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Advanced Biopolymeric Systems for Drug Delivery

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Advanced Biopolymeric Systems for Drug Delivery

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Preface

At present, drug delivery research and development are recognized as one of the fields of vital importance in biomedical and healthcare applications. Designing and development of competent drug delivery systems are now the main focus of drug delivery researchers and scientists. The innovation in biomaterial sciences and engineering allows the exploration and exploitation of various advanced biomaterials, which possess some important biomaterial characteristics like biodegradability, biocompatibility, environment responsiveness, etc. For this, biopolymers are modified or functionalized to make these as advanced materials for improved drug delivery.

The current book entitled "**Advanced Biopolymeric Systems for Drug Delivery**" covers the recent innovations in the developments of various advanced biopolymeric systems like gels, in situ gels, hydrogels, interpenetrating polymer networks (IPNs), polyelectrolyte complexes (PECs), graft co-polymers, stimuli-responsive polymers, polymeric nanoparticles, nanocomposites, polymeric micelles, dendrimers, liposomes, scaffolds, etc., and their applications in drug delivery. This volume is a collection of 15 chapters by the academicians and researchers of various fields across the world. A concise account on the contents of each chapter has been described to provide a glimpse of the book to the readers.

Chapter 1 entitled "*Biopolymers for Drug Delivery*" describes a wide variety of biopolymers such as cellulose, alginate, chitin, chitosan, pectin, gellan gum, guar gum, locust bean gum, tamarind gum, sterculia gum, natural starches, gelatine, collagen, albumin, carrageenans, hyaluronic acid (hyaluronan), and chondroitin sulfate. The uses of these biopolymers in drug delivery have been comprehensively reviewed.

Chapter 2 entitled "*Critical Points in Biopolymeric-Controlled Release Matrix Systems*" deals with different issues of controlled release matrix systems based on different biopolymers.

Chapter 3 entitled "*Biopolymeric Gels in Drug Delivery*" presents a review of biopolymeric gels, their preparation, characterization, and most importantly their applications in modern drug delivery taking into account the recent innovations.

Chapter 4 entitled "*In Situ Polymeric Gels for Topical Drug Delivery*" summarizes various potential advantages and disadvantages associated with in situ gel formulations designed for topical applications along with in situ gel formation mechanisms, factors, preparation methodologies, polymers, characterizations, and topical drug delivery applications.

Chapter 5 entitled "*Stimuli-Responsive Polymeric Systems for Smart Drug Delivery*" presents a general description of smart drug delivery systems based on the use of stimuli-responsive biopolymers as because these biopolymers comprise the particularity of responding to small physical or chemical stimuli leading to a macroscopic alteration in their structure/properties.

Chapter 6 entitled "*Smart Polysaccharide Hydrogels in Drug Delivery and Release*" deals with sustainable issue of smart polysaccharide hydrogels, which are trending to appear in advanced drug delivery applications. It is worth discussing this topic to bring forward and unwrap such advanced findings for keen inventors.

Chapter 7 entitled "*Polysaccharide-Based Nanoparticles: Nanocarriers for Sustained Delivery of Drugs*" presents the latest developments in the last five years in the drug delivery field using polysaccharide-based nanoparticles as sustained drug-releasing nanocarriers.

Chapter 8 entitled "*Polysaccharide-Based Nanocarriers for Oral Delivery of Insulin in Diabetes*" specifically describes the current challenges for oral delivery of insulin, polysaccharide-based nanocarriers loaded with insulin that can be used for targeted delivery of insulin with enhanced bioavailability, non-toxicity, and effectivity along with its future prospects.

Chapter 9 entitled "*Interpenetrating Polymer Networks in Sustained Drug-Releasing*" presents a detailed overview of the characteristics and recent successful applications of interpenetrating polymer networks (IPNs) in sustained drug delivery devices.

Chapter 10 entitled "*Biopolymeric Nanocomposites in Drug Delivery*" offers the most recent significant researches on various biopolymeric nanocomposites in drug delivery applications using biomacromolecules including chitosan, carboxymethyl chitosan, alginate, hyaluronic acid, cellulose, carboxymethyl cellulose, starch, gellan gum, gum acacia/gum arabic, guar gum, gelatin, chondroitin sulfate, pectin, and collagen.

Chapter 11 entitled "*Biopolymeric Micelles*" specifically describes about the background, properties, and characterization of biopolymeric micelles along with their applications in drug delivery and targeting.

Chapter 12 entitled "*Liposomes for Advanced Drug Delivery*" summarizes the recent advances in liposomal drug delivery systems and their applications for advanced drug delivery.

Chapter 13 entitled "*Dendrimers for Advanced Drug Delivery*" covers the recent advances in dendrimer technology, applications of dendrimers in drug delivery/targeting, and associated cytotoxicity issues.

Chapter 14 entitled "*Nanofibers for Filtration Applications*" focuses on nanofibers by electrospinning method and their applications for filtration. More specifically, antimicrobial nano-fibrous membranes (as antimicrobial filters, fibers

for oil spill cleanup, and fibers for nanoparticles removal from aqueous solution) developed from electrospun polymers, and their applications have been discussed.

Chapter 15 entitled "*Marine Polysaccharides Systems for Drug Delivery Applications*" discusses about marine polysaccharides like alginate and chitosan along with their modified derivatives for various drug delivery applications.

We would like to convey our sincere thanks to all the authors of the chapters for providing timely and valuable contributions. We thank the publisher—**Springer Nature**. We specially thank **Dr. Mayra Castro, Dr. Shadia Ikhmayies**, and **Mr. Ashok Arumairaj** for their invaluable support in the organization of the editing process right through the beginning to finishing point of this book. We gratefully acknowledge the permissions to reproduce copyright materials from various sources. Finally, we would like to thank our family members, all respected teachers, friends, colleagues, and dear students for their continuous encouragements, inspirations, and moral supports during the preparation of the current book. Together with our contributing authors and the publishers, we will be extremely pleased if our endeavor fulfills the needs of academicians, researchers, students, polymer engineers, biomedical experts, pharmaceutical students, and drug delivery formulators.

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About the Editors

Dr. Amit Kumar Nayak is currently working as an associate professor at Seemanta Institute of Pharmaceutical Sciences, Odisha, India. He has earned his PhD in Pharmaceutical Sciences from IFTM University, Moradabad, Uttar Pradesh, India. He worked as a senior research associate at IIT, Kanpur, in a CSIR sponsored project. He has over 12 years of research experience in the field of pharmaceutics, especially in the development and characterization of novel biopolymeric drug delivery systems. His recent research focus is the development of ceramic bone-implantable drug delivery for osteomyelitis therapy. Till date, he has authored over 113 research and review publications in various high impact peer-reviewed journals and 76 book chapters and seven books to his credit. Overall, he has earned highly impressive publishing and cited record in Scopus (*h*-index: 34) and in Google Scholar (*h*-index: 38, i10-Index: 93). He is serving as the "editorial board member" of journals (Current Drug Delivery and Drug Delivery Letters) and also, as the permanent reviewer of many international and national journals of high repute. He has presented his research work at several conferences. He has received University Foundation Day Research Award-2019 by Biju Patnaik University of Technology, Odisha. He has qualified GATE (Pharmaceutical Sciences) in 2006. At present, he is guiding two PhD scholars. He has performed as examiner and paper setter in various universities. He is a life member of the Association of Pharmaceutical Teachers of India (APTI) and a registered pharmacist.

Dr. Md Saquib Hasnain has over nine years of research experience in the field of drug delivery and pharmaceutical formulation analyses, especially systematic development and characterization of diverse nanostructured drug delivery systems, controlled release drug delivery systems, bioenhanced drug delivery systems, nanomaterials, and nanocomposites employing quality by design approaches and many more. Till date, he has authored over 40 publications in various high impact peer-reviewed journals, 70 book chapters, and nine books to his credit. He is also serving as the reviewer of several prestigious journals. Overall, he has earned highly impressive publishing and cited record in Google Scholar (*h*-index: 15).

He has also participated and presented his research work at over ten conferences in India, and abroad. He was also the member of scientific societies, i.e., Royal Society of Chemistry, Great Britain, International Association of Environmental and Analytical Chemistry, Switzerland, and Swiss Chemical Society, Switzerland.

Biopolymers for Drug Delivery

Md Saquib Hasnain, Syed Anees Ahmed, Saad Alkahtani, Milan Milivojevic, Chandi Charan Kandar, Amal Kumar Dhara, and Amit Kumar Nayak

Abstract Recent research and developments in the field of biopolymers direct the successful formulations of various novel and smart drug delivery devices with enhanced therapeutic efficacy, better patient compliances, and cost-effectiveness. In the drug delivery field, a variety of biodegradable polymers are being extensively used as these biopolymers are degraded biologically to non-toxic components inside the body. An appropriate understanding of various potential attributes, such

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as extraction methodology and sustainable production, chemistry, surface characteristics, rheology, bulk properties, biocompatibility, biodegradability, etc., of biopolymers can help in the designing of various biopolymer-based drug delivery systems. In this chapter, a wide variety of biopolymers and their uses in drug delivery have been comprehensively reviewed.

Keywords Biopolymers · Biopolysaccharides · Excipients · Drug delivery

1 Introduction

Over the last several centuries, biopolymers, the most versatile grade of biomaterials, have already been amended our everyday lives [1]. Although within only past 30 years, a significant distinction was noticed in the research and development of biomedical applications using various kinds of biopolymers [1–3]. The convergence of biopolymer technology and pharmaceutical research has resulted in a step-change in the designing and development of different newer kinds of drug delivery systems for the attainment of improved therapeutic efficacy as well as better patient compliances [4, 5]. Drug delivery refers to the methods, formulations, and techniques, to safely and effectively processing of the therapeutic agents within the body to accomplish the desired therapies [6, 7]. Different drug delivery systems are developed based on the interdisciplinary methods integrating the fields of polymer sciences, pharmaceutics, bioconjugate chemistry, and molecular biology while aiming at the new thoughts and approaches for regulating basic pharmacokinetics, pharmacodynamics and non-specific toxicity to enhance the biorecognition and therapeutic efficacy [8–12]. At present, about 60 million patients throughout the globe are gaining from the innovative drug delivery technologies via providing better and more effectual action of drugs necessary to counter various diseases [13]. The physicochemical nature and low-molecular weight of drugs characteristically confer the potential to deliver the drugs to the desired site of the body. The indiscriminate delivery of drugs, however, contributes to a low concentration of drugs at the site of the action required, systemic side effects, and a greater risk of the need for higher doses to bring about the optimal therapeutic responses [4]. A short half-life and rapid renal clearance of low molecular weight drugs, together with other factors, such as protein binding, lipophilicity, and ionizability, may result in the need for frequent administration of dosage forms to achieve the therapeutic effect and thereby, this can cause high dosage associated systemic side effects [1].

In general, various kinds of drugs are processed together with the inert compounds to formulate dosage forms are called excipients [14]. In formulations of drug delivery dosage forms, the excipients are usually added to enhance bioavailability and patient compliances. Such drug delivery excipients are of different types like emulsifiers, stabilizers, thickeners, viscosity enhancers, lubricants, diluents, disintegrating agents, coating agents, matrix formers, release retardants, mucoadhesive agents, gelling agents, film formers, etc. [13, 14]. These drug delivery excipients are

known as inert in nature because these do not exert the therapeutic actions or modify the biological actions of drugs. The current consensus is, however, that these excipients influence the rate and extent of drug absorptions, and thus, the pharmaceutical properties of these substances affect the bioavailability of drugs. The drug delivery field as a whole has experienced a range of diversified and intense researches on the modulation and absorption of drugs to attain optimal therapy [1, 7]. The development of new drug delivery systems not only offers additional benefits to those discussed above; but, may also make possible the use of various poorly soluble drug candidates to be formulated and finally to be administered by means of different kinds of dosage forms [6]. In the current chapter, a wide variety of biopolymers and their potential uses in drug delivery applications have been briefly reviewed.

2 Drug Delivery Systems

Drug delivery systems are the approaches for the delivery of drug candidates to specific body sites so that the drugs can be released at a desired rate [6]. Such a system through which the loaded/encapsulated drug is released and capable of producing significant therapeutic action is defined as a drug delivery system [7]. Various kinds of drug delivery carriers include nanoparticles, nanocapsules, microparticles, microcapsules, micelles, dendrimers, biocomposites, spheroids, beads, gels, hydrogels, films, patches, implants, scaffolds, etc., in which different drugs are loaded [1, 6]. Therefore, the primary purpose of the biopolymeric carriers is to deliver drugs to the desired sites of actions facilitating the protection of drugs from damaging or degradation, especially protein and peptides. In general, damaging and/or degradation of proteins and peptides may cause alteration in their chemical structure [15]. This occurrence may cause the inactivation of such drug candidates, which can inhibit the drug from reaching the site of actions. The model drug delivery system must be biocompatible and competent in attaining high loading of drugs, safe and easy to administer [6]. The important most challenge in the formulation of various biopolymers made controlled drug delivery system is the rational selection of polymer(s) [13]. To formulate various drug delivery systems, different natural, semi-synthetic and synthetic polymers have been used.

Biopolymers are the polymers derived/extracted from the living organisms [16]. In other words, biopolymers are the polymeric biomolecules made of several monomeric units, which are generally covalently bonded to configure a macromolecular polymeric structure. During the past few decades', a variety of biopolymers have already been explored, which are derived/extracted from microorganisms, plants, and animals [17–21]. These biopolymers have also been exploited for the designing of various types of drug delivery systems [4, 5, 22–26]. However, it is very difficult for the categorization of biopolymers used in controlled drug-releasing applications because of their inherent structural complexity.

In general, biopolymers can be classified as biodegradable polymers and non-biodegradable polymers. Biodegradable polymer-based dosage forms gradually

degrade within the body and therefore, these are being used in the formulation of drug delivery systems [16]. In contrast, non-biodegradable polymers are lacking of the recycling facility, and hence, these are rarely used [16, 27]. The important most challenges in the formulation of various biopolymer made controlled drug delivery system is the rational selection of biopolymer(s), which necessitate a comprehensive understanding of surface as well as bulk characteristics of biopolymers that can be functional in the designing of drug delivery systems to attain optimal therapeutic efficacy [6, 28]. Furthermore, to meet up above discussed issues, the biopolymeric drug delivery systems require comprehensive biochemical characterizations along with the detailed preclinical assessment [29].

3 Biopolymers

3.1 Cellulose

Cellulose is one of the widely used biopolysaccharides derived from numerous naturally occurring renewable resources, including plant fibers (such as cotton, hemp, jute, wood fibers, etc.) [30]. It is well-known as the major composition of various plant cell walls [31]. Recently, cellulose is also produced by certain bacteria [30, 32]. Cellulose is a linear unbranched biopolysaccharide comprising of (1 → 4)-linked D-glucose units (Fig. 1) and numerous parallel molecules of cellulose forming the crystalline microfibril structure [32]. The crystalline microfibril structure is physically strong and characterized by highly resistant to the enzymatic attacks. These microfibrils are aligned to provide the cell wall structure [31]. Cellulose extracted from fibrous raw materials like cotton and wool can be physico-mechanically disintegrated to powdered cellulose, which is being utilized as filler material in the pharmaceutical tablets [33]. Good quality powdered cellulose produces microcrystalline cellulose when it is treated by hydrochloric acid. Microcrystalline cellulose is favored over powdered cellulose as it is more free-flowing and non-fibrous, in nature. Additionally, microcrystalline cellulose is used in tablets as diluents or filler/binder for both granulation and direct compression processes [34]. In vivo, cellulose is poorly biodegradable, but hydrolyzable cellulose can be produced by altering the higher-order structural features of cellulose [35]. The simplicity of transforming native cellulose in

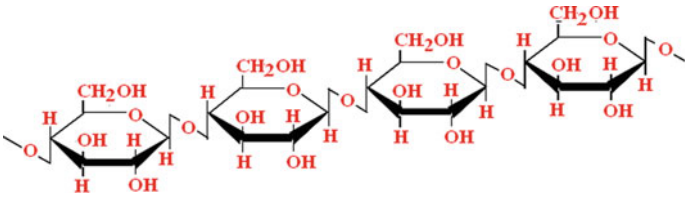

Fig. 1 Molecular structure of cellulose

different derivatives makes it a smarter biopolymeric raw material for diversified biomedical applications. Esterification, etherification, crosslinking, graft copolymerization, etc., are the means of preparation of cellulose derivatives [32]. Etherification process yields cellulose derivatives like carboxymethyl cellulose (CMC) and hydroxypropyl methylcellulose (HPMC), while the esterification of cellulose results in the derivatives like cellulose nitrate, cellulose acetate, and cellulose acetate phthalate [32, 36]. For membrane-controlled release systems, such as enteric coating and the use of semi-permeable membranes for osmotic pump delivery systems, these cellulose derivatives have found useful.

HPMC is an off-white coarse powder or granules are capable of swelling in the aqueous environment to form non-ionic and viscous colloidal solutions [36]. It is a multifunctional biopolymer possessing stability over a wider pH ranging. The viscosity of HPMC is found dependent on the molecular weight, composition, and concentration. Various grades of HPMC are employed in many applications such as stabilizer, suspending agent, coating agent, binding agent, release retardant, matrix former, viscosity enhancer, etc. [34, 37, 38]. Ethylcellulose is another type of cellulose derivative and water-insoluble biopolymer [39]. Depending on the manufacturing process, the number of ethyl groups can vary. Ethylcellulose is a powder of tasteless and free-flowing, in nature. It is a stable biopolymer possessing moderately hygroscopic quality [33, 34]. Chemically, ethylcellulose is alkali resistant; however, it is comparatively more sensitive than the cellulose esters in the acidic milieu. It undergoes the oxidative degradation at the high temperatures, in the presence/occurrence of sunlight or ultraviolet light [36]. Ethylcellulose is extensively used in many pharmaceutical formulations both oral as well as topical administrations [36, 39]. The important most uses of ethylcellulose includes hydrophobic coating agents onto granules and tablets [33, 34, 36]. Some recent researches on the uses of cellulose and its derivatives for drug delivery applications are presented in Table 1.

3.2 Chitin and Chitosan

Chitin is a naturally occurring biopolymer, which is extracted from crustacean shells, including crabs, shrimps, and lobsters [47]. Chitin even occurs in certain microorganisms, yeast, and fungi. The exoskeleton of crustaceans comprises 15–20% of dry weight of chitin. Chitin is recognized as a renewable bioresource found in nature [21, 47]. In the molecular structure of chitin, as the primary structural unit, 2-deoxy-2-(acetylamino) glucose is present.

Chitosan is produced by the alkaline *N*-deacetylation of chitin [47]. Chemically, the chitosan molecule comprises randomly distributed $\beta(1 \rightarrow 4)$-linked D-glucosamine and *N*-acetyl-D-glucosamine (Fig. 2). Chitosan merely refers to a family of copolymers with different fractions of acetylated units. Although chitin is insoluble in several solvents, it is soluble at a pH of less than 6.5 in most of the organic acid solutions, including acetic acid, formic acid, and tartaric acid [47–49]. However, it is insoluble in both sulphuric acid and phosphoric acid. The aqueous

Table 1 Recent researches on the uses of cellulose and its derivatives for drug delivery applications

Cellulose and cellulose derivatives based drug delivery systems	Drug(s)	References
Matrix tablets made of alginate, HPMC and microcrystalline cellulose	Bisoprolol fumarate	Malakar et al. [37]
In situ crosslinked alginate matrix tablets for sustained release prepared using microcrystalline cellulose	Salbutamol sulfate	Malakar et al. [40]
Chitosan-HPMC matrices as carriers for hydrodynamically balanced capsules	Moxifloxacin HCl	Verma et al. [41]
Floating capsules containing alginate-HPMC-based beads	Salbutamol sulfate	Malakar et al. [42]
Gastroretentive hydrodynamically balanced system made of HPMC	Ofloxacin	Nayak et al. [38]
Ethyl cellulose microparticles	Metformin HCl	Maji et al. [39]
Alginate-HPMC and alginate-sodium CMC buccal patches	Atenolol	Rath Adhikari et al. [43]
Alginate-methyl cellulose mucoadhesive microcapsules	Gliclazide	Pal and Nayak [44]
Alginate/HPMC-based in situ gelling ophthalmic system	Gatifloxacin	Liu et al. [45]
CMC/graphene oxide bio-nanocomposite hydrogel beads	Doxorubicin	Monireh and Hassan [46]

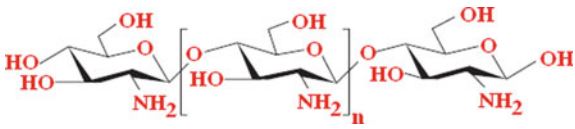

Fig. 2 Molecular structure of chitosan

solubility of chitosan depends on the presence of free amino groups and *N*-acetyl groups in the molecular structure of chitosan [46]. Because of the presence of many free amino groups, chitosan is capable of crosslinking and this crosslinking property has been exploited to produce hydrogels [50]. Chitosan is reported as an antimicrobial polymer. It is also known as biocompatible and biodegradable biopolysaccharide. On the account of its biocompatibility and biodegradability characteristics, chitosan is being utilized as biopolymeric excipients in the formulations of various kinds of pharmaceutical dosage forms including inhalable powders, matrix tablets, transdermal and buccal films or patches, microparticles, nanoparticles, pellets, gels, implants, etc. [1, 13, 21, 34]. During the past few decades, chitosan and chemically modified (functionalized) chitosan have been employed as the biopolymeric excipients in the fabrication of numerous drug delivery carriers [21, 47, 50]. Some of the important and widely pharmaceutically used modifications chitosan

Table 2 Recent researches on the uses of chitosan for drug delivery applications

Chitosan-based drug delivery systems	Drug(s)	References
Chitosan succinate and chitosan phthalate microspheres for oral delivery	Insulin	Ubaidulla et al. [51]
Chitosan–gelatin films	Tyrosol and ferulic acid	Benbettaïeb et al. [52]
Chitosan-HPMC matrices as carriers for hydrodynamically balanced capsules	Moxifloxacin HCl	Verma et al. [41]
Chitosan-tamarind seed polysaccharide interpenetrating polymeric network microparticles	Aceclofenac	Jana et al. [50]
Photoresponsive chitosan conjugated prodrug nanocarrier	5-fluorouracil	Horo et al. [53]
Chitosan-egg albumin nanoparticles for oral drug delivery	Alprazolam	Jana et al. [54]
Carbopol gel containing chitosan-egg albumin nanoparticles for transdermal delivery	Aceclofenac	Jana et al. [55]
Polysorbate 80 coated crosslinked chitosan nanoparticles for brain targeting	Ropinirole HCl	Ray et al. [56]
On-chip made chitosan nanoparticles for cancer therapeutics	Paclitaxel	Majedi et al. [57]
Magnetic stimuli-responsive chitosan-based drug delivery biocomposite for multiple triggered release	Vancomycin	Harris et al. [58]

include acylation, alkylation, sulfation, thiolation, phosphorylation, carboxyethylation, carboxymethylation, *N*- or *O*-quaternarization, chitosan reductive amination with phosphorylcholine glyceraldehydes, grafted copolymerization of chitosan [47–50]. Chitosan phthalate and chitosan succinate have been employed to formulate microspheres for the oral delivery of insulin [51]. Chitosan succinate is often more hydrophilic than the chitosan phthalate. The comparative pharmacological effectiveness of insulin-containing microspheres made of chitosan phthalate and chitosan succinate is reported to produce approximately three-folds more significant action than the oral administration of insulin [51]. For oral delivery systems of protein and peptide drugs, novel hydrogels made of various chitosan derivatives have been developed and evaluated. Some recent researches on the uses of chitosan for drug delivery applications are presented in Table 2.

3.3 Alginate

Alginic acid (often known as alginate or algin) is an anionic polysaccharide occurred in the brown algae cell walls, wherein it constitutes a viscous gum by interacting

with water [21, 59]. It soaks up water rapidly and is also capable of producing highly viscous hydrocolloids. The color of alginate varies from white to brownish-yellow. Alginate molecules consist of (1 → 4)-linked L-guluronic acid (G) and D-mannuronic acid (M) residues in the alternating chains (Fig. 3a). The geometries of the G-block regions, M-block regions, and alternating regions are substantially dissimilar because of the specific shapes of these monomers and their linkage modes in the alginate molecular structure [60]. In particular, the G blocks are buckled, whereas the M blocks are alike an extended ribbon structure. By the influence of several divalent as well as trivalent metal cations, such as Zn^{2+}, Ca^{2+}, Ba^{2+}, Cu^{2+}, Cd^{2+}, Pb^{2+}, Al^{3+}, Fe^{3+}, etc., sodium alginate (i.e., sodium salt of alginic acid) undergoes the ionotropic gelation [59–61]. Ionotropic gelation as well as crosslinking of sodium alginate is accomplished primarily through the exchange of monovalent sodium ions present in the sodium alginate with the divalent and trivalent metal cations, and the stacking of these guluronic groups to form characteristic the "egg-box" modeling structures [62]. Divalent and trivalent metal cations induce the inter-polysaccharide binding at the crosslinking sites, which are known as junction zones [61, 62]. These crosslinking metal cations (divalent and trivalent) interact with the sodium ions of sodium alginate and thereby bring together the two polymer chains to form crosslinked alginate of insoluble nature. These crosslinking metal cations are actually accommodated in the interstices of two polyuronate chains possessing a close ion-pairing with the carboxylate anions of the sodium alginate molecules and sufficient coordination as a result of other electronegative oxygen atoms [59]. The ionotropic gelation interaction in-between alginate with divalent calcium ions is shown in Fig. 3b.

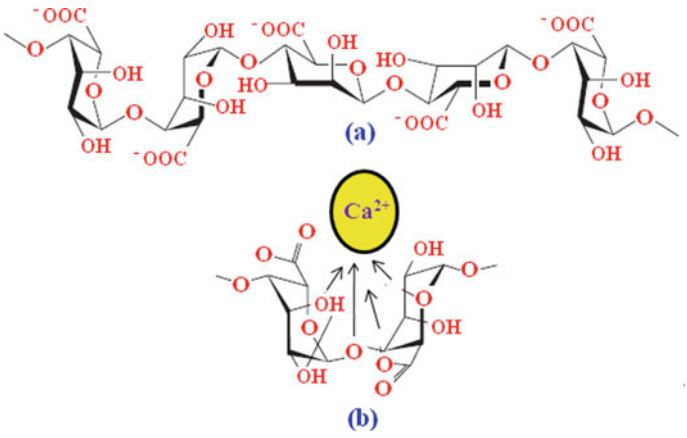

Fig. 3 **a** Molecular structure of alginate and **b** ionotropic gelation of alginate by calcium ions

Alginates are commonly used biopolymers as pharmaceutical excipients in various kinds of pharmaceutical dosage forms, such as tablets, capsules, gels, emulsions, buccal patches, beads, microparticles, nanoparticles, etc., due to their advantageous physicochemical characteristics such as solubility, viscosity, crosslinking, sol–gel transformation, etc., and favorable biological characteristics, such as biocompatibility, biodegradability, bioadhesion, immunogenicity, etc. [42–45, 60, 63]. Recent years, different tailor-made alginate-based materials, such as crosslinked alginate, oxidized alginate, thiolated alginate, grafted alginate, etc., are being synthesized and used to formulate various improved and smart biopolymeric systems for drug delivery [64–66]. Recently, other biomaterials (both bioorganic and/or bioinorganic) have been combined/blended with the alginate matrices to modify the drug-releasing over a longer period [61–63, 67–69]. Some recent researches on the uses of alginates for drug delivery applications are presented in Table 3.

3.4 Gellan Gum

Gellan gum is well-known as an important microbial biopolymer. It is occurred by the fermentation (aerobic) of *Pseudomonas elodea*, a Gram-negative bacterium [88]. Gellan gum is an anionic natured biopolysaccharide. The molecular structural feature of gellan gum is described as the repeating sugar units containing α-L-rhamnose, β-D-glucose, and β-D-glucuronate. These α-L-rhamnose, β-D-glucose, and β-D-glucuronate are present in the molecular formula of gellan gum in the molar ratios of 1:2:1 [89]. The native form of gellan gum is two types: acyl gellan gum and acetyl gellan gum [88]. Both the low-acyl gellan gum is capable of producing hydrogels by the influence of di- and trivalent metal cations [90, 91]. On account of biocompatibility, biodegradability, nonallergic, hydrophilicity, and mucoadhesivity of gellan gum, it is currently exploited as a biopolymeric excipient in drug delivery [88, 89, 92]. During last few years, gellan gum has been exploited in the development of various drug delivery dosage forms, such as tablets, hydrogels, beads, microparticles, nanoparticles, films, etc., via different routes of administrations (for example, oral, topical, nasal, buccal, ophthalmic, vaginal, etc.) [89, 92]. In recent years, it has also been employed for designing and developing a variety of nanoformulations for the effectual delivery/targeting of drugs [92–95]. Some recent researches on the uses of gellan gum for drug delivery applications are presented in Table 4.

3.5 Pectins

Pectins are non-starch natural polysaccharides. These are water-soluble, biocompatible, and biodegradable polysaccharides [101]. Pectin occurs in the plant cell walls and is industrially extracted from various plant resources, such as citrus peels, sugar beetroots, apple pomaces, etc. [102–105]. These are employed as food additives,

Table 3 Recent researches on the uses of alginates for drug delivery applications

Alginate-based drug delivery systems	Drug(s)	References
In situ crosslinked alginate matrix tablets for sustained release prepared using microcrystalline cellulose	Salbutamol sulfate	Malakar et al. [40]
Hard gelatin capsules containing alginate and other hydrophilic polymers	Theophylline	Malakar and Nayak [70]
Zinc alginate-carboxymethyl cashew gum microbeads	Isoxsuprine HCl	Das et al. [64]
Linum usitatisimum polysaccharide-alginate mucoadhesive beads	Diclofenac sodium	Hasnain et al. [71]
Tamarind seed polysaccharide-alginate beads	Metformin HCl	Nayak et al. [72], Nayak and Pal [73]
Alginate-ispaghula husk beads	Gliclazide	Nayak et al. [74]
Alginate-PVP K 30 microbeads	Diclofenac sodium	Nayak et al. [75]
Oil-entrapped buoyant alginate beads containing magnesium stearate	Ibuprofen	Malakar and Nayak [76]
Oil-entrapped buoyant alginate beads by emulsion–gelation method	Cloxacillin	Malakar et al. [77]
Calcium alginate-gum arabic beads	Glibenclamide	Nayak et al. [78]
Jackfruit seed starch-alginate beads	Pioglitazone	Nayak et al. [79]
Jackfruit seed starch-alginate mucoadhesive beads	Metformin HCl	Nayak and Pal [80]
Fenugreek seed mucilage-alginate mucoadhesive beads	Metformin HCl	Nayak et al. [81]
Modified starch (cationized)-alginate beads	Aceclofenac	Malakar et al. [65]
Soluble starch-blended Ca^{2+}-Zn^{2+}-alginate composites-based microparticles	Aceclofenac	Nayak et al. [82]
Zinc alginate-okra gum blend beads	Diclofenac sodium	Sinha et al. [83]
Okra gum-alginate blend mucoadhesive beads	Glibenclamide	Sinha et al. [84]
Alginate nanocapsules	Testosterone	Jana et al. [85]
Alginate-PVP-nanohydroxyapatite composite matrices	Diclofenac sodium	Hasnain et al. [86]
Alginate hydrogel core-shell systems for combination delivery	Ranitidine HCl and aceclofenac	Jana et al. [87]

Table 4 Some recent researches on the uses of gellan gum in drug delivery applications

Gellan gum based drug delivery systems	Drug(s)	References
Sustained drug-releasing pellets made of gellan gum and polyvinyl pyrrolidone as binding agents	Theophylline	Barbosa and Ferraz [96]
Ispaghula mucilage-gellan gum mucoadhesive beads	Metformin HCl	Nayak et al. [90]
Fenugreek seed mucilage-gellan gum mucoadhesive beads	Metformin HCl	Nayak and Pal [91]
Jackfruit seed starch-blended gellan gum mucoadhesive beads	Metformin HCl	Nayak et al. [97]
Tamarind seed polysaccharide-gellan gum mucoadhesive beads	Metformin HCl	Nayak et al. [98]
Unsaturated esterified alginate-gellan gum microspheres	Aceclofenac	Jana et al. [99]
pH-dependent drug-releasing novel gellan gum beads	Naproxen	Osmałek et al. [100]
Gellan gum/PVA nanofibers for gastroretentive/mucoadhesive drug delivery	Ofloxacin	Vashisth et al. [93]
Gellan gum nanohydrogel for combination therapy in cancer treatment	Paclitaxel and prednisolone	D'Arrigo et al. [96]
Self-assembled gellan gum nanohydrogel	Prednisolone	D'Arrigo et al. [94]

thickeners, stabilizers, emulsifiers, and gelling agents [101]. Pectins are reported as primarily linear polymers composed of D-galacturonic acid residues, which are linked via α-(1, 4) glycosidic linkages (Fig. 4). The main chain of D-galacturonic acid residues also possesses irregular the rhamnose groups that interrupt the configuration of the chain-helix and α-L-rhamnopyranose via the α-(1–2) linkage with an approximately few hundred to about one thousand building blocks per pectin molecule in proportion to an average molecular weight of 50,000–180,000, approximately [101–105]. The occurrence of carboxylic acid groups of D-galacturonic acid residue is generally esterified by a methoxy group. High methoxy pectins are capable of forming gels in an acidic environment by the addition of a higher quantity of sucrose (>50%) [101]. In contrast, the low methoxy pectin is generally capable of forming

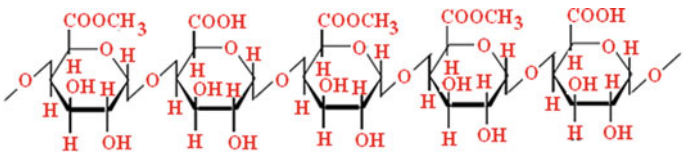

Fig. 4 Molecular structure of pectin

Table 5 Some recent researches on the uses of pectins in drug delivery applications

Pectin-based drug delivery systems	Drug(s)	References
Pectinate-poly (vinyl pyrrolidone) beads	Aceclofenac	Nayak et al. [107]
Calcium pectinate-fenugreek seed mucilage mucoadhesive beads	Metformin HCl	Nayak et al. [102]
Calcium pectinate-ispagula mucilage mucoadhesive beads	Metformin HCl	Nayak et al. [104]
Jackfruit seed starch-pectinate mucoadhesive beads	Metformin HCl	Nayak et al. [105]
Calcium pectinate-tamarind seed polysaccharide mucoadhesive beads	Metformin HCl	Nayak et al. [103]
Mucoadhesive-floating zinc-pectinate-sterculia gum interpenetrating polymer network beads	Ziprasidone HCl	Bera et al. [108]
Plantago ovata F. husk mucilage-Zn^{+2}-pectinate controlled release matrices	Aceclofenac	Guru et al. [109]
Pectin beads loaded with chitosan–iron microspheres for colonic specific delivery	Ciprofloxacin	Reynaud et al. [110]
Pectin-coated nanoliposomal delivery	Phloridzin	Haghighi et al. [111]
Pectin-coated liposomes	Vitamin C	Zhou et al. [112]

gelled polymeric structures by the ionotropic gelation process by the influence of specific divalent cations (for examples: Zn^{2+}, Ca^{2+}, etc.) and this ionotropically-gelled matrices have been used for drug delivery [62]. Pectins of different sources have already been used as the potential pharmaceutical excipients for the many years in various formulations of drug delivery dosage forms, such as tablets, gels, hydrogels, nanoparticles, microparticles, beads, films, patches, scaffolds, etc. [102–106]. In recent years, low methoxy pectin has extensively been employed to formulate several ionotropically-gelled pectinate particulates in the form of microparticles and beads for sustained drug-releasing and multi-unit floating drug delivery systems [102–105, 107–109]. Recent years, various mucoadhesive biopolymers have been exploited as blends with low methoxy pectin to formulate mucoadhesive multiple-unit particulates (microparticles and beads) for various drugs [103–105, 107]. In addition, considering the colon-specific property of pectin, a wide range of pectinate-based systems have been developed and evaluated for colonic drug delivery/targeting systems [106]. Some recent researches on the uses of pectins for drug delivery applications are presented in Table 5.

3.6 Gum Arabica

Gum arabic is a plant-derived natural biopolymer extracted from *Acacia* (family, Leguminosae) [113]. It possesses a complex and branched polysaccharidic structural feature containing sugars like galactose, arabinose, rhamnose, glucuronic acid,

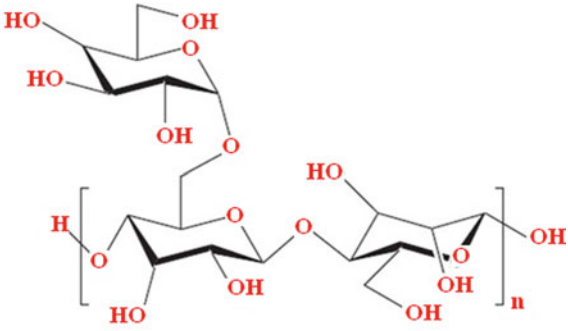

Fig. 5 Molecular structure of guar gum

etc. [78]. It also contains some extents of moisture, and protein. Gum arabic is extensively used as thickening agent, emulsifier, and suspending agent in various food preparations and cosmetic products [114]. During the past few decades, by reason of the potential benefits of cost-effectiveness, biodegradability, and biocompatibility, gum arabic has already been used as pharmaceutical as well as drug delivery excipient [78, 113]. It has proved its potential as tableting excipient in various pharmaceutical tablets for the delivery of drugs [115]. Gum arabic has already been used to formulate microparticles and nanoparticles for improved drug delivery [78, 116].

3.7 Guar Gum

Guar gum is an example of a plant-derived biopolymer of non-ionic, biocompatible, and biodegradable in nature [117]. It is extracted from *Cyamopsis tetragonoloba* seeds (family; Leguminosae) [117, 118]. Chemically, guar gum exhibited a linear polysaccharidic chain composed of (1 → 4)-β-D-mannopyranosyl units possessing α-D-galactopyranosyl units linked by (1 → 6) linkages (Fig. 5) [118]. Guar gum possesses the capability of gel formation in aqueous solutions. It has already been used as a thickener, suspending agent, stabilizer, and emulsifier in various food and pharmaceutical applications [117, 119]. Guar gum is extensively used to formulate hydrophilic matrices for drug delivery [119]. It is used as colon-specific matrices because of its enzymatic degradation at the colonic fluids [120].

3.8 Locust Bean Gum

Locust bean gum is a biopolymer extracted from the seeds of carob tree (*Ceratonia siliqua*) and that's why it is also known as carob bean gum [121–123]. Chemically, it is galactomannan category of biopolysaccharide containing galactose and mannose (1: 4) [121]. The molecular structure of locust bean gum comprises of (1, 4)-linked

β-D-mannopyranose backbone possessing the branch points at 6-positions, which is linked to α-D-galactose [122]. It is less soluble in the cold water and soluble in the hot water. It possesses the capability of producing heavy viscous solutions even at the lower concentrations, and this characteristic was found unchanged by salt addition, alteration of pH, or temperature [123]. It is biocompatible, biodegradable nonteratogenic and nonmutagenic, in nature [121]. It has been exploited as biopolymeric excipients in various drug delivery dosage forms [122, 123]. Because of its mucoadhesive nature, locust bean gum is used in the formulation of various mucoadhesive drug delivery systems [124, 125].

3.9 Tamarind Gum

Tamarind gum is extracted from the tamarind (*Tamarindus indica* L.; family: Leguminosae) seed kernel powder by various established extraction methodologies [126, 127]. Chemically, it is a galactoxyloglucan and its molecular structure is composed of (1 → 4)-β-D-glucan skeleton, which reported to be substituted with side chains of α-D-xylopyranose and β-D-galactopyranosyl (1 → 2)-α-D-xylopyranose linked (1 → 6) to glucose residues, where glucose, xylose and galactose units are present (2.8:2.25:1.0) [128, 129]. Tamarind gum is an aqueous soluble biopolysaccharide [130]. During the past few decades, it has been exploited as binder, gel-forming agent, thickening agent, emulsifying agent, mucoadhesive agent, and release modifier in various drug delivery systems [126, 127, 131]. In the present literature, a variety of multiple-unit particulate carriers for the delivery of different drugs have been reported [130–135]. Furthermore, because of the hydrophilicity and mucoadhesivity, tamarind gum has been used in the formulation of mucoadhesive drug delivery systems [133]. Recent years, tamarind gum has been functionalized and functionalized tamarind gum has been evaluated as excipients in different drug delivery dosage forms [136].

3.10 Sterculia Gum

Sterculia gum or karaya gum is a plant-derived biopolymer extracted from the exudates of plant—*Sterculia urens* (family: sterculiaceae) [137]. It is a partially acetylated biopolysaccharide and also, composed of three dissimilar chains. The 1st chain (i.e., approximately, 50% of the total gum) comprises four galacturonic acid repeating units, L-rhamnose at the reducing end and β-D-galactose branch. The 2nd chain (i.e., approximately, 17% of the total gum) comprises an oligorhamnan possessing D-galactose and D-galacturonic acid branch. The last or 3rd chain comprises (i.e., approximately, 13% of the total gum) comprises D-glucuronic acid with galactose, rhamnose, and uronic acid [138]. Sterculia gum is reported to

possess various potential characteristics for biomedical applications like biocompatibility, biodegradability, nonallergic, nonteratogenicity, nonmutagenicity, aqueous solubility, etc. [137]. In addition, it is also reported to exhibit antimicrobial property [138]. It also possesses high viscosity, good acidic stability, and excellent swelling ability [139]. Since long, sterculia gum is well-known as a natural biopolymeric excipient, which is has been used to formulate various tablets, microparticles, beads, hydrogels, buccoadhesive drug delivery systems, etc. [137–140]. In recent years, several multiple-unit particulate drug delivery carriers have been developed [138, 139]. Some of these have been designed for gastroretentive drug delivery by floating and/or mucoadhesive approaches [108, 141, 142].

3.11 Natural Starches

Starches are the important class of naturally derived biopolymers well-known for their various useful applications in the biomedical fields including drug delivery, regenerative medicine, etc. [35]. Starches are the reserve carbohydrate storage occurred in the plant parts like cereals, root vegetables, rhizomes, seeds, tubers, and corms as microscopic granules with characteristically shapes and sizes, which are of origin-specific, in nature [143]. Natural starches are usually extracted from maize, potato, wheat, rice, etc. Starch molecules are the glucose monomers that occurred as insoluble granules in the plant cell chloroplasts. Chemically, starch molecules are consisting of α-amylose (20–30%) and amylopectin (70–80%) [35, 65]. Various naturally occurring starches are already reported as cost-effective, biocompatible, and biodegradable in nature [80, 97, 143]. Nevertheless, after oral ingestion, native starch alone is about completely broken down. The current on starch has focused the exploration of different nonconventional natural starch sources with their physico-chemical, structural, and functional properties facilitating a wider-ranging of potential industrial applications [105, 143]. During the past few decades, a significant volume of natural starches have already been used as pharmaceutical excipients in the formula of several drug delivery dosage forms like tablets, hydrogels, beads, microparticles, nanoparticles, etc. [143, 144]. Recently, various nonconventional starch sources have been identified and from these identified sources, various useful starches have already been extracted. Recently, these plant-derived natural starches have been used to formulate various biopolymer beads and microparticles for sustained drug-releasing applications [65, 97, 105, 143, 144].

3.12 Gelatin

Gelatin is a colorless and flavorless protein-based biopolymer extracted from collagen as the by-products of animals and fishes [145–147]. It is translucent and brittle (when it is in dried form). Gelatin is widely used as gel-forming agent, and thickener in

Table 6 Some recent researches on the uses of gelatin in drug delivery applications

Gelatin-based drug delivery systems	Drug(s)	References
Semi-interpenetrating hydrogels from carboxymethyl guar gum and gelatin	Ciprofloxacin	Ghosh et al. [148]
Chitosan–gelatin films	Tyrosol and ferulic acid	Benbettaïeb et al. [52]
Liposomes entrapped in chitosan–gelatin hydrogels	Calcein	Ciobanu et al. [149]
Gum arabic aldehyde-gelatin nanogels for breast cancer therapy	Curcumin	Sarika and Nirmala [116]
Mucoadhesive buccal tablets based on chitosan–gelatin microparticles	Propranolol HCl	Abruzzo et al. [150]
Gelatin nanoparticles for ocular delivery	Moxifloxacin	Mahor et al. [151]
Gelatin liposomes for HIV therapy	Stavudine	Nayak et al. [152]
Gelatin conjugate microparticles for the treatment of tuberculosis	Isoniazid and rifampicin	Manca et al. [153]
EGFR-targeted gelatin nanoparticles for systemic administration in an orthotopic pancreatic cancer model	Gemcitabine	Singh et al. [154]

the manufacturing of foods, pharmaceuticals, and cosmetics [146]. It is obtained by means of the partial hydrolysis of collagen, which is extracted from connective tissues, bones, and to some extent from the animal intestines of domestic cattle and pigs [147]. Gelatin is well considered as a rich source of proline, glycine, and hydroxyproline as all these amino acids are generally present in the polymeric chain. Gelatin is available in two forms: type A and type B. According to the mechanism of gelatin hydrolysis, acid hydrolyzed gelatin is known as type A gelatin; while the base-catalyzed gelatin is designated as type B gelatin [147]. Gelatin is often characterized and recognized as a special and smart biopolymer with sol–gel transition characteristics because of its thermoreversible (temperature-responsive) property. It is used pharmaceutically in both the hard and soft gelatin capsules [148]. Gelatin is being used in the drug delivery system due to its swelling property by producing hydrogels [149, 150]. In addition to these properties, gelatin is capable of forming films. It is also employed for microencapsulation and formulation of nanoparticles for the uses in the delivery of various drugs [116, 148, 151, 152]. Some recent researches on the uses of gelatin in drug delivery applications are presented in Table 6.

3.13 Collagen

Collagen is one of the well-known natural proteins that occurred in both animals and fishes [145]. It mainly occurs in the connective tissue of mammals. About 25–35% of total mammalian proteins are composed of collagen [1]. Almost 13 forms of collagen are being extracted, which differ in the helix length, nature, and size

of the non-helical portions [155]. Connective tissue mammals containing fibrous collagen such as skins and tendons are usually used as raw materials for the extraction of natural collagen. Microspheres and transdermal drug delivery systems made of collagen as a biopolymeric excipient are used to deliver a variety of drugs [156, 157]. Collagen is also utilized to prepare polymeric carriers to deliver human growth hormones, growth factors, immune stimulants, etc. [146, 157]. The drawbacks of collagen as a biopolymer for drug delivery include the expensive extraction procedure and variability of extracted collagen (for example, crosslinking density, fiber size, impurities, and hydrophilicity) [156].

3.14 Albumin

Albumin is well-known as a multifunctional natural protein-based biopolymer, which is being used as an excipient to formulate biopolymeric carriers for drug targeting and improving the pharmacokinetic profiles of various protein and peptide drugs [158]. It is the plasma protein exhibiting the most abundance in the plasma (35–50 g/L; human serum). It occurs in the liver, where it is biosynthesized for every gram of liver at 0.7 mg/h rate, approximately [158, 159]. The biological functions and binding characteristics of human serum albumin (HSA) are of multi-folds. HSA is capable of binding a larger number of drugs, such as indole compounds, sulphonamides, penicillins, benzodiazepines, etc. [159, 160]. HSA is recognized as a protein that is accountable for osmotic colloidal pressure of blood. When HSA is broken down, the amino acids facilitate nutrition to the peripheral tissues [159].

Ovalbumin is known as a highly functional protein frequently employed in the designing of food matrices [158]. Chemically, ovalbumin is a monomeric phosphoglycoprotein composed of 385 residues of amino acids [158, 159]. The molecular weight of ovalbumin is 47,000 Da in water at 25 °C and an isoelectric point of 4.8 [158]. It is readily available as compared to other proteins and its production is expensive. Besides, ovalbumin shows the capability of forming gel networks and stabilizing the emulsions. It has the potential to be used as the biopolymeric excipient in the formulation for controlled drug-releasing carriers, due to its pH-and temperature-responsive characteristics [159]. Bovine serum albumin (BSA) is another category of albumin derived from bovine serum. It has a molecular weight of 69,323 Da and an isoelectric point of 4.7 in the water at 25 °C [158]. Due to its medical significance, abundance availability, low cost of production, ease of purification, characteristic ligand-binding properties, and wider applicability for the pharmaceutical uses, it is extensively used for drug delivery applications. HSA may be a supplement for BSA to prevent potential in vivo immunological reactions [160]. It is a highly soluble monomeric globular protein comprising of 585 amino acid residues with 66,500 Da of relative molecular weight [158]. As it is incredibly robust towards pH, temperature, and organic solvents, it is not like the typical proteins. Such properties of HSA and its preferential up taking by the tumors and inflamed tissues, easy availability from the natural resources, biodegradability, and biocompatibility make it a potential

Table 7 Some recent researches on the uses of albumin in drug delivery applications

Albumin-based drug delivery systems	Drug(s)	References
Albumin nanoparticles	Gabapentin	Wilson et al. [162]
Human serum albumin nanoparticles	Lapatinib	Wan et al. [163]
Chitosan-egg albumin nanoparticles for oral drug delivery	Alprazolam	Jana et al. [54]
Carbopol gel containing chitosan-egg albumin nanoparticles for transdermal delivery	Aceclofenac	Jana et al. [55]
Human serum albumin nanoparticles	Cabazitaxel	Qu et al. [160]
Albumin nanoparticles for antiviral therapy	Acyclovir	Suwannoi et al. [161]
Albumin nanoparticles for treatment of ovarian cancer	Albendazole	Noorani et al. [154]
Drug-conjugated albumin nanoparticles	Gemcitabine	Kushwah et al. [165]
Glutathione-conjugated bovine serum albumin nanoparticles for brain-targeted drug delivery	Asiatic acid	Raval et al. [166]

biopolymeric candidate for drug delivery [161, 162]. The increased uptaking ability of albumin-based nanoparticles by the solid tumors is attributable to the pathophysiology of tumors, characterized by hypervasculature, angiogenesis, damaged vascular architecture, and defective lymphatic drainage [159]. Some recent researches on the uses of albumin in drug delivery applications are presented in Table 7.

3.15 Carrageenans

Carrageenans belong to the family of linear sulfated polysaccharides that are extracted from the red edible seaweeds [167]. These polysaccharides are comprised of (1 → 3)-linked-D-galactose and (1 → 4)-linked α-D-galactose units that are alternately substituted and modified to 3,6-anhydrous derivatives, on the basis of their sources and the extraction process [167, 168]. Three major forms of carrageenans are identified based on their sulfate-linked D-galactose unit patterns that are variously substituted by the sulfate. These are called kappa (κ), iota (ι) and lambda (λ) carrageenans [168–170]. All these carrageenan molecules are extremely flexible and these wind around each other to configure a double-helical structure at a higher concentration. A specific advantage is associated with the use of carrageenans because these are thixotropic in nature having a time-dependent shear thinning capacity [170, 171]. Due to their strong ionic property, carrageenans show a high degree of reactivity for proteins [167, 168]. Recent years, several modifications of carrageenans have been researched and used for drug delivery applications [171].

3.16 Hyaluronic Acid

Hyaluronic acid (hyaluronan) is a natural biopolymer extracted from animal origin. In the year of 1934, it was discovered in the bovine vitreous humor [172]. Hyaluronic acid is commercially extracted/isolated from different animal sources, especially, from synovial fluid, skin, umbilical cord, rooster comb, etc. [173]. Recently, it is being produced from bacteria via the fermentation. Chemically, hyaluronic acid molecules comprise uronic acid and amino sugar. Within the molecules of hyaluronic acid, disaccharides (D-glucuronic acid and D-*N*-acetyl glucosamine) are connected together via the alternating pattern of β-(1 → 4) and β-(1 → 3) glycosidic bonds [174]. The enzymatic degradation of hyaluronic acid is mainly catalyzed by the actions of enzymes like hyaluronidase, β-*N*-acetyl-hexosaminidase, and β-D-glucuronidase [172]. Several favorable characteristics of hyaluronic acid such as enhanced viscoelastic and rheological characteristics, poly-anionic nature, biodegradability, biocompatibility, nonimmunogenicity, etc., lead it as a biopolymeric material for the use in drug delivery to develop various drug delivery systems [172, 175]. The uses of hyaluronic acid have extensively been evaluated in parenteral, nasal, ophthalmic, and implantable drug delivery systems [175–177].

3.17 Chondroitin Sulfate

Mostly, chondroitin is available as chondroitin sulfate [178, 179]. Chondroitin sulfate is sulfated glycosaminoglycan containing residues of D-glucuronic acid and *N*-acetyl D-galactosamine [180]. It is generally extracted from the cartilage materials of cow, pig, shark, etc. Attributable to its biodegradability and biocompatibility, it has been extensively used in the management of osteoarthritis and also, in tissue regeneration applications [181, 182]. During the past few years, chondroitin sulfate has also been exploited as a potential biopolymer in drug delivery and drug targeting [179, 182, 183]. It has been employed to formulate various drug carriers loaded with many drugs for controlled releasing and targeting of drugs [184, 185]. Recent years, it is being used for the development of various biopolymer-based targeting of anticancer drugs to treat various cancers [185].

4 Conclusion

The recent advancements in the biopolymer sciences find a considerable direction towards the development of many novel and smart drug delivery systems, which are capable of producing improved therapeutics along with better patient compliances. A suitable consideration of various potential attributes such as extraction methodology

and sustainable production, chemistry, surface characteristics, rheology, bulk properties, biocompatibility, biodegradability, etc., of biopolymers can help in the designing of different drug delivery applications. It is anticipated that various improved and versatile drug delivery carriers will possibly be formulated, evaluated, and successfully used in the near future as a result of continuous research and development in the field of new biopolymer explorations and exploitations. There are several potential obstacles and prospects to convert sensitive/responsive biopolymers from the research laboratory to the clinic, despite the many advances in the biopolymeric research. In this chapter, a wide variety of biopolymers and their uses in drug delivery have been comprehensively reviewed. In addition to this, how the biopolymers support the formulations of advanced drug delivery systems with enhanced drug delivery performance has been reviewed. Hence, it is obvious that the usefulness of biopolymers possesses an exciting future in the field of drug delivery.

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Critical Points in Biopolymeric-Controlled Release Matrix Systems

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Abstract Natural polymers have been extensively employed by the pharmaceutical industry due to their good safety profile, biocompatibility and biodegradability as well as the fact that they come from renewable sources. However, they show some disadvantages such as high solubility and low thermal stability which must be overcome in order to develop effective controlled release matrix systems. In this chapter, three different types of biopolymers have been considered: natural polymers, chemically modified natural polymers, and new polymers based on natural products. These new products have been studied as alternatives to traditional synthetic excipients. Different tools have been employed to characterize their rheological properties as well as their suitability to be employed as controlled release excipients. Critical points of matrix systems prepared with dextran and with new polymers derived from sugar-based monomers have been explained according to percolation theory. Some of the new polymers studied show outstanding properties as controlled release excipients and, some of them, also as excipients for colon-specific drug delivery devices.

Keywords Biopolymer · Controlled release · Critical points

1 Introduction

Polymeric matrix systems are the excipients most widely utilized by the pharmaceutical industry in order to formulate oral-controlled release pharmaceutical dosage forms, the main reason being their low cost and simple manufacturing process.

Natural polymers have been used for decades as pharmaceutical excipients due to their good safety profile, biocompatibility and biodegradability as well as the fact that they come from renewable sources in contrast with traditional polymers derived from

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petroleum which have an exhaustible nature. Polysaccharides, peptides, proteins, resins, and related compounds are the main types of biopolymers employed in pharmaceutical technology. Nevertheless, these materials show some disadvantages such as high solubility and low thermal stability which must be overcome to develop effective controlled release matrix systems. Chemical modifications of these polymers as well as new polymer based on natural products are interesting approaches in order to develop new materials with enhanced biocompatibility and biodegradability. Particularly, carbohydrates are convenient raw materials since they are inexpensive, readily available, and show high stereochemical diversity [1].

According to the ICH Q8 directive, dealing with pharmaceutical development, design space is defined as the multidimensional combination and interaction of input variables and process parameters that have demonstrated to provide assurance of quality of a pharmaceutical formulation [2]. Critical points are very important tools to properly define the design space of a formulation, so their establishment is essential to formulate dosage forms that accomplish the standards of quality [3]. The application of percolation theory in pharmacy studies the critical points of different systems that correspond to critical concentrations of the components of the systems related to geometrical phase transitions, known as percolation thresholds. The vicinity of a percolation threshold of a component is an area of great variability that must be avoided in the formulation of robust dosage forms, since a component starts to have a stronger influence on the properties of the system, starting to extend from one side to the other sides of the system. Therefore, abrupt changes in the behavior of the system are expected in these areas. Numerous studies have been carried out applying percolation theory to pharmaceutical systems since 1987, when Leuenberger and coworkers firstly applied it to the design of solid dosage forms [4]. The behavior of controlled release hydrophilic and inert matrices manufactured with the most employed commercial polymers and more recently with new biopolymers has been explained according to these concepts.

The purpose of this chapter is to review different controlled release matrix systems based on biopolymers described in the literature. Three different types of biopolymers have been considered: natural polymers, chemically modified natural polymers, and new polymers based on natural products. Critical points of matrix systems prepared with dextran and with new polymers derived from sugar-based monomers have been explained according to percolation theory.

2 Controlled Release Matrix Systems

Controlled release matrix systems are monolithic or multiparticular systems in which the drug is dispersed in a polymeric excipient. These systems are intended to deliver drugs locally or systemically at a predetermined rate during a specified period of time. As it is well known, the advantages of these dosage forms are a reduction in the fluctuations of the drug plasma levels, an improvement of patient compliance, an increase in the efficiency of the treatment and/or a reduction in adverse effects [5].

Depending on the nature of the polymer employed and on its interaction with the biological media, there are three different types of matrix systems: inert, hydrophilic, and lipidic matrix systems. Moreover, matrix systems can also contain a mixture of inert and hydrophilic polymers showing particular release properties [6].

2.1 Inert Matrix Systems

Inert matrices are constituted by one or various polymers that act as a skeleton in which the drug is dispersed. These systems do not disintegrate in contact with the gastrointestinal fluids, so the drug is released by diffusion through the initial pores of the matrix and the pores that are formed when the drug is dissolved. Therefore, drug release rate from these systems depends on different factors such as porosity of the matrix, size of the pores, and tortuosity. Polymers employed in the manufacture of inert matrices must meet different requirements such as showing compatibility with the drug and other excipients, lacking of toxicity, and being insoluble in the gastrointestinal fluids [7].

2.2 Hydrophilic Matrices

Hydrophilic matrices consist of a dispersion of a drug in a hydrophilic polymer that in contact with gastrointestinal fluids swells, forming a gel or a colloid of high viscosity. Factors such as swelling rate, rate of penetration of water through the matrix, rate of dissolution of the drug, rate of diffusion of the drug through the swelled material, and erosion of the matrix influence the drug release kinetics from these systems [8]. Polymer concentration, polymer properties, drug content, drug and excipient relative particle size, and compression pressure have also demonstrated to have an influence in the drug release rate [9].

2.3 Lipidic Matrices

These systems are also called “insoluble matrices” or “cereus matrices” and consist of a drug suspended or dissolved in a lipidic excipient in which the drug is imbibed. These excipients are in general of natural origin and physiologically well tolerated. Drug is released by diffusion or erosion depending on the digestible nature of the excipient employed [10]. Saturated polyglicolicglycerices (Gelucire®), fat acids and alcohols, and low molecular weight esters and waxes are among the excipients forming this type of matrices.

3 Percolation Theory

Percolation theory describes emergent properties related to the connectivity of large numbers of objects. These objects typically have some spatial extent, and their spatial relationships are relevant and statistically prescribed [11]. It is, therefore, a statistical theory that studies disordered or chaotic systems.

The beginnings of this theory go back to the Second World War when Flory and Stockmayer made use of it to explain the polymerization process that takes place when chemical bonds are formed between molecules to form a net that connects the whole system. However, the publications of Broadbent and Hammersley in 1957, dealing with a critical point of porosity of antigas masks made of carbon granules above which these masks carried out an effective decontamination, are considered the starting point of percolation theory [12–14]. Since the 1970s, authors as Essam and Gwilym developed the theory to study critical phenomena but it was not until 1987 when percolation theory was first applied to the pharmaceutical sciences, corresponding the first publications in this area to professor Hans Leuenberger and coworkers [4, 15–20]. Since that moment percolation theory has been employed to explain the existence of critical points in pharmaceutical formulations.

3.1 Important Concepts

Supposing a square lattice whose positions can be occupied by different components, a cluster is defined as a group of neighbor positions occupied by the same component. Positions are considered neighbors when they have one side in common but not if they only touch in a corner. It is assumed that the occupation of the lattice is random. Considering that there are N squares in the lattice and that p is the probability of a site to be occupied by a particular component, pN is the number of occupied squares and $(1 - p)N$ is the number of squares empty. As p increases from small to large values, there is a moment when neighbor occupied positions extend from the top to the bottom and from the left side to the right side of the lattice. The cluster formed this way is called a percolating or infinite cluster.

Percolation threshold (p_c) is other important concept of percolation theory and is defined as the concentration of a component at which there is a maximum probability of appearance for the first time of a percolating cluster of this component [12]. In systems constituted by various components, as pharmaceutical formulations, each component has its own percolation threshold. In order to simplify these systems, a matrix tablet can be considered as a binary system containing drug and excipient. Depending on their volume ratio, one or both components constitute a percolating cluster existing two percolation thresholds (p_{c1} and p_{c2}).

The geometrical lattices that better describe the behavior of pharmaceutical tablets are the body-centered cubic lattice (site percolation threshold: 24.64) and the simple cubic lattice (site percolation threshold: 31.16) [11].

At the percolation threshold of a component, this component spans the whole system and starts to have a stronger influence on its behavior. This is the reason why some properties of the system may experience an abrupt change in the vicinity of the percolation threshold. Consequently, percolation thresholds are related to critical points of the formulation which must be taken into account in order to formulate robust dosage forms [21].

3.2 The Fundamental Equation of Percolation Theory

It is well known that there is a relationship between percolation thresholds and critical points of the systems, so it is interesting to know the equation that describes the behavior of the system in the vicinity of the percolation threshold. Initially, this equation is only considered to be valid in the proximity of the percolation threshold ($p_c \pm 10\%\ p_c$). However, it has been observed that the fit of the experimental data to the equation is usually wider.

According to percolation theory, a system property X at the percolation threshold, p_c, follows a power law:

$$X = S(P - P_c)^q \tag{1}$$

where S symbolizes the scaling factor and q the critical exponent which depends on the property of the system which is being studied [18].

3.3 Different Percolation Models

The first percolation model described was the "bond percolation." This model is based in a lattice with all the sites occupied, where there is a probability "p" that two neighbor sites are bond. Therefore, a cluster in this model is considered as a group of bonds connected between them [22]. However, site percolation models are more general and therefore they have been more extensively studied. In these models, the squares in the lattice are occupied with a probability p and empty with a probability $(1 - p)$. The site-bond percolation model is a more complex model that combines both types of percolation. In this model, each position in the lattice has a probability p_s of being occupied and there is a probability p_b for two occupied neighbor sites being bond.

The process of compaction during tablet formation can be considered a combination of site and bond percolation phenomena [20]. The bonding of the particles during compaction can be described as a bond percolation phenomenon. However, the evolution of the porosity of the powder and its decrease during compaction can be better described as the site percolation phenomenon [23].

Finally, continuum percolation model considers that the components are not distributed into discrete lattice sites. This model considers a continuum distribution function of the components so that a regular lattice underlying the system is not needed [24].

3.4 Percolation Theory as a Tool to Study Controlled Release Formulation Critical Points

The knowledge of the critical points related to the formulation is necessary in order to have a robust understanding of the behavior of pharmaceutical systems, since critical points constitute natural limits of the design space. There are numerous research works studying the percolation threshold of different drugs and excipients. These studies confirm the existence of changes in mechanical or rheological properties, conductivity, water uptake, or dissolution rate of the systems near these percolation thresholds [25–30]. Therefore, the vicinity of drug and excipient percolation thresholds must be avoided to obtain robust pharmaceutical formulations. The influence of different factors such as percentage and particle size of drug and polymer or the existence of mixtures of polymers in the percolation thresholds has been studied. Particle size has demonstrated to be the more important factor affecting critical points in the case of matrix tablets.

In order to apply the percolation theory to the study of controlled release matrix tablets, it is important to know that in the case of inert matrices the ideal formulation is a bicoherent system, i.e., drug and matrix-forming polymer should be above their percolation threshold. These percolation thresholds are generally around 30–35% v/v of the corresponding component [8, 31, 32]. This way the inert matrix polymer forms an inert skeleton controlling the drug release and avoiding disintegration of the matrix that would cause the immediate release of the drug. Additionally, to avoid a therapeutic failure, the drug plus the initial porosity, i.e., the total porosity of the matrix, must also percolate the system to assure a complete release of the drug dose. Otherwise, drug is distributed in isolated clusters, so only the drug fraction contained in clusters connected with the outer surface of the tablet can be released.

In the case of hydrophilic matrices, the hydrophilic polymer must be above its percolation threshold. This way the polymer in contact with the biological fluids forms a coherent gel layer controlling the drug release rate. Below the polymer percolation threshold, the polymer is forming isolated clusters that are unable to form a continuous gel layer, so the polymer erodes and generally, the matrix disintegrates, leading to an abrupt release of the drug in a similar way as an immediate release tablet [5].

4 Matrix Systems Containing Natural Polymers

4.1 Dextran as Controlled Release Matrix-Forming Excipient

Dextran is synthesized from sucrose by dextransucrases, glucansucrases, and glucosyltransferases, produced by bacteria such as Leuconostoc or Streptococci growing in sugar juice. This polymer consists of glucose homopolysaccharides containing a high number of consecutive alfa-(1-6) linkages in their major chains. They also possess side chains coming from alfa-(1-2), alfa-(1-3), or alfa-(1-4) branch linkages.

Combined matrix tablets were prepared by Castellanos-Gil et al. [32] with ternary mixtures of commercial native dextran (DT), HPMC K4M CR, and lobenzarit disodium (LBD). The formulations contained different amounts of excipient (dextran:HPMC always in proportion 4:1 w/w):10, 15, 20, 30, 40, 50, 60, and 70%, w/w and a constant dosage: 150 mg of drug. Binary systems DT:LBD were prepared with the same polymer amounts (range 10–70%, wt/wt) with respect to LBD. Tablets were obtained by direct compression varying the compression force in order to obtain different levels of initial porosity (0–30%).

Better flowability values were observed in binary and ternary powder mixtures as the amount of dextran increased. Levels of initial porosity were lower for binary tablets than for ternary systems when tablets with equal % (v/v) of polymer were compared. This can be due to the better compressibility index of dextran (CI = 18.8) with respect to HPMC (CI = 24.6).

A slower drug release rate can be observed in ternary tablets in comparison with tablets containing only native dextran as excipient. This fact is due to a synergy between the two polymers employed in the same concentrations in controlling the drug release [33].

With respect to the mechanism of drug release, an anomalous diffusion mechanism was observed for the matrices studied. Moreover, the application of the Peppas–Sahlin equation revealed a lower contribution of the erosion in comparison with the diffusion process.

According to percolation theory, the release kinetic constants studied show a critical behavior as a function of the volumetric fraction of the components in the ternary matrix tablets. The percolation threshold of the polymer mixture dextran-HPMC (4:1 w/w) was estimated between 22.34% (v/v) and 33.10% (v/v). Above this concentration of polymer mixture, a percolating cluster of the excipients would be obtained, resulting in a control of the drug release.

The influence of the initial porosity in the different batches was studied revealing a faster drug release rate as the initial porosity level increased. However, this parameter has shown to have little influence in the excipient percolation threshold of the hydrophilic matrices. This finding has been supported later by the studies carried out by Aguilar-de-Leyva et al. who investigated the effect of the initial porosity on the critical points of hydrophilic HPMC-carbamazepine matrix tablets [27].

5 Chemically Modified Natural Polymers

5.1 Tapioca Starch as Controlled Release Excipient

Tapioca starch is derived from the roots of the mandioca plant (*Manihotesculenta* Crantz) that is a perennial woody tree belonging to the spurge family whose content in starch is up top 80% of the dried weight of the root. This plant is widely cultivated in Asia, Africa, and Latin America, so tapioca starch is highly available in the world and extensively used for different industrial applications, including its use as pharmaceutical excipient [34].

As it is well known, starch consists of two major components: amylose, a primarily linear polysaccharide with α(1–4)-linked D-glucose units and amylopectin, a highly branched molecule, with α(1–4)-linked D-glucose backbones and about 5% of α(1–6)-linked branches [35]. The content of amylose in tapioca starch varies between 18 and 24% [34].

Native tapioca starch has been used as filler, tablet disintegrant, and binder for the preparation of pharmaceutical compressed tablets. However, it shows some disadvantages for compression such as its low compactibility, poor flow, and elastic behavior. Moreover, native starches are susceptible to erosion by α-amylase in the gastrointestinal tract, failing to prolong the drug release. Consequently, natural starches need to be modified in order to overcome these limitations to act as excipient for controlled drug delivery [36]. A range of suitable monomeric and polymeric products can be used to easily modify starch employing physical and chemical methods. In this sense, Casas et al. [37] synthesized and characterized new graft copolymers derived from tapioca starch and hydroxypropyl tapioca starch in order to evaluate its suitability for direct compression matrix tablets. These new copolymers were compared with the native starches. The hydrophobic monomer ethyl methacrylate (EMA) that can be easily polymerized, shows good biocompatibility, and non-toxic behavior, was selected for the grafting. Copolymers were obtained by free radical copolymerization of EMA and different starches (tapioca starch—TS and hydroxypropyl tapioca starch—THS) following the procedure described by Echeverria et al. [38]. TSEMA and THSEMA were obtained. These products were dried using two different methods: drying in a vacuum oven (OD) or freeze-drying (FD).

Particle size distribution of the carbohydrates and the grafted polymers were determined by sieving. Larger mean particle size for grafted polymers can be appreciated. A broader and more symmetric distribution for copolymers, especially for THSEMA products was observed.

The flowability of the polymers was determined employing an automated flowmeter system consisting of a glass funnel connected to a balance and a computer with the adequate software. Poor flow properties have been observed for native tapioca starch, being the small particle size of TH and THS responsible for the results. The copolymers also showed poor flow properties, showing OD copolymers better results because of their smoother surface.

Tablets were prepared with the different polymers and copolymers employing an instrumented single-punch tablet machine. Samples of 500 mg of powder were preweighed and manually fed into a 12 mm die. Tablets with a constant crushing force of 70–80 N were obtained. Different parameters involved in compression process were determined, revealing that graft copolymers require significantly lower applied pressure (P) for the preparation of tablets. Low lubrication values (R) were obtained for all polymers, so it would be necessary the addition of a lubricant when using these copolymers as excipients for direct compression. The total deformation and the total elastic deformation values for the new polymers are similar and lower, respectively, in comparison with the most widely used commercial excipients for direct compression.

With respect to the physical assays, tablets prepared with the different polymers accomplish the guidelines detailed in the European Pharmacopoeia in relation with the weight uniformity test. A crushing force value between 70 and 80 N was obtained for all the tablets. Tablets prepared with the copolymer display higher thickness and diameter in comparison with tablets prepared with the native starch, which was attributed to higher axial and radial expansion. Finally, copolymer tablets show lower friability and larger disintegration times.

In relation with the microstructure of the matrices, their pore size distribution was determined by mercury intrusion–extrusion porosimetry. Tablets prepared with the copolymers show higher porosities in comparison with tablets prepared with native starch in agreement with their higher thickness. Additionally, a clear difference in the drying process has also been observed, displaying FD copolymers higher porosities and lower mean and median pore diameters.

Although native starches are not appropriate for controlled drug delivery systems, mainly because of their fast release properties in physiological fluids, based on the good results obtained for the crushing strength and the large disintegration time of the obtained tablets prepared with the copolymers, Casas et al. [39] studied the ability of these copolymers to act as controlled release matrix-forming polymers. For this purpose, a release study of matrix systems prepared with the copolymers and theophylline anhydrous as model drug was carried out, comparing the results with those obtained for tablets prepared employing tapioca and hydroxypropyl tapioca starch as raw materials. The influence of the carbohydrate nature, the drying process, and the compression force employed (70–80 and 140–150 N) on the release process was also evaluated.

500 mg of mixtures containing 24% w/w of theophylline anhydrous, 75% of polymer (TS, THS, TSEMA, and THSEMA), and 1% w/w of stearic acid were compressed into tablets employing an instrumented single-punch tabletting machine. The powder was preweighed and manually fed into a 12 mm die. Tablets were prepared at two different crushing strengths (70–80 N and 140–150 N) in the case of the mixtures containing copolymers. Tablets containing as raw material TS or THS were compressed only at 70–80 N because it was not possible to obtain tablets with a higher crushing strength using these excipients.

The release study was carried out during 12 h in distilled water. Matrices prepared with carbohydrates TS and THS released 100% of the drug in the first hour, showing complete disintegration whereas matrices containing copolymers did not release the total amount of drug at the end of the assay. TSEMA matrices released a lower amount of drug in comparison with THSEMA matrices. Moreover, a slight erosion of the tablet surface at the end of the assay was observed at both compression forces for THSEMA while TSEMA matrices remained practically intact probably due to the better binding properties of these copolymers.

The influence of the drying method and the compression force was only significant in the case of THSEMA matrices, so matrices prepared at 70–80 N and freeze-dried displayed a higher drug release according to its higher porosity.

Tablets prepared with the copolymers behave as inert matrices being the diffusion process the main mechanism controlling the drug release.

5.2 Waxy Maize Starch as Controlled Release Excipient

The suitability of waxy maize starch to be employed as pharmaceutical excipient for controlled drug delivery was investigated by Marinich et al. [40]. This type of starch has several advantages such as an increased storage stability and higher ability to control the drug release in comparison with other starches. However, waxy maize starch is usually chemically modified in order to improve its properties to be employed as pharmaceutical excipient. In this sense, hydroxypropyl starch was chosen as a chemical modification that leads to a higher hydrophilic character and therefore a higher swelling power. On the other hand, grafting of the waxy maize starch (MS) and hydroxypropyl starch (MHS) with ethyl methacrylate (EMA) was also studied in order to obtain copolymers that combine the good properties of starch and synthetic polymers.

Copolymers were synthesized by free radical copolymerization of EMA and (MS) and (MHS) following the procedure described by Echeverria et al. [38]. The products obtained were also dried using two different methods: drying in a vacuum oven (OD) and freeze-drying (FD).

Particle size distribution of the carbohydrates and the grafted polymers were determined by sieving. Larger mean particle sizes were observed for graft copolymers that also showed a broader and more symmetric distribution especially in the case of MHSEMA.

The flowability of the polymers was determined employing an automated flowmeter system. The best flow properties were exhibited by FD-MHSEMA. A complete lack of flow characterized the other products, probably due to the smaller particle sizes with prevalence of fine particles.

Matrix tablets weighing 500 mg were compacted employing an instrumented single-punch tablet machine with 12 mm flat-faced punches. The powder was manually fed into the die and prepared at a crushing force of 140–150 N in the case of the

copolymers. Tablets prepared with the carbohydrates could not be prepared at this crushing force so a slightly lower pressure interval was employed (120–130 MPa). Tablets were prepared without including any other excipient in order to get intrinsic information of the polymeric material. Low lubrication ratio values (R) were also obtained for all the studied polymers, being necessary the use of lubricants when employing the copolymers in the manufacture of matrix tablets.

In relation with the physical assays, all tablets showed good results for the weight uniformity test. Tablets prepared with the copolymer displayed a higher thickness which might be related to a higher axial and radial expansion in comparison with the raw material. Higher crushing force was found for tablets prepared with the copolymer. These tablets also showed lower friability values and disintegration times larger than 30 min, what make them potential candidates for controlled drug delivery systems.

The porosimetry study revealed that all the tablets prepared show mesopores and that carbohydrate tablets display smaller porosities than copolymer tablets, which are in agreement with the thickness data.

In order to investigate the potential use of the new copolymers for controlled drug delivery, Marinich et al. [41] studied the mechanism governing drug release from matrix systems prepared with74% w/w of polymer, 24% w/w of either anhydrous theophylline (a slightly water-soluble drug) or diltiazem hydrochloride (a freely water-soluble drug) as model drugs, and 1% w/w of stearic acid.

500 mg tablets were compressed in an instrumented single-punch tablet machine using a 12 mm die. The target crushing strength was 140–150 N.

Drug release studies were carried out in distilled water over 12 h. Matrices containing MHSEMA copolymers showed a faster drug release in comparison with MSEMA derivatives for both drugs which could be due to the higher hydrophilic character of MHSEMA copolymers. A faster drug release is also observed for matrices prepared with diltiazem HCl, with a complete drug release for all the formulations at the end of the dissolution test. This fact is attributable to its higher aqueous solubility. Moreover, a slight erosion of the tablet surface is also observed for these matrices. Therefore, to obtain a controlled drug delivery system employing diltiazem HCl, it would be necessary to employ MSEMA copolymers. On the other hand, theophylline matrices remain nearly intact after the dissolution process showing a much slower drug release rate.

The almost constant erosion front movement and the absence of swelling confirm that the tablets prepared with the new copolymers behave as inert matrix systems where the drug is released by diffusion through the porous structure.

In summary, it can be concluded that the new copolymers MSEMA and MHSEMA could be employed as directly compressible tabletting excipients for sustained release.

6 Matrix Systems Containing Polymers Based on Natural Products

Polymer chemistry has experienced a great advance in the last years due to the requirement of new biocompatible and biodegradable materials for specific biomedical applications. Traditional polymers derived from petroleum show low biodegradability and biocompatibility. Moreover, they are derived from exhaustible resources.

Researchers are paying increasing attention to renewable resources. This is the reason why new methods of synthesis of a great structural variety of polymers have been designed and developed based on natural renewable resources.

Biomass plays an important role among the renewable resources and concretely carbohydrates are excellent raw materials because of their abundance and availability [42].

The development of novel polymers having similar characteristics to those of the industrial polymers but synthesized from sugar-based monomers derived from renewable raw materials is an interesting approach. Moreover, the synthetic polymers obtained can be able to mimic the structure and function of biological polymers. These biodegradable and biocompatible polymers can be obtained by incorporating sugar-derived units into traditional step-growth polymers such as polyamides, polyesters, and polyurethanes [1].

Natural sugars have many advantages as raw materials since they are abundant, show structural diversity and multiple functionalities, are non-toxic, and their hydrophilic nature assures the hydrolytic degradability.

6.1 Matrix Systems from New Functionalized Polyurethanes

The structure of polyurethanes (PUs) contains three basic components: a polyol, diisocyanate, and a chain extender. The polyol, commonly called soft segment, is usually polyethers or polyesters, with chain ends terminated by hydroxyl groups and a low glass transition temperature (i.e., <25 °C). The chain extender is usually a small molecule with either hydroxyl or amine end groups and the diisocyanate is a low molecular weight compound that can react with both the polyol and the chain extender. The chain extender and the diisocyanate components constitute the hard segment of the polymer [43].

Two different groups of polyurethanes must be considered: bio-inert and biodegradable polyurethanes. Bio-inert polyurethanes show outstanding chemical stability, abrasion resistance, and mechanical properties so they are frequently employed in medical devices and artificial organs. On the other hand, biodegradable polyurethanes are usually employed as implants for tissue repair and as drug

delivery systems [44]. These polyurethanes are being widely studied in biomedicine due to their low toxicity, potential biodegradability, biocompatibility, and versatile structures [45].

Degradability of polyurethanes involves hydrolytic, enzymatic, and oxidative pathways and is also being extensively investigated in the biomedical community [43, 46]. This process can be accelerated through the introduction of hydrolyzable linkages [47]. Moreover, disulfide bonds, which are a linking structure frequently found in biological systems, can also be introduced into polyurethane skeletons. This approach has been proposed as an alternative method to enhance degradability of polyurethanes since disulfide linkage can be cleaved by the action of the natural tripeptide γ-glutamylcysteinyl-glycine (glutathione, GSH) [48].

6.1.1 PU[(iPr)Man-DTDI] as Matrix-Forming Polymer for Sustained and Site-Specific Drug Release in the Gastrointestinal Tract

Campiñez et al. [49] have studied the ability of a novel biodegradable polyurethane PU[(iPr)Man-DTDI] to act as controlled release matrix-forming polymer for both the oral drug delivery and the colon targeting. This novel polyurethane combines the good properties of PUs with the introduction of disulfide linkages into their skeleton in order to increase the polymer biodegradability. It has been successfully synthetized by the reaction of 3,4-O-isopropylidene-D-mannitol with 2,2′-dithiodiethyldiisocyanate. The incorporation of the sugar monomer D-mannitol into the polymer backbone contributes to enhance properties such as biodegradability and biocompatibility [1].

Preformulation studies of the polymer were carried out in order to determine its suitability to be employed in the preparation of matrix tablets by direct compression. With this purpose, the SeDeM method, developed by SuñéNegré et al., was applied to the polyurethane [50]. This method considers different rheological parameters of the powder whose values are normalized and are classified in different groups depending on the property that they are measuring (dimension, compressibility, flowability/powder flow, lubricity/stability, and lubricity/dosage).

Table 1 shows the rheological parameters studied applying the SeDeM method.

One of the main objectives of the SeDeM method is to build a diagram that visually shows the characteristics of the powder to be processed by direct compression. For this purpose, the rheological parameters are determined applying the methods indicated in pharmacopeias or based on usual practice in Pharmaceutical technology [51].

After the determination of the rheological parameters, they are normalized applying a factor with the aim of making their values be in a scale from 0 to 10. These normalized values are known as radius values *r* and are plotted in the SeDeM diagram obtaining a polygon by connecting the radius values with lineal segments. This polygon illustrates the characteristics of the powder for direct compression. In this case, the SeDeM diagram has been made with 11 parameters.

Table 1 Limit values accepted for the SeDeM diagram parameters and factor applied to transform each parameter into radius values (r)

Incidence	Parameter	Limit Values	Factor Applied to v
Dimension	Bulk density	0–1 g/ml	10v
	Tapped density	0–1 g/ml	10v
Compressibility	Inter-particle porosity	0–1,2	10v/1,2
	Carr index	0–50 (%)	v/5
Flowability/poder flow	Hausner ratio	3–1	(30-10v)/2
	Rest angle	50–0 (°)	10-(v/5)
	Powder flow	20–0 (s)	10-(v/2)
Lubricity/stability	Loss on dryinga	0–10 (%)	10-va
	Higroscopicity	20–0 (%)	10-(v/2)
Lubricity/dosage	Particles < 45 μm	50–0 (%)	10-(v/5)
	Homogeneity index	0–0,02	500v

Reproduced from Campiñez et al. [49]

Three indexes based on the SeDeM diagram are also calculated in order to determine the suitability of a powder for direct compression: Parametric index (IP) is calculated according to Eq. (2).

$$\mathrm{IP} = \mathrm{No.}\ \rho \geq 5 / \mathrm{No.\,Pt} \tag{2}$$

where No. $p \geq 5$ indicates the number of parameters whose values are equal to or higher than 5 and No. Pt indicates the total number of parameters studied.

The acceptability limit would correspond to:

$$\mathrm{IP} \geq 0.5$$

Parametric profile index (IPP) corresponds to the mean r value of all parameters. The acceptability limit corresponds to:

$$\mathrm{IPP} = \mathrm{mean}\ r \geq 5$$

Good compression index (IGC) was calculated following Eq. 3.

$$\mathrm{IGC} = \mathrm{IPP} * f \tag{3}$$

where f is a reliability factor and was calculated with Eq. 4.

$$f = \mathrm{polygonarea/circlearea} \tag{4}$$

The acceptability limit was calculated by Eq. 5.

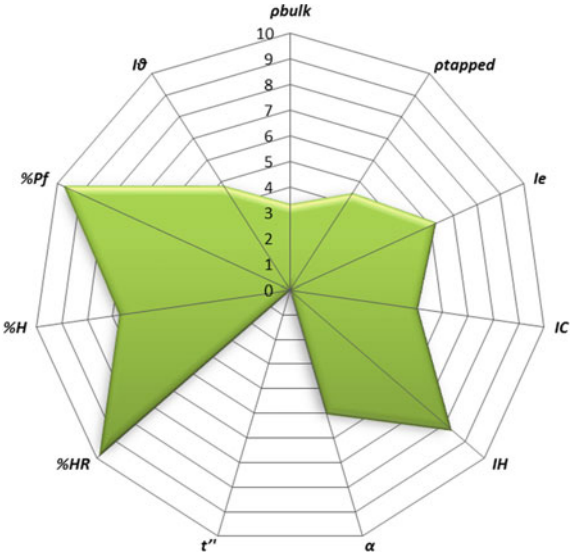

Fig. 1 SeDeM diagram for PU[(iPr)Man-DTDI]. Reprinted from Campiñez et al. [49] Copyright © 2017 Elsevier

$$\text{IGC} = \text{IPP} * f \geq 5 \tag{5}$$

The results obtained for the parametric index (IP), the parametric profile index (IPP) (mean radius), and the good compression index for PU[(iPr)Man-DTDI] were 0.54, 5.78, and 5.45, respectively. Figure 1 shows the SeDeM diagram for this polyurethane.

The results obtained indicate that the PU[(iPr)Man-DTDI] can be considered a direct compression excipient, with rheological properties clearly better than most of the traditional pharmaceutical excipients.

Binary matrix tablets containing 10, 20, and 30% of PU[(iPr)Man-DTDI] with two different molecular weights 40,000 Da (PU5) and 90,000 Da (PU5′) and theophylline anhydrous as model drug were prepared by direct compression. The different formulations were subjected to a dissolution test consisting of four phases, simulating pH, and transit times through the gastrointestinal tract up to the proximal colon [52]. A reductive environment was created in the last phase, trying to mimic the colon ambient. This reductive environment is created working under argon atmosphere and adding glutathione to the dissolution medium. This way a better simulation of the physicochemical conditions existing in the colon is achieved.

Figure 2 shows the dissolution profiles of the batches prepared with the new polyurethane.

A decrease in the drug release rate is observed as the concentration of polymer increases in the formulation. A good ability to control the drug release can be appreciated since tablets containing only 10% of polymer with the two molecular weight release less than 80% of drug after four hours of assay. On the other hand, a significant influence of the molecular weight of the polyurethane on the drug release rate

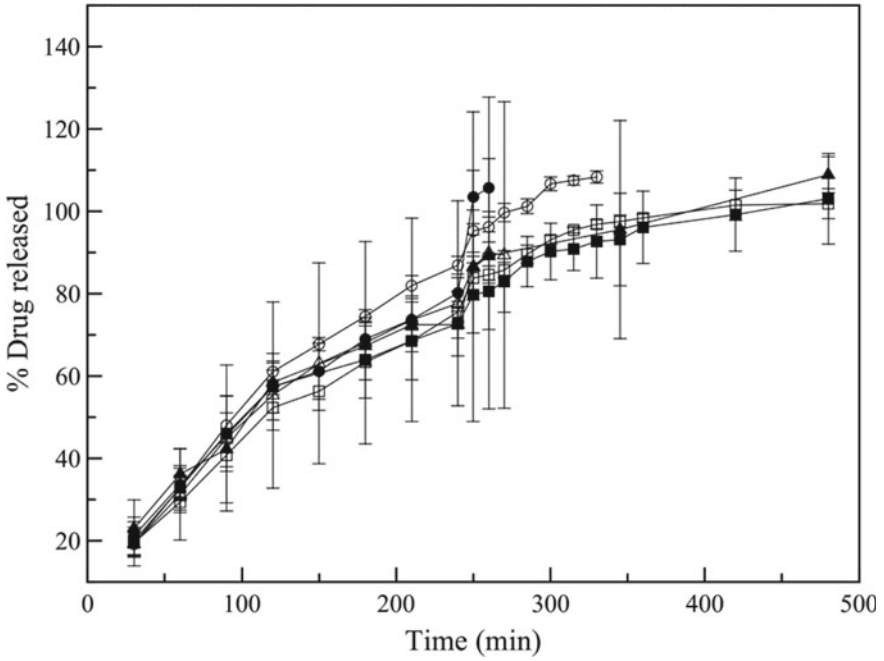

Fig. 2 Dissolution profiles prepared with 10% (filled circle), 20% (filled triangle), and 30% (filled square) w/w of PU[(iPr)Man-DTDI] with a molecular weight of ca. 40,000 Da (PU5), and with 10% (empty circle), 20% (empty triangle), and 30% (empty square) w/w of PU[(iPr)Man-DTDI] with a molecular weight of ca. 90,000 Da (PU5′)

has not been clearly appreciated in the release profiles although a higher degree of polymerization of the excipient is normally related to a slower drug release rate. It is possible that other formulation factors, such as rheological properties, compactibility, compressibility, or particle distribution inside the matrix, are masking this influence.

An increase in the drug release rate was noticed when the dosage forms were exposed to the colon simulating phase, what can be attributed to an increase of the biodegradability of the disulfide linkages of the polymer in the reductive environment. This effect is more clearly appreciated for batches 4–6 containing polymer PU5´with a lower molecular weight. This fact can be explained because a lower degree of polymerization facilitates the access of the dissolution medium to the disulfide bonds of the polymer, making them more susceptible to the reductive reactions. Moreover, the drug release rate constants for the colonic phase of the assay are higher than the constants for the first phase, supporting the hypothesis of the degradation of the disulfide bonds of the polymer in the reductive environment. In relation to the drug release mechanism, diffusion predominates during the stomach and jejunum phase whereas erosion is the main mechanism in the ileum/colon phase.

With respect to the percolation threshold of the polyurethane PU[(iPr)Man-DTDI], a lower degree of variability and a slower drug release can be appreciated for

batches containing 30% of polyurethane, so that the polymer percolation threshold is estimated to be between 20 and 30% w/w of polymer. Moreover, a lower increase in the drug release rate in the colonic conditions of the assay, attributed to a lower biodegradability of the disulfide bonds due to a lesser susceptibility to the reductive conditions can be observed for batches containing 30% w/w of polymer in Fig. 2. This fact can be explained by the lower exposure of the drug to the release medium when the polymer is above its percolation threshold, forming a coherent insoluble network throughout the system.

The excipient efficiency (EE) for controlling the drug release as modified by Casas et al. [53] has been calculated for the novel polyurethane. This parameter is determined as the ratio between the total porosity of the system and the slope of Higuchi's equation corrected by the drug solubility as can be observed in Eq. 6.

$$\mathrm{EE} = (\varepsilon / k_{\mathrm{H}}) * \ (1/(1.963 - 0.246 \ln \mathrm{Cs})) \tag{6}$$

where EE is the efficiency of the excipient, ε is the total porosity of the matrix tablet, k_{H} is the Higuchi rate constant, and Cs is the drug solubility.

This parameter, first proposed by Caraballo, is able to quantify the capability of an excipient to control the drug release and must be calculated in formulations above the drug and excipient percolation thresholds [53]. The values obtained for the batches 3 and 6, containing 30% w/w of PU5 and PU5′, respectively, are 7.66 and 7.43 ($\mathrm{min}^{1/2}\ \mathrm{mg}^{-1}$ mL). These values are quite high in comparison with the obtained for commercial excipients widely employed as inert matrix-forming excipients such as, for example, Eudragit RS PM (5.59 $\mathrm{min}^{1/2}\ \mathrm{mg}^{-1}$ mL).

In summary, the novel excipient PU[(iPr)Man-DTDI] (PU5) shows adequate rheological properties to be processed by direct compression in the formulation of matrix tablets according to the SeDeM method. Moreover, this polymer shows a good ability to control the drug release as reflected in both the dissolution profiles and the value of the *excipient efficiency*. Finally, this polymer could be a potential candidate for colon targeted drug delivery systems.

6.1.2 PU (Dithiodiethanol-DTDI) as Matrix-Forming Polymer for Sustained and Site-Specific Drug Release in the Gastrointestinal Tract

The ability of the new biodegradable polyurethane PU (dithiodiethanol-DTDI) to act as controlled release matrix-forming polymer for both conventional oral route and colon targeted drug delivery has also been studied by Campiñez et al. [49]. In the case of this novel polyurethane, disulfide linkages have also been included in its backbone with the aim of increasing polymer biodegradability. The polymer has been synthetized by the reaction of 2,2′-dithiodiethanol with 2,2′-dithiodiethyldiisocyanate. The SeDeM method was also applied in the preformulation studies of this polymer, obtaining the following results for the parametric

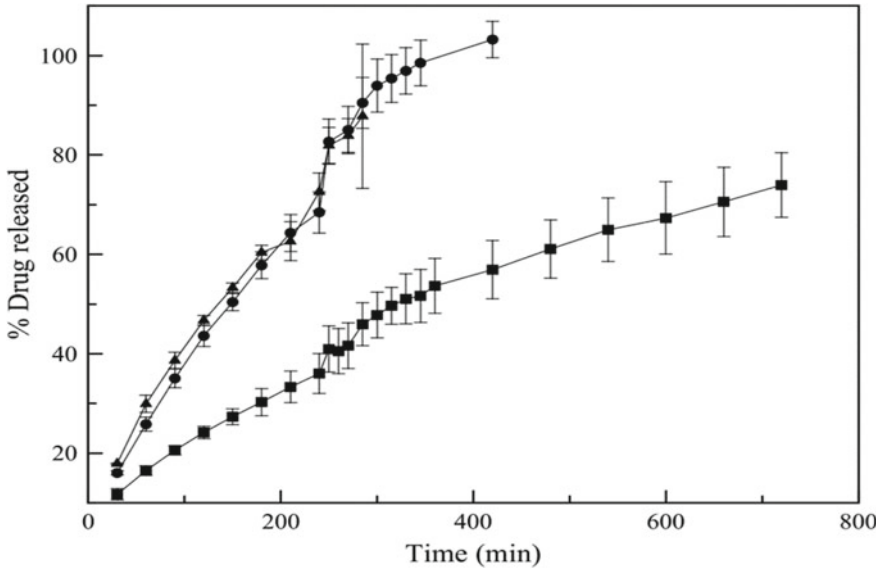

Fig. 3 Dissolution profiles prepared with 10% (filled circle), 20% (filled triangle), and 30% (filled square) w/w of PU (dithiodiethanol-DTDI)

index (IP), the parametric profile index (IPP) (mean radius) and the good compression index (IGC): 0.54, 5.34, and 5, respectively. These results also indicate that the PU (dithiodiethanol-DTDI) shows good rheological properties to be processed by direct compression.

Binary matrix tablets containing PU (dithiodiethanol-DTDI) and theophylline anhydrous were prepared and subjected to the gastrointestinal dissolution assay proposed by Ferris et al. [52]. The dissolution profiles showed a drastic decrease in the drug release rate for tablets containing 30% w/w of polymer that release around 60% of drug after 8 h of assay (see Fig. 3).

The same amount of drug is released for batches containing 10 and 20% w/w of polymer after 3 h of assay what reveals that the polymer percolation threshold is also between 20 and 30% w/w for this polyurethane.

The biodegradability of the disulfide linkages of the polymer in the reductive environment is also confirmed by the increase in the release kinetic constants in the colonic phase of the assay. The diffusion mechanism also predominates during the stomach and jejunum phase while erosion is the main mechanism in the ileum/colon phase.

A clearer increase in the drug release rate in comparison with the polymer PU[(iPr)Man-DTDI] can be observed when the polymer reaches the colonic phase. This increase is likewise more evident in the case of batches containing 10 and 20% of polymer, i.e., below the polymer percolation threshold, since the disulfide bonds of the polymer are more exposed to the action of the reductive environment in these batches for the same reasons explained in the previous section.

The value obtained for the *excipient efficiency* is 8.66 ($min^{1/2}$ mg^{-1} mL), revealing a good capacity of the polymer to control the drug release.

The results obtained indicate that PU (dithiodiethanol-DTDI) has quite good rheological properties to be employed as matrix-forming polymer by direct compression. Moreover, the polyurethane is a candidate to be employed in controlled release formulations and also in colon targeted drug delivery systems.

6.1.3 Polyurethane PU (TEG-HMDI) as Matrix-Forming Excipient for Controlled Drug Delivery

This polymer was obtained according to Ferris et al. [46] by the reaction of triethyleneglycol (TEG) with hexamethylenediisocyanate (HMDI). The study of different rheological parameters revealed adequate flow and compressibility properties. Binary matrix tablets containing 10, 20, and 30% w/w of PU (TEG-HMDI) and theophylline anhydrous were prepared by direct compression. Matrix tablets with a high crushing strength were obtained [54]. Moreover, an outstanding high ability to control the drug release is observed since tablets containing only 10% w/w of polymer release around 90% of theophylline after 8 h. A sudden decrease in the release rate is observed when the polymer concentration increases to 20% w/w since these batches releaseless than 60% of drug after 8 h of assay. This fact indicates that the polymer percolation threshold is between 10 and 20% w/w of polymer.

The analysis of the release data according to the different kinetic models reveals that the drug is released predominantly by the diffusion mechanism.

This polymer is a promising candidate to be employed as matrix-forming polymer by direct compression due to its good compactibility properties and to its high ability to control the drug release.

6.1.4 Polythiourethane-D,L-1,4-Dithiothreitol-Hexamethylene Diisocyanate [PTU(DTT-HMDI)] as Controlled Release Matrix-Forming Polymer

Campiñez et al. [55] studied the ability of the polyurethane [PTU(DTT-HMDI)] to act as controlled release matrix-forming polymer. This polyurethane has been synthetized by the reaction of D,L-dithiothreitol with hexamethylenediisocyanate (HMDI). The SeDeM method was applied in order to investigate its suitability to be employed as a direct compression excipient. The results obtained for the parametric index (IP), the parametric profile index (IPP) (mean radius), and the good compression index (IGC) are 0.36, 4.87, and 4.59, respectively. Concretely, the values of the IPP and the IGC are very close to the adequate values for direct compression without addition of flow agents, what is not usual for controlled release excipients that normally have poorer rheological properties.

Four batches of binary inert matrix tablets weighing 250 mg and having 9 mm diameter were prepared with 10, 20, 30, and 40% w/w of [PTU(DTT-HMDI)] and

theophylline anhydrous by direct compression. The different batches were subjected to a 8 h dissolution assay in distilled water showing [PTU(DTT-HMDI)] a noticeable ability to control the drug release since batch containing 10% w/w of polymer only releases 93% of theophylline in 6 h. The increase in the polymer concentration resulted in a significant decrease in the drug release rate. Concretely, tablets containing 40% w/w of the polymer only released 43% of theophylline after 8 h of assay. Diffusion was the mechanism governing drug release in all the batches prepared.

The polymer percolation threshold was estimated for the inert matrices prepared as it is important to know the critical points of the formulation which are areas of high variability that must be avoided in order to obtain robust formulations. This polymer percolation threshold has been estimated based on the intra-batch variability in the drug release. Below the polymer percolation threshold, there is not an inert skeleton controlling the drug release, so a higher variability in the drug release rate is observed. Based on this approach, the polymer percolation threshold was estimated between 20% w/w and 30% w/w of PTU(DTT-HMDI).

The results obtained show that this polymer can be considered an excellent candidate for controlled release inert matrix-forming excipient.

The particular release mechanism of the sustained-release matrices prepared with PTU(DTT-HMDI) and PU(TEG-HMDI) have been studied by Campiñez et al. [56] with the objective of explaining the remarkably high ability of these polymers to control the drug release. A comparison between the experimental results of the drug release profiles of the binary matrix tablets of theophylline and polyurethanes and the in silico simulation of these data was carried out employing the F-CAD software, which is an innovative formulation tool based on cellular automata.

An unexpected behavior of the drug dissolution rate was found with the increase in the polymer concentration in the matrix systems. This leaded to a disagreement between the initial in silico estimations and the experimental values. This unexpected behavior was studied in depth in order to reveal the mechanism that these polymers employ to control the drug release. It was hypothesized that the unpredicted behavior could be due to a change in the effective diffusion coefficient, being the tortuosity the main factor responsible for a diffusion-controlled release mechanism through a surrounding porous meshwork [57]. Scanning electron microscopy (SEM) was employed to measure tortuosity experimentally. The calculated tortuosity values were employed to correct the estimations of the drug dissolution rate. In this case, a good agreement was found between in silico and in vitro release profiles.

On the other hand, SEM images were also employed to study the polymer distribution in the tablets. It could be observed that the particles of the polymer surround the theophylline particles as the concentration of the excipient increases. Practically a continuous barrier surrounds effectively the drug particles similarly to a continuous system from the point of view of percolation theory, leading to a decrease in the polymer percolation threshold.

In summary, the tortuosity and the particular distribution of the polymers around the drug particles forming a mechanical barrier are responsible for the outstanding

high ability of these polymers to control the drug release during 8 h with a concentration of only 10% w/w. These characteristics, together with the good biocompatibility, biodegradability, and non-toxicity of these polyurethanes, make them promising candidates to design controlled release systems.

6.1.5 PU{[(Ar(S-NH2)3)20-DiT80]-HMDI}

This polymer is anamine-based copolyurethane that forms part of the stimulus-responsive sugar-based polyurethanes able to be degraded by tripeptide glutathione under physiological conditions. The enhancement of the degradability of this polymer has also been achieved by the introduction of disulfide linkages into the polymer backbone. This polymer has been investigated as matrix-forming polymer for colon targeting drug delivery. For this purpose, a sustained-release formulation of the polymer containing methotrexate was studied by Ferris et al. [52]. This formulation was prepared by mixing a powder blend containing 98% of Fast Flo lactose, 1% of aerosol, and 1% of magnesium stearate in a turbula mixer and suspending it in THF. On the other hand, a solution of methotrexate and the polymer in THF was prepared. The solution was mixed with the suspension and the THF was removed. The final mixture was compressed and the tablets obtained were later coated with Eudragit FS 30D up to a final weight gain of 1%. The formulation was subjected to a release assay consisting of four phases simulating pH and transit times through stomach, jejunum, distal ileum, and proximal colon (as explained in Sect. 6.1.1).

An increase in the release rate, typical of degradation-driven processes was observed with a total drug released of 50% after 48 h. This fact shows an impressive capacity of the polymer to control the drug release although this release rate is not the most suitable for colon drug delivery. Nevertheless, the inclusion of channeling agents in the formulation would favor water penetration after the dissolution of the Eudragit coating layer what would increase the drug release rate in the colon.

PU{[(Ar(S-NH2)3)20-DiT80]-HMDI} showed an outstanding ability to control the drug release employed at very low concentrations, even below 5% w/w in a tablet containing 92% w/w lactose. This result makes this polymer an excellent candidate for controlled drug delivery systems in different types of formulations, not only for colon targeting.

7 Conclusions

In summary, a group of new polymers derived or synthesized from natural products is being introduced in the pharmaceutical field as alternatives to traditional synthetic excipients. In general, those new polymers show good biocompatibility, biodegradability, and very low toxicity.

Different approaches have been employed to predict their behavior during the production of pharmaceutical solid dosage forms (SeDeM expert system) and during

the drug release process (estimation of their critical points, in vitro and in silico studies of their release mechanism). This would facilitate the estimation of the design space of the pharmaceutical formulations containing these excipients, according to the quality by design approach and the ICH Q8 guideline.

As it has been described during this chapter, some of them, especially a group of new polyurethanes and polythiourethanes, show outstanding properties as controlled release excipients and, some of them, also as excipients for colon-specific drug delivery devices.

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Biopolymeric Gels in Drug Delivery

Moumita Das Kirtania, Nancy Kahali, and Arindam Maity

Abstract Biopolymers or the natural polysaccharides like alginate, chitosan, pectin, cellulose and their derivatives, etc., have been used in recent research studies for a number of significant advantages like their biocompatibility, biodegradability, safety, and cost-effectivity. They have been evaluated in a number of formulation strategies including matrix tablets, microencapsulation, nanoparticulate delivery, targeted drug delivery in various parts of the gastrointestinal tract according to pH or microbial population, etc. Further, they have been extensively utilized in the formation of gels by physical or chemical cross-linking methods for advanced drug delivery. Such biopolymeric gels find applications not only in controlled or targeted drug delivery but also in biomedical fields. Such gel formulations would provide controlled or targeted drug release based on their physicochemical properties including thermal sensitivity, pH sensitivity, analyte sensitivity or presence or absence of microbial population, etc. Recent inventions in this field include the smart gels which produce significant changes in drug delivery with minimum changes in the environment or the in situ gels which remain in the liquid state outside the body and would turn into gel at body temperature, once delivered. Further, modified or grafted biopolymers have been tried out for the formation of stable gels with favorable physicochemical properties for better control on drug delivery. The present chapter would present a review of the potential biopolymeric gels, their preparation, characterization, and most importantly their applications in modern drug delivery taking into account the recent innovations in the area.

Keywords Biopolymer · Gel · Drug delivery

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1 Introduction

Biopolymers can be defined as the polymeric substances produced from natural resources either by chemical synthesis of biological matter or by biosynthesis of living organisms [1–4]. The main advantage of biopolymer is its capability of degradation when it comes into contact of living microorganisms. This phenomenon has gained popularity in recent years in pharmaceutical, industrial, and medical fields [5]. Further, due to their biocompatible nature, they have created an interesting impact on drug delivery systems [6, 7].

In pharmaceutical field, polymeric gels have been established as promising delivery systems to overcome the challenges of drug delivery. Gels are generally semisolid and homogeneous formulations consist of medicinal dispersion in satisfactory hydrophilic or hydrophobic three-dimensional (3D) network [8, 9]. These formulation have attained popularity due to easy preparation. They also provide close contact between therapeutic element and the site of action followed by controlled delivery of drug in different routes. Generally, gels are classified into two types: (a) hydrogels and (b) organogels. Hydrogels are hydrophilic 3D polymeric network that binds with great volume of water or biological fluids without dissolution of polymer [10, 11]. Immobilization of gelator fibers with organic liquid phase followed by formation of 3D network is known as organogels or oleogels [12].

On the basis of the responsive nature, novel gels are generally distinguished by two different types: stimuli-responsive and non-responsive. The former one swells when exposed to external stimuli, like pH, temperature, magnetic field, ionic strength and the later one swells after engulfing water. Gels that counter more than one environmental stimulus are known as multiresponsive gels [9, 13].

2 Classification of Gels

Due to the versatile characteristics and wide background of applications, novel gels are classified as follows:

2.1 Hydrogels

These are hydrophilic 3D polymer networks, which are closer to the extracellular matrix of cells [9, 14]. From decades in the field of drug delivery system, hydrogels contribute their promising aspects. Due to biocompatibility, pliability, presence of higher volume of water, and broad range of applications, they have gained the popularity in the sphere of drug delivery system from since 50 years [14–20]. Hydrogels can be synthesized in number of classic chemical processes, which involves one

step approaches, such as polymerization and aligned cross-linking of multifunctional monomers. The synthesis also involves various techniques associated with reactive groups of polymer molecules, which result in their cross-linking as well as possible reactions between polymers and cross-linking agents. As the hydrogels are 3D hydrophilic polymer networks, they have capability of swelling and de-swelling in aqueous media and thereby retain high volume of fluid in swollen condition [19, 21]. Hydrogels perform volume transformation markedly in the presence of different physical and chemical factors like light, pressure, magnetic field, sound and pH, ionic strength, molecular species as well as composition of solvent [19, 22].

The first synthetic hydrogel for biological application was established by Wichterle and Lim in 1960 [23]. Later on hydrogels have come into application in different fields, such as agriculture, [24] drug delivery systems, [25, 26] ophthalmic products, [27] dehydration of coal, [28] food additives, [29] pharmaceuticals, [30] biomedical background, [31, 32] tissue engineering, [33] and regenerative medicines, [34] Moreover, hydrogels are also used in separation of biomolecules or cells, [35] wound dressing, [36] as well as biosensor [37].

2.2 Emulgels

Emulgel has now widely emerged as a topical drug delivery system. If adequate efforts are applied in its formulation development with topically effective drugs, it would prove to be a great achievement for derma care and cosmetology. Emulgels are defined as an emulsion of w/o or o/w type, which is converted to gel form followed by addition of gelling agent [38, 39]. Emulsion itself acts as a controlled release system in which drug is encapsulated in an internal phase and thereby moves toward the external phase to the skin, from where it can be absorbed gradually in a controlled manner. Internal phases function as drug reservoir and release the drug to the external phase for a longer period of time. Gel possesses cross-linked network form that catches tiny drug particles and produces controlled release. Owing to its mucoadhesive nature, it extends the period of contact time of medication on the skin. Emulgel acts as dual controlled release system as it possesses the characteristics of both emulsion and gel [39].

There are several marketed emulgels available, which have been widely used as antifungal, topical corticosteroids, anticancer, exfoliating, and anti-inflammatory medications [8, 40].

2.3 Microgels

The term ‘microgel’ was first introduced by Baker by implementing cross-linked polybutadiene latex particles [41]. Basically, microgels are defined as micron-sized gel, which is having cross-linked network structure possessing particle size range

higher than 1 micron. Furthermore, microgels are composed of colloidal dispersion of gel and solvent [42]. Due to strong physical forces, microgels have their steady construction [43].

Microgels are widely used in the field of oral and non-oral drug delivery system, [44–46] topical drug delivery system [8, 47–50], etc.

2.4 Nanogels

In recent years, nanogels have emerged as promising hydrophilic formulations for entrapment of guest molecules having the capacity to respond to external stimuli that may be possibly used for multiple applications. Nanogels are 3D polymeric hydrogel-based cross-linked network having nanoscale range with a capacity to carry large volume of water in the absence of aqueous media [8, 51]. Nanogels can be prepared by synthetic, natural polymers and combination of both. By altering the composition of nanogels, their size, shape, amphiphilicity, charge, and softness can be modified [52]. Nanogel triggers drug release at target site. However, owing to their speciality, nanogels offer number of advantages, such as biocompatibility, swelling capability, biodegradability, high drug loading capability, enhanced efficacy over renal excretion [8].

Nanogels have wide number of applications in the field of cancer treatment. As compared to single responsive nanogels, multistimuli-responsive nanogels are very effective for targeted drug delivery in cancer [53, 54]. Moreover, nanogels are used in local anesthesia, [55] Alzheimer's disease, [56] gene therapy, [57] neurodegenerative diseases, [58] and rheumatic disorders [59].

2.5 In Situ Gel

In situ gel is one of the most elegant drug delivery systems that stimulates establishment of various medical and biomedical controlled delivery systems. In situ gel appears in liquid form at ambient temperature and markedly change based on different factors like: change in pH and alteration of temperature. Moreover, it simultaneously changes its appearance when it comes to the contact of body fluid [60]. In situ gelation is a mechanical process of gel formation at the target site after application [61]. The advantage of in situ gels includes excellent thixotropic characteristics, enhanced contact time of drug, decrease frequency of drug administration, quick absorption and rapid onset of action, low dose strength, minimized systemic and local effects, direct penetration to systemic circulation and central nervous system (CNS) as well as possible administration through rectal, vaginal, oral, ocular, and intraperitoneal routes [62, 63].

In situ gels are used as in antibiotic formulations to overcome the problems associated with eye drops [64], used as an antitussive and anti-angiogenic agent [65].

2.6 Vesicular Gel

Vesicles are small-scale carriers composed of a number of amphiphilic molecules like lipids, surface active agents and block polymers. Vesicles are generally made up of hydrophilic core bordered by bilayer of amphiphiles. They have gained attraction for their exclusive delivery system of drugs, pharmaceuticals, food nutrients, fragrances and dyes in cosmetics and textiles, and so on. Vesicular gel enables topical drug delivery via niosomes, liposomes, ethosomes, novasomes, and other vesicular system. Vesicular system provides innumerable applications of locally acting drugs on dermal delivery as well as transdermal delivery for systemic effect. Hence, non-invasive route has gained popularity over oral route from decades [8].

3 Biopolymeric Gels

These are molecular coils which proceed through coil helix transformations; either produces network or enables the network to establish via lateral helix alliance [66]. Different levels of structural heterogeneity are shown by biopolymer gel networks. At one degree, where polysaccharide network strands are thick (e.g., agarose gel), such network may be considered as a microphase separation. On the other hand, where a network represents itself to be necessarily molecular, large-scale variation of network density repeatedly occurs in both the cases of associative and particulate gels. The gels thus are made heterogeneous over long-scale distance and opaque [66, 67].

The biopolymeric gels are widely used in the field of agriculture [68], food, and pharmaceuticals [69]. On the other side, the gels prepared with polymeric blends have wide ranges of applications in pharmaceutical, cosmetics, food, and biotechnological background [8, 70].

Recent research has been focused on natural biopolymers and biopolymer gels, various types of gel formulations due to the immense benefits that could be achieved from such delivery systems targeting several diseases; for local as well as systemic action; for drug delivery and medical devices; for various routes of drug delivery including oral, rectal, vaginal, topical nasal, or buccal. Few of such studies would be highlighted in the next section concerning several biopolymers.

3.1 Guar Gum

Pandey et al. prepared o/w type of emulsion gels using aqueous solutions of guar gum and xantham gum together with sunflower oil for the administration of combinations of probiotics and drugs. The emulgels were characterized by FTIR, fluorescence microscopy, XRD, DSC, evaluated for mechanical properties and disintegration studies. The encapsulated probiotic *Lactobacillus plantarum* 299v was found to be viable in the emulgel formulation when stored under different conditions of temperature, 4 °C, 20 °C, and −196 °C. Further, when the drug metronidazole was loaded on to the probiotic emulsion gels, sustained release of the drug was produced [71].

An in situ gelling ophthalmic delivery system was developed by Bhowmick et al. [72] using poloxamer-407, xanthan gum, and guar gum in a ratio of 3:7 which was sufficient to convert the poloxamer, used in concentrations less than 18% from sol to gel at temperatures below the body temperature. Further, the gums added helped the formulations to retain the drug for longer duration than the poloxamer alone.

Tetrakis(2-hydroxyethyl)orthosilicate (THEOS) which is a hydrophilic silica precursor was combined with hydroxypropyl guar gum (HPGG) which is a hydrophilic guar gum derivative to obtain a biocompatible sol–gel silica matrix which can be used for the delivery of drugs or biomolecules. The addition of HPGG not only catalyzed the sol–gel transition of THEOS in water yielding a homogeneous gel, with much shorter gelation times but also affected the mechanical strength of the gels. When Vit B12 was encapsulated within the formulation, it produced a sustained release. The release properties were further dependent on the concentration of HPGG, with lower rates of release with higher amounts of the gum derivative [73].

3.2 Xanthan Gum

Anionic gels containing agarose along with carbomer 934 and xanthan gum were applied to produce electric field induced drug delivery that would follow zero-order drug release. The gel content and the strength of the electric current were observed to affect the drug migration under the effect of the applied electric field [74].

A nanoemulgel was designed for the nasal delivery of the antiepileptic drug carbamazepine containing oil/surfactant as oleic acid and labrasol in a ratio of 1:5 and 0.1% xanthan gum as the mucoadhesive agent which was anionic in nature. The prepared formulations were characterized with respect to the size of the droplets, the drug release and drug uptake as well as mucoadhesion properties. Further, in vivo studies were conducted on animal model using albino mice to evaluate the anticonvulsant activity induced by chemical and electrical means after the application of the nasal gel. Drug uptake reached up to 65% within an hour. Thus, an alternative means for the delivery of the drug could be developed which has erractic absorption on oral administration [75].

Chlorhexidine gels containing 10% doxycycline hyclate and xanthan gum were evaluated for use along with scaling and root planning for the treatment of chronic periodontitis. The results showed marked improvements in the patients when the gel was applied in the treatment [76].

Cross-linked gel beads with xanthan gum and sodium alginate entrapping diclofenac sodium as the model drug were developed. The presence of hydrogen bonds between xanthan gum and sodium alginate resulted in difference of physicochemical properties of the beads, like higher drug entrapment efficiency, higher water uptake, and swelling in distilled water pH 6.8 phosphate buffer. However, in increased concentrations of the gum, drug release increased [77].

In a novel study, an aerogel prepared with methoxy pectin and xanthan gum was placed as a coating on medical grade stainless steel and evaluated for orthopedic applications on osteoblast cells derived from human bones. The gelation was produced using ethanol and then dried. Drugs such as indomethacin and diclofenac sodium were added in the gel coatings, and the release was obtained till a period of 24 h. The delivery system was proven to be biocompatible and thus has potential to be used for clinical purposes [78].

Lamotrigine was added into polymeric solutions of gellan and xantham gums, so as to produce in situ gels in the nasal cavity, which would improve the bioavailability of the drug, bypassing the first pass effect, and increase residence time due to higher mucoadhesion. In vitro and ex-vivo studies were conducted for the formulations. The in vitro studies showed immediate drug release with a maximum of 97% within 20 min. The ex-vivo studies showed sustained drug release over a period of 12 h with greater permeability compared to the control batch. The formulations were stable for 45 days when temperature maintained within $4 \pm 2^{\circ}$ C [79].

Mucoadhesive nasal inserts were prepared with a number of water-soluble polymers like sodium alginate, carrageenan, Carbopol, chitosan, polyvinyl pyrrolidone, hydroxypropyl methylcellulose (HPMC) K15M and E5, sodium carboxy methylcellulose, and xanthan gum. It was observed that the polymers with low molecular weights dissolved and released the drug quickly, whereas the inserts prepared with high molecular weight polymers like xantham gum, HPMC K15, or carbopol decreased the drug release rate [80].

Xanthan gum and locust bean gum were used to produce gels loaded with vesicles composed of non-ionic surfactants and a model drug to evaluate topical drug delivery compared to other marketed topical gel formulations. The developed formulations matched the marketed products with respect to mechanical integrity and strength and produced sustained release but improved permeability through the skin as it was loaded with permeation enhancing vesicles. Further, the formulations were stable for a period of about one year without the addition of any preservatives [81].

HPMC K100 and xanthan gum were used to prepare in situ gels encapsulating loratidine for nasal delivery. The gels had mucoadhesive characteristics. The temperature for the sol-to-gel transformation for the formulations varied between 33.1 ± 0.43 and 34.8 ± 0.82 °C, and the gelling time ranged from 4.0 ± 0.21 to 11.3 ± 0.22 s. The pH of the formulations was favorable such that they produced no mucosal irritation. The drug release was sustained for a period of around 10 h. The gels were stable

for about six months under accelerated stability testing. Thus, the prepared formulations had the potential to be used as mucoadhesive gels to improve bioavailability of drugs [82].

Microemulsion formulations of Repaginate, a class II hypoglycemic drug was gelled using xanthan gum for improvement of its bioavailability by improving the residence time and permeation of drugs. Ex-vivo permeation tests were conducted using rat skin for both the microemulsion and microemulsion gel formulations. They showed 12.30 and 10.97 fold increase in permeation across the membrane compared to normal drug suspension. In vivo studies on Sprague Dawley rats confirmed the efficacy of the developed formulations to control glucose level [83].

3.3 Shellac

In situ gels and microparticles were developed using bleached shellac and different solvents like dimethyl sulfoxide (DMSO), N-methyl pyrrolidone (NMP), and 2-pyrrolidone (PYR) encapsulating the model drug doxycline hyclate. The drug and solvent release from the microparticles were slower than that of gels. The drug release rates were minimum when 2-pyrrolidone (PYR) was used as the solvent and was chosen as the solvent which gave the best sustained release from in situ gels with good biodegradation properties [84].

In situ gels comprising of bleached shellac, ethylcellulose and Eudragit RS were developed using N-methyl pyrrolidone as solvent for possible use in periodontitis treatment. The formulations could be easily administered through injection and could inhibit various bacterial species owing to the antibacterial activity of N-methyl pyrrolidone. They could form in situ gels in vitro [85].

Three types of oleogels were formed with hydrophilic polymer like HPMC, with shellac, and with emulsion droplets and were compared with respect to various physicochemical properties. They were characterized with respect to their process of preparation, their mechanical strength and rheological properties and the response of the oleogels to differences in temperature, water content, or shearing force [86].

3.4 Alginate

Beads produced from alginate aerogels are known to have a highly porous structure nanostructure. In a study, dried beads were produced from alginate cryogels, xerogels, or aerogels under different gelation conditions like aqueous or alcoholic solutions of calcium chloride and different drying conditions like freeze drying, supercritical drying, or oven drying. The effect of such gelation or drying methods on the physicochemical properties and stability of the beads were studied. The alginate aerogels were found to be suitable after 3 months of storage at 25 °C and 65% relative humidity [87].

Beads from alginate aerogels with cross-linked iron (III) were developed, and ibuprofen and ascorbic acid were loaded. When the drug release was tested in HCl (pH 2) and phosphate buffers (pH 6.8), the release was found to be faster in phosphate buffer. Further, incorporation of ascorbic acid in some of the formulations increased the drug release as the iron (III) to iron (II) cross-linking was reduced by the acid and led to the erosion of the matrix [88].

Microparticles with size less than 50 μm were prepared from alginate aerogels cogelled with pectin with low methoxyl pectin and k-carrageen an, dried using supercritical CO_2 and loaded with drugs like ketoprofen and quercetin. The release of drugs from the microparticles was relatively improved than from alginate particles due to larger surface area and superporous characteristics of the aerogel. Further, alginate having bioadhesive properties and the formulations may be applied for mucosal delivery with improved absorption [89].

Aerogel microspheres were also developed with polysaccharides like alginate, starch and pectin, loaded with drugs like ketoprofen or benzoic acid and their release characteristics tested in HCl and phosphate buffers. Controlled drug release from alginate aerogel microspheres could be obtained depending on the composition of matrix. Drug release was observed to be based on both diffusion and erosion of alginate matrix [90].

Nanoparticles based on nanogels prepared from alginate and chitosan as biopolymers were developed for corneal delivery for treating glaucoma. Timolol maleate was used as the model drug. The particles gave sustained release for a period of 24 h after a burst release during the first hour in the drug dissolution studies. The size of the particles ranged from 80–100 nm. Promising results were also obtained from the ex-vivo permeation studies conducted through Franz diffusion cell and fluorescent microscopy where it was observed that the drug permeation from the formulations was twice than that from pure drug [91].

Smart nanogels were developed from alginate derivatives linked to iron oxide nanoparticles and loaded with doxorubicin which would have magnetic resonance imaging properties for diagnosis of disease as well as target tumor cells for therapeutic activity as they were loaded with drug. They were relatively safe to normal tissues [92].

Cisplatin-loaded alginate nanogels were developed for targeting macrophages for treating artherosclerosis. Cisplatin served as the therapeutic agent as well as the cross-linking agent for alginate molecules. The formulation showed a pH-dependent drug release with 100% release within 48 h at pH 5, whereas the release was even less than 15% at pH 7.4. The drug uptake was evaluated on macrophage and human cell lines. Further, it was observed that the nanogels were selectively taken up by macrophage cells rather than human cell lines [93].

Alginate along with a thermosensitive polymer poly(N-isopropylacrylamide) was used to develop smart nanogels in situ with cystamine as cross-linker. The developed nanogels gave abrupt swelling upon temperature increase in the environment of the cells from 25 to 37 °C. Due to the increase of temperature, the nanogels could be easily taken up by cancer cells. Further, due to the presence of acidic and reducing

conditions in the cells, the drug release from the nanogels was accelerated. Thus, the therapeutic activity of anticancer drugs would be improved to a high extent [94].

In a similar study, gels were prepared by adding poly(N-isopropylacrylamide) or poly(N-isopropylacrylamide-co-acrylic acid) into alginate (AG) emulsion nanodrops and fixed and stabilized with cystamine dihydrochloride. The developed gels showed thermosensitivity, pH sensitivity, and redox sensitivity. The formulations loaded with anticancer drug were taken up by cells and released drug due to thermal changes. Further, the acidic and reducing environments in the cells cause accelerated drug release leading to enhanced toxicity of the drug [95].

Smart nanogels comprising of branched alginate-polyethyleneimine copolymer were used to not only enhance drug delivery but also track the passage of the delivery system through fluorescence spectroscopy. The fluorescence emitted varied with pH γ irradiation. Doxorubin loaded on to the gels was released in a time-dependent manner which was significantly higher in the presence of glutathione and at lower pH than in acidic pH or absence of glutathione. The drug-loaded gels were actively taken up by HeLa cells as confirmed by fluorescence microscopy. Further, the nanogels were much less cytotoxic and hemocompatible [96].

In situ gels using alginate using cystamine as a cross-linker were prepared and loaded with doxorubicin as a model drug which has poor cellular uptake and release characteristics. The nanogels were cytocompatible and had > 95% encapsulation efficiency. The release from the nanogels under reducing conditions of the cells was high. The nanogels were actively taken up by osteosarcoma cell line CAL-72 cells. The cell uptake and death were significantly higher from the developed nanogels compared to free drug [97].

Pressure-sensitive nanogels prepared with alginate cross-linked by modified β-cyclodextrin were developed and utilized for better therapeutic management with 5-fluorouracil which suffers from low cellular uptake. The prepared nanoparticles from the nanogels were cytocompatible with 82% encapsulation efficiency. The in vitro drug release from the formulation was pressure sensitive which indicates that the drug release in vivo would be stimulated by intravascular pressure. They were actively taken up in colon cell lines HT-29 cells. Significantly higher amounts of drug were taken up by the cells and resulted in cell death compared to free drug [98].

Aldehyde-alginate was cross-linked with gelatin by inverse mini-emulsion technique to develop nanogels in the presence of borax due to Schiff's base reaction. Spherical particles of the nano range were obtained which were found to be cytocompatible and hemocompatible and thus non-toxic to the body. Such formulations can be thus used targeted drug delivery with fewer side effects [99].

Curcumin-loaded alginate aldehyde-gelatin nanogels were developed and characterized to improve the bioavailability of the medicament. The nanogels had a high encapsulation efficiency > 82% and gave a controlled release of drug over a period of 48 h. Nanogels were found to be cytocompatible and were actively taken by MCF-7 cells which were confirmed by confocal laser scanning microscopy [100].

Biocompatible alginate nanogels have been used as suitable carriers for protein or peptide drugs. However, low encapsulation efficiency and higher release in alkaline pH have been observed due to larger pore size of the nanogel structure. In this study,

a novel on-chip method has been devised where the pore size of the gel could be modulated by synthesis of the gels using microfluidic platforms with cross-junction microchannels. For fluid flow ratio of 0.2–2, the size of the nanogels ranged from 68 to 138 nm. Increase in the flow ratio increased the size and decreased the compactness of the formulations. Therefore, the porosity of the gels could be controlled effectively by this method to modulate drug release under different conditions [101].

Nanosized liposomes were used to prepare nanosized cross-linked alginate gels for various therapeutic applications. Alginate was entrapped within the core of nanoscale liposomes and then placed in a calcium chloride containing buffer solution with elevated temperatures which resulted in the absorption of calcium ions by the liposomes to cross-link the alginate in the core. Thereafter, the lipid layer was removed by surfactants and nanoscale alginate gels of size range 120–200 nm resulted. In a similar way, different size of nanogels can be prepared using different sizes of liposome template [102].

3.5 Chitosan

Chitosan-based gels were applied on second degree burns in rabbits to study the wound healing rates. Chitosan has well-known wound healing properties. It was observed that compared to the control group there was better wound healing including healed epidermis and normal melanocyte production [103].

A biodegradable, safe, and biocompatible biomaterial with bioadhesive properties which would stop bleeding and help to bind tissues was developed by reacting chitosan with oxidized dextran. A biocompatible gel was produced as a result which was non-toxic and showed good adhesive properties on tissues. The gel did not swell in phosphate buffer. The in vivo efficacy of the produced gel was demonstrated in a rabbit model with liver injury. The gel can also be used for drug delivery [104].

Myricetin was loaded on to chitosan nanogels with a particle size of 100–300 nm. Fickian drug release was accompanied with swelling and erosion in acidic medium. Further, the bioavailability of the drug was found to improve when administered in rats via the oral route. The formulation showed no cytotoxicity in MTT assay [105].

Chitosan gels with mucoadhesive properties encapsulating antifungal agents like econazole and miconazole nitrates were developed and evaluated for possible vaginal use. Various grades of chitosan with differing molecular mass and viscosity were used. Several evaluation studies were conducted on the developed gels to determine their mechanical strength, rheological properties, and syringe ability, in vivo retention in vagina in rats, mucoadhesive properties, release studies, and studies to demonstrate anticandidal effect. After evaluating all the formulations, the gels prepared with medium-molecular weight chitosan were optimized as it showed suitable mucoadhesive and release properties and effective vaginal retention times [106].

Film-forming gels have the specific advantage of protecting the skin and to provide continuous release at the target site. Thus, a chitosan-based film-forming gel encapsulating the drug ketoprofen was developed with various skin permeation enhancers and evaluated for various physicochemical characteristics. Skin permeation study was conducted in Franz diffusion cell using excised rat skin. In vivo studies in rheumatoid arthritis-induced animal model were also conducted. The gel was found to form the film well in the skin permeation study. Oleic acid was found to act as a useful skin permeation enhancer compared to others. In the in vivo study, significant anti-inflammatory and analgesic activities were reported [107].

Such film-forming chitosan gels have also been produced containing tyrothricin and evaluated in various wound types and burns. Once solidified, the chitosan layer protected the wound and healed it gradually. The wound size was measured periodically after induction and results compared with negative control where no drug was applied and positive control where sodium fusidate ointment and marketed tyrothricin gel were applied. The developed gel formulation demonstrated significantly better results than negative and positive controls for various types of wounds, which may be due to better occlusion properties of chitosan [108].

Photocytotoxic agents like Toluidine blue O (TBO) have been in use to produce toxic effects on tumor cells. Thus, TBO was incorporated in 4% chitosan gels containing Tween 80 as a permeation enhancer for management of oral cancer. The formulations were characterized with respect to physicochemical properties like mucoadhesion, viscosity, etc., and in vitro release or mucosal retention and in vivo penetration studies through mucous layer. The 4% chitosan gels with 5% Tween 80 and 1% TBO had good mucoadhesion properties. The release of TBO was sustained by Tween 80 and allowed greater mucosal retention times. The formulation also improved tumor cell death by apoptosis [109].

Nanoemulsions were prepared containing Labrafac PG + Triacetin as the oil phase, Tween 80 and polyethylene glycol (PEG 400) as surfactant and co-surfactant, respectively, and characterized with respect to physicochemical properties, ex-vivo skin permeation and deposition studies. The optimized emulsion was then incorporated into 1–3% chitosan gel for preparing nanoemulsion gels. Curcumin was used as the model drug and entrapped within both the nanoemulsion and the nanoemulsion gel formulations, and both the formulations were compared with respect to wound healing characteristics. The permeation of curcumin was higher in case of the nanoemulsion, whereas the retention of curcumin on skin was significantly higher in case of the gel formulation [110].

Nanofibers have been found to be beneficial for accelerated wound healing as they can induce hemostasis, induce cell growth, and absorb the exudates from wound. Chitosan nanofibers have been prepared for the above purpose with their surface modified with arginine and electrostatically interacted with sodium alginate under different pH conditions with an average diameter of 100–150 nm as observed by scanning electron microscope. The release of arginine from the nanofibers took place at a sustained rate. The formulation was viscous and could spread quite well and therefore easily applied in the wound area. The wound healing properties observed

were significantly improved in in vivo rat model when compared to control groups [111].

Chitosan gel-containing Lysostaphin was developed and evaluated against multidrug resistant Staphylococcus aureus. The antibacterial activity of the developed gel formulation was evaluated using agar well diffusion method and ex-vivo porcine skin model. Both the studies showed significant reductions in bacterial count [112].

Hydrogel beads of succinyl chitosan were prepared and stabilized with glycopolymeric network and loaded with anticancer drug doxorubicin. The drug release was sustained for more than 15 days with zero-order release profile [113].

Moxifloxacin was loaded on to niosomes and entrapped within chitosan gel for topical drug delivery. The formulations were evaluated for various physicochemical characteristics, and activity on the pathogens like *Pseudomonas aeruginosa* and *Staphylococcus aureus* was studied by agar well diffusion methods. The optimized formulation demonstrated a drug entrapment efficiency of 73%, and sustained drug release of 47% in 8 h. The gel formulations exhibited improved sustained release characteristics compared to niosomal formulations. The niosomes showed greater activity toward *P. aeruginosa,* while the noisome containing gel formulations showed greater activity toward *S. aureus* [114].

Acrylic-based nanocapsules with cationic and anionic characteristics were loaded onto chitosan gels for vaginal delivery which is a challenging route. Nile red was used as the model drug which is lipophilic in nature. The formulations were characterized with respect to pH and viscosity and evaluated in porcine vaginal mucosa. The formulations were found to be retained for prolonged periods of time and penetrate the vaginal membrane better. The gels were found to be sufficiently viscous and had an acidic pH of about 4.5 in both the formulations containing cationic and anionic nanocapsules. The mucoadhesion on the vaginal mucosa was found to be better than control without any nanocapsules. The penetration of gels with cationic nanocapsules was better than anionic ones [115].

Biocompatible chitosan gel along with cationic protamine sulfate, an arginine-rich protein was used for controlled delivery of DNA. Protamine has been known to be beneficial for effective cell penetration and localization in the nucleus. The formulations were characterized with respect to DNA entrapment efficiency, release, release kinetics, and swelling studies. The hydrophilic nature of the gel particles was assayed by Rose Bengal partition assay method. Further, the formulations were found to be non-hemolytic and therefore can be used in devices that stay in contact with blood [116].

3.6 Inulin

Inulin plasma clearance data were determined and compared for inulin solution given through i.v and i.m routes and an inulin/poloxamer gel formulation administered through i.m route. It was found that the clearance values of inulin in case of the gel

formulations were significantly reduced compared to inulin solutions given through i.v and i.m routes [117].

3.7 Cellulose

Cellulose gels were produced with tetramethylguanidine as the cross-linking agent in ratios of 1:1, 1:2, and 1:3 which gave stable formulations. Such gels would be beneficial for drug delivery [118].

Aerogels were prepared with cellulose and polyethoxydisiloxane resulting in polymer networks, and they were characterized using two different methods like molecular diffusion and pressure difference induced forced flow. The latter method resulted in significantly reduced impregnation times. The specific surface area of the gel network was evaluated using nitrogen adsorption analysis method and was found to increase by threefold compared to organic–inorganic composites [119].

A mucoadhesive cellulose polymer gel formulation encapsulating the antifungal agent miconazole was prepared and characterized for drug delivery in the buccal cavity. The gel was cross-linked with triethanolamine and evaluated with respect to ex-vivo permeation study. The texture of the formulations was found to be consistent over a period of 90 days. Greater diameters of zones of inhibitions of the antifungal gel were observed when compared to marketed formulations. Thus, stable formulations with improved residence times in the oral mucosa were developed [120].

Sodium carboxymethylcellulose was used along with microcrystalline cellulose to formulate a mucoadhesive nanogel formulation. Few nanofillers were also incorporated in the nanogels like MMT-clay or porous starch for a stable structure. The formulations were able to achieve better controlled release compared to other nanogels [121].

One of the recent promising methods for gastric emptying tests is the alternate current biosusceptometry (ACB). It is sensitive, easy to perform, non-invasive, and economic. In a study, formulations with magnetic properties such as Mn-Zn ferrite nanoparticles, nanoparticles modified with dextrose, and cellulose gel-containing ferrite nanoparticles were developed to function as tracers in gastric emptying tests. When evaluated in rats, the ferrite nanoparticles were pH-sensitive along the length of the gastrointestinal tract, while nanoparticles modified with dextrose were found suitable for rapid gastric emptying tests. The cellulose gel formulation on the other hand was found to be sufficiently bioadhesive and retained in stomach and easily detected by ACB analysis [122].

Ibuprofen was loaded onto oxidized cellulose gels containing nanofibrils and compared with marketed products for topical delivery. The gels were evaluated using silicone membrane and pig skin by in vitro tests and in human volunteers by in vivo tests. The permeation of the drug from the gels was similar to that of the marketed products as observed from the in vitro or in vivo tests [123].

In a study based on preparation of cellulose aerogels, zinc chloride tetrahydrate was used which was later removed from the gel by using solvents such as alcohol,

acetone, water, or isopropanol. It was further observed that aerogels washed with acetone had a significant increase in surface specific area compared to those washed with water [124].

Novel topical cellulose-based gel formulations were developed in order to minimize the loss of viscosity after sterilization in autoclave. Initially, viscous gels were produced with methylcellulose and hypromellose entrapping a protein molecule; however, they lost their viscosity after autoclaving. When edetate disodium was added into the formulations, the loss of viscosity was minimized in the presence of 0–100 ppm of hydrogen peroxide. However, when methionine was added, the loss of viscosity could be completely prevented in the presence of 0–50 ppm of hydrogen peroxide [125].

Aqueous NaIO4 was used to partially oxidize cellulose gel and then reacted with polyallylamine for formation of Schiff's base. Three different gel formulations were prepared by the method with a content of amino groups such as 0.35, 0.59, and 0.96 mmol/g cellulose, and protein retentions were evaluated and compared with DEAE-cellulose gel-containing amino groups in the ratio of 1.07 mmol/g cellulose. It was observed that the protein retention was much higher in case of the developed gel formulations. Further pairs of proteins such as human and bovine serum albumins which have similar isoelectric points and molecular weights could be effectively separated using the developed gels, which may be due to the high density of polyallylamine [126].

In a novel study, cellulose polymer was modified with different concentrations of HMDI and this modified polymer was then added to castor oil to form oleogels due to the reaction of the polymer with the ricinoleic fatty acid chain hydroxyl groups. When characterized, the oleogels were found to possess suitable viscosity and thermal-resistant properties [127].

Lysine-based surfactants were added to ethyl (hydroxyethyl) cellulose gels which reduced their cytotoxicty which was tested on HeLa cells. The polymer interacted with the surfactant molecules to form mixed micelles due to which they became more biocompatible. The biocompatibility of the gels was improved with the most hydrophilic or longest chain surfactant molecule [128].

Cellulose sulfate vaginal gel formulation was tested in a clinical study on 1398 women of sub-Saharan Africa in order to test their efficacy to prevent HIV infection. The studies indicated that the cellulose sulfate was not able to prevent HIV infection in the tested women and was in no way better than placebo [129].

3.8 Pectin

In a novel study, the efficacy of preactivated thiolated pectin for buccal delivery of lidocaine was evaluated in a gel formulation and compared with other pectin and thiolated pectin formulations with respect to drug release and other physicochemical properties like viscosity, swelling, and mucoadhesive properties. Thiolated pectin was cross-linked resulting in gel formation due to the presence of thiol groups and

did not require any excipient for the cross-linking reaction, whereas pectin could not do so. Viscosity of the gels formed with thiolated pectin was increased by 92 times and that of preactivated thiolated pectin increased by 4958 times than pectin gels. Gels swelled in water but would not dissolve for several hours. Further, mucoadhesive properties improved significantly. Higher retention of drug in the buccal mucosa and sustained release properties of the novel gel indicated that the gel formulation would be promising for buccal delivery [130].

Beads were prepared from calcium pectin-silica gel using the ionotropic gelation method entrapping mesalazine for controlled release in colon. Increasing the amount of sodium silicate led to higher gel strength and a decrease in swelling of the beads. Further, when the reaction time with calcium chloride was increased up to 1 h, sustained release properties were improved [131].

Pectin-calcium gels have the property of adhesion on gram positive bacterial cells like *Bacillus subtilis*. Pectins obtained from various sources were used in the study. The adhesion was attributed to the high molecular mass, length of carbohydrate chain, and low degree of methyl esterification [132].

A pulsatile capsule was developed for colon-targeted delivery. The capsule was impermeable and filled with an immediate release tablet containing the drug 5-aminosalicylic acid and had a plug at the capsule opening which was prepared with high-methoxy pectin and lactose or low-methoxy pectin and hydroxypropylmethyl-cellulose. In vitro release profile showed rapid release after a lag time and adding pectinase or rat cecal contents to the medium shortened the lag time for drug release. In the in vivo studies, it was observed that the plasma concentration for the drug could be detected after a lag time of 6 h which showed that it would be suitable for colon-targeted drug delivery [133].

In a novel study, spherical aerogel particles were produced via the jet cutting method using chitosan, amidated pectin, and sodium alginate. Gels were produced by diffusion method in calcium chloride solution and by internal setting method using calcium carbonate as the cross-linking agent; citric and acetic acids were used for adjusting pH. The aerogel particles thus produced had a size range of 400–1500 μm and a specific area of $500 m^2/g$ [134].

In a study, ketoprofen-loaded tablet formulations were prepared by adding pectin/dextrin mixtures to microparticles of zinc pectinate for controlled drug delivery in the colon. The formulations were characterized and optimized using factorial design. It was observed that the release was sustained when the microparticles were added in the formulations. The in vitro release studies were conducted by mimicking the pH and gastric retention times throughout the gastrointestinal tract. Lag times ranging from 4.125 to 4.85 h were observed, whereas the time taken for 50% drug release was in the range of 7.45–8.70 h. The formulations were able to achieve controlled release and were better by 5.28–37.82 folds than calcium pectinate beads [135].

Pectin gel had been used for adsorption and removal of methylene blue, but the adsorption rate was low. Therefore, particles of pectin microgel were prepared and used for the adsorption of methylene blue. It was found that the microgel particles

had a high adsorption rate and therefore would be beneficial for methylene blue removal from samples [136].

Aerogel microspheres were prepared with biopolymers like alginate and pectin and cross-linked with calcium ion and dried by lyophilization. It was observed that on increasing the pectin amount the porosity and solubility of the microspheres increased and on increasing the alginate concentration, the microspheres were stiffer. The microspheres were able to achieve controlled release of the encapsulated agent proanthocyanidins and those with higher pectin contents showed higher antioxidant activity [137].

Modified pectins were obtained from callus cultures and when cross-linked with higher concentrations of calcium chloride resulted in gels with higher degree of rhamnogalacturonan I branching of pectin. Such a cross-linked pectin structure could achieve retarded release of encapsulated prednisolone in simulated gastric and intestinal media, whereas a rapid release pattern was observed in simulated colonic medium from which it may be concluded that the resulting gel would be suitable for colonic delivery [138].

Gels with double network were prepared with sugar beet pectin and isolates from soy protein by laccase catalysis and application of heat. It was observed that the gels had improved water holding capacities and mechanical strength, and therefore, such gels could be effectively used for delivery of various components [139].

Floating emulsion gel beads were prepared by emulsion gelation methods with pectin and wax, where the wax added in mixtures of pectin and olive oil was melted, homogenized, added to the cross-linking solution of calcium chloride and the formed beads after washing were dried. Metronidazole was used as the model drug and loaded onto the beads. When the amount of oil used was sufficient, the beads floated on the simulated gastric fluid. Various types of waxes were used in the study. When water-soluble waxes were used, the drug release increased, but when water insoluble waxes were used, the drug release was reduced significantly. However, the incorporation of waxes in the formulation resulted in sustained drug release from the gel beads, while they floated for prolonged periods of time [140].

4 Conclusion

From the above chapter, it was observed that there are innumerable natural polymers with significant benefits which are used for preparation of different biopolymeric gel formulations entrapping active agents and used for drug delivery or other biological applications. Such biopolymeric gel formulations have immense opportunities for further research for targeting different disease models. Further research on discovery and development of new biopolymers is also the call of the day. However, a further research should be focused on proper in vivo studies, clinical, and toxicological study to ensure the safety and efficacy of biopolymeric formulations. Overall, it can

be concluded that biopolymers hold significant potential with respect to targeting new disease models, development of novel formulations, and medical device and ensure safety and efficacy for the benefit of the common man.

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In Situ Polymeric Gels for Topical Drug Delivery

Paramita Paul and Gouranga Nandi

Abstract Hydrogels have been considered as a potential drug carrier not only in case of peroral devices but also in a variety of ophthalmic, transdermal, oral mucosal and even injectible preparations due to their simplicity in preparation and smartness in the modulation of residential time, degree of drug absorption, local bioavailability, drug release, various physical properties of the devices, etc. In situ gel formulations have been considered as an effective approach to this problem associated with viscous hydrogel-based formulations. An in situ gel formulation remains as low-viscous solution or dispersion with sufficient flowability in the container at ambient condition and gets converted into a highly viscous gel state in the physiological conditions immediately after administration. This chapter summarizes the potential advantages and disadvantages associated with in situ gel formulations designed for topical applications along with various mechanisms of transition, factors, preparation-methods, polymers, characterizations, and drug delivery applications.

Keywords In situ gel · Topical drug delivery · Polymer · Hydrogels

1 Introduction

Hydrogels have been considered as a potential drug carrier not only in case of peroral devices but also in variety of opthalmic, transdermal, oral mucosal and even injectible preparations due to their simplicity in preparation and smartness in modulation of residential time, degree of drug absorption, local bioavailability, drug release, various physical properties of the devices, etc. For example, hydrogel-based skin, buccal-mucosal, ophthalmic or otic preparations possess higher the residential capacity

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over relatively longer period in order to promote a better degree of drug absorption from the site of application because of their higher viscosity. Hydrogels can be defined as three-dimensional polymeric semisolid matrices with a significantly large amount of water content within it. A wide number of natural polysaccharides such as sodium alginate, chitosan, gellan, xanthan, pectin, etc. are capable of forming hydrogels, which are easily available, economic, biocompatible and biodegradable. But, specially, gel formulations designed for ophthalmic, nasal or otic administration suffer from poor flowability and non-uniformity of dosing. In situ gel formulations have been considered as an effective approach to this problem associated with viscous hydrogel-based formulations. An in situ gel formulation remains as low-viscous solution or dispersion with sufficient flowability in the container at ambient condition and gets converted in to a highly viscous gel state in the physiological conditions immediately after administration. This chapter summarizes the potential advantages and disadvantages associated with in situ gel formulations designed for topical applications along with various mechanisms of transition, factors, preparation-methods, polymers, characterizations and drug delivery applications.

2 Advantages of In Situ Forming Mucoadhesive Polymeric Delivery Systems

In situ gelling systems consist of polymers which are applied as solutions or suspensions that are capable of rapid sol-to-gel transformation triggered by external stimulus such as pH, temperature and ionic strength in the environment upon instillation [1]. The in situ gel has a numbers of merits and demerits that are enumerated below [1, 2].

1. Improved local bioavailability
2. Reduced concentration of drug in dose
3. Ease of administration
4. Reduced dosing frequency
5. Improved patient compliance and comfort
6. Easy formulation steps lowers manufacturing cost and investment
7. Increase ocular residence time
8. Overcome first-pass metabolism if given as in situ nasal gel [3]
9. Overcome the problem of Rapid washout during lachrymation in eyes (ophthalmic preparation).

3 Mechanisms of Formation of In Situ Gel

In situ gels are the hydrogel systems that are applied as liquids (solutions or suspensions) at room temperature but undergo sol-to-gel transformation, also called gelation, due to change in specific physico-chemical parameters like pH, temperature and

ionic strength in the environment etc. [1]. Several mechanisms may lead to formation of in situ gel. The probable mechanisms include temperature modulated, pH-triggered, ion-activated, chemical material-sensitive, photopolymerization, solvent exchange, electric-sensitive, magnetic field-sensitive, ultrasonic-sensitive and, ionic cross-linkage etc. [2, 4]. Some of the important mechanisms are described below.

3.1 Temperature Modulated In Situ Gelling

Temperature modulated or thermo-activated in situ gel formulations do not required external heat other than the body temperature for sol-to-gel transformation. The solution is liquid at room temperature (20–25 °C) and it converted into gel when applied in the body fluid and reaches to body temperature (35–37 °C) [5, 6]. The temperature above which polymer solutions converted to gel and below which it remains as solution is referred to as lower critical solution temperature (LCST). Similarly the temperature above which polymers remain as solution form and converted to a gel upon cooling is known as upper critical solution temperature (UCST) [7–11]. For this mechanism, some temperature-sensitive polymers are employed that exist as a liquid form below its low critical solution temperature (LCST) and undergoes gelation when the temperature reaches above the LCST or environmental temperature [4, 5, 12].

Generally naturally derived polysaccharides do not attribute thermal responsiveness. Thus, various strategies were adopted to confer thermo-sensitivity property to polysaccharides such as (i) chemical modification, e.g. methylation of cellulose, (ii) formation of interpenetrated networks with other polymers featuring thermo-responsiveness, and (iii) complex formation with hydroxylated salts [7].

Polymers which show temperature induced gelation are poloxamers/ pluronics, cellulose derivatives [HPMC, ethyl (hydroxy ethyl) cellulose (EHEC), methyl cellulose], xyloglucan, tetronics, etc. [5, 13]. Polysaccharides that possess thermoresponsive characteristics include agarose, carrageenan, and gellan gum etc. A synthetic polymer that has been extensively researched for its thermoresponsive properties is poly(*N*-isopropylacrylamide) (PNIPAM), which has an LCST of 32 °C [11].

3.2 pH-Induced In Situ Gelling

In this mechanism the change in pH plays a vital role in sol-to-gel transformation. pH-induced in situ gel requires polymers which possess acidic or alkaline of ionizable groups are called as polyelectrolyte within the chain molecule and undergoes a sol-gel phase transition on change from a low pH to high pH environment [4–6]. Polysaccharides may have some ionogenic groups like carboxylic acid moieties in alginates or amine groups in chitosan whose ionization sometimes may depend on the pH of the medium. Depending upon the ionization in the presence of water,

polymers thus become polyelectrolytes with either positively charged (for chitosan) or negatively charged (alginates) [7]. For example, the formulation that exists as a normal solution at pH 4.4 gets transformed into gel at the pH of lachrymal fluid (pH 7.4) [5].

Some of the pH-sensitive polymers are polyacrylic acid (PAA) (Carbopol®, Carbomer) and its derivatives, cellulose acetate phthalate (CAP) latex, polymethacrilic acid (PMA), polyethylene glycol (PEG), chitosan, albumin, gelatin, etc. [5, 6, 14].

3.3 In Situ Gel Formation Due to Chemical Reaction

3.3.1 Ion-Activated In Situ Gelling

In ion-activated in situ gel systems gelation of the instilled solution is encouraged by the change in ionic strength. The osmotic gradient across the surface of the gel influences the rate of gelation thus this process is also called as osmotically triggered in situ gel systems. The polymer undergoes a sol-gel transition triggered by mono or divalent cations such as Na^+, Mg^{2+} and Ca^{2+} present in tear fluid [5, 15, 16].

Generally anionic polymers are used in the formation of ion-sensitive drug delivery system. Polymers that exhibit osmotically induced gelation include gelrite (or gellan gum), tamarind gum hyaluronic acid, alginates, etc. [1, 5]. Other polymers such as MC and HPMC are used to increase the effect of anionic polymer [16].

3.3.2 Enzymatically Crosslinking

In situ formation catalyzed by natural enzymes has not been studied widely but it has some advantages over chemical and photochemical approaches. For example, under physiologic conditions, an enzymatic process operates efficiently without need for potentially harmful chemicals like monomers and initiators. Adjusting the amount of enzyme provides a convenient mechanism for controlling the rate of gelling, which allows the mixture to be injected before gel formation [5].

3.3.3 Mickael Addition

Michael addition is an addition of nucleophiles (macromolecules with multiple terminal amine or thiol groups) to α, β-unsaturated ketones, or esters. This reaction process takes place under aqueous conditions with high efficiency without the formation of any side products, making it a suitable approach for crosslinking in hydrogel synthesis. The nucleophiles macromolecules cross-link with electrophilic macromolecules functionalized with alkene groups with adjacent electron-withdrawing groups, such as vinyl sulfone, acrylate, or methacrylate [17]. In situ hydrogels

were formed under physiological conditions by Michael type addition upon mixing aqueous solutions of vinyl sulfone functionalized dextrans and multifunctional mercaptopoly(ethylene glycol) with thiol groups at a concentration of 10–20% w/v. The gelation time varied from 0.5 to 7.5 min, depending on the degrees of substitution, concentration, dextran molecular weight, and mercaptopoly(ethylene glycol) with thiol group functionality [18].

3.3.4 Schiff Base Reaction

A Schiff base is usually produced by chemical reaction of amines, hydrazides, or hydroxylamines with aldehydes or ketones to form imine, hydrazone, or oxime linkage. In aqueous conditions formation of Schiff base occurs without using additional chemicals or catalysts. It also shows pH-dependant controllable reaction rates. Therefore, this is a simple approach to produce in situ forming hydrogels [17]. The chemical crosslinking agents, due to their toxicity to cells, are the major barriers in the use of injectable in situ forming polymer scaffolds. However, in situ forming biodegradable hydrogel by self-crosslinking of water-soluble *N*-succinyl chitosan and oxidized for hyaluronic acid (aldehyde hyaluronic acid) can be prepared successfully without utilizing any extraneous chemical crosslinking agents. Here, the process of in situ gelation occurred by the Schiff base reaction between amino and aldehyde groups of polysaccharide derivatives [19].

3.3.5 Photopolymerization

The photopolymerization method, also termed as UV irradiation method, utilizes some electromagnetic radiations such as ultraviolet light for the formation of in situ gel. A solution of monomer or reactive macromer and photoinitiator is to be injected into a tissue site and electromagnetic radiation is applied there to transform into gel [5]. The polymers with polymerizable functional groups are capable of dissociating in the presence of some suitable photoinitiators like acrylates or other polymers. Generally, long-wavelength ultraviolet and visible wavelengths are used. Short wavelengths are not used due to their biological harmfulness and its limited penetration into tissue. In this approach, ketones such as 2,2-dimethoxy-2-phenyl acetophenone are used as the initiator for ultraviolet photopolymerization. Camphorquinone and ethyl eosin initiators are used as visible light systems [5, 6].

Tyagi et al. have developed a light-activated polycaprolactone dimethacrylate and hydroxyethyl methacrylate based in situ gel containing bevacizumab using 365 nm UV light and 2,2-dimethoxy-2-phenylacetophenone) as a photoinitiator [20]. Spread of the gel in the rabbit eyes and in vivo delivery in rat eyes was monitored noninvasively using a fundus camera and Fluorotron Master™ [20].

Higham and co-workers [21] found that gelation of alginate in the presence of calcium carbonate ($CaCO_3$) particles and a photoacid generator (PAG) undergoing ionic crosslinking upon ultraviolet (UV) irradiation using in situ dynamic rheology.

The PAG is photolyzed upon UV irradiation, resulting in the release of free calcium ions for ionic crosslinking. The viscous and elastic moduli during gelation are found to be dependent on the intensity of UV irradiation, exposure time, alginate concentration, and the ratio between alginate and calcium carbonate [21].

Recently, Kamoun and his group have worked on grafting of poly (vinyl alcohol) (PVA) with glycidyl methacrylate (GMA) by the trans-esterification reaction via introducing methacryloyl groups into PVA chains. Later, UV-photopolymerization method was adopted for photocrosslinking the water-soluble PVA grafted GMA (PVA-g-GMA) using a photoinitiator Irgacure 2959 [22].

4 Factors Affecting the In Situ Gel Formation

A number of mechanisms lie behind the formation of in situ gel that has been described previously. Thus the transformation from sol to gel depends on the many factors such as changes in pH, presence of ions, ultraviolet irradiation, etc. given in Fig. 1 [3].

4.1 Ultraviolet Irradiation

Gel time decreases as irradiation intensity of the UV light increases because a larger concentration of photoinitiator will be photolyzed upon UV irradiation.

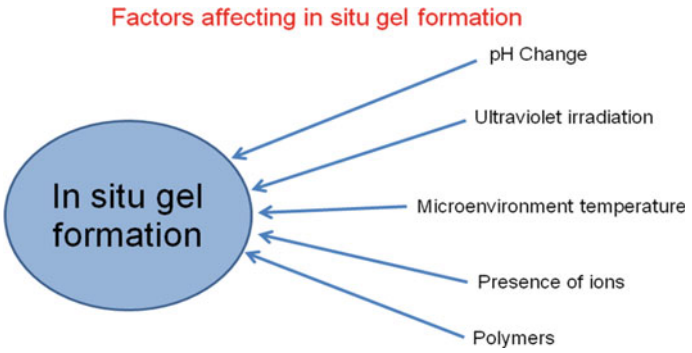

Fig. 1 Factors affecting the in situ gel formation

5 Various Methods of Preparation of Sol

5.1 Dispersion Method

The polymer capable of in situ gelling and other polymers as viscosity enhancers are dissolved in distilled water and a solution of the drug is mixed with it in order to get a homogeneous dispersion. Finally, the pH of the dispersion is adjusted to 6.5 with 0.1 N HCl acid. Makwana et al. prepared an ophthalmic sol of ciprofloxacin hydrochloride using the dispersion method [1].

5.2 Cold Method

In this method, gel-forming polymer (s) is slowly dissolved in a specific amount of water maintained at around 4 °C temperature with continuous stirring by a magnetic stirrer. The temperature of the water is maintained during the preparation and the solution is kept overnight in the refrigerator. The polymer such as poloxamer (407 and 188) having aqueous solubility at cold temperature is suitable for cold method. Other polymers such as viscosity modulators are dispersed in the previous polymer solution. The preservatives may be added after dissolving them in hot water and subsequent cooling. Drug may be added in the polymeric dispersion directly with stirring if it is sufficiently soluble in water, otherwise, the drug is made solubilized in water using solubilizer and then added to the polymeric dispersion. Finally, pH is adjusted. Chaudhary et al. reported the preparation of oral in situ gel of acyclovir employing this method [2].

6 Polymers Used in the Preparation of In Situ Gels for Topical Drug Delivery

List of some polymers used in formulation of in situ gels are given in Table 1.

6.1 Ion-Activated Systems

Ion-activated in situ ocular gelling systems exhibit their sol-gel transition due to crosslinking with polyvalent cations such as Ca^{2+} and Mg^{2+} present in lachrymal fluids. This transition imparts higher viscosity to the formulation and subsequently better adherence with the corneal surface. The examples of most commonly used ion-activated polymers in ophthalmic preparation include sodium alginate, pectin, and gellan gum.

Table 1 Polymers used in formulation of in situ gel

Type of in situ gelling systems	Polymer(s) used	Model drug	Major outcomes	References
Thermosensitive	Poloxamer F127 and carbopol 934P	Brinzolamide	A sol-gel transition at 33.2 ± 1.1 °C sustained release of drug over 8 h	[23]
	Pluronic (PF-127 and PF-68) and sodium alginate	Ofloxacin	In vivo evaluation in rabbits showed improved ocular retention performance of 20% (w/w) Pluronic F127 compared to Pluronic F68	[24]
	Pluronic F-127 HPMC K4M	Ketorolac tromethamine	Enhanced ocular availability and prolonged ocular residence time	[25]
	Pluronic F127, Pluronic F68, and sodium alginate	Lomefloxacin	Exhibited a sustained release profile over 8 h	[26]
pH-responsive	Calcium alginate with HPMC K4M and E50LV	Ciprofloxacin	Sustained drug release	[1]
	Carbopol and chitosan	Timolol Maleate	Exhibited a sustained release over 24 h	[27]
	Carbopol 940 combined with HPMC and HPMC K15M	Gatifloxacin	Provided sustained drug release over an 8 h period	[28]
	Carbopol/HPMC	Moxifloxacin	Exhibited enhanced precorneal residence time and ocular bioavailability	[29]

(continued)

Table 1 (continued)

Type of in situ gelling systems	Polymer(s) used	Model drug	Major outcomes	References
Ion-activated	Alginate with HPMC	Gatifloxacin	Improved ocular bioavailability and longer residence time in aqueous humor than conventional ophthalmic solutions	[30, 31]
	Hydroxypropyl β-cyclodextrin complexed gellan gum and κ-carrageenan	Fluconazole	Exhibited controlled release of fluconazole along with good bioadhesiveness	[32]
	Gellan gum	Terbinafine hydrochloride	Significantly higher C_{max}, and T_{max}, and longer mean residence time and enhanced bioavailability	[33]
	Gellan gum and carrageenan	Antisense oligodeoxynucleotide	Significantly greater reduction in wound size, the least stromal oedema, and hypercellularity	[34]
Multi-stimuli-responsive	Sodium alginate and methylcellulose (Ion and pH-sensitive)	Sparfloxacin	Rapid gelation upon raising pH to 7.4, in vitro controlled drug release over 24 h, significantly improved corneal permeation	[35]

(continued)

Table 1 (continued)

Type of in situ gelling systems	Polymer(s) used	Model drug	Major outcomes	References
	Carboxymethyl chitosan (CMC) and poloxamer (pH-induced and thermosensitive)	Nepafenac	Sol-gel transition temperature of 32–33 °C and sustained the drug diffusion rate	[36]
	Chitosan with gellan gum (pH-sensitive and ion-activated polymer)	Timolol	Improved transcorneal drug permeation and longer residential at the corneal surface	[37]
	Sodium alginate and chitosan (Ion and pH-triggered)	Levofloxacin	Better retention time	[38]

6.1.1 Sodium Alginate

Alginate is an anionic linear polysaccharide obtained from brown algae, which is chemically (1-4)-linked block copolymer of β-D-mannuronate (M) and α-l-guluronate (G) [39]. Sodium alginate gets transformed into a viscous gel due to crosslinking by Ca^{2+} ions present in lachrymal fluid having pH 7.4. The ratio of β-D-mannuronic acid and α-L-glucuronic acid determines various properties of the polymer such as the mechanical strength, porosity, etc. Alginate having a high guluronic acid content shows a better gelling capability and therefore, lower concentration of polymer is sufficient to form a stiff and consistent gel.

6.1.2 Pectin

Pectin is another example of anionic polysaccharides having ion-activated gelling property, which is chemically composed of D-galacturonic acid residues linked by α-(1,4) linkages. Low methoxy pectins having a degree of esterification less than 50% are more susceptible to gelation in presence of free Ca^{2+} ions, where, calcium ion gets linked covalently with two $–COO^-$ groups of adjacent galacturonic acid chains [40]. Formulation of ophthalmic in situ gel with pectin has been reported in a US patent.

6.1.3 Gellan Gum

Gellan gum is an anionic hydrophilic exocellular hetero-polysaccharides secreted by the bacterium *Sphingomonas elodea*, which chemically consists of a repeating tetrasaccharide unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucose residues [41]. Gellan molecules have several hydrophilic groups such as hydroxyl and carboxylic groups, which often interact with other polymers through hydrogen bonding and/or electrostatic attractions. Low-acetyl gellan shows to undergo gelation in the presence of mono, di, or trivalent cations. The lachrymal fluid contains Na^+, Mg^{2+}, and Ca^{2+} which are supposed to induce sol-gel transformation of gellan when instilled in the form of liquid solution into the cul-de-sac. Formulation of gellan with optimized concentration of calcium gluconate has shown the formation of gel with higher strength compared to that with gellan alone [42]. Gellan has been found to exhibit in situ gelation upon activation by both ions and temperature. The proposed mechanism of in situ gelation comprises the formation of double-helical junction zones, subsequent aggregation of the double-helical segments, formation of hydrogen bond with water, and complexation with cations resulting in a 3-D network [16].

6.2 pH-Responsive System

The pH-responsive systems usually utilize polymers containing an acidic group such as carboxylic or sulfonic group or a basic group such as ammonium group which either accept or donate protons in response to change in pH in the surrounding medium. At lower pH such as pH 4.4 at which most of ophthalmic drugs are stable, the formulation remains as a thin solution with sufficient flowability but gets transformed in to gel in lachrymal fluid (pH 7.4) when instilled in eye sac. The examples of most commonly used pH-sensitive polymers in ocular formulation include polyacrylic acid (Carbopol 940), polycarbophil, and cellulose acetate phthalate [43].

6.2.1 Carbopol (Polyacrylic Acid)

Carbopol (CP) is a poly (acrylic acid) polymer that exhibits a sol-gel phase transition in aqueous solution due to rise in the pH above its pKa (5.5). The carboxylic groups of CP accept and donate protons at lower pH and higher pH, respectively. Therefore, at higher pH, carboxylic groups present as $–COO^-$ resulting in swelling and enhancement in molecular entanglement due to the electrostatic repulsion between the negatively charged carboxylate ions, which finally causes the sol-gel transition. Ocular formulation can utilize this property of carbopol along with its mucoadhesiveness in order to increase ocular residential time. Carbopol exhibits its mucoadhesive capacity through the interaction with mucin molecules via electrostatic

attraction, hydrogen bonding, and hydrophobic interaction. But the major disadvantage of carbopol as ocular excipient is its irritable nature on corneal membrane. Combinations of carbopol with other polymers such as cellulose derivatives, chitosan, etc. have been suggested to minimize this problem [15].

6.3 Temperature-Dependent System

6.3.1 Poloxamers (Pluronic)

These are block polymer consisting of poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide). Poloxamers possess amphiphilic characters due to the presence of hydrophilic ethylene oxide domains and hydrophobic propylene oxide domains. These polymers exhibit temperature and concentration-dependent gelling character. At the temperatures near our body temperature (37 °C) and concentrations above 15% w/w, a transformation from sol to gel has been found. The proposed mechanism of the gelation includes gradual dissolution followed by enhanced micellar aggregation and polymeric entanglement at elevated temperature. Poloxamers are available in the market in different physical states having different molecular weights and the liquid, semisolid and solid forms are designated as L, P, and F, respectively. The most commonly used grades are poloxamer 188 (F 68), 237 (F 87), 338 (F 108), 407 (F 127). Poloxamer F-127 (molecular weight 12,000 Da; PEO: PPO 2:1) exhibits low viscosity below 4 °C and exists as semisolid at body temperature. It also shows better solubility in cold water due to the formation of hydrogen bonding at lower temperatures [4, 44].

6.3.2 Xyloglucan

Xyloglucan obtained from the partial hydrolysis of tamarind seed polysaccharide by β-galactosidase exhibits temperature-sensitive gelling capacity in dilute aqueous solution. The degree of galactose degradation influences the sol-gel transition temperature [45]. Xyloglucan with galactose-elimination of more than 35% shows the gelation [46].

6.3.3 Cellulose Derivatives

Cellulose is a polysaccharide composed of β (1 → 4) linked D-glucose units of varying number from several hundred to more than ten thousands. Methyl cellulose (MC), hydroxyethyl cellulose (HEC), hydroxypropylmethyl cellulose (HPMC), and sodium carboxymethyl cellulose (SCMC) are commonly used in the formulation of in situ gel for topical applications [46]. At lower concentrations from 1 to 10%, the aqueous solutions of the cellulose derivatives exist as low-viscous liquid but form a

viscous gel at higher temperatures. Methylcellulose shows sol-gel transition at the temperature ranging from 40 to 50 °C whereas HPMC from 75 to 90 °C. These higher transition temperatures are not suitable for in-or in situ gelling formulation for various topical applications such as ocular delivery. A variety of physical and chemical modifications of cellulose derivatives have been reported in order to lower the transition temperature [47]. For example, low hydroxypropyl molar substitutions in HPMC and addition of sodium chloride in MC solution have shown to decrease the transition temperature to 40 °C and 34 °C, respectively [48, 49].

6.3.4 Chitosan

Chitosan is a cationic polysaccharide containing amine group obtained from the partial deacetylation and depolymerization of chitin extracted from the exoskeletons of arthropods such as crustaceans, etc. This biodegradable, biocompatible, and mucoadhesive polymer has been shown to have many potentials in various biomedical applications. Chitosan-based temperature-sensitive in situ gels with various polyols such as glycerol, ethylene glycol, and sorbitol have been reported [50]. Thiolated chitosan exhibits in situ gelling capacity due to oxidation of thiol groups at physiological pH-values and subsequent formation of intra and intermolecular disulfide linkages.

6.3.5 Poly (*N*-Isopropylacrylamide)

Poly (*N*-isopropylacrylamide) (PIA) has been widely reported to be useful as temperature-responsive polymer. Aqueous solution of this polymer remains as transparent solution at ambient temperature but gets transformed in a viscous gel at about 32 °C. Hsiue et al. developed nanoparticles of epinephrine using linear as well as crosslinked PIA and evaluated for activity and residential time [51]. The formulations with the combination of linear PIA and crosslinked nanoparticles showed six-fold and eight-fold longer compared to conventional eye drop, respectively.

6.3.6 Viscosity Builder

Some ocular formulations have been found to utilize different cellulose derivatives such as hydroxypropylmethyl Cellulose (HPMCK4M and E5 0LV) in order to improve the consistency of the in situ gel and also to modulate the drug release from the gel. HPMC is semisynthetic, inert, pseodoplastic, and non-toxic polymer having high swelling capacity, which has been used widely as a wonderful good carrier for different pharmaceutical applications [1].

6.4 Nano-In Situ Gelling Systems

Nanotechnology being a most emerging field has also been explored in situ gelling systems with the objective of modulating physicochemical properties of drugs, extending ocular residence time, improving ocular bioavailability, drug release as well as overall efficacy of the formulations [52]. Fabrication of drug-loaded nanoparticles and subsequent dispersion in an in situ gelling vehicle which undergoes sol-gel phase transition upon exposure to physiological condition has been suggested to obtain triple benefit of in situ gel such as longer ocular residential time, sustained drug release and improved ocular bioavailability. A curcumin-loaded ocular nanogel formulated with cationic nanostructured lipid carriers and thermosensitive gelling agent has been reported, where the formulation has been evaluated for the in vitro drug release, corneal permeation, ocular irritation, and pre-ocular retention. The pharmacokinetic parameters were also studied in the aqueous humor by microdialysis technique. The area under the curve (AUC) obtained from the nanogel was found to be 9.24-fold greater than that from curcumin solution, which indicates a significantly enhanced bioavailability [53].

Ahmed et al. reported a formulation of ketoconazole nanoparticles prepared with a biodegradable polymer, poly(lactide-co-glycolide). The nanoparticles were then dispersed in an in situ gelling vehicles for ophthalmic topical administration. A sustained drug release pattern and improved anti-fungal activity were exhibited by the formulation. They also reported another in situ gel formulation of ketokonazole with alginate-chitosan nanoparticles which revealed higher drug permeation through corneal epithelial cell lines [54]. List of some in situ gel systems containing nanoparticles are summarized in the Table 2.

7 Characterization and Evaluation of In Situ Gel

The developed formulations were evaluated for clarity, pH measurement, gelling capacity, drug content, rheological study, and in vitro drug release [1].

7.1 Clarity Test

Clarity test was observed by visual inspection under good light, viewed against a black and white background, with the contents set in motion with a swirling action. Also, it was observed for the formation of turbidity or any unwanted particles dispersed in the solution [60].

Table 2 List of some in situ gel systems containing nanoparticles

Type of nanocarriers	Polymers used	Model drugs	Major outcome	References
Ion-activated-liposome	Gellan gum	Timolol	Rapid decrease in intraocular pressure and significantly longer duration of action	[55]
Temperature-sensitive nanoemulsion	Poloxamer 407 and 188	Loteprednol	Longer residence time and improved (2.54 fold) bioavailability compared to marketed formulation	[56]
Temperature-sensitive nanoemulsion	Poloxamer 407	Dorzolamide	Non-irritating and higher therapeutically efficacy	[57]
pH-responsive nanoparticles	Carbopol 934	Acetazolamide	Higher permeability, longer corneal residence time and extended release along with improved in vitro efficacy	[58]
Ion-triggered-microemulsion	Deacylated gellan gum	Cyclosporine A	Exhibited 3 times greater bioavailability	[59]

7.2 Gelling Capacity

The gelling capacity of the prepared formulation was determined by placing a drop of the formulation in a beaker containing 50 mL of freshly prepared concentrated calcium chloride solution and was visually observed for gelling time.

7.3 pH Measurement

Each formulated batch, pH was measured using pH meter which was previously calibrated using standard buffers of pH 4 and pH 7 as per the established procedure.

7.4 Determination of Viscosity of Sol and Gel

Viscosity of the formulation at the solution state as well as a gel state is measured using a suitable multiple-point viscometer such as cup and bob or cone and plate viscometers. The higher viscosity of the gel state compared to that of solution establishes the sol-gel transition and in situ gelation. The temperature of the sol as well as gel should be considered during the determination of viscosity in order to characterize the rheology of the formulation in physiological environment. Bhowmik et al. [61] determined the sol-gel transition temperature from the viscosity versus temperature curve, which they measured the viscosity of the formulation at various temperatures.

7.5 Sol-Gel Transition Time

The time required for conversion from sol to gel in situ should be considered for the overall performance of the gel formulation. For example, an ophthalmic in situ gel formulations having a longer onset of gelling may be washed out quickly compared to another one having a short onset. Bhowmik et al. described a method to determine the onset of gelling (gelling time), in which 1 mL of in situ gelling sol of various formulations maintained at 25 °C were placed in a dialysis membrane (presoaked with simulated tear fluid, STF) bound at one end of a thin-walled glass cylinder with 11 mm internal diameter. The cylinder containing the sol was then immersed into a water bath maintained at 37 °C. Sol-gel transition time was then noted by manual observation through frequent-tilting of the glass cylinder [61].

7.6 Gel Strength

A method was described by Yong et al. for the determination of gel strength, in which a quantity of 30 g of the gel was taken in a 50 mL graduated measuring cylinder and allowed to get converted in to gel in a water bath at 37 °C temperature. The time taken by the cylinder to get submerged by 5 cm downward through the gel after application of 50 g weight with the help of a cylinder was measured. This time period is considered the strength of the gel [62].

7.7 Determination of Sol-Gel Temperature (Tsol-Gel)

Chaudhary et al. described a method of determining the sol-gel transition temperature for an oral in situ gel formulation, where the sol is taken in a test tube and placed

in water bath maintained at 37 ± 5 °C for 2 min. A thermometer is sub-immersed in the sol inside the test tube. The temperature at which sol gets converted to gel is noted. In the case of formulations containing polymers having pH sensitivity such as carbopol, the sol is taken in the test tube containing phosphate buffer solution of pH 6.8. After thorough mixing, the test tube is placed in the water bath. The limitation of this method is that the setting of the gel is observed visually by turning the test tube [2].

7.8 Determination of pH

Conventional pH meter is used to determine the pH of the gel. The pH meter is calibrated before the determination and the measurement is carried out in triplicate to obtain an average pH of the gel.

7.9 Spreadability Test

The gel formed in situ should have optimum spreadability over the surface whereon applied for the intention of application. Lardy et al. described a method of determining the spreadability of the gel where approximately 1 g of gel is placed at the center of a glass plate with the dimension of 20 cm × 20 cm and covered with another one plate of similar dimension. A weight of 1000 g is then carefully applied on the upper side of the plate, which results in the spreading of the gel in between the plates. After 1 min interval, the weight is withdrawn and the diameter of the spreading area is measured in cm [63].

7.10 Mucoadhesion Studies

Mucoadhesive property of the in situ gel formulation was determined by Chaudhary et al. [2]. A modified physical balance was used in their study. Porcine oral mucosa (used as biological membrane) was fixed under one pan of the balance with the help of cyanoacrylate glue after hydrated with 100 μL of phosphate buffer pH 6.8 maintained at 37 ± 1 °C. 1 g of the gel was stuck to the outer bottom surface of an inverted beaker of 250 mL capacity and the beaker was fixed with glue. The pan with the membrane was lowered and touched to the gel. A preload weight of 20 g was placed on the pan in order to allow the formation of mucoadhesive interaction for a period of 3 min. At the end of the period, the preload was then removed, and gradually the weight was increased in another pan until the detachment of the gel from the membrane surface. The total weight required for the complete detachment was noted.

7.11 Ex vivo Permeation Study

Xiang et al. described an Ex vivo method for determination of the drug permeation through the biological membrane in their study with transbuccal delivery of 2′,3′-dideoxycytidine [64]. Franz diffusion cells along with porcine oral mucosa as a biological membrane were used for the study. Porcine oral mucosa was collected freshly, washed with distilled water, stored in phosphate buffer of pH 7.0 at 4 °C and used within 3 h from its collection. The receptor chamber was stirred magnetically at 600 rpm during the study. The membrane was placed in between the donor and the receptor compartment. The temperature was maintained at 37 ± 1 °C. The gel was placed in the donor compartment and the aliquots were withdrawn from the receptor compartment at predetermined intervals to analyze the amount of drug permeated. After each withdrawal, equal volume of fresh media (phosphate buffer of pH 7.4) maintained at 37 ± 1 °C was added in the receptor compartment to maintain the sink conditions.

7.12 Drug Content

1 mL of the developed formulation was dissolved in 100 mL phosphate buffer (pH = 7.4) followed by spectrophotometric estimation of the aliquot to determine drug concentration.

7.13 In Vivo Residential Study for Ophthalmic In Situ Gel

The main objective of the in situ gel formulation is to increase the residential time at the site of application and thereby improve the efficacy through higher degree of absorption, higher drug bioavilability, sustained release, etc. Therefore, the formulation should be evaluated for its residential time. Bhowmik et al. [61] performed an in vivo study for evaluation of their formulation containing atropine sulfate using rabbit model. New Zealand albino rabbits of either sex with weights of 2.9–3.6 kg were taken for the study. The animals were kept in restraining boxes throughout the total course of time for each experiment. All tests were carried out in the same room under standard lighting conditions. The animals were acclimatized prior to starting of the experiment and the basal pupil diameters of the eyes were measured three times using a metric ruler to establish a baseline for both eyes. The differences in pupil diameters were calculated for each pair of results. The mean was utilized for the conversion of post instillation data to the baseline-corrected values. The in situ gel-forming solutions were cooled prior to filling the pipette to facilitate the procedure.

Developed in situ gel solution with 16% poloxamer, 0.225% xanthan gum, 0.525% guar gum and atropine sulfate (test), 16% poloxamer, 0.225% xanthan gum, 0.525% guar gum vehicle (without drug as control) and Topin® (standard) were applied in each of the three rabbits. First, 50 μL of control vehicle was instilled in the left eye of each rabbit to reduce the effect of the polymer if any, followed by administration of test solution or Topin® to the right eyes. Administration of the solutions was done by placing in the lower conjunctivital sac, at the middle between the inner and outer canthus. Pupil diameters were measured at predetermined time points and the differences were calculated using baseline-corrected values. The degree of the total therapeutic response of the in situ gel along with the area under the percentage increase in pupil diameter (AUC) was calculated using trapezoidal rule. The efficiency of the gel formulations was determined by the peak mydriatic response, peak response time, and the AUC after instillation of the respective formulation. The duration of mydriatic response has been defined as the time interval between administration of the solution and the time at which the pupil diameter returned to its normal pretreatment value. The study exhibited a tenfold increase in pharmacological response and a 4.5-fold increase in the duration of response from the formulation containing 16% poloxamer, 0.225% xanthan gum, 0.525% guar gum compared to Topin®.

7.14 In Vitro Drug Release Study

Dissolution studies of samples were performed using Franz diffusion apparatus and phosphate buffer (pH = 7.4) as a dissolution medium. Phosphate buffer with pH7.4 will simulate the lachrymal fluid. The temperature was maintained at 37 ± 0.5 °C with the speed of rotation maintained at 100 rpm. The samples were withdrawn at various time intervals and analyzed spectrophotometrically for the drug content. Percentage drug release in case of in situ gel of ciprofloxacin hydrochloride was found to be 67.02% release in 7 h from an ophthalmic solution formulated with sodium alginate and HPMC [1]. Thus the in vitro dissolution test indicated the sustained release nature of in situ gel of ciprofloxacin hydrochloride.

8 Applications of In Situ Gel as a Mode of Drug Delivery

In situ gels offer the primary requirements of a successful controlled release product with improved patient compliance. Preparation of in situ gel for their applications using a variety of drug delivery routes, such as oral, ocular, nasal, otic, vaginal, and injection. Depending on the routes of application, the characterization of in situ gel has to be determined to ensure that the prepared preparation met the standard. A list of in situ gel for the delivery by different topical route with the corresponding mechanism of formation of gel, polymers used and advantages have been summarized in Table 3.

Table 3 The polymeric in situ gel for topical delivery of drug, mechanism of sol-gel transformation and their advantages

Topical delivery route	Mechanism of forming in situ gel	Drug	Polymers used	Advantages	References
Ophthalmic	Ionic-sensitive	Linezolid	Hydroxypropyl guar gum (HPG) and xanthum gum (XG), hydroxyethyl cellulose (HEC), carbopol, and sodium alginate (SA)	Increase the retention time, sustained drug release	[65]
Ophthalmic	Ionic-sensitive	Moxifloxacin hydrochloride	SA, Hydroxy propyl methyl cellulose (HPMC)	Increase residence time of the drug	[66]
Ophthalmic	Thermosensitive	Atropine sulphate	XG, guar gum (GG), poloxamer-407	Sustained drug release, enhanced bioavailability by enhancing the precorneal residence time and decreased frequency of administration	[61]
Ophthalmic	Light-activated	Bevacizumab	Polycaprolactone dimethacrylate, hydroxyethyl methacrylate	In situ gel formation in the suprachoroidal space	[20]
Ophthalmic	Ion-sensitive	Dorzolamide	Chitosan nanoparticles, SA	Prolonged residence time on corneal region enhance the bioavailability and efficacy of drug for the treatment of glaucoma	[67]
Ophthalmic	Ionic-sensitive	Ketotifen	Deacetylase gellan gum	Increase the residence time of the formulation and prolonged drug release	[68]
Ophthalmic	Temperature-triggered	Neomycin sulphate	Poloxamer 407, HPMC	Sustained release of drug	[69]

(continued)

Table 3 (continued)

Topical delivery route	Mechanism of forming in situ gel	Drug	Polymers used	Advantages	References
Ophthalmic	Ion-sensitive	Curcumin	Pluronic P123 or D-a-tocopheryl polyethylene glycolsuccinate (TPGS) mixed micelle, gellan gum	Improve corneal permeability prolong ocular retention time	[70]
Ophthalmic	pH-triggered	Norfloxacin	Carbopol-940, HPMC E50LV, HPMC E4M and HPMC K4M	Increase contact time, controlled release of drug, decrease the frequency of administration to get greater therapeutic effect	[71]
Ophthalmic	Ion-activated	Ciprofloxacin hydrochloride	SA and HPMC K4M and E5 0LV	Improves ocular bioavailability Ease of administration Enhance patient compliance Sustained drug delivery	[1]
Ophthalmic	Thermosensitive	Latanoprost	Chitosan, gelatin	Biocompatible and sustained release of drug improved patient compliance and efficacy of treatment of glaucoma by controlling ocular hypertension	[72]
Ophthalmic	Thermoresponsive	Dexamethasone sodium phosphate, tobramycin sulfate	Poloxamer 407 and HPMC K4M	Prolong the precorneal residence time, ocular bioavailability and decreases the frequency of administration of dosage form	[73]

(continued)

Table 3 (continued)

Topical delivery route	Mechanism of forming in situ gel	Drug	Polymers used	Advantages	References
Ophthalmic	Ionic-sensitive	Ketoconazole	Poly(lactide-co-glycolide) nanoparticles, alginate, chitosan, poloxamer 407/carbopol 940, HPMC	Enhance drug permeation through epithelial cell line, sustained and enhanced drug release, enhanced anti-fungal activity	[54]
Ophthalmic	Temperature modulated	Nepafenac	Silica nanoparticles containing chitosan-poloxamer (Pluronic F127) or Pluronic F68-Pluronic F127	Improve drug retention time sustained drug release and higher ex vivo corneal permeation	[74]
Ophthalmic	Thermoresponsive	Pilocarpine hydrochloride	Cellulose nanocrystals, triblock poloxamer copolymer	Sustained release of encapsulated drug	[75]
Topical	Schiff base reaction	Epidermal growth factor, bovine serum albumin	PEG-grafted chitosan, PEG-dialdehyde	Increase therapeutic effectiveness in wound healing treatment	[76]
Topical	Thermosensitive	Pycnogenol	Poloxamer 188, Poloxamer 407	Enhanced wound healing activity	[77]
Topical	Chemical material-sensitive	Ac2-26 (N-terminal derived peptide of Annexin A1)	Alginate-pectin nanospray dried particles	Exudate absorption of the powder and improve wound care armamentarium	[78]

(continued)

Table 3 (continued)

Topical delivery route	Mechanism of forming in situ gel	Drug	Polymers used	Advantages	References
Otic	Thermosensitive	Ciprofloxacin hydrochloride, dexamethasone sodium phosphate	Poloxamer 407, Klucel HF (hydroxypropyl cellulose) and Natrosol 250M (hydroxyethyl cellulose)	Reduce the frequency of dosing, prolongation of release of both the drugs for the management of otits media	[79]
Otic	Thermoreversible	Lomefloxacin hydrochloride	Poloxamer 407, methocel K100M, methocel K4M, carbopol 974P	Chronic suppurative otitis media	[80]
Oral mucosa	pH-triggered and ion-activated systems	Clotrimazole	pH-triggered- carbopol 934P (0.2–1.4% w/v) and HPMC Ion triggered- gellan gum (0.1–0.75% w/v) along with HPMC E50LV	Prolong buccal residence time enhanced therapeutic effects	[81]
Oral mucosa	Temperature and pH trigged	Acyclovir	Poloxamer 407, poloxamer 188, carbopol 934, and HPMC K-100	Increase the residence time and thus the bioavailability of drug	[2]
Oral mucosa	Temperature, ion, and pH-sensitive	Moxifloxacin Hydrochloride	Poloxamer 407, gellan gum, and carbopol 934P	Improved local action for the treatment of periodontitis	[82]
Nasal	Temperature-responsive	Loratadine	HPMC K-100 and XG	Conquer the first-pass metabolism enhanced bioavailability of the drug	[3]
Nasal	Ion-activated	Salbutamol sulphate	Gellan gum, HPMC	Rapid onset of action and avoids the first-pass metabolism. Improved therapeutic effectiveness	[83]

(continued)

Table 3 (continued)

Topical delivery route	Mechanism of forming in situ gel	Drug	Polymers used	Advantages	References
Nasal	Thermoreversible	Geniposide	Poloxamers (p407, p188) and the hydroxypropyl methylcellulose	Increase residence time, and render mucoadhesive	[84]
Nasal	Temperature and pH dual-responsive	Huperzine A	Pluronic F127, pluronic F68, and chitosan	Impart the formulation for brain-targeting ability in comparison to the drug alone by the intranasal route	[85]
Vaginal	Thermosensitive	Clotrimazole-β-cyclodextrin complex	Pluronic F127, Carbopol 934 and HPMC	long residence time at the application site	[86]
Vaginal	Ion-activated	Clindamycin HCl	HPMC and gellan gum		[87]
Vaginal	pH-responsive	Iron (II) gluconate dehydrate and doxorubicin hydrochloride	Aldehyde-functionalized chitosan and N-succinyl chitosan	Increasing the residence time of the system	[88]

Table 4 List of some marketed in situ ocular gel

Brand name of the product	Polymer(s) used	The type of in situ gelling system	Manufacturer	References
Timoptic-XE® (Timolol maleate ophthalmic gel-forming solution)	Gellan gum	Ion-activated	Merck Pharmaceuticals, USA	[89]
Pilopine HS® (pilocarpine hydrochloride ophthalmic gel)	Carbopol 940	pH-responsive	Alcon laboratories, inc. USA	[16]
Akten® (Lidocaine hydrochloride)	HPMC	Temperature-sensitive	Akorn Inc., Lake Forest, IL	[90]
AzaSite (azithromycin ophthalmic solution)	Poloxamer 407	Temperature-sensitive	InSite Vision	[91]
Timoptol-LA (Timolol maleate)	Gellan gum	Ion-activated	Laboratories Merck Sharp and Dohme	[15]
Virgan (Ganciclovir)	Carbopol® 974	pH-responsive	Laboratoires THEA-France	[15]

8.1 Ophthalmic delivery

Delivery of drugs using in situ gelling systems is one of the promising approaches to improve the ocular retention time and ocular bioavailability. Stimuli-responsive polymers such as pH-sensitive polymers, thermosensitive polymers, and ion-sensitive polymers are used to form in situ ophthalmic gel after instillation of the aqueous solution on the eye surface [4, 70]. In situ gel containing ciprofloxacin hydrochloride has been developed using polymers like sodium alginate and hydroxy Propyl Methyl Cellulose (HPMC). Sodium alginate undergoes instantaneous gel formation due to the formation of calcium alginate by virtue of its interaction with divalent cation (Ca^{2+}) present in lachrymal fluid (pH 7.4). Alginate can be ionically crosslinked in the presence of divalent cations. HPMC K4M and E50LV were incorporated as a viscosity enhancer to further aid in the accomplishment of sustained drug delivery [1]. Ion-sensitive in situ gels were prepared when curcumin-loaded Pluronic P123 or D-α-tocopheryl polyethylene glycolsuccinate (TPGS) mixed micelle was added in gellan gum to improve corneal permeability and also to prolong ocular retention time [70]. List of some marketed in situ ocular gel is given in the Table 4.

8.2 Delivery to Oral Mucosa

An in situ gelling system containing acyclovir was developed to increase the residence time and the bioavailability of the drug for the treatment of oral infection caused by

herpes simplex virus. The formation of in situ gel composed with polymers such as poloxamer 407, carbopol 934, and HPMC was trigged by Temperature and pH [2].

8.3 Topical Delivery in Skin

Topical delivery of in situ gel-forming agents are generally used for the treatment of wound healing [76–78]. Kim et al. [76] have worked with poly (ethylene glycol) (PEG) grafted with varying lengths and densities of chitosan to form PEG-grafted chitosan (PEG-*g*-chitosan) with tunable architecture. In situ hydrogel was formed by Schiff base reaction between PEG-*g*-Cs and PEG-dialdehyde [76].

8.4 Nasal Delivery

Drug delivery through the nasal route is a very convenient route of drug administration as it has numerous advantages such as improved patient compliance, avoids first-pass metabolism, and also provides a high degree of absorption as well as transport of substances. The nasal route delivered geniposide to the brain directly through the olfactory region [92]. Mucoadhesive in situ nasal gels containing loratadine was formulated using different polymeric ratios of hydroxypropyl methylcellulose (HPMC K-100) and xanthan gum and evaluated with the aim to conquer the first-pass metabolism and enhanced bioavailability of the drug [3].

8.5 Otic Delivery

Thermosensitive in situ gel has been successfully developed and characterized by a number of researchers to deliver antimicrobial agents such as ciprofloxacin, lomefloxacin for the management of Chronic suppurative otitis media [79, 80]. After otic delivery of in situ gelling systems, it undergoes sol-to-gel phase transition in the ear cavity and is strong enough to withstand shear forces in the tympanic cavity and have a long residence time in the ear. Polymers like poloxomer 407 are used as the thermoresponsive polymer and HPMC, HEC area added to build up the viscosity and prolong the residence time.

9 Conclusion

A variety of innovative and appreciable approaches have been reported in the past few years to overcome the problems associated with conventional strategies for topical and ocular drug delivery. The in situ gel systems have been considered as one of the most promising strategies for the design and fabrication of prolonged-release ocular and mucosal drug delivery devices in order to improve ocular bioavailability, therapeutic efficacy, and reduce systemic absorption and toxicity. Incorporation of drug-loaded nanoparticles in in situ gel system has been another thrust area of topical drug delivery, which offers better modulation of physical and pharmacological aspects of drug delivery devices. The choice of the excipients in ophthalmic and otic formulations is very critical and always demands the use of non-toxic additives with high safety level. In this issue, the application of biopolymers especially biopolysaccharides in formulation of in situ gel should be highly appreciable. However, extensive studies are essential to evaluate the possible toxicity of nanoparticles in the case of the formulation with the intention of long-term use (glaucoma drugs). In addition, problems such as blurred vision and discomfort feeling are found to associate with the in situ gel due to high viscosity. These result in a faster elimination due to rebound tear secretion and reflex blinks. Therefore, the viscosity should be optimized without compromising the overall efficacy and safety issues of the formulations. Quality-by-Design (QbD) approach may be beneficial in this regard. Consequently, further works are required to explore this promising drug delivery system for the clinical application of most of ophthalmic and topical drugs. In not-too-distant future, innovation of novel, smart, and more reliable in situ gel-forming polymers is required, which may be amenable to some biochemical markers associated with the disease conditions of topical tissues including eyes.

References

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Stimuli-Responsive Polymeric Systems for Smart Drug Delivery

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Abstract This chapter provides a general description of smart drug delivery systems (DDSs) based on the use of stimuli-responsive polymers. Smart DDSs have the distinctiveness of carrying out the release of therapeutics at the target sites in a spatially controlled manner. This means that the drug is released with suitable speeds exclusively at the site of action. Specifically, smart DDSs ensure that the drug is not freely extravagate during blood circulation, and only released at specific sites (organs/tissues) where these nanocarriers accumulate through an active or passive targeting strategy. Various polymers-based nanomaterials offer new opportunities for the preparation of smart DDSs due to their unique nanoscale properties and specific bio-functions. In this way, there is a special type of polymers called 'stimuli-responsive', 'intelligent', 'smart' or 'environmental-sensitive' polymers, because they have the particularity of responding to small physical or chemical stimuli leading to a macroscopic alteration in their structure/properties. The basis of the different stimulus-sensitive polymers used in the preparation of intelligent DDSs will be presented in the different sections of this chapter taking into account the stimulus that trigger polymer alteration and their specific applications in drug delivery.

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1 Introduction

The general concept of the drug delivery systems (DDSs) is focused on the formulations and devices used to transport therapeutic drugs in the body in a safe and efficient manner, satisfying accordingly the desired therapeutic effects.

Many publications have been made, and several conventional DDSs have already been investigated, among which many of them are already being used commercially (https://www.fda.gov/Medicaldevices/). However, it is well known that these systems may have systemic side effects as a result of the lack of specificity and control in the release, and bio-distribution of the medication. Due to these limitations, advanced or smart controlled DDSs have been developed with the advantage of releasing therapeutics at the target site in a spatially controlled manner. This means that the drug is released with suitable speeds exclusively at the site of action. Specifically, smart DDSs ensure that the drug is not freely extravagate during blood circulation, and only released at specific sites (organs/tissues) where these nanocarriers accumulate through an active or passive targeting strategy.

Therefore, these new systems can intelligently and effectively induce the dosage frequency, while maintaining the concentration of the drug in specific organs/tissues for a longer period of time. The behaviour of smart DDSs allows to give fascinating properties since they decrease the fluctuations in the concentration of the drug. Therefore, its toxicity is reduced, and the therapeutic efficacy results are enhanced [1].

Nanomedicine can be considered the basis of innovative delivery techniques that offer great benefits to patients and new markets for the pharmaceutical industry [2–4]. Various nanomaterials offer new opportunities for the preparation of smart DDSs due to their unique nanoscale properties and specific bio-functions. However, those nanomaterials that could be used as drug carriers must meet fundamental safety and therapeutic efficacy requirements, such as being biocompatible and biodegradable, stable in physiological conditions, having high drug loading capacity and low toxicity. Other important condition for those systems that have demonstrated to fulfil the above-mentioned requirements is the feasibility of scaling up, which will be necessary once they are in condition to be applied clinically (Fig. 1). Today, materials that can be used in the preparation of smart DDSs are polymers, liposomes, hybrid nanoparticles, exosomes, among others.

In this chapter, we are focused on the use of polymers and polymers-based devices because we believe it is the most promising development in drug delivery. In this way, there is a special type of polymers called '*stimuli-responsive*', '*intelligent*', '*smart*' *or* '*environmental-sensitive*' *polymers*, because they have the special feature

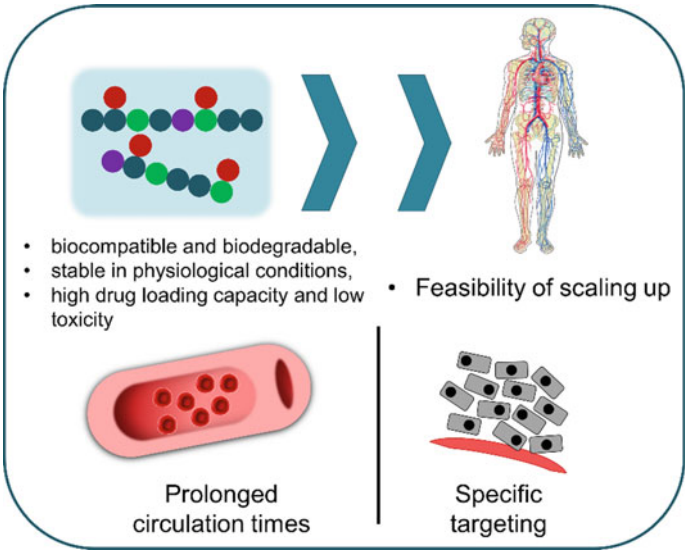

Fig. 1 Main properties of polymers to be used in DDSs

of responding to small physical or chemical stimuli leading to a macroscopic alteration in their structure/properties. Smart polymers are becoming increasingly important in the fields of controlled drug delivery, biomedical applications and tissue engineering, and it is often beneficial to employ polymers that can respond to stimuli. These polymers exhibit a nonlinear response to a small stimulus which could be varied from swelling/contraction to disintegration. The most fascinating features of the smart polymers arise from their versatility and tuneable sensitivity. On the other hand, the wide variation of polymer sources and their combinatorial synthesis make it possible to tune polymer sensitivity to a given stimulus within a narrow range. Therefore, development of smart polymer systems may lead to more accurate and programmable drug delivery.

These developed designed smart or stimuli-responsive nanoplatforms can respond to physical, chemical and/or biological stimulus as shown in Fig. 2. The physical stimuli including temperature, magnetic field, ultrasound, light, electric pulse and high-energy radiation can be applied externally. Chemical stimuli could be pH variations or redox gradient [5], which are related to the disease pathological characteristics. Biological agents can be hormone level, enzyme concentration, small bio-molecules as glucose, among others. All type of stimuli could be used to trigger or enhance the drug release at diseased areas.

It is important to denote that the selection of the polymer that will be part of the smart DDS depends on several factors, such as: (i) the ability of the components to form stable colloidal systems in biological fluids; (ii) the requirements of adequate surface functionality (loads, hydrophilicity, targets); (iii) the authorization for the application of the components, ease of use and processing. Design in relation to

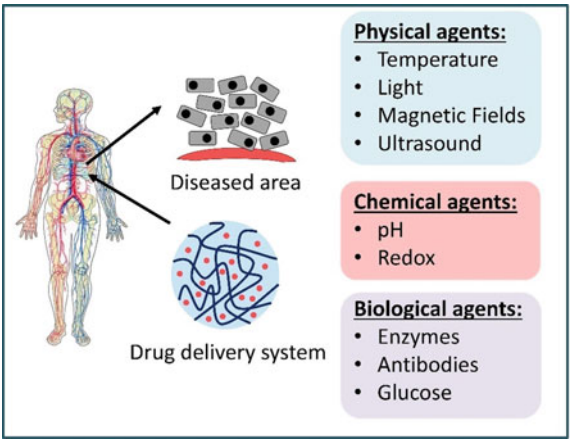

Fig. 2 Classification of the different types of stimuli to which a smart DDS can respond

what is desired for its application is essential. For example, a DDS to release an antibiotic for eye treatment should be designed to stay in the eye membrane (bio-adherent) and release the drug at the tear pH. On the contrary, if one were creating a DDS to administer an anticancer component to the colon, then it should be designed to resist the pH of the mouth, stomach and small intestine, but that can decompose and release the drug into the colon at alkaline pH [6].

In this chapter, we will describe the most studied smart DDSs for drug delivery and discuss the most recent developments in the field in relation to its structure/property relationship. Furthermore, the fundamentals of the conformational changes that can take place on different types of stimuli-responsive polymeric systems will be analyzed.

1.1 Physical Stimuli

1.1.1 Thermo-Responsive DDSs

Among the available polymeric materials, thermo-responsive polymers are high versatile materials because they allow a precise control of the response towards thermal changes. Temperature displays a critical role in nature, and thermal changes can take place spontaneously in living beings. Otherwise, heating can be applied externally in a non-invasive manner [7]. In the first case, it is worthy to highlight that tumours and areas of inflammation typically display abnormal temperature gradients as compared with those of normal ones [8–12]. Spontaneous temperature fluctuations also occur during day and night cycles [7].

The most widely studied type of thermo-responsive polymers are those which undergo a solution liquid–liquid phase transition at which their solubility in water dramatically changes in response to variation of the temperature [7, 13]. In this sense,

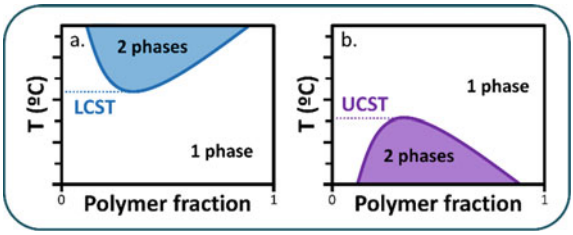

Fig. 3 Phase transitions of LCST (**a**) and UCST thermo-responsive polymers (**b**)

there are two main types of thermo-responsive homopolymers. If the polymer goes from be completely miscible with solvent to become insoluble upon heating, the phase transition takes place at lower critical solution temperature (LCST). On the contrary, if it becomes soluble upon heating, it defines an upper critical solution temperature (UCST) (Fig. 3) [14].

Below the transition temperature, an aqueous solution of a LCST polymer is clear and homogeneous because the polymer is perfectly soluble in water. Above the LCST, the polymer becomes hydrophobic and water insoluble, and consequently, the solution appears cloudy [13]. Therefore, this macroscopic effect allows researchers to define a transition temperature called cloud point temperature (T_{CP}). On the contrary, UCST polymers are water soluble above the T_{CP} and hydrophobic below this temperature.

The thermo-responsive behaviour depends on the solvent interaction with the polymer and the hydrophilic/hydrophobic balance within the polymer molecules [15]. The general mechanism of this hydrophilic/hydrophobic balance for LCST polymers in water will be firstly illustrated. Below T_{CP}, the polymer chains and surrounding water molecules are bounded together by hydrogen bondings, which means that the polymer is hydrated and solubilized resulting in a one-phase system. While temperature gets higher, the hydrogen bonds become weaker, and consequently, the polymer chains become poorly solubilized. Finally, polymer aggregation takes place giving the formation of two immiscible liquid phases [16].

Hoogenboom et al. explained the weakening of the hydrogen bondings with temperature from a thermodynamic point of view taking into account the free energy of mixing (Eq. 1) [7, 14, 16, 17]:

$$\Delta G_{\text{mixing}} = \Delta H_{\text{mixing}} + T.\Delta S_{\text{mixing}} \tag{1}$$

At lower temperatures, the free energy of mixing should be a negative value because the polymer is hydrated in water. In this situation, hydrogen bondings between polymer chains and water molecules give a favourable enthalpy contribution to the free energy of mixing but contribute unfavourably to the entropy of mixing because they induce enhanced ordering of the system. The entropy term of free energy equation ($T.\Delta S$) increases with heating until that the free energy of mixing turns positive at the critical solution temperature, which is macroscopically

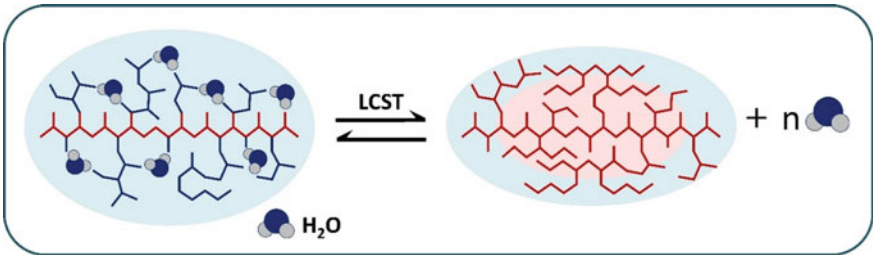

Fig. 4 Conformational changes before and after LCST thermo-sensitive polymer (Reprinted with permission from Lutz et al. [18]. Copyright © 2007 American Chemical Society [18])

manifested in phase separation. In this new condition, water molecules are expelled from the polymer structure into the bulk water leaving behind partially dehydrated polymer chains allowing the formation of polymer–polymer interactions. During this process, the polymeric material changes from hydrophilic to hydrophobic nature (Fig. 4), which also produce a change in the conformation of those polymer chains. In the hydrophilic state, polymer chains tend to be in a hydrated coiled conformation, whereas in the hydrophobic form, polymer chains acquire a globular conformation.

Among the thermo-sensitive polymers, poly(N-isopropylacrylamide) (PNIPAAm) is the most studied one because it has a LCST around body temperature (~32 ºC), and most cytocompatibility and tissue compatibility studies involving PNIPAAm-based materials have yielded promising results [14]. Nevertheless, PNIPAAm has some disadvantages that complicate the regulatory approval of PNIPAAm-based materials for biomedical use as the highly toxic nature of the NIPAAm monomer, the lack of a clear degradation pathway and the strong hysteresis of the thermal solubility transition [19–22].

In a second place, it is poly(N-vinylcaprolactam) (PVCL) which also has a LCST around body temperature and a suitable bio-compatibility to be used in bio-technological applications [23]. It is well known that PVCL ring is stable and does not hydrolyze in water at high temperature, whereas the amide group of VCL monomer is more susceptible to hydrolysis [21].

Furthermore, an emerging class of thermo-responsive polymers are polymers made of oligo ethylene glycol (OEG) side chains. Lutz et al. have demonstrated that by combining OEG monomers of different hydrophilicities, the LCST can be modulated in order to prepare thermo-responsive NGs on demand [14, 18, 24−27]. These co-polymers exhibit excellent bio-compatibility and more uniform thermal profile (heating and cooling cycles are completely reversible) than PNIPAAm [25, 28]. Finally, it is worth to highlight that OEG methacrylates are less prone to hydrolysis than NIPAAm and VCL [14].

For the case of UCST polymers, another enthalpic term needs to be introduced in the Gibbs free energy equation to understand the behaviour: ΔH for supramolecular association of the polymer chains [7]. In this case, the polymer chains have

strong associative interactions that must be broken in order to produce dissolution. The supramolecular associative interaction strength decreases with the increase of temperature, giving a dominant hydration term and thus, leading to dissolution of the polymer. Consequently, it is agreed that an UCST behaviour arises from strong polymer−polymer and solvent−solvent interactions compared to weak polymer−solvent interactions [29].

In comparison with LCST polymers, UCST ones are considerably less investigated. Seuring et al. summarize the main reasons that may explain this low popularity among thermo-responsive polymers [29]. On the one hand, UCST can be observed in certain conditions which are little interesting for biomedical applications: outside the 0 to 100 °C range, only high ionic strength or low pH. On the other hand, the UCST is very sensitive to electrolytes and concentration, which is an unfortunate feature for pharmaceutical interests.

However, there is a kind of UCST polymers which is promising for medical application: those which are based on hydrogen bonds. They show that the thermal behaviour in pure water and physiological conditions allows facile tuning of the phase-separation temperature and can be synthesized from simple building blocks. Examples are poly(N-acryloylglycinamide), poly(methacrylamide) or co-polymers of (meth)acrylamide. In this sense, many efforts must be done in this field for the development of novel polymeric materials with a robust UCST transition in aqueous solution.

1.1.2 Photo-Responsive DDSs

One interesting alternative in the field of smart polymeric systems is the design of light-responsive polymers. These systems undergo a reversible or irreversible change in conformation, polarity, amphiphilicity, charge, optical chirality or conjugation in response to a light stimulus. Reversible molecular switches undergo a reversible isomerization upon light irradiation, the most common groups employed are azobenzenes, spiropyran, diaryl ethane or coumarin. However, irreversible chromophores are cleaved from the polymer chain upon light exposure (e.g., o-nitrobenzylphotolabile protecting group). Light-responsive systems provide intrinsic advantages against pH, temperature, electric or magnetic stimuli-responsive systems, such as non-contact and remote spatiotemporal control, and they can be easily dosed to achieve the desired response. Light-switchable systems can realize ‘on-demand’ or pulsatile delivery of drugs by precisely changing the parameters of the light including intensity, wavelength, irradiation time and area [30]. Among the several stimuli exploited in smart polymeric systems, light stimuli-responsive remains quiet unstudied, and nonetheless, the different types of irradiation have drawn significant attention due to the ease and precise tune of its intensity, the ability to control the exposure duration and tissue location and the non-invasiveness of the employed technique [31].

There are several mechanisms of light-induced molecular changes in these systems to achieve a photo-controllable release of a cargo. Generally, drug molecules release

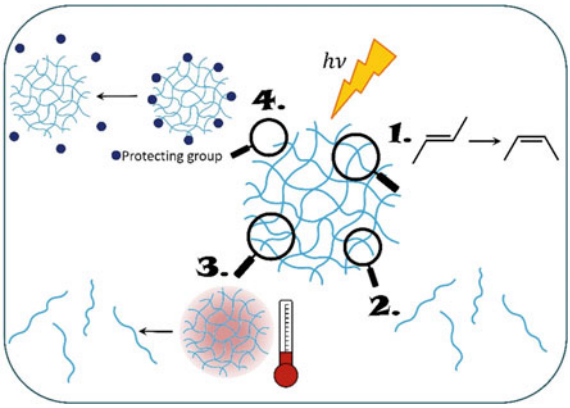

Fig. 5 Release mechanisms of light-sensitive polymeric systems. Mechanistic pathway 1 is reversible; 2, 3 and 4 are irreversible

owing to the physical or chemical changes of carriers, and the change mechanisms of light-responsive carriers can be divided into four types: (1) molecular structure change via a photo-isomerization effect, (2) polymer backbone photo-degradation, (3) physical disruption via a photo-thermal effect and (4) chemical degradation via a photo-chemical effect (Fig. 5).

1. *Photo-isomerization* is related to a conformational change in a rotational restricted bond, more common, a double bond. Usually, it is considered as a reversible change (the molecule undergoes internal rearrangements) such as the azobenzene groups, in which the trans double bond, –N = N–, suffers a reversible trans–cis isomerization as a response to light stimulus. The isomerization process can be reversed with visible light or heat. Nevertheless, photo-isomerization can be an irreversible process, if accompanied with a cleavage of the chromophore group upon photo-induced structural transformation [32].
2. *Polymer backbone photo-degradation* enables drug release via light-triggered degradation of the polymer chains.
3. *Physical disruption via a photo-thermal effect* occurs when a light-sensitive molecule is in the structure of the polymeric system. Light absorption generates a local heat point which induces a thermal disruption of the polymer achieving the controlled release of a cargo molecule.
4. *Chemical degradation via a photochemical effect* is related to a photo-labile bond. Examples of these systems are those which have a o-nitrobenzyl employed as a protecting group, and this group is fragmented upon irradiation, leading to the release of the molecule of interest and degradation of the protecting group [33].

In the past few years, a large variety of photo-responsive systems have been designed to achieve a controlled and sustained release of a wide variety of different structural compounds, owing to their non-invasiveness and the possibility of spatiotemporal control. Chromophores are therefore the key component of light-sensitive DDSs [34]. These systems can be designed to achieve response to a specific

wavelength, ultraviolet (UV), visible or near-infrared (NIR). Molina et al. synthesized a novel polymeric NIR absorbing material based on a biocompatible thermo-responsive nanogel that is semi-interpenetrated with polyaniline, which causes the nanoparticle to strongly absorb NIR radiation. After irradiation, the nanocomposites generates heat, inducing a local hyperthermia used for photo-thermal cancer therapy [35].

Therefore, light-responsive systems can respond to ultraviolet (10–400 nm), near-infrared (700–950 nm) or visible light. Nonetheless, the biggest disadvantages of UV responding systems lie in the low penetration depth of high-energy photon (10 mm) due to the high absorption and scattering properties of chromophores in tissue; another disadvantage of far UV photon relies in the possibility to ionize or cleave covalent bonds, causing the photo-destruction of active molecules. Taking this into account, UV and visible light-responding systems become unsuitable to be used for intradermal applications, and these systems can only be employed for topical usage which can be irradiated directly. NIR light presents low absorption and scattering throughout soft tissue, which cause a high depth penetration, about 10 cm. The lower absorption by tissue and photo-active molecules is reflected in a minimal harm to the tissue itself, becoming NIR light methods less cytotoxic and more suitable to be applied in clinical applications. One interesting alternative lies in materials with the capability to convert NIR absorbed photons into heat, which can be used to trigger the release of a loaded cargo molecule from the polymeric NIR responsive system. Although, finding suitable materials in terms of bio-compatibility and biodegradability remains a challenge in light-responsive polymeric systems.

Attractiveness of light-responsive systems lies in the versatile ways to applied external stimuli. These systems can realize pulsatile delivery of drugs or by a one-time irradiation, and the desired response is regulated by the parameters of the light employed such as intensity, wavelength, time and area of irradiation. In addition, light irradiation can be narrowly focused on specific sites to trigger or activate the release event triggered by photo-sensitiveness-induced structural changes in the system. By employing light release mechanism, therapeutic efficiency is enhanced along with selectivity and reduction of side effects [36].

Light-sensitive systems can contain drugs or cargo molecules retained inside the porous structure of the polymer by capping agents. These agents are cleaved or destroyed in presence of an external stimuli like UV or visible light. Knezevic et al. synthetized a sulforhodamine 101 loaded mercaptopropyl-functionalized mesoporous silica nanoparticles employing $Ru(bpy)_2(PPh_3)$-moieties as capping agent, and when irradiated with visible light, it causes the release of the cargo molecule and the capping species [37].

An alternative mechanism to photo-induce changes is the two-photon NIR triggered mechanism, in which the simultaneous absorption of two NIR photons induce chemical reaction. The usage of infrared light minimizes scattering in the tissue. Due to the usage of two-photon absorption, this technique presents a high suppression of the background signal, and due to the low energy of NIR photons, it presents a high penetration depth, which are considered one of the biggest advantages of this mechanism and also present high 3D spatial resolution [38]. Guo et al. synthetized

poly-thiophene nanoparticles with excellent physical–chemical properties, including great water dispersibility, high pH and photo-stability, a great $^1O_2$ quantum yield and a imaging detection depth up to 2100 μm, and these polymers have potential properties to be employed in two-photon excited photo-dynamic therapy [39].

Photo-thermal therapy (PTT) can also be employed as a light-activated mechanism. Molecules with the capability to absorb irradiation, most often IR, get to an excited state, and the decaying produced by vibrational or rotational relaxation produces heat, which leads to changes in the systems. The usage of this techniques present some advantages such as the possibility to combine photo- and thermal-responsive system, enhanced cytotoxicity and employ low-energy radiation which is less harmful to cell and tissues. PTT can be combined with photo-dynamic therapy, generating reactive oxygen species, showing higher cytotoxic efficacies and enhanced damage to tumoral cells [40]. Feng et al. developed conjugated polymer nanoparticles (CPNs) with tumour targeting and fluorescent detection, by successfully combining photo-dynamic therapy with photo-thermal therapy. Two polymers with strong absorption were co-loaded into one CPN, when irradiated CPNs show synergistic therapeutic efficacy [41].

1.1.3 Magnetic-Responsive DDSs

The magnetic field can penetrate in the body tissue in non-invasive way, and in fact, currently the iron oxide-based magnetic nanoparticles, such as magnetite, maghemite, among other, are widely used as contrast agents for magnetic resonance imaging (MRI) [42]. However, the magnetic-responsive approach to smart DDSs has recently been investigated. The combination of the magnetic nanoparticles with polymer systems has been studied to develop composite structures with synergistic properties, where magnetite-responsive DDSs obtained may have potential applications for both diagnostic and therapeutic therapy, which is known as theragnostic systems [43].

On the one hand, magnetic nanoparticle could produce magnetic hyperthermia which is the process for generating heat by two mechanisms: intrinsic rotational motion (Brownian) and extrinsic motion (Neel). That is to say, thermal rotation of the particle's magnetic moment and relaxation via diffusion, under the influence of external high-frequency [42]. Local hyperthermia dissipates heat into the surrounding tissues and can cause tumour inhibition. Heating in the range of 46–56 ºC causes thermo-ablation by direct cell necrosis, while at temperatures up to 41–45 ºC, apoptosis processes can be activated [44]. Currently, hyperthermia is an approved treatment as a therapy for cancer; however, it is necessary to combine with other treatment, such as chemotherapy. For example, NanoTherm® is a product that is already on the market to hyperthermia therapy, and several others are in the pre-clinical phase [45].

Furthermore, polymers combined with magnetic nanoparticles can undergo thermodynamic phase/conformational transitions depending on their LCST/UCST

followed by swelling/collapse, as described above in Sect. 1.1. Therefore, this phenomenon is induced by magnetic heating, and it can produce drug release [46, 47].

Therefore, magnetic-responsive DDSs give the possibility of smart delivery of the drug both guided by the magnetic field and/or temperature-responsive release. A clear example of the potential of magnetic-responsive DDSs is super-paramagnetic iron oxide (Fe_3O_4) nanoparticles (SPIONs) synthesized by Thirunavukkarasu et al. They have combined SPIONs with a temperature-sensitive polymer matrix of poly(lactic-*co*-glycolic acid) (PLGA), and then, doxorubicin was loaded. The experiments performed in vitro showed that as the temperature increases as consequence of exposure to the magnetic field, the drug release percentage increases. 39% of drug was released at 37 °C, while 57% of drug was released at 45 °C (after 24 h). Furthermore, synergistic effect of the system was demonstrated in vivo by studying antitumor efficacy against CT26 tumour-bearing mice. Multifunctional nanoparticles showed higher tumour inhibition effect than DOX or SPIONs/PLGA alone. Similarly, the study was followed by MRI by taking advantage of to the sensitivity of magnetic-responsive DDSs [48].

1.2 Chemical Stimuli

1.2.1 pH-Responsive DDSs

Probably, one of the most studied stimuli to design DDSs is pH due to the variations which take place in the human body. For example, pH changes in gastrointestinal tract can range from pH 2 in the stomach, pH 7 within the colon and up to pH 8.2 in the lower duodenum [1]. Additionally, different pHs are presented at cellular level; the cytosol (7.4), Golgi apparatus (6.4), endosomes (5.5–6.0) and lysosomes (4.5–5.0) [43]. In the same way, there is a remarkable difference between pH recorded in tumour tissues or in tissues that undergo an inflammatory process (below 7.0) and the extracellular pH of blood and healthy tissues (7.4) [34]. These pH variations have allowed to design a wide range of smart DDSs on demand with excellent performance and minimum side effects of drugs.

In order to design pH-responsive DDSs, polymers with ionizable groups in their backbone structure are employed because they can accept or release hydronium ion in response to environmental pH changes [49]. Many kinds of pH-dependent mechanisms of action can take place in smart DDSs, but all of them are based on acid/base equilibrium between weak species present in the DDSs and ions of the medium. Specifically, in biological media there are two main mechanisms of action for DDSs, the first one based on pH-labile polymer-drug bonds and the second based on ionizable pH-sensitive groups present in polymeric chain [34].

In the first case, either the DDSs are formed through of pH-labile chemical bonds or the drug molecules are linked to cleavable linkages. These bonds are stable at physiological pH, but at sudden changes in pH, for example acidic environments exhibited by tumour or cellular microenvironment, they can be hydrolyzed and release the drug

[50]. Some pH-labile bonds used are hydrazone, Schiff-base, acetal, cis-acotinyl or β-thiopropionate, among others functionalities [51]. Hydrazone ($R^1R^2C = NNH_2$) is one example of the most studied linkers, and it is stable at neutral pH (in the blood) but is rapidly destroyed in the acidic environment. Bae et al. synthesized a system based on this kind of bonds; this system is currently in phase I trials for advanced solid tumours or soft tissue sarcoma. It consists in micelles from PEG-poly(l-aspartic acid) block co-polymers with either DOX or Epirubicin covalently attached to P(l-Asp) via pH-labile hydrazone bonds. This system exhibits a smart pH-responsive release, with the 50% of the drug release at pH 5 after 48 h and no significant release at physiological pH (7.4). These micelles exerted enhanced tumour-infiltrating activity and effective antitumor activity with extremely low toxicity [52].

In the second case, the DDSs are made of monomers with ionizable pH-sensitive groups like as, weak acid (carboxylic acid) or base (amines). The drug release results from the disassembly of the carrier, either through hydrolytic degradation or through changes in the physicochemical properties of polymer chains. According to the polyelectrolyte of which smart DDSs are made, they can be classified into anionic or cationic pH-responsive DDSs. Anionic ones are ionized when environmental pH is above the pKa, leading to an increase in the swelling, and this pH-responsive DDSs are schematized in Fig. 6. In turn, cationic ones are ionized at pH values below the pKb, which increases the swelling due to electrostatic repulsions [53]. Some examples are listed below.

The polyelectrolytes mostly used are poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA) and poly(dimethylaminoethyl methacrylate) (PDMAEMA), among others [54]. These polyelectrolytes should have groups with pKa or pKb that corresponds with pH of the interest site of release. The ionization state of these species results in conformational changes which affect the affinity of the polymer chains for the solvent, as well as, the interaction between polymer chains themselves. This phenomenon is given by electrostatic repulsive forces, by creating a large osmotic swelling force that produces either the disassembly of the chains or the swelling of polymeric networks [53]. In addition to the reversible swelling/contraction produced by changing the pH of the surrounding solution, a great advantage of these pH-responsive DDSs is the possibility of modifying the action range by simply varying the nature and

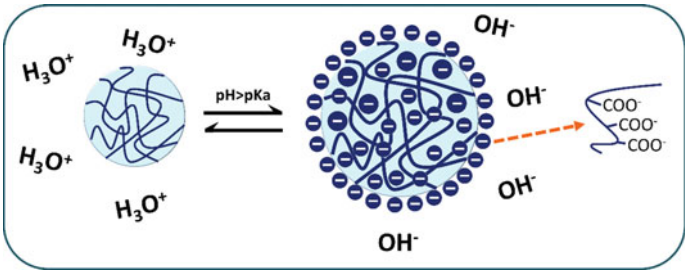

Fig. 6 Schematic change of anionic pH-responsive DDSs

proportion of the co-monomers employed [34]. An example of these pH-responsive DDSs was designed by Dolatabadi-Farahani et al. who prepared spherical hydrogel beads by addition of aqueous sodium alginate and alginate-*N*, *O*-carboxymethyl chitosan (NOCC) solutions into $CaCl_2$ solution. They found that this system has high sensitivity to pH, for example, in basic media (pH 7.4), the swelling degree of hydrogels was much higher than in acidic media (pH 1.2). Given pH changes along the gastrointestinal tract these pH-sensitive polymeric hydrogels are ideal for colon drug delivery [55].

1.2.2 Redox-Responsive DDSs

Redox reactions are widely found in nature, playing major roles in every type of mechanism, and a well-known redox couple is the glutathione(GSH)-GSH disulfide, which is the major redox couple found in animal cells [34]. GSH concentrations in cell environment are controlled by the NADP/NADPH redox couple [56] and glutathione reductase. The higher concentration of GSH inside cells can be successfully used to achieve redox sensitivity from responsive polymers. Moreover, tumour tissues have a greater concentration of GSH than the healthy ones, so tumours are considered as a reducing environment, which reinforces the role of GSH to specifically trigger drug release in tumour cells [34]. Yu Tian et al. developed a tumour-selective drug delivery nanogel with redox response. The nanogel is composed of hyaluronic acid to achieve tumour target, poly-ethylene glycol to enhance bio-stability, and cystamine, which provides the disulfide bond to successfully respond to GSH concentrations. These nanogels have been probed to possess selective and responsive drug release, converting them into promising therapeutic platforms for cancer treatment [57].

Some antibody–drug conjugates, which can respond to intracellular redox conditions, are in clinical phase II/III for breast cancer (Trastuzumab-DM1) [58].

Redox-sensitive systems become a potential trigger to achieve drug release from polymeric systems to take place inside cells, providing some advantages over other stimuli-responsive systems, such as the release of the loaded molecule directly into the nucleus or cytosol, enhanced stability in the extracellular environment where GSH concentrations decreases, etc. [56].

Disulfide bonds (–S–S–), a labile bond prone to be cleaved by GSH, can be used to achieve redox responsiveness. A large variety of GSH-responsive polymer have been already studied [59]. As a consequence of the polymer undergoing the redox reaction, the polymeric structures swell or disassemble, and the loaded molecule is released.

The design of redox-sensitive systems may be achieved by different designs, Shuang Bai et al. designed a sensitive dual-redox-responsive prodrug-based star-like polymer, responding to GSH and reactive oxygen species (ROS). These present micellar systems enhanced tumour penetration. In the tumour micro-environment, where GSH level are higher, the micellar structure disintegrates promoting camptothecin drug release, an anticancer drug. This systems exhibits a high and selective release of the loaded drug and a high inhibition tumour rate [60]. YunusKurtoglu et al.

developed a N-acetyl cysteine(NAC)-poly(amidoamine) dendrimer conjugate with a disulfide linkage and evaluated the release kinetics in presence of GSH, cysteine and bovine serum albumin. The drug-dendrimer conjugate exhibits a high stability in simulated medium and delivers around 60% of its NAC payload within 1 h at intracellular GSH concentrations, and does not release the drug at extracellular GSH concentration [61].

Micellar polymeric systems are one of the most studied systems that can provide redox sensitiveness, nonetheless, other systems have been studied, GSH-responsive crosslinked materials, either the crosslinker is present in the core [62] or in the shell [63], nanomaterials systems coated with mesoporous silica [64] also have been studied, and liposomes [65].

1.3 Biological stimuli

1.3.1 Enzyme-Responsive DDSs

Enzymes are bio-molecules that act as catalysts for chemical reactions and are involved in almost all intracellular metabolic processes of living systems. Enzymes selectively act on molecules called substrates which have specific recognition domains for the enzyme involved in a certain metabolic process [66]. These high selective and specific enzyme–substrate interactions are the main driving force for the development of enzyme-responsive DDSs [67]. In addition, the regulatory activity of enzymes can be exploited, since it decreases/over-expressed in pathological situations [68].

For the development of enzyme-responsive DDSs, there are two main approaches; the first is based on nanocarriers sensible to enzymatic changes. In this case, the most commonly used enzyme-specific species are peptides or sugars whose cleavage is given by the action of esterases or proteases [1]. Within this group of DDSs, enzymatically degradable polymers or enzymatically sensitive linkers between the drug and the polymer are employed; the release is triggered by direct action of enzymes on the smart DDSs [69]. The second approach is based on the surface modification of the DDSs with molecules that confer enzymatically triggered changes of the physical properties of the smart DDS in solution and results in controlled release of the drug [43]. The great advantage of enzyme-responsive DDSs is their bio-recognition because it offers high selectivity and sensitivity which are fundamental in the field of nanomedicine. However, one disadvantage is that their construction requires the use of enzyme-specific species as peptides which are relatively expensive. And consequently, scaling up of these smart DDSs is hindered.

An example of these enzyme-responsive DDSs was designed by Radhakrishnan et al. In this case, DDS consists in dual enzyme-responsive hollow nanocapsules and assembles through layer by layer method to deliver doxorubicin specifically in cancer cells. The stimuli-responsive components of nanocapsules are polypeptide protamine that degrades in the presence of protease enzyme trypsin, and glycosaminoglycan

chondroitin sulphate that degrades in response to hyaluronidase, both enzymes are normally over-expressed under specific pathological conditions. These nanocapsules showed minimal drug release when kept in pH 7.4 PBS buffer, but released the drug molecules at high rate in the presence of any of enzymes [70].

1.3.2 Antibodies-Responsive DDSs

Antibodies are glycoproteins used by the immune system to identify and neutralize foreign elements such as bacteria and viruses. In the structure of the antibodies, there is a small region that allows to identify and specifically bind their unique antigen. The antibodies are widely used in immunological assays due to their high specificity, stability and versatility. Nowadays, these features are the reason of the increase of their use for the development of smart DDSs.

The specific linkage between antibodies and their antigen is given by weak and non-covalent bonds, such as hydrophobic and electrostatic interactions, hydrogel bonds and Van der Waals forces [71]. The action approach of antibodies-responsive DDSs is that the antigen–antibody binding acts as a dynamic crosslinking between the polymer chains, and in other words, it would be a switch on/off button to release the drug. In the absence of the antigen of interest, the smart DDSs do not release the drug and remains collapsed because of high crosslinking density. Otherwise, if the free antigen is present in the medium, the antigen–antibody crosslinks decrease. Consequently, the network swells followed by drug release [34]. Despite the high efficiency of the antibodies-responsive DDSs, they are rarely used due to the high costs that involve obtaining antibodies, and so, few examples are found in the literature. One of them is the antigen-responsive hydrogel designed by Lu et al. which may have potential applications as drug delivery devices or bio-sensors. Polymerizable antibody Fab′ fragment (fragment from monoclonal antifluorescein BDC1 antibody) was co-polymerized with N-isopropylacrylamide (NIPAAm) and N,N′-methylenebis(acrylamide) (MBAAm; crosslinker). Results showed that binding of the antigens to the Fab' fragment caused reversible changes in the swelling which was depending on Fab' content, temperature and pH of the medium. When the hydrogels were exposed to free antigens, significant reversible volume changes were observed for the hydrogel containing 50% (w/w) Fab′ fragment at 33.7 and 36.8 °C in acetate buffer (10 mM, pH 5.0), respectively, but not at 27.7 °C or in PBS buffer (10 mM, pH 7.4). On the contrary, for the cases of pure NIPAAm hydrogel and the gel containing 10% (w/w) Fab′ fragment, no noticeable reversible volume changes were observed [72].

2 Conclusions and Outlook

As far as stimuli-responsive smart DDS is concerned, they are a very important emerging area of drug delivery.

Beyond the promising properties displayed by this type of materials, as its versatility, safety and others that have already been described, it is possible to combine polymeric materials with other materials, such as inorganic nanoparticles or fabricate co-polymers to confer to the final structure response to more of one stimulus, such as pH and temperature. Therefore, smart DDSs offer the possibility of designing personalized or patient-based therapies, which could be a very important advance in treatments of diseases with a high incidence of mortality, such as cancer. In this way, there is a special interest in the development of smart DDSs for cancer therapy since these systems allow the drug delivery specifically towards cancer cells giving special protection of drug under circulation. The success in achieving this specificity is crucial to destroy cancer cells even if they had undergone metastasis.

However, the most of smart polymeric drug delivery systems and their applications have not yet made the clinical transition. This means that there are still some critical points that have to be considered. The most important reason is the response time of the polymer; in most cases, it happens in a too slow time, and therefore, fast-acting polymer systems are required, including their exact reproducibility. The toxicity of some synthetic polymers is another problem.

This chapter has summarized the most important concepts and recent advances in the development of smart DDSs.

Despite the fact that much remains to be done in order for these systems to be applied, and hence, move to the stage of scaling up and commercialization, we strongly believe that the more studies on these issues are carried out, the less time will be required for smart DDSs to demonstrate their potential as successful clinical candidates.

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Smart Polysaccharide Hydrogels in Drug Delivery and Release

Harshani Iresha and Takaomi Kobayashi

Abstract Smart hydrogels having extreme biocompatibility and drug loading ability are used in drug release (DR) applications under external stimuli like ultrasound (US). For the smart medicine hydrogels used in US-triggered DR, hydrogel matrix has functionalities like non-toxicity and biocompatibility. In addition, the DR behavior can be controlled by US exposure. It is known that in cancer chemotherapy, protein and gene delivery, and tissue regeneration, such smart hydrogel medicine plays a vital role as drug carriers and release. The hydrogels fabricated from polysaccharides like cellulose and chitin, which retain high content of water and medicine in the polymeric networks, exhibit excellent bio- and cyto-compatibilities and are mainly introduced for DR. It is also reviewed that, from such medicine hydrogels, external stimulant promotes accelerated DR by stimuli like temperature, pH, and enzymes. Especially, US-stimulated DR by cellulose and chitin hydrogels are reviewed as smart polysaccharide hydrogels.

Keywords Cellulose hydrogel · Chitin hydrogel · Drug release · Ultrasound · Biocompatibility

Abbreviations

ATB	Agave tequilana Weber bagasse
BSA	Bovine serum albumin
CH	Cellulose hydrogel
ChH	Chitin hydrogel
DD	Drug delivery

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DMAc	N,N–Dimethylacetamide
DMSO	Dimethyl sulfoxide
DR	Drug release
EtO	HEthanol
H_2SO_4	Sulfuric acid
HCl	Hydrochloric acid
LiCl	Lithium chloride
MCH	Mimosa-loaded cellulose hydrogel
NaOCl	Sodium hypochlorite
NaOH	Sodium hydroxide
NMMO	N-methylmorpholine-N-oxide
RMSSR	Root mean square surface roughness
SCB	Sugarcane bagasse
SEM	Scanning electron microscope
SPBM	Surface scanning probe microscope
TBAF	Tetrabutylammonium fluoride
WC	Water content

1 Introduction

Smart hydrogels, as the name implies the smart function of polymeric hydrogels, are remarkable in stimulant-driven drug delivery (DD), drug release (DR) applications, and other biomedical uses. Such applications in medical uses are in the pinnacle of the evolution of science, technology, and engineering, providing valuable and unique solutions for a number of difficulties found in therapeutic medicine. For example, in cancer chemotherapy, injectable hydrogel systems have been developed instead of conventional intravenous chemotherapy and thus bring advantages such as minimizing drug toxicity to other organs by releasing drug on to the targeted site promoted by various stimulants. Similar advancements can be experienced in protein and gene delivery, and tissue regeneration. In these fields, smart hydrogels play a vital role as drug carriers containing a polymeric network changed by an external stimulant. This specialty is the driving force for controlled DR or DD from smart hydrogels as drug carriers. Stimulants such as ultrasound, pH, temperature, enzymes, light, and magnetic fields are some of the main stimulants used in DD and DR applications. To response and promote the accelerated but controlled DR and DD under respective stimulant, there are a number of interesting natural and synthetic polymeric matrices developed. For sustainable issue, smart polysaccharide hydrogels are trending to appear in biomedical applications. It is worth discussing this topic to bring forward and unwrap such advance findings for keen inventors.

1.1 Smart Polysaccharide Hydrogels

Smart polysaccharide hydrogels are developed and fabricated from biomass sources which are freely available in nature. Cellulose and chitin are abundant natural polymers in the world [1, 2]. Those can be extracted from various natural sources including plants and animals. These natural polymers bring advantages over other synthetic polymers especially in medical applications. The most impressive advantages are sustainability and exhibiting excellent biocompatibility and cytocompatibility [3–5], outstanding biodegradability [6–8], providing biosafety due to nontoxic nature, and outstanding mechanical properties due to its chemical structure formed with strong inter- and intra-molecular hydrogen bonds. In addition to these, chitin exhibit wound-healing property [9]. Collectively, these are favorable and applicable with valuable properties for biomedical applications leading as new medical inventions as well as substitutions to existing conventional practices.

It is well known that cellulose is the world's most abundant polymer which is available in many natural resources. Cotton is almost 100% of cellulose, 35–50% of dry weight accounts for the cellulose from plant cell walls [10], and bacterial cellulose [11]. Moreover, recent research revealed excellent recoverability of cellulose from natural waste materials remaining after major productions, e.g., sugarcane bagasse [3, 12] after sugar refinery, *Agave tequilana* Weber bagasse [4] after production of tequila, and rice husks [13]. Cellulose is a linear homopolymer composed on D-glucopyranose linked by β-1,4-glycosidic bonds (Fig. 1a).

Chitin is also a linear polysaccharide composed of β-(1 → 4)-2-N-acetyl-D-glucosamine units (Fig. 1b). Chitin is the second most abundant natural polysaccharide in the world [14]. Chitin can be obtained from exoskeletal of marine crustaceans such as shrimps, crabs, lobsters and krill [2], exoskeletal of other arthropods [15], cell walls of fungi and yeast [16], and nanofiber chitin from mushrooms [17].

Chemical structures of cellulose and chitin bring linearity, toughness, and fibrous nature to these polysaccharides. However, both the cellulose and chitin are insoluble in common solvents including water, ethanol, etc. This insolubility is a major problem associated with cellulose and chitin for further processing in various applications. Nowadays, this problem has been overcome after introducing different solvents to dissolve these high molecular weight polysaccharides. Thus, both polysaccharides were developed for applications such as drug carriers [18, 19] and scaffold materials

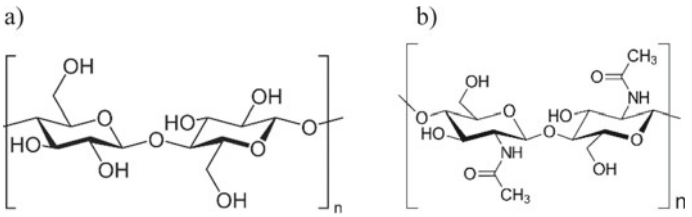

Fig. 1 Chemical structure of **a** cellulose and **b** chitin

for tissue regeneration [3, 4, 20]. The procedures of cellulose and chitin extraction, and cellulose and chitin hydrogel fabrication will be discussed in brief in the following sections.

1.1.1 Extraction Procedure of Cellulose and Chitin and Fabrication of Their Hydrogels

Depending on the composition of cellulose or chitin sources, the extraction procedures and/or conditions can be varying. However, cotton can be used without further extraction steps [18]. In general, cellulose extraction from plant sources or waste biomasses consists of four main steps. They are preliminary washing, lignin elimination, hydrolysis, and bleaching [21]. Tovar-Carrillo et al. [4] extracted cellulose successfully from *Agave tequilana* Weber bagasse (ATWB). The bagasse (Fig. 2a) was converted to cellulose hydrogel (Fig. 2c) through NaOH treatment for the elimination of lignin, then H_2SO_4 for the hydrolysis process, and NaOCl for bleaching. Similar process was applied for the extraction of cellulose from sugarcane bagasse [12].

Chitin extraction is differing from the cellulose extraction. Jiang and Kobayashi [19] and Nguyen et al. reported chitin extraction from crab shells with three main

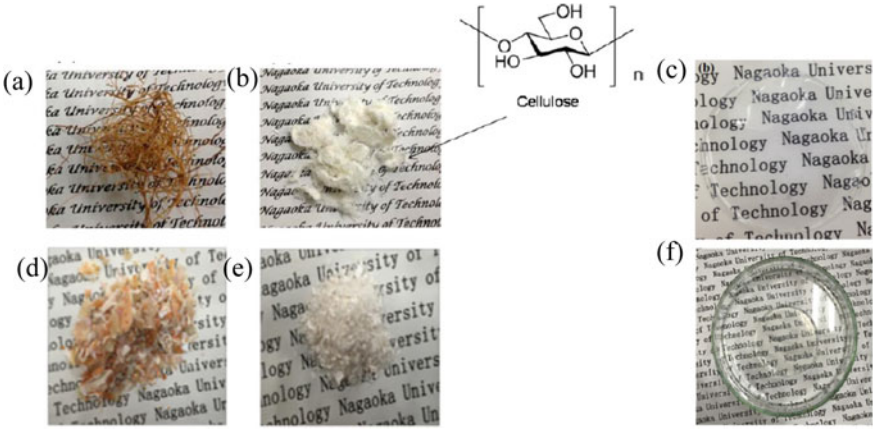

Fig. 2 Pictures of **a** ATWB before treatment and **b** cellulose extracted from ATWB after bleaching [4] (Reprinted with permission from Industrial & Engineering Chemistry Research, 52, Tovar-Carrillo et al., Fibroblast Compatibility on Scaffold Hydrogels Prepared from Agave Tequilana Weber Bagasse for Tissue Regeneration, 11,607–11,613, Copyright © 2013 American Chemical Society), **c** wet cellulose hydrogel [18] (Reprinted with permission from Ultrasonics Sonochemistry, 32, Jiang et al. [18], Ultrasound stimulated release of mimosa medicine from cellulose hydrogel matrix, 398–406, Copyright © 2016 Elsevier) **d** crushed crab shell, **e** chitin extracted from crab shells, and **f** wet chitin hydrogel [22] (Reprinted with permission from Journal of Applied Polymer Science, 136 (11), Nguyen. et al., Chitin-halloysite nanoclay hydrogel composite adsorbent to aqueous heavy metal ions, 47,207. Copyright © 2018 Wiley Periodicals, Inc.)

steps: demineralization using 1 N HCl, deproteinization using 1 N NaOH, and decolorization using EtOH. Chitin with 29.7% of average yield [19] was obtained using this procedure. To prepare their hydrogels, it is necessary to be dissolved in a proper solvent.

There are several solvents for cellulose and chitin. N-methylmorpholine-N-oxide (NMMO) [23], *N,N*-Dimethylacetamide in the presence of lithium chloride (DMAc/LiCl) [24], tetrabutylammonium fluoride and dimethyl sulfoxide (TBAF/DMSO) [25], Alkali with Urea [26], and ionic liquids [27] are some solvents used for cellulose dissolution. However, these solvent systems operate under extreme process conditions, e.g., 120 °C in NMMO, −12 °C in alkali/urea, microwave in ionic liquids. Among these, DMAc/LiCl solvent is considered as universal for dissolving both cellulose and chitin under ambient conditions with simple dissolving procedures [24]. Thus, DMAc/LiCl solvent was widely used for cellulose hydrogel (CH) and chitin hydrogel (ChH) [18, 19].

Procedure of cellulose and chitin dissolution in LiCl/DMAc is extending with three consecutive solvent exchange steps using abundant of distilled water, EtOH and DMAc, by soaking and stirring for 24 h in each solvent, sequentially [3, 4, 12, 28]. After stirring in each solvent, the cellulose/chitin was filtered using an adapter glass filter under vacuum [4]. After the solvent exchange steps, the cellulose/chitin was vacuum dried at room temperature prior to dissolve in LiCl/DMAc. As the final step, to dissolve 1 g of cellulose/chitin, 6 g of LiCl and 93 g of DMAc were used and stir until fully dissolve (for 1 day or more) [3, 4, 12, 22] to obtain a clear viscous liquid with 1 wt% of concentration of cellulose/chitin.

By using such CH or ChH solution, hydrogel can be fabricated using phase inversion method under water vapor [19, 22] or ethanol vapor [4, 12] atmosphere. 10 g of cellulose/chitin was poured into a petri dish and kept still in a sealed container filled with (20–40 ml) EtOH or water. During this period, the coagulated gel form of cellulose/chitin, i.e., cellulose/chitin hydrogel, was obtained by the phase inversion. As shown in Fig. 2c, f, CH and ChH are colorless and transparent hydrogels.

1.1.2 Properties of Cellulose and Chitin Hydrogel

CHs and ChHs prepared using LiCl/DMAc by phase inversion method exhibit excellent biocompatibility, mechanical properties, flexibility, and high-water retention ability. However, quantitatively, these properties differed depending on the treatment conditions, dissolution media, etc.

For example, CHs prepared from cellulose extracted from SCB the water content (WC) of CHs ($WC = \left[\left(W_{wet} - W_{dry}\right)/W_{dry}\right] \times 100$,) were increased in 300–500% depending on the degree of chemical treatment [12]. When the concentration of NaOCl bleaching agent was increasing from 0, 1, 2.5, 5.0, 7.5, and 10 vol%, mechanical properties of the hydrogels were enhanced. Tensile strength was increased from 38 N/mm^{2}to 56 N/mm^{2}when the LiCl loading was increasing from 0 to 10 vol% [28]. This was due to the improved interactions of cellulose fibrils by the action of LiCl/DMAc [29]. It was seen that the CHs prepared with cellulose

solution in LiCl/DMAc showed higher tensile strength (66 N/mm^2) as compared to NaOH (27 N/mm^2) and NaOH/Urea (21 N/mm^2) systems [20]. In these three solvent systems, the WC was also higher in LiCl/DMAc system than in NaOH and NaOH/urea system. In LiCl/DMAc system to dissolve cellulose, an increase in LiCl concentration caused an increase in mechanical properties of CHs while decreasing the WC. At higher LiCl concentrations, there were cellulose fibrils that tend to aggregate thus polymer network acts against tensile forces [4], while this aggregation restricts the water retention in the matrix.

Cellulose and chitin hydrogels are popular in medical application due to their superior cytocompatibility and biocompatibility. Thus, numerous advanced researches were reported with such polysaccharide hydrogels. Scaffold from bacterial cellulose derived from *Acetobacter xylinum*, was investigated for in vivo biocompatibility, means no inflammation to host tissues, thus confirm the applicability as a scaffold for tissue engineering applications [30]. Further, chitin nanogels [31] and α-chitin hydrogel/hydroxyapatite composites [32] are biocompatible scaffolds for bone and wound tissue engineering applications. In the latter, cell viability, cell attachment, and cell proliferation were studied by MG 63, Vero, NIH 3T3, and nHDF cells for exhibiting superior cytocompatibilities to four types of cells.

CHs prepared from cellulose extracted from ATWB [4], SCB [3], bamboo [20], and wood pulp [33] were reported for their cytocompatibility and biocompatibility. Among them, Karla et al. reported cytocompatibility study using fibroblast cells (NIH 3T3 cells) adhesion on to the CHs prepared from ATB cellulose, at different LiCl concentrations (4, 6, 8, 10, and 12 wt%). With the cell culture time, the cell density was increased and compared to the control (standard polystyrene dish), the cell density is higher at all LiCl concentrations. Further, according to reflectance microscopic images of CHs, the cell growth direction was comparable with the cellulose fiber arrangement [4]. Figure 3 shows phase-contrast light images of cell culture dishes of CHs from bamboo cellulose, dissolved in different solvents: DMAc/LiCl, NaOH, and NaOH/urea. CHs prepared from cellulose dissolved in DMAc/LiCl show similar cell growth like standard polystyrene dish while the CHs from other solvents.

CHs from SCB cellulose were successfully proved its excellent in vivo biocompatibility by Nakasone et al. [3]. CHs were placed in the intraperitoneal of female ICR mice. Water intake, food intake, and body weight changes were monitored week by week. Mice group with implanted CHs showed growth pattern similar to control group of mice and insignificant increases/decreases were noted in water and food intake measures. Also, post-mortem examination revealed no internal inflammations in the implantation sites of mice during each week observations after the implantation.

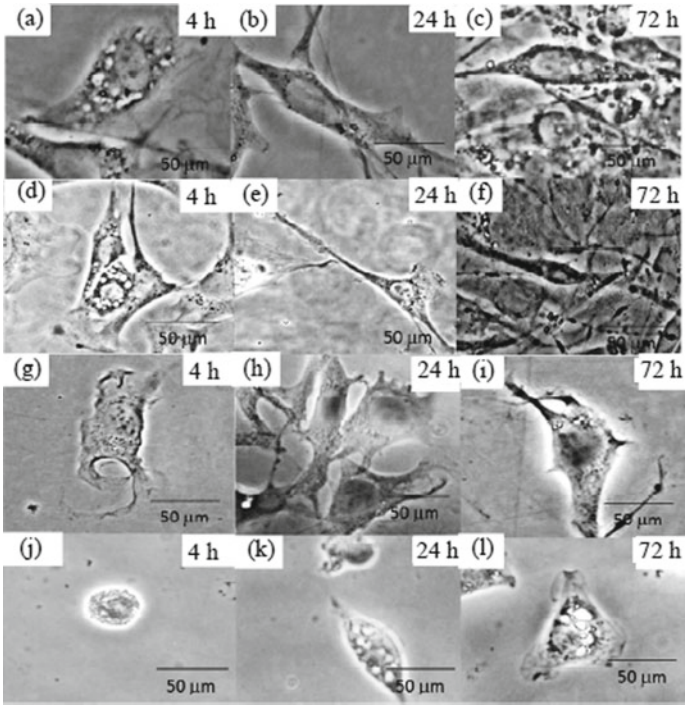

Fig. 3 Phase-contrast light images of **a–c** polystyrene dish used as the control with cell culture, and CHs prepared from cellulose extracted from bamboo dissolved in **d–f** DMAc/LiCl, **g–i** NaOH and **j–i** NaOH/Urea. The cell culture time is 4 h, 24 h, and 72 h, in ascending order of alphabet [20] (Reprinted with permission from Tovar-Carrillo et al. [20]. Copyright © 2013 authors)

1.2 Cellulose and Chitin Hydrogels in Drug Delivery and Drug Release

Polysaccharide hydrogels are not only used in tissue regeneration and other biocompatible applications. Those are well exhibited for applications in smart DD and DR. Evolutional research on smart hydrogels in DR applications was reported recently, as shown by pH- and ion-sensitive cationic cellulose hydrogel [34], thermo- and pH-responsive bacterial cellulose/acrylic acid hydrogel for bovine serum albumin (BSA) release [35], and chitin nanogel system conjugated with CdTe quantum dots (QDs) for DD, bioimaging, and biosensing, i.e., multifunctional nanogel system [36]. Likewise, some of the recent SH-based DR applications are summarized in Table 1. Here, cellulose and chitin hydrogels which are already having cyto- and biocompatible properties provide the additional DR or DD capability as a medicine matrix with smart functionality.

Despite in the above-mentioned hydrogel materials, cellulose and chitin were applied for DD and DR, and there was quietly less research by using pure cellulose

Table 1 Summary of different polysaccharide-based hydrogels for DD and DR applications under different stimulants

Polysaccharide hydrogel	Drug	Stimulant	References
Cellulose hydrogel	Mimosa	US	[18]
Chitin hydrogel	Gallic acid	US	[19]
Cationic cellulose hydrogels	Diclofenac sodium	pH- and ion-sensitivity	[34]
Bacterial cellulose/acrylic acid hydrogel	Bovine serum albumin	Temperature and pH	[35]
Chitin nanogels conjugated with MPA-capped-CdTe-Quantum dots	Bovine serum albumin	pH	[36]
Hydroxypropylmethyl cellulose films	Nicotine	pH and ionic strength	[37]
Kappa-carrageenan/polyvinyl alcohol hydrogel	β-carotene	pH	[38]
Bacterial cellulose/acrylamide-based hydrogel	Theophylline	Released to phosphate buffer (pH 7.4) at 37 °C	[39]
Cellulose nanocrystals-gelatin hydrogels	Theophylline	Released to simulated gastric fluid (HCl at pH 1.2) at 37 °C	[40]
Carboxymethyl cellulose/carboxymethyl β-cyclodextrin hydrogel	Tetracycline	Released to PBS buffer (pH 7.4), at 37 °C	[41]
Carboxymethylcellulose sodium/cellulose hydrogel	Bovine serum albumin	Released to phosphate buffer (pH 7.4) at 37 °C	[42]
Chitin/PLGA blend microspheres	Bovine serum albumin	Released to PBS buffer (pH 7.4) at 37 °C	[43]
Cellulose hydrogel and chitin hydrogel	Nicotine	US	[44]
Chitosan/alginate beads	Indomethacin	pH	[45]
Poly(ethylene glycol)/carboxymethyl chitosan hydrogel	5-fluorouracil	pH	[46]
Carboxymethyl chitosan/poly(N-isopropylacrylamide) semi-interpenetrating polyampholyte hydrogel	Coenzyme A	Temperature and pH	[47]
Thiolated hydroxypropyl cellulose nanogels		Temperature and redox	[48]
Bacterial cellulose nanofiber/sodium alginate hybrid hydrogel	Ibuprofen	pH and electric field	[49]

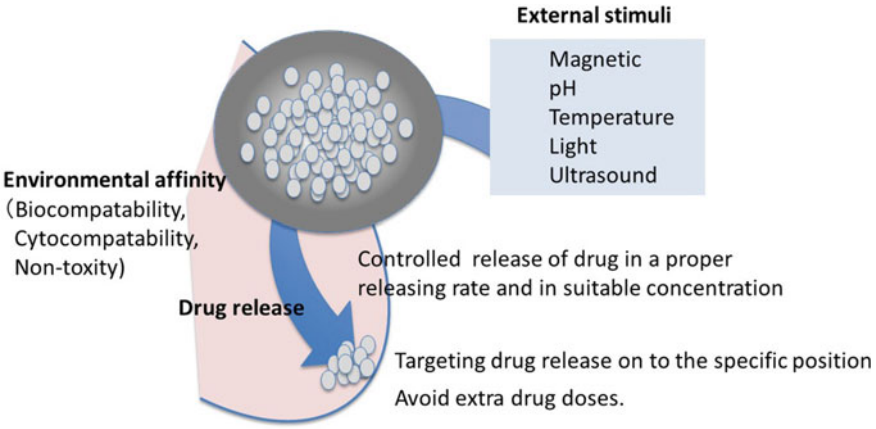

Fig. 4 Schematic drawing emphasize the smart DR from SHs

and chitin matrices. Thus, mostly both cellulose and chitin were chemically modified or composited physically with other materials. On this point, CH and ChH as drug carriers for stimulated-driven DR applications are quietly smart. Figure 4 illustrates such hydrogels with medicine. The hydrogel matrix has good environmental affinity like biocompatibility, cytocompatibility, and non-toxicity. Those valuable properties make the matrix suitable for human and animals. Like below, medicine release can be triggered by US from outside to body manipulation, at variable US output power and frequencies. Here, the breakage of hydrogen bonding between the drug and the matrix can be promoted. In the example of US release, mimosa-entrapped cotton cellulose hydrogel [18] and gallic acid-loaded chitin hydrogel [19]. US-stimulated drug carries are reported. In this section, the US-triggered DR by cellulose and chitin hydrogel matrices are explained extensively.

In the mimosa-loaded cellulose hydrogel (MCH) was prepared using cotton as the cellulose source. The mimosa release behavior from MCH was studied under US at different US powers (0, 5, 10, 20, and 30 W) and different frequencies (23, 43, and 96 kHz). The research reveals the mimosa release under US exposure. The mimosa release rate was 0.03 μg/ml.min without US and 0.15 μg/ml.min at 30 W/43 kHz US. As increased with the US power, the mimosa release rate was thus controlled by the US powers and by the US frequencies. Mimosa is a medicine extracted from mimosa plant [50] and has a value of wound healing. Therefore, mimosa release from CHs is valuable for surgical treatments and other wound-healing applications.

Similarly, gallic acid (GA) exerts biomedical advantages as an antimicrobial agent, an antioxidant, and an antihyperglycaemic, anticancer, and wound-healing agent [51]. This drug hydrogel was observed the GA release behavior under US [19]. This also proved an enhanced and controlled drug release by US exposure. Also, when the US power was increasing, the GA release was enhanced (Fig. 5). The release rates were 0.07 μg/ml.min and 0.51 μg/ml.min, without US and with US at 30 W/43 kHz conditions at 25 °C, respectively. Moreover, when the GA concentration inside the

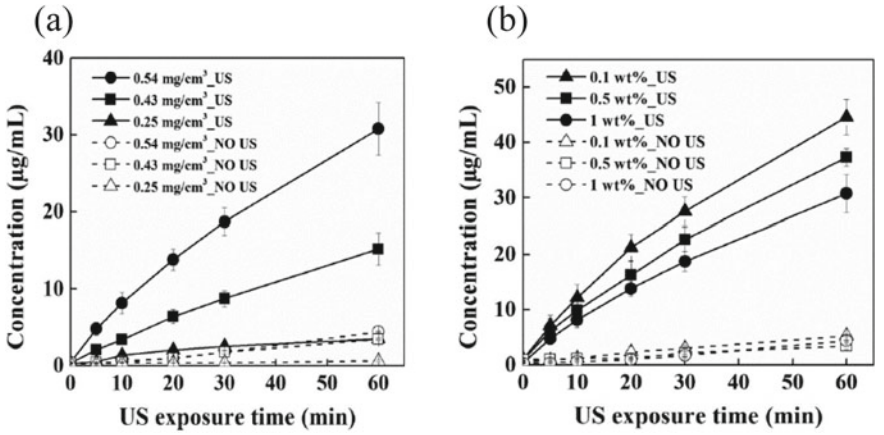

Fig. 5 GA release behavior from ChHs **a** loaded with different GA concentrations (0.25, 0.43, and 0.54 mg/cm^3) and 1 wt% chitin and **b** prepared with different chitin loading (0.1, 0.5, and 1.0 wt%) with 0.54 mg/cm^3 GA loading Hydrogels were exposed to US at 30 W/43 kHz conditions [19] (Reprinted from Materials Science and Engineering C, 75, Jiang and Kobayashi, Ultrasound stimulated release of gallic acid from chitin hydrogel matrix, 478–486. Copyright © 2017 Elsevier)

ChH was varying, the release amount was significantly differed. Here, the GA loading caused to decrease the storage modulus (G') of the chitin matrix thus the release was enhanced concomitantly with GA concentration [19]. This was evidence that the medicine interacted with the chitin hydrogel matrix through hydrogen bonding.

When the concentration of polysaccharide in the drug hydrogel matrix was increased, the density of the hydrogel was also increased. Denser hydrogel network arrangement was further confirmed by the cross-sectional scanning electron microscopic (SEM) images of hydrogels as shown in Fig. 6. According to this dense structure of the drug hydrogel, at higher polysaccharide concentrations, the drug release can be restricted.

The US-triggered release of mimosa and GA was identified as excellent smart hydrogel systems for DR. Both systems were confirmed in the DR behavior due to the breakage of hydrogen bonds of the drug-polysaccharide matrix as seen by deconvoluting FT-IR spectra for the hydrogen bonding region cellulose and chitin. Here, analysis shows that the US exposure broke the hydrogen bonds between the drug and the hydrogel [18, 19].

Figure 7a, b shows generalized two-dimensional (2D) correlation FT-IR spectrums of GA-loaded ChH which was analyzed by "2D Shige" software [52]. This analysis was suggested seven peaks related to the NH and OH stretching region of GA-chitin and these peaks were assigned as seen in the caption of Fig. 7.

Similar analysis was carried out for the mimosa-cellulose hydrogel film [18]. The results confirmed the hydrogen bond break promoted by US and for releasing mimosa at a higher rate compared to no US conditions.

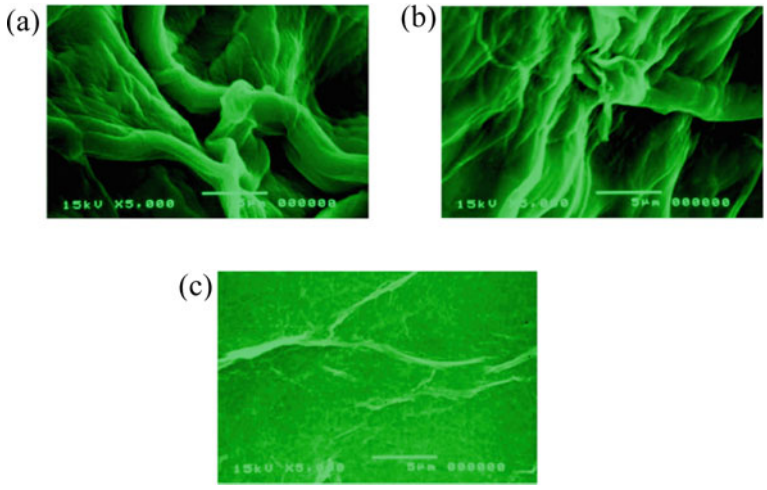

Fig. 6 Cross-sectional SEM images of GA-loaded chitin matrices prepared with **a** 0.1 wt% **b** 0.5 wt% and **c** 1.0 wt% of chitin concentrations [19] (Reprinted from Materials Science and Engineering C, 75, Jiang and Kobayashi, Ultrasound stimulated release of gallic acid from chitin hydrogel matrix, 478–486. Copyright © 2017 Elsevier)

1.3 Conclusion

Polysaccharide hydrogels are smart hydrogels which show extreme biocompatibility and cytocompatibility. Among various types of polysaccharide hydrogels, CHs and ChHs show their smart behavior in DR applications. Thus, US-stimulated DR is remarkable in CH and ChH matrices and these findings expose the applicability of CHs and ChH in various surgical and biomedical applications as drug carriers. Collectively, cellulose and chitin hydrogels are proper smart hydrogels for DR and DD applications which have good mechanical properties and more importantly which can be easily fabricated using under simple procedures [6, 7, 8, 13, 22, 34, 45, 52].

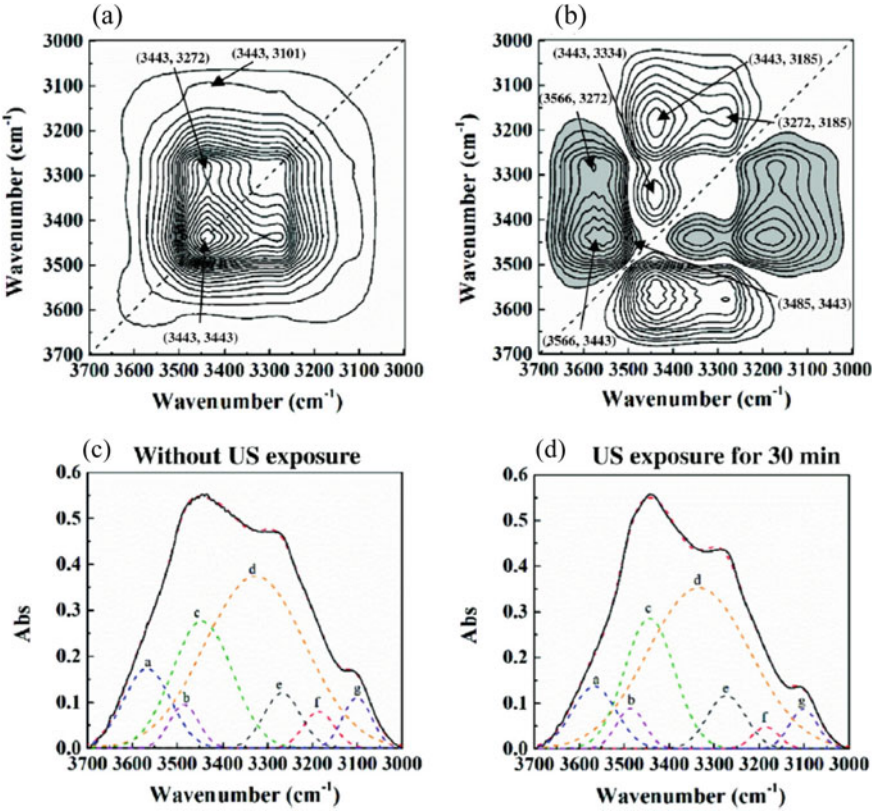

Fig. 7 **a** Synchronous and **b** asynchronous 2D correlation FT-IR spectra for GA-loaded ChH. Deconvolution results of hydrogel **c** without US and **d** with US (30 W/43 kHz for 30 min) [19]. a—3566 cm^{-1}—free OH groups in chitin molecules, b—3485 cm^{-1}—hydrogen bonds formed between OH groups and water molecules, c—3443 cm^{-1}—OH stretching of hydrogen bonds in chitin-chitin, d—3334 cm^{-1}—OH stretching of chitin-GA interaction, e—3272 cm^{-1}—free NH groups of chitin, f—3185 cm^{-1}—NH groups in hydrogen bonds of GA-chitin, and g—3101 cm^{-1}—NH groups in hydrogen bonds of chitin-water (Reprinted from Materials Science and Engineering C, 75, Jiang and Kobayashi, Ultrasound stimulated release of gallic acid from chitin hydrogel matrix, 478–486. Copyright © 2017 Elsevier)

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Polysaccharide-Based Nanoparticles: Nanocarriers for Sustained Delivery of Drugs

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Abstract Polysaccharides are considered as the most promising natural materials for their unique physicochemical properties and excellent biocompatibility. They are biodegradable, non-toxic, abundant, and inexpensive biopolymeric precursors for preparing materials of choice in various industries. Many biomedical applications of polysaccharide nanomaterials (PNM) have been explored. PNM have the potential to be used as nanometric carriers for the sustained/controlled delivery of drugs. Sustained delivery through PNM has improved the utility of many drugs like 5 aminosalicylic acid, diclofenac sodium, ranitidine hydrochloride, and hormonal drugs while alleviating their toxic side effects. This chapter summarizes the recent developments in the field of PNM based drug delivery systems.

Keywords Polysaccharide · Nanoparticles · Nanocarriers · Sustained delivery of drugs

1 Introduction

Since last decade, nanoparticles have been utilized for diversified applications for their intriguing properties [1]. The conversion of micromaterial to nanomaterial imparts many new properties to a material. These properties are dependent on the shape and surface area to volume ratios of the nanomaterials [2] which have modulating effect on the chemical, mechanical, optical, and electrical properties of the materials [3]. Polysaccharide nanomaterials (PNM) have been designed in various shapes [4] like nanorods, nanowires, nanocages and nanoflakes, and various physical and chemical methods such as nanoprecipitation [5], solvent dissolvation [6], emulsification [7], self-assembly [8], free-radical polymerization [9], and green synthesis [10] have been used for their syntheses.

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Polysaccharides are the macromolecules which consist of various monosaccharide units. These units are linked together through glycosidic linkages [11–13]. They are abundant, economic and renewable materials and are being used in various fields for their unique biological and chemical properties including nontoxicity, biodegradability, hydrophilicity, biocompatibility, and polyfunctionality [14].

Though polysaccharides do hold many advantages over synthetic materials, there are many limitations in their use. Their uncontrolled hydration and easy microbial contamination often impair their use in their natural form. Hydrophilic biopolymers can be modified into amphiphilic biopolymeric matrices which are capable of being exploited as entrapping agents in delivering the active principle compound to the targeted site. Modification of polysaccharides includes grafting, functionalization, conversion to nanoparticles, nanocarrier, etc. Nowadays, PNM are being used as drug carriers as they increase the solubility and permeability of many effective drugs, which are otherwise difficult for oral administration [15]. Apart from drug delivery systems, PNM offer many diversified applications in various fields (Fig. 1).

Delivering a drug to the targeted organ requires a suitable approach, formulation, technology, and system such as to transport the pharmaceutical product safely while retaining its maximum therapeutic effect. The potent drug can be encapsulated or

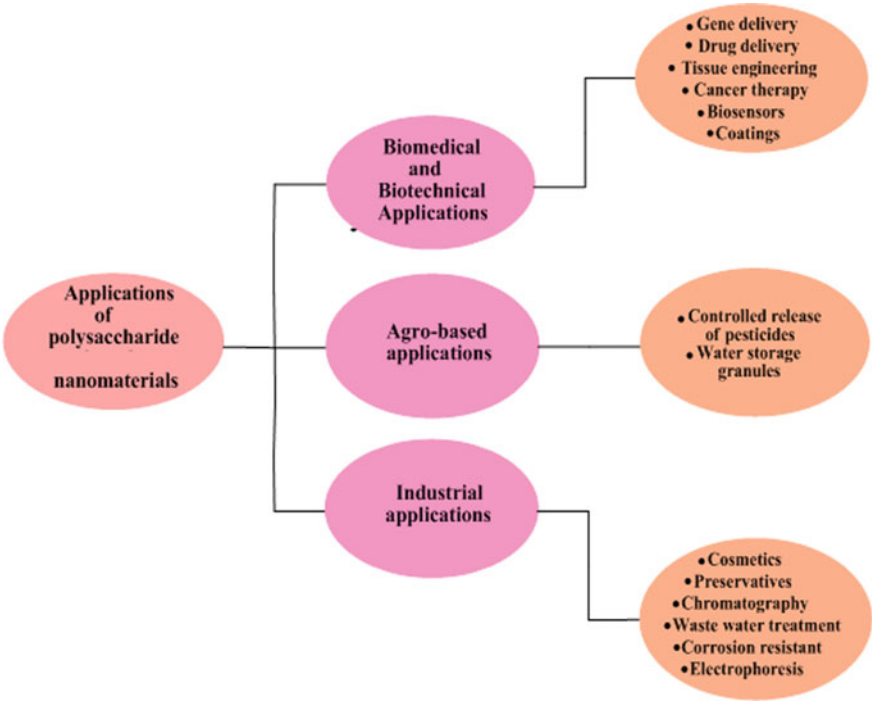

Fig. 1 Various applications of polysaccharide nanomaterials

adsorbed within a suitable matrix for better solubility, biocompatibility, biodegradability, and bioavailability [16–19]. The drug entrapped within PNM can be delivered in an uninterrupted manner, without getting affected from the harsh gastrointestinal fluids and enzymatic degradation, while allowing the active principle to reach at the site of action, that too in a sufficient concentration [20].

The use of PNM is advantageous in drug delivery as they cause improved bioavailability, dose reduction, increased stability, and reduction of the side effects. This chapter is written with the aim of summarizing the studies on the preparation and development of PNM and their application in the field of drug delivery. As a voluminous amount of research has been carried on drug delivery using PNM, the papers published in the last five years only will be considered in this chapter to give a glimpse of the current research in the field and for exploring future avenues of this field of research (Table 1).

2 Polysaccharides

Polysaccharides are the carbohydrates materials consisting of large polymeric oligosaccharide units which are linked together through glycosidic linkages. Large number of reactive groups, high molecular weight, and varying chemical compositions of polysaccharides offer diversified properties for exploitation in numerous fields. On the basis of ionic charges, polysaccharides can be classified as neutral polysaccharides (Guar gum, starch, dextran etc.), positively charged polysaccharides (Chitosan) and negatively charged polysaccharides (alginate, xanthan). Based on the structural characteristics, several methods have been devised for the preparation of PNM such as nanoprecipitation, polyelectrolyte complexation, self-assembly, etc. (Fig. 2). A number of polysaccharides have been utilized in designing the nanomaterials for drug delivery. Table 1 summarizes the nanomaterials derived from different polysaccharides along with its use in drug delivery.

2.1 Neutral Polysaccharides

2.1.1 Cellulose and Cellulose Derivatives

Cellulose is a linear homopolymer consisting of $\beta(1 \rightarrow 4)$ linked D-glucose repeating units. It is the most widely distributed polysaccharide on earth. It originates mainly from the cell walls of plants but is also found in algae, oomycetes, and bacterial biofilms [21, 22]. Apart from being harmless to mammals, cellulose and its derivatives are biodegradable, biocompatible, and possess properties that can be utilized for various applications in industries [22–24].

Table 1 List of PNM used for drug delivery

S. No.	Polysaccharide	Size (nm)	Drug delivered	References
Cellulose-based nanoparticles				
1	Acetylated Carboxymethyl cellulose (CMC)	150	Doxorubicin	[30]
2	Alginate-cellulose nanocrystal	100	Rifampicin	[35]
3	Cellulose	213–730	Camptothecin	[25]
4	CMC and chitosan	<50	5-fluorouracil	[26]
5	CMC	3	Doxorubicin	[27]
6	Cellulose hydrogel and lipid nanocarrier	150	Doxorubicin	[28]
7	Cellulose nanocrystal rods	118	Cis-aconityl doxorubicin	[29]
8	CMC-hydroxy apatite	60–80	Dexamethasone	[31]
9	Cellulose nanocrystals	–	Ketorolac tromethamine	[34]
10	Cellulose nanocrystals	380	Neurotensin	[36]
11	CMC hydrogel	–	Tetracycline	[37]
12	CMC-rosin gum hybrid	267	5-Aminosalicylic acid	[40]
13	Methylcellulose	151	Docataxel	[33]
14	Polyvinyl alcohol/CMC-ZnO	191–210	Erythromycin drug	[32]
15	Quaternized cellulose	20–50	Anti-cancer therapy	[24]
Starch-based nanoparticles				
16	Carboxymethylated starch nanocrystals	217	Naproxen	[42]
17	Crosslinked starch nanoparticles	21	Diclofenac sodium	[45]
18	Hydroxyethyl starch-deoxycholic acid	197	Flavonoid Morin	[43]
19	Polylactic acid and hydrophilic dextrin	–	Ornidazole ~97% and ciprofloxacin ~98%	[46]

(continued)

Table 1 (continued)

S. No.	Polysaccharide	Size (nm)	Drug delivered	References
20	Starch/gum nanocomposites	109	Sal B	[44]
Guar gum based nanoparticles				
21	Carboxymethyl guar gum	208	Rhodamine B	[48]
22	Guar gum coated chitosan nanoparticles	230–310	Anti-tubercular drugs	[49]
23	Guar gum/chitosan/polycaprolactone	–	Rifampicin	[50]
24	Guar gum-g-polyacrylamide	13–90	Transdermal drug delivery system	[51]
Dextran-based nanoparticles				
25	Dextran	10–150	Piroxicam drug	[52]
26	Dextran-*g*-poly(*o*-nitrobenzyl acrylate)	30	Nile red and doxorubicin	[53]
27	Dextran	125–150	Paclitaxel	[54]
28	Dextran	120	Doxorubicin hydrochloride	[55]
Miscellaneous neutral polysaccharides				
29	Carboxymethyl and amine derivative of galactomannan	<100	Dorzolamide hydrochloride	[56]
30	Katira gum nanoparticles	100	Bromelain	[57]
Chitosan-based nanoparticles				
31	Amphoteric derivative of chitosan	–	Ronidazole	[65]
32	Alginate/chitosan particles	440	Tobramycin	[78]
33	Blending of chitosan lactate with polyvinyl alcohol	–	Ciprofloxacin	[61]
34	β-cyclodextrin-grafted carboxymethyl chitosan hydrogels	–	Acetylsalicylic acid	[79]

(continued)

Table 1 (continued)

S. No.	Polysaccharide	Size (nm)	Drug delivered	References
35	Chitosan hydrogel	–	Bovine serum albumin and 5-Fluorouracil	[69]
36	Chitosan nanogels	60–70	Doxorubicin	[58]
37	Chitosan and gum arabic	250–290	Curcumin	[75]
38	Chitosan and poly(2-acrylamido-2-methylpropanesulfonic acid)	255–390	Doxorubicin	[55]
39	Chitosan and nitrosalicylaldehyde	–	Chemotherapy	[60]
40	Chitosan and poly(ethylene glycol)-block-poly (propylene glycol)-block-poly(ethylene glycol)	–	Metformin (MET) drug and MCM-41 or MCM-41-APS	[63]
41	Chitosan, alginate or pectin based nanoparticles	590	Drug against oral ailments	[64]
42	Chitosan	–	Curcumin	[73]
43	Chitosan hydrogel	200–300	Curcumin	[76]
44	Chitosan and acrylic acid	115	Curcumin	[14]
45	Chitosan, CMC and graphene oxide	500	5-fluorouracil	[67]
46	Chitosan and polylactic-co-glycolic acid	250	Streptozocin	[66]
47	*N*-naphthyl-*N*,O-succinyl chitosan and *N*-octyl-*N*,O-succinyl chitosan	120–338	Curcumin	[74]
48	Chitosan and locust bean gum	318	Aceclofenac	[66]
49	*N*-trimethyl chitosan and sodium carboxymethylxanthun gum	–	Ciprofloxin	[62]
50	*N*-succinylhydroxybutyl chitosan	–	Bovine serum albumin	[70]
51	Chitosan with phospholipids	120	Curcumin, diclofenac and vitamin B12	[77]

(continued)

Table 1 (continued)

S. No.	Polysaccharide	Size (nm)	Drug delivered	References
52	Poly (ethylene glycol) methyl ether and chitosan	–	Paclitaxel and 5-fluorouracil	[71]
53	Poly(acetylantipyrine-chitosan)	–	Methotrexate drug	[72]
Alginate-based nanoparticles				
54	Alginate nanocarrier	20–40	Sunitinib	[82]
55	Chitosan/algiante nanoparticles	60	Quercetin	[81]
Cashew-based nanoparticles				
56	Acetylated cashew gum	179	Indomethacin	[9]
57	Acetylated cashew gum		Diclofenacdiethylamine	[84]
58	Aloevera polysaccharide/acrylonitrile	50	5-amino salicylic acid	[91]
59	Xanthan gum nanoparticles	150	Mesalamine	[87]

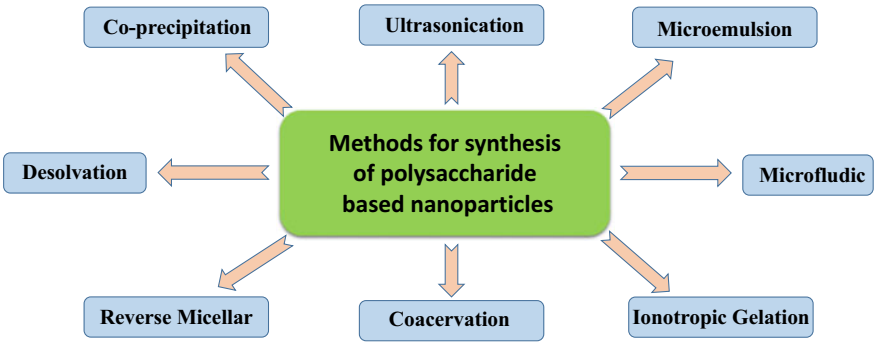

Fig. 2 Techniques for synthesis of PNM

Esterification has been used for preparing the conjugates of testosterone, ergocalciferol, and DL-α-tocopherol hemisuccinate with methylcellulose, hydroxyethyl cellulose and (hydroxypropyl) methylcellulose. These have been used for the sustained release of a potent anti-cancer drug "camptothecin," which is known for its antiviral activity. The drug was encapsulated in the cellulose nanoaggregates (1.7–13.0 wt%). Sustained release of the drug was observed for over 150 h and cytotoxicity study against MCF-7 cancer cells proved that the nanoparticles were suitable candidates for chemotherapy [25].

Bio-nanocomposite beads consisting of carboxymethyl cellulose (CMC) and chitosan (CS) are reported. CMC is known for its poor mechanical performance which has been improved through nanocomposite formation. In this study, zinc oxide nanoparticles were incorporated into CMC beads and then they were coated with a layer of CS via a self-assembly technique which led to the formation of core–shell polyelectrolyte complexes. Bio-nanocomposite beads exhibited pH sensitivity when loaded with anti-cancer drugs, 5-fluorouracil (5-FU). The beads were found efficient in carrying colon-specific drug [26].

A polyelectrolyte magnetic nanocarrier was developed using carboxymethyl cellulose polymer which enhanced the delivery and uptake of doxorubicin in MCF7 breast cancer cells and reduced the unfavourable toxic side effects of the drug. The efficiency of the delivery system was evaluated by loading and release studies which confirmed the excellent behaviour of the carrier. Biological assay studies like protein-particle interaction, haemolysis assay, cytotoxicity study, cellular uptake, and apoptosis analysis were also performed [27].

A novel hybrid biomaterial has been developed by combining bacterial cellulose hydrogel and lipid nanocarrier which was then loaded with cationic or neutral doxorubicin as the model drug [28]. The drug-loaded carrier was analyzed for in vitro drug release using MDA-MB-231 cells and was also assayed in vivo using an orthotopic breast cancer mouse model. Nanocarriers loaded with cationic Dox showed low encapsulation efficiency (48%) which was accompanied by the fast release of the drug while higher encapsulation (97%) and sustained drug release was witnessed when neutral Dox was loaded. Taking advantage of the differential drug release, a

mixture of cationic and neutral Dox was encapsulated within the nanocarriers and was assayed in vivo. A significant reduction of tumour growth was observed with minimal local drug toxicities and metastasis incidence.

Fluorescence-visible rod-like nanomedicines having enhanced cellular uptake and intracellular drug controlled release are reported [29]. The synthesis was based on cis-aconityl doxorubicin labelled cellulose nanocrystal rods. Aminated cellulose nanocrystal rods were also developed and were used as the prodrug to study the sustained drug delivery profiles over 40 h. The cumulative drug release increased from 36 to 80% with a decrease in pH value from 7.4 to 5.0. The prodrug revealed great potential for fluorescence-visible drug delivery system having greater cellular uptake as well as intracellular drug release because of its rod-like structure, suitable aspect ratio, and acid-triggered drug release.

The delivery of chemotherapeutics to the tumour tissue with minimum harsh side effects is yet another achievement [30]. The researchers have reported the synthesis of nucleolin targeted hybrid nanostructure which was fabricated from doxorubicin-encapsulated hollow mesoporous silica nanoparticles coated with acetylated carboxymethyl cellulose. To study the guided drug delivery to nucleolin overexpressed cancerous cells, the nanoparticles were covalently conjugated to aptamer and high loading capacity, smart characteristics, and desirable anti-cancer potential of the drug were achieved.

In situ dexamethasone (Dex) encapsulated metal–organic frameworks of 60–80 nm size have been synthesized [31]. These were efficiently integrated with carboxymethyl cellulose-hydroxyapatite nanocomposite for the development of three dimensional localized drug delivery system. In vitro release behaviour of Dex was examined in phosphate-buffer solution. The nanocomposite released Dex molecules much slower than the metal–organic framework. The release study was sustained for 4 weeks and the cytocompatibility studies showed that the nanocomposite was compatible to MC3T3 cells, thus is a promising material for therapeutic as well as load-bearing orthopedic applications.

Nanocomposite fibrous mats containing erythromycin drug have been crafted by crosslinking polyvinyl alcohol/carboxymethyl cellulose-ZnO with 2% glutaraldehyde vapour and 3% $AlCl_3$ alcoholic solution [32]. In vitro release study revealed that the erythromycin was slowly released from the nanocomposite fibrous mats, which indicated that the mats are suitable biomaterial for wound dressings.

Another anti-cancer drug, docataxel is widely used as an anti-mitotic agent. To obtain its better efficacy, the properties and low aqueous solubility of the drug need improvement. Chung et al. [33] have developed an injectable formulation of this drug using surfactant-free, low molecular weight methylcellulose (hydrophobically modified cellulose derivative) which was derived by the enzymatic degradation of crude methylcellulose. Docataxel was efficiently loaded to this formulation which showed a sustained release profile of the drug. Therapeutic effect of the drug was also enhanced in comparison to the commercially available docataxel, indicating the formulation is promising for the effective delivery of insoluble antitumour drug.

Non-toxic nanocomposite biofilms have been synthesized from cellulose nanocrystals (isolated from jute waste) [34]. In vitro permeation studies were

performed via Franz diffusion cell method which revealed that the nanocomposite biofilms are capable of the diffusion mediated sustained drug release of ketorolac tromethamine and can also be used for edible packaging.

Rifampicin-loaded alginate-cellulose nanocrystal hybrid nanoparticles (of size 100 nm) were prepared [35]. The nanoparticles reduced the barriers to oral delivery of the drug and protected it from the harsh intestinal gastric conditions to offer sustained release to the target organs. The swelling property of the drug was found to be pH-dependent. The nanoparticles showed high encapsulation efficiency and have shown a sustained release profile of the drug. MTT assay revealed the non toxic nature of the nanoparticles. Thus the nanoparticles can be used as a efficient carrier for treating *Mycobacterium tuberculosis.*

Diabetic foot ulcer is a serious threat to human beings and is a fatal disease. It can be controlled by the use of neurotensin which is an inflammatory modulator in wound healing. Its cytocompatibility was much improved by loading into polylactide–co-polyglycolide and cellulose nanocrystals nanofiber membranes [36]. The sustained drug release was studied for two weeks. It was established that diabetic foot ulcers can be treated by the use of drug-loaded membranes which not only released the drug in a controlled manner but also led to a more rapid healing.

Currently, available wound dressings have disadvantages such as lack of antibacterial activity, insufficient mechanical properties, inadequate amount of water vapour, and oxygen flow. However, the use of hydrogels in these dressings can minimize these shortcomings because of the strong swelling ratio, wet environment, and cooling sensation of the hydrogels besides these qualities they are capable of absorbing the wound exudates. Targeting this, Rakhshaei and Namazi [37] have designed flexible nanocomposite hydrogel films using zinc oxide impregnated mesoporous silica with carboxymethyl cellulose (CMC) hydrogel. Silica and CMC were crosslinked by citric acid to avoid the cytotoxicity of conventional crosslinkers. The drug delivery efficiency of these hydrogels was checked using tetracycline as a broad-spectrum antibiotic and it has been concluded that the nanocomposite hydrogel has the potential to be used as the promising wound dressing material with sustained drug delivery properties.

Another biocompatible hydrogel having a double-membrane structure has been prepared from cationic cellulose nanocrystals and anionic alginate [38]. The hydrogel behaved as an efficient biomedical drug carrier for oral administration as well as for dressings of wounds. The double-membrane structure of the hydrogel had chemically-modified cellulose nanocrystals in the inner membrane which was responsible for the sustained release of the drug as it provided the nano-obstruction effect" and "nano-locking effect". Two drugs were loaded into different membranes of the hydrogel to ensure the co-delivery of the complexing drugs. The varied drug release behaviours from two membranes (rapid release of the drug present in the outer membrane and sustained and prolonged release of the drug present in the inner layer) revealed that one drug was initially released quickly followed by the slow release of another drug. The synergistic release effect of the drug is interesting.

Nanocomposite hydrogels from the quaternized cellulose and cationic cellulose nanocrystals have been prepared by You et al. [39]. These nanocomposite hydrogels

exhibited high mechanical strength, high extension in degradation, and sustained drug release. Such properties are the result of the strong interaction between cellulose nanocrystals and quaternized cellulose chains which were crosslinked by β-glycerophosphate. Nanocomposite hydrogels were tested for in vitro degradation, cytotoxicity, sustained release of doxorubicin, and in vivo biocompatibility to ascertain their potential for biomedical application. In vivo study was done by injecting drug-encapsulated hydrogels beside the tumours of liver cancer xenografts bearing mice. The results have revealed that the hydrogel can be used as localized and sustained drug delivery depot systems for anti-cancer therapy.

Carboxymethyl cellulose-rosin gum hybrid nanoparticles have been synthesized via nanoprecipitation method [40]. The nanoparticles were found thermally stable and crystalline with an average size of ~267 nm. The authors utilized the nanoparticles for the colon targeted in vitro release of mesalamine (5-aminosalicylic acid), which is an anti-inflammatory drug for treating bowel disease or Crohn's disease. This drug is used for treating mild inflammation in the lower gastrointestinal tract but due to its solubility and dependency on the pH of the aqueous system, it can easily permeate into the upper gastrointestinal tract and very low amount of drug can reach the colon. This limitation was completely dealt with by loading it on nanohybrids of CMC and rosin gum. The drug release study revealed that a negligible amount of drug was released in a simulated gastric fluid of upper gastrointestinal tract within first 2 h in comparison to its sustained release in the intestinal fluid of colon for up to 12 h. It is reported that 72% of the loaded drug was released in a controlled manner in contrast to the native CMC or rosin gum. The nanohybrid proved to be efficient for enhancing the bioavailability of drug in colon.

2.1.2 Starch

Starch is one of the most abundant polysaccharides which is known for its edible and cost-effective properties. It is being extensively used for the synthesis of nanoparticles which have been utilized in various industries and biomedical fields [41].

Nanocarriers for poorly soluble drugs (naproxen) have been developed from Acha (*Digitaria exilis*) starches [42] by hydrolyzing them with H_2SO_4 and treating with monochloroacetic acid and sodium hydroxide. The carboxymethylated starch nanocrystals were thus obtained. It was found that the drug loading content of the native starch and the modified starch nanocrystals was more than 50% and the loading efficiency was above 75%, while the nanocrystals showed sustained release of naproxen.

A novel amphiphilic polymer, hydroxyethyl starch-deoxycholic acid loaded with flavonoid "morin" has been synthesized for in vivo treatment of hyperuricemia in a rat model [43]. Systemic administration of the polymer showed a noticeable longer half-life and systemic exposure was also high in comparison to the free drug morin.

When the nanoparticles were injected into a rat suffering from hyperuricemia, the nanoparticles decreased the serum uric acid level by increasing the uricosuric action thereby reducing the hyperuricemia-associated inflammation in kidney of rats. The in vivo circulation time of morin was also prolonged which increased the drug's therapeutic efficacy.

Nanoparticles of uniform size and shape were prepared from starch/gum nanocomposites [44] for the controlled delivery of salvianolic acid B. Different food gums were individually added to short-chain glucans along with salvianolic acid B which resulted in the formation of Sal B embedded starch nanoparticles. The size of starch nanoparticles was reduced by 50% (to 45 nm) when chitosan and rosin gums were added. The authors also reported the in vitro release of Sal B from the nanocomposites. The release occurred in a sustained and prolonged manner over a period of 12 h.

Crosslinked starch nanoparticles have been used for transdermal delivery of diclofenac sodium [45]. Cost-effective starch nanoparticles were synthesized via nanoprecipitation method using tween 80 where diclofenac sodium was crosslinked with starch and sodium tripolyphosphate. The drug entrapment efficiency was found to be 95% and the drug release was sustained up to 6 h which indicated that the nanoparticles were efficient in carrying the drug. The nanoparticles resulted in controlled release and successful permeation for the transdermal delivery of non-steroidal anti-inflammatory drugs.

Biodegradable crosslinked hydrogel has been synthesized by free-radical polymerization technique using hydrophobic polylactic acid and hydrophilic dextrin in the presence of crosslinker *N,N*-methylene bisacrylamide, and potassium persulfate as initiator [46]. The hydrogel synthesis was optimized by varying the concentration of the crosslinker and the sample with higher crosslinking and lower equilibrium swelling was considered as the optimum sample. Ciprofloxacin and ornidazole were selected as the model drugs to study the in vitro release from the hydrogel matrix in various buffer solutions at 37 °C. The same research group [47] prepared novel stimuli-sensitive covalently crosslinked hydrogel via Michael type addition reaction from dextrin, N-isopropylacrylamide, and *N,N′*-methylene bis(acrylamide) and used it for controlled drug release application. Equilibrium swelling studies in various pH media have confirmed the stimulus responsiveness of the hydrogel and the gel strength and the gelation time were evaluated by the rheological study. Noncytotoxicity and biodegradability tests were performed using human mesenchymal stem cells and hen egg lysozyme respectively. Ornidazole and ciprofloxacin model drugs were evaluated for the in vitro and in vivo drug release studies from the hydrogels. The hydrogel was found to be an excellent alternative for a dual-drug carrier. Stability study indicated that the drugs (ornidazole ∼97% and ciprofloxacin ∼98%) in tablet formulations were stable up to 3 months.

2.1.3 Guar Gum

Guar gum is a non-ionic polysaccharide that is derived from the seeds of *Cyamopsis tetragonolobus* plants of family Leguminosae. Structurally, its backbone consists of linear chains of $\beta(1 \rightarrow 4)$–D-mannopyranosyl units to which D-galactopyranosyl units are linked by $\alpha(1 \rightarrow 6)$ linkages. Guar gum is well known as a disintegrant in its solid dosage forms and for its binding properties.

Nanoformulations of carboxymethyl guar gum have been synthesized via ionic gelation method where trisodium trimetaphosphate was used as the cross linker [48]. The average size of the synthesized nanoparticles was ~208 nm. The nanoparticles were loaded with rhodamine B (80% drug loading capacity) which was used as the model drug. pH-dependent drug release behaviour was studied by performing experiments in simulated gastric and intestinal fluids. The nanoformulation was absolutely non-toxic at the concentration <0.3 mg/mL and thus is a biocompatible nanodrug carrier.

Guar gum coated chitosan nanoparticles have been synthesized in which the galactomannan subunit of guar gum was loaded with antitubercular drugs having therapeutic potential against tuberculosis [49]. The nanoparticles were synthesized using ionotropic gelation technique combined with spray drying. The particle size of the optimized material ranged from 230–310 nm and the material had the highest cell uptake potential. Biphasic pattern of in vitro drug release behaviour having initial burst and then sustained release of drug was studied. Histopathology study showed no lung tissue abnormality on the drug-loaded nanoparticle treated group. The synthesized material may be used as a promising drug carrier for selective drug delivery with minimal side effects.

Hydrogel having inter-connected micelle core as hydrophilic inner and guar gum/chitosan/polycaprolactone as hydrophobic outer core was formulated [50]. It was employed for the delivery of water-insoluble drug "rifampicin". UV–vis spectrometer was used to study the in vitro drug release pattern of the hydrogel-based miceller system. It showed mucoadhesive properties and was efficacious for intracellular alveolar macrophage treatment. It showed no toxic effect when it was not loaded with drug, but cytotoxicity study indicated its higher activity against THP-1 cells.

Guar gum-g-poly(acrylamide) nanocomposite was synthesized by free-radical polymerization using potassium persulphate as an initiator [51]. They fabricated transdermal membranes via solution casting technique in which different wt % of nanosilica and diltiazem hydrochloride were incorporated into the synthesized copolymer. All the transdermal membranes were evaluated for in vitro drug release study and it was found that the nanocomposite containing 1 wt % nanosilica exhibited the best drug release results. It showed 8.58 and 24.76% drug release after 5 and 20 h, respectively. Furthermore, the nanocomposite formulation displayed non-irritant behaviour and good cytocompatibility which are the basic requirement for an efficient transdermal drug delivery system.

2.1.4 Dextran

Dextran is a water-soluble polysaccharide which consists of glucose moieties that are linked mainly through α-1,6 glucosidic linkage while it also contains some α-1,3-glucosidic linkage to form long branched chains. It is medicinally used for reducing blood viscosity and as a volume expander in anaemia.

Nanohydrogel has been synthesized through electrostatic polycation–polyanion interactions between the cationic moiety of pulllulan and anionic dextran sulphate [52]. It was formed very easily and was soluble in water due to polyionic nature. The size and surface charge of the synthesized nanoparticles was controlled by varying polycation/polyanion ratio. They are colloidally stable, spherical in shape and had hydrodynamic diameters of 10–150 nm. This nanohydrogel system was used to deliver "piroxicam" drug which got effectively entrapped inside the hydrophobic core and was released in a controlled manner. The synthesized biocompatible nanohydrogel system was effectively taken up by the cells.

Photosensitive core/shell nanoparticles are reported by [53], which were proved as very efficient drug delivery nanocarrier. Dextran-*g*-poly(*o*-nitrobenzyl acrylate) copolymers were synthesized from hydrophilic backbone of dextran to which photosensitive grafts of poly(*o*-nitrobenzyl acrylate) were attached by using two different processes. In the first process, nanoprecipitation method was employed, while second process involved emulsion/organic solvent evaporation method. Nile red and doxorubicin release studies from the nanoparticles were performed in the presence of UV irradiations. The study concluded that the nanoparticles are suitable for being used as drug nanocarrier.

Drug "paclitaxel" is known as the most important advancement in chemotherapy but with disadvantages of low solubility and weak permeability. Bakrania et al. [54] have developed a nanoformulation using dextran in conjugation with paclitaxel to overcome its adverse effects. Multiple therapeutic pathways were targeted to fabricate a specific organ targeted nanosystem. Cytotoxic study revealed that the formulation was safe for various cell lines. The maximum cellular uptake (at 60 min post-treatment) was demonstrated by green fluorescence lighting up of the nuclear membrane. The mechanistic approach of the nanoformulation to target nuclear membrane showed a synergistic release of β-interferon at the target organ.

pH-sensitive dextran/mesoporous silica nanoparticles are reported [55]. Dextran polysaccharide behaved as a "gatekeeper" while synthesizing a drug delivery system for controlled intracellular release of an anti-cancer drug (doxorubicin hydrochloride). Dextran was oxidized by $NaIO_4$ to obtain three kinds of dextran dialdehydes which were then coupled with mesoporous silica nanoparticles via pH-sensitive hydrazone bond. It was found that at pH 7.4, the dextran dialdehydes blocked the pores of the nanoparticles to prevent the release of the drug. However, in a weakly acidic environment (pH $\sim$5.5), the hydrazone ruptured and the drug was released from the carriers. The drug loading capacity, entrapment efficiency, and release rate were studied and the optimum performance carrier was selected for further in vitro cytotoxic and cellular uptake studies. The nanocarrier showed excellent pH sensitivity

by entering HeLa cells to release the drug intracellularly due to the weakly acidic pH and killed the cells. Thus, the reported nanocarrier showed potential application for cancer therapy.

2.1.5 Miscellaneous Neutral Polysaccharides

Carboxymethyl and amine derivative of *Leucaena leucocephala* galactomannan has been used for the preparation of nanoparticles by Mittal and Kaur [56]. The synthesized bioadhesive polymeric nanoparticles were employed for the ocular delivery of dorzolamide hydrochloride (DRZ) which is used in glaucoma treatment. 2-factor, 3-level central composite experimental design was used for the preparation and optimization of the sample. Sample showed sustained release and higher corneal permeation during transcorneal permeation (in vitro release studies and ex vivo studies)when compared to conventional formulation of dorzolamide eye drops.

Katira gum nanoparticles loaded with bromelain have been synthesized [57]. A three-level optimization process was used for the synthesis of the nanoparticles. In vivo anti-inflammatory activity was studied using carrageenan-induced rat paw oedema method. This study showed enhanced anti-inflammatory potential. The enhanced activity may be attributed to increased absorption due to a decrease in particle size. The drug encapsulation within nanoparticles gave protection to bromelain from acid proteases present in the medium.

2.2 Cationic Polysaccharide

2.2.1 Chitin/Chitosan

Chitosan, a cationic polysaccharide, is one of the most biologically rich biopolymers which is obtained from the natural chitin (found in the exoskeletons of arthropods and in fungal cell walls). It possesses native amine groups that are positively charged and its backbone consists of randomly distributed β-(1 → 4)-linked *N*-acetyl-D glucosamine and D-glucosamine units [14].

Chitosan has been modified for the delivery of doxorubicin [58]. The modification was done with a chain transfer agent followed by polymerization of 2-hydroxyethyl methacrylate monomer which was subsequently reacted with maleic anhydride. The product thus obtained was grafted with a crosslinking agent, *N,N′* bis(acryloyl)cystamine to obtain redox-sensitive nanogels. The nanogels were suitable for cancer treatment.

Complex spherical nanoparticles with average diameters ranging from 255 to 390 nm have been synthesized from cationic chitosan and anionic poly(2-acrylamido-2-methylpropane sulfonic acid) [59]. Doxorubicin drug was loaded on the nanoparticles with high loading and encapsulation rates. The in vitro release studies proved that the release of drugs can be managed by adjusting pH of the release media.

A new drug delivery system has been developed from chitosan and nitrosalicylaldehyde via in situ hydrogelation in the presence of a model drug [60]. In vitro release of the drug was checked under artificial conditions and in vivo release was done on rats. The biodegradability of the system was established by enzymatic degradation. The prolonged release of drugs was observed with an efficient therapeutic effect over 5 days. The system provided a practical approach for sustained drug delivery for local chemotherapy.

Drug-loaded composite hydrogels have been prepared by the blending of chitosan lactate with polyvinyl alcohol followed by crosslinking with glutaraldehyde [61]. The hydrogel was evaluated for the sustained release of hydrophilic drugs such as ciprofloxacin. Investigations proved that the sustained release of the drug (from the hydrogels) inhibited the growth of *Escherichia coli* bacteria. The cell cytotoxicity was also studied by in vitro cell activity of L929 cells which confirmed that the fabricated hydrogels are compatible with cells and facilitate cell adhesion. The hydrogels proved suitable for anti-effective coatings, wound dressing, and sustained delivery of drugs.

Hydrogel consisting of *N*-trimethyl chitosan and sodium carboxymethyl xanthan gum is reported for the controlled release of ciprofloxacin [62]. Ciprofloxin drug was entrapped within the gel without any significant interaction and the encapsulation efficiency increased with an increase in the drug concentration. In vitro release study in phosphate buffer saline had a constant rise in cumulative drug release while the highest release amount reached about $96.1 \pm 1.8\%$ in 150 min, while the gel with high drug loading efficiency ($3.52 \pm 0.07\%$) demonstrated faster and higher release rate than that of gel containing a smaller amount of drug ($0.44 \pm 0.01\%$). The zone of inhibition against bacteria *E. coli* was found to be higher (67.0 ± 1.0) in comparison to the reference antibiotic, gentamicin (28 ± 0.5).

Biocompatible nanocomposite films have been crafted by blending chitosan and poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol), metformin (MET) drug and MCM-41 or MCM-41-APS [63]. These nanocomposites were formulated to study the controlled release of metformin. The results showed that on increasing the amount of MCM-41 or MCM-41-APS, the elongation at break was reduced but the tensile stress of the films was improved. The release of the drug was significantly increased within 22–24 h after which the slow release of the drug was sustained up to 15 days. Overall, the nanocomposite showed significant hydrophilicity, hydrolytic stability, biocompatibility, mechanical, and drug release properties.

Treatment of oral ailments is a challenge as most of the pharmaceutical drugs have low residential time in oral cavity. Goycoolea et al. [64] have synthesized chitosan,

alginate, or pectin based nanoparticles through self-assembly by ionotropic gelation using oppositely charged crosslinkers (tripolyphosphate or zinc). The nanoparticles could significantly enhance the residential time of the drugs. The nanoparticles were subjected to cytotoxicity tests against buccal cells (TR146) and the stability in medium stimulating pH and concentration of saliva. Most cytocompatible formulation for oral usage was obtained with chitosan nanoparticles.

Colitis and chronic foul-smelling diarrhoea are caused due to a flagellated protozoan parasite, called *Tritrichomonas foetus* which colonizes the feline colon. It can be treated by ronidazole which rapidly gets absorbed in the small intestine but has been reported to cause neurotoxicity in some cats. The delivery of this drug (to colon) has been controlled by the amphoteric derivative of chitosan [65]. The in vitro release profile of the drug has clearly demonstrated that the coated ronidazole tablet was released less than 2% in the physiological environment of the stomach and small intestine.

Smart self-regulated insulin delivery systems are required to achieve glycemic control and for decreasing long term micro and macrovascular complications. An injectable nano-complex formulation has been developed for closed-loop insulin delivery during subcutaneous administration in response to increased blood glucose levels [66]. The nano-complex was synthesized by mixing oppositely charged chitosan and polylactic-co-glycolic acid (PLGA) nanoparticles. Negatively charged PLGA particles were found to decrease micro-environmental pH by producing gluconic acid in the presence of glucose molecules. Positively charged chitosan nanoparticles were prepared with loading of insulin using ionic gelation method. In vivo evaluation of nano-complex formulations in streptozocin induced diabetic rats showed that after subcutaneous administration, significant glycemic regulation was observed up to 98 h.

Hybrid aerogels of chitosan, carboxymethyl cellulose, and graphene oxide were prepared using calcium ions as crosslinker [67]. Chitosan and carboxymethyl cellulose are pH-sensitive and thus have been utilized as the carriers for the pH-controlled delivery of 5-fluorouracil which is an effective chemotherapeutic agent for cancer treatment. The drug release studies showed that hybrid aerogels are potent materials for drug delivery.

Aceclofenac-loaded interpenetrating polymeric network nanocomposites have been prepared by crosslinking of chitosan and locust bean gum with gluteraldehyde [68]. The formation of nanocomposite was confirmed by spectral studies and the chemical compatibility between the drug and the polymer. As the amount of locust bean gum was increased, the drug entrapment efficiency was decreased from 72 to 40%, and larger particles of 372–485 nm size were produced. This result was in contrast to what obtained on increasing the chitosan concentration. However, maximum drug entrapment efficiency of 78.92%, with the smallest size of 318 nm, was obtained when the mass ratio of locust bean gum to chitosan was 1:5. This nanocomposite showed the slowest drug release profile in phosphate buffer solution (pH 6.8) up to 8 h. This formulation had high efficiency as it suppressed the release of drugs at low pH indicating its usefulness in minimizing the gastrointestinal side effects. This carrier may provide medication in a slow and sustained manner.

Chitosan has also been modified into a semi-interpenetrating network hydrogel which was responsive to pH, temperature, and salinity [69]. The network was fabricated by free-radical polymerization of acrylic acid, oligo (ethylene glycol) methacrylate and 2-(2-methoxyethoxy) ethyl methacrylate. Bovine serum albumin and 5-Fluorouracil were evaluated for the sustained release of drug from the hydrogel and the results indicated that the amount of drug released was comparatively low in acidic pH and high in neutral pH. The release rates for bovine serum albumin and 5-Fluorouracil were slower at 37 °C than that at 25 °C. Cytotoxic studies showed that the hydrogels had negligible toxicity to normal cells but the drug-loaded hydrogels remained highly toxic for LO2 and HepG2 cancer cells.

A series of thermo and pH-sensitive *N*-succinylhydroxybutyl chitosan hydrogels have been synthesized and were loaded with bovine serum albumin drug [70]. The drug was released from the hydrogels in phosphate buffer saline (pH 7.4). The hydrogels released 93.7% of the drug after incubation for 24 h, while at pH 3.0, 24.6% drug was released. The release of the drug from hydroxybutyl chitosan was also checked and the results showed that about 70.0% of the drug was released at pH 3.0 and pH 7.4. The hydrogels had significant properties to be used as a soluble drug carrier which has pH-sensitive drug release profile for oral drug delivery.

A dual-drug delivery system has been reported for cancer treatment [71] in which poly (ethylene glycol) methyl ether and chitosan were self-assembled to form nanogels. These were evaluated for the release of a combination of drugs, Paclitaxel, and 5-Fluorouracil. 50% of Paclitaxel was entrapped in the nanogels while the entrapment efficiency of 5-Fluorouracil was found to be 10%. The release profiles of either of the drugs were found to be associated with the hydrophilicity characteristics of polyethylene glycol. The nanogels exhibited a controlled release for both the drugs.

pH and thermal responsive hydrogels have been prepared using chitosan and 4-chloroacetylantipyrine in DMF/H_2O by [72]. The reaction led to the formation of poly(acetylantipyrine-chitosan) which was heated with glutaraldehyde for crosslinking to form the hydrogels. Equilibrium swelling studies of the hydrogels were done at different temperatures in solutions of pH 2.1 and 7.4. Methotrexate drug was loaded on the hydrogels and the release studies were performed in solutions of pH 2.1 and 7.4. The results indicated that the hydrogels may find use in drug delivery.

Plants derived drugs show excellent chemotherapeutic effectiveness with low toxicity, but they fail to scale through phyto-drug discovery channel as they lack suitable drug delivery systems. The bioavailability, stability, and effectiveness of these drugs can be enhanced by loading them on compatible carriers. Olayinka et al. [73] have reported chitosan-based drug delivery carriers which contain Curcumin as phyto-drug model. The synthesis has been performed in two ways, either via ionotropic gelation with tripolyphosphate or via polyelectrolyte complexation with alginate. It was found that the encapsulation efficiency, rate of Curcumin release, and mean release time in the gastric fluid was dependent on the pH of the chitosan solution, Curcumin/alginate/tripolyphosphate concentration, and crosslinking time. Curcumin erosion was reduced by 30% through the incorporation of alginate while it increased

the release time by 180 min. The study confirmed that the radical scavenging activity ratio of Curcumin was significantly increased by encapsulation in chitosan.

Colon targeted delivery of Curcumin was also studied by Woraphatphadung et al. [74] who modified chitosan into pH-sensitive *N*-naphthyl-*N*,O-succinyl chitosan and *N*-octyl-*N*,O-succinyl chitosan polymeric micelle carriers. Curcumin was entrapped by physical methods like dialysis, co-solvent evaporation, and O/W emulsion where the dialysis method showed the highest Curcumin loading capacity. The loading capacity was also increased when the initial amount of Curcumin was increased from 5 to 40%. The particle sizes of all the Curcumin loaded micelles were found to be in the range of 120–338 nm. The release characteristics of Curcumin were pH-dependent. Only 20% of Curcumin was released from all the prepared micelles in simulated gastric fluid. However, the release amount was increased significantly (upto 50–55%) in simulated intestinal fluid and up to 60–70% in a simulated colonic fluid. Curcumin loaded chitosan modified micelles showed highest anti-cancer activity against HT-29 colorectal cancer cells. The micelles were found to be stable upto 90 days, thus showed excellent potential for the delivery of Curcumin to the colon.

Nanoparticles for Curcumin delivery have been fabricated using chitosan and gum arabic by the polyelectrolyte complexation method. It was revealed that 1:1 mixing ratio of the two biopolymers (at pH 4.0) can form monodisperse, hydrophilic, and highly positively charged colloidal nanoparticles [75]. During storage, the encapsulation efficiency and Curcumin loading content was 90% and 3.8% respectively, with an 85% retention rate. The nanoparticles significantly improved the stability while the release of Curcumin in a simulated gastrointestinal environment was delayed. These results indicated that the nanoparticles are the model carrier to deliver Curcumin.

Chitosan has been modified for Curcumin delivery [76]. Poly-(*N*-isopropylacrylamide) was grafted onto chitosan backbone using a coupling reaction. Cytotoxic study was done using CellTiter-Blue® cell viability assay in NIH-3T3 and HeLa cells. Curcumin was encapsulated in the spherical nanogel particles and maximum loading was achieved using an incubation method. The study revealed that Curcumin loaded nanogels have the potential to be used for delivery systems.

Magnetic nanoparticles have been prepared by graft copolymerization of chitosan with acrylic acid followed by grafting of ethylenediamine derivative of β-cyclodextrin [14]. The nanoparticles were evaluated for the sustained and controlled release of anti-cancer drug, Curcumin. The drug delivery system was tested to check the effect of pH on the encapsulation of Curcumin and it was found that pH 5 was optimum for the drug loading as maximum hydrogen bonding and Van der Waal's interactions were feasible at this pH. The swelling of the nanoparticles was found to be highest at pH 7.4 which led to the optimum drug release. The cytotoxicity study was also carried out on 3T3-L1 and MCF-7 cells which indicated the potential and biocompatibility of the drug delivery system.

Electrospun hybrid nanofibers have been prepared by mixing chitosan with phospholipids [77]. The fibers have been used as platforms for the delivery of transdermal drugs. The stability of the nanofibers was extended for at least 7 days in phosphate buffer saline solution. Cytotoxicity studies revealed that the nanofibers have suitable

biocompatibility. Fluorescence microscopy study showed that L929 cells seeded on top of the hybrid have a similar metabolic activity to the cells seeded on tissue culture plate (control). Curcumin, diclofenac, and Vitamin B_{12} were used as the model drugs to study the release profile from the hybrid nanofibers. These fibres have the potential to be used for transdermal drug delivery system.

Cystic fibrosis is one of the most life-threatening diseases which are affected by the administration of antibiotics. This disease is led by the pathogenesis of chronic infection with *Pseudomonas aeruginosa* and Tobramycin is the treatment for this infection. Another challenge in the treatment of this infection is the thickened mucus which is accumulated in the pulmonary environment. To deal with this challenge, Hill et al. [78] have prepared alginate/chitosan particles via precipitation and Tobramycin was loaded on them. The release study revealed that both the uptake and in vitro release of sufficient Tobramycin took place to inhibit *P. aeruginosa.* The alginate/chitosan particles were functionalized with secretory leukocyte protease inhibitor which helped to inhibit the inflammatory response associated with lung infections and thus enhanced their interaction with cystic fibrosis mucus in vitro.

A series of β-cyclodextrin-grafted carboxymethyl chitosan hydrogels have been crafted by Kono and Teshirogi [79]. The synthesis involved carboxymethyl chitosan and carboxymethyl β-chitosan in the presence of *N*-hydroxysuccinimide and water-soluble carbodiimide as a crosslinker. Due to the presence of (cyclodextrin) in the structure, the synthesized hydrogels showed enhanced absorption characteristics towards acetylsalicylic acid. The amount of acetylsalicylic acid absorbed by the hydrogels was increased with an increase in the amount of cyclodextrin in the hydrogels. In addition, the hydrogels provided a slower release of the entrapped acetylsalicylic acid in comparison to the release profile of a solely CMC-containing hydrogel.

2.3 Anionic Polysaccharide

2.3.1 Sodium Alginate Based Polysaccharide

Alginate is a linear and anionic polysaccharide obtained from marine algae in the form of alginic acid or bacterial source through treatment with aqueous alkali solutions. The major composition of alginate contains blocks of α-1,4-L-guluronic acid and β-1,4-D-mannuronic acid in a varying ratio [80].

Chitosan/alginate nanoparticles have been synthesized by encapsulation of Curcumin diethyl diglutarate using emulsification and ionotropic gelation [81]. The drug-encapsulated nanoparticles showed enhanced physicochemical stability against UV irradiation, thermal treatment, and enzymatic degradation as compared to the free drug along with greater stability, bioaccessibility, and digestibility. The in vitro release profile showed sustained release and the release pattern best fitted with the Korsmeyer–Peppas kinetic model, indicating the Fickian diffusion mechanism.

Quercetin has been loaded on the alginate coated chitosan nanoparticles through ionic gelation method [19]. TEM image demonstrated crystalline morphology and particle size of ~60 nm. An evident change in the morphology of the nanoparticles was revealed on Quercetin encapsulation. The release study demonstrated a controlled release of Quercetin from the nanoparticles for 24 h. This release profile was attributed to the fact that the drug was loaded at higher concentrations within the core and alginate coating at the outer shell region acted as a physical barrier in the drug release.

Novel Sunitinib entrapped alginate nanocarrier has been fabricated with the help of ionic gelation method by [82]. In vitro drug release study was performed by dissolution method which showed sustained release of Sunitinib. TEM image revealed that the size of nanocarrier was about 20–40 nm and the particles had spherical shape. Drug encapsulation efficacy was reported to be 98.48%.

2.3.2 Cashew Gum

Cashew gum is an anionic polysaccharide obtained from the trees of *Anacardium occidentale.* The polysaccharide mainly consists of D-Galactose as the main chain to which side chains of D-glucose are attached by 1 → 3 linkages. Other monosaccharides like D-arabinose, D-rhamnose, and D-glucuronic acid are present as the terminal units [83].

Self-assembled nanoparticles of acetylated cashew gum have been synthesized through the dialysis of an organic solution (DMSO) against water (a non-solvent) [9]. The synthesis was confirmed by different spectral techniques which indicated that the average size of the nanoparticles was 179 nm. Indomethacin was used as a hydrophobic model drug and was incorporated into the hydrophobized nanoparticles to study the controlled drug release from the nanoparticles.

Dias et al. [84] have also reported the synthesis of nanoparticles from acetylated cashew gum using nanoprecipitation and dialysis methods. The nanoparticles synthesized by the dialysis method had larger average size as compared to those synthesized by nanoprecipitation method, but the latter exhibited better stability and yield. The nanoparticles were loaded with diclofenac diethylamine drug and the efficiency of the drug release was evaluated which was over 60% for the nanoparticles synthesized through either of the routes. Cytotoxic studies revealed that the nanoparticles had no significant effect on the cell viability, hence they were considered to be biocompatible. The nanoparticles also showed more controlled release (as compared to the free drug). Transdermal permeation of drugs was also reported to reach 90% penetration.

2.3.3 Xanthan Gum

Xanthan gum is an extracellular heteropolysaccharide containing anionic unit. It is typically derived from corn (can also be from soy or wheat) that has been pooped out by a bacteria that produces rot on various vegetables. The main composition of

xanthan gum consists of two mannose and one glucoronic acid side chain linked to 1,4 D-glucose backbone [85, 86].

Methacrylic acid has been crosslinked with xanthan gum via self-assembly method to craft nanoparticles by Malviya et al. [87]. The authors have incorporated poly(methacrylic acid) (PMA) into xanthan gum backbone at –OH sites through free-radical polymerization method. A schematic mechanism has also been proposed to demonstrate the mechanism for the synthesis. Potassium persulphate/ascorbic acid redox reaction generated $SO_4^{-\bullet}$ which formed primary free radicals ($OH^{\bullet}$) after interacting with water molecules. These primary radicals ($OH^{\bullet}$) created active free-radical sites on to the polysaccharides backbone which invited PMA chains to adhere through free-radical copolymerization. The PMA grafts complexed with xanthan gum due to hydrogen bond interaction and as a result, the self-assembly occurred to form 'micelle' like nanoaggregates. The thermally stable nanoparticles showed porous and rough morphology with an average size ~150 nm. The nanoparticles could effectively load mesalamine drugs where it exhibited 65.43% encapsulation efficiency in 24 h time. The COO– and OH– groups at the interaction sites of the nanoparticles associated with NH– and COOH– groups (through hydrogen bonding/physical interactions) at the drug molecule. The structure of the network controlled the swelling of the nanoparticles which, in turn, helped in the sustained release of the enclosed drug at the target pH of the gastrointestinal tract. The release of mesalamine was also dependent on the percent crosslinking and pH of the buffer solutions. Drug release profile followed zero-order kinetics and non-Fickian diffusion mechanisms [87].

2.3.4 Aloevera Polysaccharide

Aloevera is an important natural cactus-like plant that grows in hot and dry climate. Its leaves possesses a water-soluble polysaccharide that has various pharmacological properties. Major components of aloevera polysaccharide are the repeating units of tetrasaccharide along with glucose, mannose, and galactose [88–90]. Its unique acetomannan structure best suits for designing nanostructures for drug delivery applications. Aloevera polysaccharide/acrylonitrile nanoflowers have been synthesized via free-radical polymerization using persulfate/ascorbic acid redox initiator and methylenebisacrylamide as the crosslinker [91]. HRTEM studies revealed the size of the thermally stable nanoflower was ~50 nm. In vitro release of a model drug (5-Aminosalicylic acid) from the nanoflowers was monitored in various buffer solutions (pH 1.2, 6.8, and 7.4) at 37 °C. The controlled release of the drug was observed up to 18 h in comparison to the crude aloevera polysaccharide for which the release exhausted within 7–8 h in all the buffer solutions. Moreover, this delivery system proved to be advantageous as it entrapped the drug at acidic pH, i.e., pH in the upper part of the gastrointestinal tract while at alkaline or neutral pH, the drug was slowly released from the matrix in a sustained manner. Only 30% drug was released in the first 3 h at pH 1.2, thereafter at pH 7.4, the release became faster. The delayed release of the 5-Aminosalicylic acid is attractive as it can reach in larger amount to colon rather being released in the upper part of the gastrointestinal tract.

3 Methods of Synthesis of PNM

The available literature reveals that several methods have been utilized to shape polysaccharide nanomaterials. The method for the synthesis is opted depending on the requirements such as particle size, stability, thermal and chemical stability of the loaded drugs, and toxic effects, etc. Different methods used in the preparation of polysaccharide nanoparticles are briefly discussed in the following section.

3.1 Self-Assembly Method

Self-Assembly is one of the most promising routes to obtain controlled nanostructured micelles from amphiphilic polysaccharide systems. These structures have a hydrophobic core and a hydrophilic shell. This method requires an aqueous environment without involving the use of harsh solvents or reaction conditions [91]. Hydrophilic polysaccharides are hydrophobically modified by introducing groups like alkyl, acryl, vinyl, etc. The amphiphiles thus obtained, spontaneously self-aggregate on dissolving in water due to intra- and/or intermolecular association between the molecules. Use of different hydrophobic/hydrophilic constituents results in the formation of nanoparticles that exhibit unique characteristics such as dynamic stability, a nanoscale radius with core–shell structure, unusual rheological features, etc. This method of synthesis provides monodispersed nanoparticles under mild reaction conditions. These nanostructures are suitable not only as nanocarriers for different hydrophobic/hydrophilic drugs but also they are used for trapping hydrophobic substances such as fluorescent probes and various proteins.

3.2 Ionic Gelation Method

Most of the polysaccharides are present in ionic forms in solution. For example, chitosan is present in cationic form due to the presence of amidogens in the molecular chain which is protonized so that it can dissolve in dilute acid solutions. Likewise, alginate is present in anionic form due to the carboxylic acid residues. Such polyelectrolytes can be aggregated and be converted into nanoparticles by crosslinking with micromolecular reagents having opposite charge via electrostatic interaction. Hence, cationic polysaccharides can be crosslinked with polyanionic substances like tripolyphosphate which is a multivalent anionic molecule. While anionic polysaccharides can be crosslinked with cations (guluronic acid units with di- or polyvalent cations). Ionic gelation method is the most frequently used method for the preparation of polysaccharide-based nanoparticles as it involves simple, non-toxic, organic solvent-free, convenient and controllable synthesis [81].

3.3 Complex Coacervation Method

This method involves reaction of two polysaccharides carrying opposite charges. Complex coacervation of oppositely charged polysaccharides has been used to prepare and strengthen polysaccharide-based nanoparticulate systems which find extensive applications in medicine technology. This method influences the pore size and network complexity of the nanoparticles thereby, improves their performance as drug carrier system. Mild preparation conditions and simple procedures are required while the structure and properties of the biochemical drugs including gene and protein are not altered [73].

3.4 Emulsification Method

This method involves the distraction of water-soluble polysaccharides in the oil phase to make oil-in-water or water-in-oil emulsion by stirring or using ultrasound. Internal or external gelation results in the formation of polysaccharide-based nanoparticles. Relatively controllable and spherical nanoparticles are obtained using this method, however, it has more complex reaction conditions and a much larger amount of organic solvents are required which limits the application of this method in nanoparticle synthesis [81].

3.5 Desolvation Method

This method of preparation of nanoparticles involves desolvation of polysaccharide through charge changes or by adding desolvating agents inducing a coacervation effect. Alcohols or salts can be used as desolvating agents depending on the nature of the drug to be trapped inside the nanoparticles. The advantage of using the desolvation method is that the nanoparticles can be produced directly in the suspension in an aqueous medium (no oily phase to extract). However, the introduction of a desolvating agent and potentially toxic molecules such as gluteraldehyde requires a purification step before using them in drug delivery systems.

3.6 Nanoprecipitation or Solvent Displacement Method

Nanoprecopitation technique involves dissolvation of the core polysaccharide in a fully or partly water-miscible solvent like acetone, ethyl acetate, etc. Then this solution is dropped into an aqueous solution that may contain surfactant. Rapid desolvation of the polysaccharide in the presence of water yields polysaccharide

nanoparticles provided that aggregation is limited. To avoid aggregate formation during precipitation, organic solutions are largely diluted which is the main drawback of this method [40].

4 Conclusion and Outlooks

Polysaccharide derived nanoparticles/hydrogels have gained much attention in the field of drug delivery. They are efficient carriers of different pharmaceutical drugs due to their unique biological and physicochemical properties. The research is focussed on developing such drug delivery systems which can control the drug release with full therapeutic effect and with minimum side effect. The syntheses of the nanoparticles involved various synthetic methods such as self-assembly, covalent and ionic crosslinking, polyelectrolyte complexation, etc. and the selection of the synthesis routes depended on the nature and properties of the polysaccharide. The modified polysaccharides possess significant active properties and functionality to be utilized as nanocarriers for various kinds of drugs. In short, polysaccharide and polysaccharide derived nanomaterial/hydrogels find many applications for in vitro and in vivo organ targeted drug delivery of various pharmaceutical compositions.

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Polysaccharide-Based Nanocarriers for Oral Delivery of Insulin in Diabetes

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Abstract Diabetes mellitus is common nowadays and its number is increasing day by day in all over the world. It is an endocrine or metabolic disorder which is characterized by high sugar levels in the blood due to insufficient levels or absolute deficiency of insulin in the body resulting in hyperglycemia as well as affecting other metabolic processes. Despite all the advancement in therapeutics, diabetes still remains a major cause of morbidity and mortality in the world. Few antidiabetic drugs along with insulin are available in the market for the treatment of diabetes, but the majority of them have massive side effects and are not satisfactory. The antidiabetic drug is either degraded by the enzymatic activities or by intestinal epithelial tight junctions which ultimately results in low bioavailability of the drug. Delivering insulin in the diabetic patients is currently invasive, i.e., painful. Nanotechnology opened a door for non-invasive delivery of insulin in diabetic person and holds other advantages like targeted delivery and controlled release. Metallic nanoparticles were highly explored for drug delivery and have received much popularity because of their uniform size and sharp size distribution in nanometer dimension. But metallic nanoparticles are thermodynamically unstable, poor corrosion resistance, non-degrading, toxic, and biologically harmful/unsafe. Recently, biopolymeric (polysaccharides/proteins) nanoparticles have revolutionized the world of drug delivery due to its high biocompatible, degradable, and safe nature. Therefore, this chapter specifically describes current challenges in delivery of insulin, polysaccharide-based nanocarriers with insulin that can be used for targeted delivery of insulin with more bioavailability, non-toxicity, and effectivity along with its future prospects.

Keywords Diabetes mellitus · Biopolymer · Nanocarriers · Insulin delivery

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1 Introduction

Diabetes is a general health problem in the world. The global number of diabetes patients has increased from 30 million in 1985 to 194 million in 2003 and is expected to grow to 333 million by 2025 [1]. Diabetes mellitus is an endocrine disorder which results an increase in blood sugar level due to inadequate insulin hormone. It is broadly classified into two categories: diabetes mellitus type 1 and diabetes mellitus type 2. Type 1 diabetes is caused due to destruction of pancreatic β cells of islets of Langerhans. Type 1 diabetes is also known as juvenile diabetes and is insulin dependent. Type 2 diabetes is also known as non-insulin dependent which is induced due to loss of sensitivity of receptors for insulin or insulin resistance.

Diabetes mellitus is spreading at an alarming rate, prompting detrimental problem if left untreated or not proper care is taken. There are number of obstacles in the fruitful treatment of diabetes due to individual and monetary expenses acquired in its treatment. Oral administration of insulin may essentially improve the personal satisfaction of diabetic patients who routinely get insulin by the subcutaneous route. Actually, oral administration of insulin in diabetes treatment offers numerous points of interest: Higher patient compliance, quick hepatic insulinization, and preventing peripheral hyperinsulinemia and prevents other unfriendly impacts, for example, hypoglycemia and weight gain. The current mode of insulin therapy is by subcutaneous injections are but the major side effects are hypoglycemia, allergy, resistance, edema, and lypodystrophy.

1.1 Insulin

Insulin is composed of two peptide chains containing 51 amino acids. Chain A and chain B which are linked together with two disulfide bonds between cysteine residues have 21 amino acids and 30 amino acids, respectively. There are certain segments in the amino acid sequence which are highly conserved and varies with species, these includes the positions of the three disulfide bonds, both ends of the chain A and the C-terminal residues of the chain B. In solution, insulin molecules can form dimers due to hydrogen-bonding between the C-termini of B chains. Additionally, they also form hexamers when dissociate from dimer form in the presence of zinc ions. Three conserved regions in insulin have been of particular interest in the primary receptor-binding surface of insulin: (i) the N-terminal and C-terminal segments of the A chain (Gly ^{A1} -Ile ^{A2} -Val ^{A3} -Glu ^{A4} and Tyr ^{A19} -Cys ^{A20} -Asn ^{A21}), (ii) the central α-helix of the B chain (especially Val ^{B12}), and (iii) and the C-terminal segment of B chain (Phe ^{B24} -Phe ^{B25} -Tyr ^{B26}).

Insulin promotes the uptake of glucose by cells and increases the synthesis of glycogen, fatty acids, and proteins. Thus, the role of insulin is the conversion of excess glucose into two storage forms, namely glycogen and triacylglycerols, and helps in maintaining glucose homeostasis. The oral administration of insulin is viewed as

the most advantageous and agreeable methods, less intrusive and easy management, prompting a higher patient compliance. In any case, the intestinal epithelium is a significant obstruction to the retention of hydrophilic medications, as they cannot diffuse over epithelial cells through lipid-bilayer cell layers to the circulation system. In this manner, consideration has been given to improving the paracellular transport of hydrophilic medications. An assortment of intestinal saturation enhancers including chitosan (CS) has been utilized for the help of the ingestion of hydrophilic macromolecules. Hence, the framework is expected to shield protein drugs from the cruel condition in the stomach and small digestive system, whenever given orally. The insulin stacked NPs covered with mucoadhesive polysaccharides may draw out their living arrangement in the small digestive system, invade into the bodily fluid layer and along these lines intervene temporarily opening the tight intersections between epithelial cells while getting to be unsteady and broken separated because of their pH susceptibility or potentially degradability. The insulin discharged from the wrecked separated NPs could then penetrate through the paracellular pathway to the circulation system. Thus, the advancement of improved oral insulin organization is basic for the treatment of diabetes mellitus to beat the issue of every day subcutaneous infusions.

Polysaccharides are natural hydrophilic polymers, which show enzymatic degradation and excellent biocompatibility. This can be easily derived from plant, animal, and microbes. They show various characteristics like they can be positively charged; negatively charged or neutral, branched or linear; their molecular weight varies from few hundred to thousand Daltons. Polysaccharides can also maintain the stability of protein and increase duration of therapeutics as well as its feasibility through non-parenteral routes. These properties make them significant carrier in bio-distribution of drugs at in vivo [2].

2 Challenges in Delivery of Insulin

Several physiological factors affect the oral administration of insulin and the main challenges include physical, chemical, and enzymatic barrier. These barriers lead to enzymatic degradation, instability in the acidic pH environment, and little bioavailability of nanoparticles because of poor dissemination over the bodily fluid layer and deficient permeation through the GI tract epithelium. Degradation of insulin takes place by the breakdown of disulfide bonds in the presence of digestive enzymes and high pH in the GI.

2.1 Chemical Barrier

The major challenge is the pH variation in the gastrointestinal tract which makes the nanoparticles highly unstable. It takes less than a minute for a nanoparticles to reach

mouth where they experience a surprising low pH moving from 6.8 to 1.2 which is followed by transition from very high acidic to low basic environment in small intestine from pH 6.5 to 8.0 [3]. The mean transit time in stomach and residence time in small intestine is around 2.5 h and 3–4 h, respectively [4]. It is shown in the studies that the particle components like proteins or lipids, polysaccharides are protonized or deprotonized which leads to the dissociation of structure of nanoparticulate [5, 6].

Thus, to improve the bioavailability of oral drug, it is essential to protect it from chemical degradation caused due to fluctuations in pH level from entry till its absorption.

2.2 Enzymatic Barrier

Efficacy of oral drug delivery is hindered by the various digestive enzymes present in gastrointestinal tract. Enzymatic barrier is another major challenge in drug delivery. As soon as the lipid and protein-based drug reach the stomach breakdown is initiated by the action of gastric enzymes like lipase and pepsin, respectively [7, 8]. It is further degraded in lumen of small intestine by pancreatic enzymes like trypsin, α-chymotrypsin, and elastase [9].

2.3 Physical Barrier

Nanoparticles are then exposed to intestinal epithelium layer which cover the gastrointestinal tract which has goblet cells, paneth cells, microfold cells, and enterocytes. This is another barrier before absorption [10]. Mucus layer produced by goblet cells covers and protects the epithelium underlined [11]. Mucus layer is a viscous mixture which is negatively charged comprising of enzymes, antiseptic, immunoglobulins, inorganic salts, and thus it can entrap molecules with low permeability and high molecular weight like insulin including those nanoparticles having hydrophobic nature and strong positive charge [12, 13].

3 Nanotechnology and Artificial Intelligence: Neoteric Approach in Drug Delivery

Nanotechnology has received much attention in recent years due to its varied applications in each and every field, especially in health care, i.e., from disease diagnosis to its treatment (Fig. 1). From this technology, early and quick diagnosis can be performed

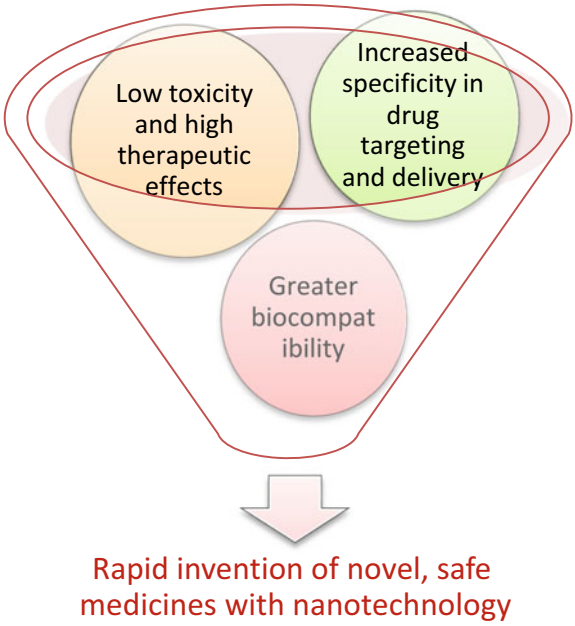

Fig. 1 Nanotechnology in development of novel, safe, and effective medicine for diabetes

along with economical treatment. Recent developments have shown that nanoparticles have great potential as drug carriers due to their small size and unique biological and physiochemical properties. Material synthesized using nanotechnology has greater surface area and quantum effects and these properties make them different from other materials. These improve the material properties like strength, reactivity, in vivo behavior, and electrical characteristics.

From past few years, there is a search for innovative technique or system through which the efficacy of targeted delivery of drugs can be increased with reduction in side effects. Because conventional drug has lot of drawbacks like toxicity, low therapeutic index, etc. Artificial intelligence (AI) tools can solve various problems like computational tasks, data interpretation, nanotechnology-related issues, and drug design with less side effects. AI could be the future as it uses wireless communication, electronic components, and power supply in a microchip implant for programmed drug delivery [14]. Continuous glucose monitoring and controlled insulin delivery may help in reducing diabetes complications. For this, insulin pump, dose calculator, and glucose meter in a device is provided for delivery of insulin and continuous monitoring [15, 16]. It requires the development of drug delivery system which is functional, stable, and biocompatible and overcome the limitations like dosage, side effects, etc. [17–19].

4 Polysaccharide-Based Nanocarriers: Possible Solution Non-invasive Delivery of Insulin

Polysaccharide-based nanocarriers have tremendous properties due to which they are extensively studied for drug delivery. Following are some polysaccharides used in drug delivery.

4.1 Alginate

It has gelation ability, biodegradable, biocompatible, and mucoadhesive. It is an unbranched polymer, anionic in nature which is composed of guluronic and mannuronic residues [20–22]. Due to its anionic nature they can interact with cationic compounds. Thus, by incorporating positively charged molecules or drugs can be used in the drug delivery system. Residence time is increased when alginate beads are coated with chitosan. Good control over the release of drugs is seen in alginate-chitosan complex rather than alginate and chitosan alone [23].

It is formed by linear block copolymerization of d-mannuronic acid and l-guluronic acid. Alginates are linear unbranched polysaccharides which contain different amounts of (1 → 4′)-linked β-d-mannuronic acid and α-l-guluronic acid residues. Alginate is biodegradable, has controllable porosity, and may be linked to other biologically active molecules. Interestingly, encapsulation of certain cell types into alginate beads may actually enhance cell survival and growth. Due to their hemostatic properties, alginate and its salts are used for wound treatment in various forms such as gel or sponge. Calcium alginate can also increase cellular activity properties such as adhesion and proliferation. Obtained from processed algae, calcium alginate, calcium–sodium alginate, collagen–alginate, and gelatin–alginate are highly absorbent natural fiber dressings. Alginate can absorb water and body fluids up to 20 times its weight, resulting in a hydrophilic gel. The formed gel is weak, but it maintains a moist wound healing environment.

4.2 Chitosan

Its structure is similar to cellulose and is composed of repeating units of D-glucosamine. It is biodegradable, bioadhesive, and non-toxic. Chitosan shows mucoadhesive properties which are due to interaction between negatively charged mucin and positively charged groups. This property can be used to enhance the absorption and penetration of nanocarriers through epithelial barriers [24]. It can be used in the nasal, oral, ocular, and transdermal administrations by modifying the functional groups [25].

4.3 Heparin

It is sulfated polysaccharide exhibiting properties of strong anticoagulant and is anionic in nature [26]. It protects the drugs from proteolytic and chemical degradation as well as controls its release from the nanoparticles. Heparin is alike chitosan which shows anticancer properties. It has the ability to restrain tumor angiogenesis and metastasis. Higher efficacy is seen by low molecular weight small heparins [27].

4.4 Hyaluronic Acid

In aqueous environment, hyaluronic acid shows good solubility and stability. They can form different structures which vary with concentrations. These are linear, non-sulfated, and negatively charged because of this used in the fabrication of nanoparticles [28]. It is an ideal lubricant in tissues and joints as it can decrease the post-operative adhesion formation. It has good potential for passive tumor targeting [29]. Additionally, HA nanoparticles have been researched as bearers to expand the porousness and cell take-up, and limit the enzymatic degradation of insulin through the oral course in animal models [30].

4.5 Dextran

Dextran has higher water solubility and is unbranched polysaccharide. What makes dextran attractive for fabricating it as nanoparticles are its properties like non-immunogenicity biodegradability, biocompatibility, and nonantigenicity [31]. For example, dextran nanoparticles have been designed for the delivery of doxorubicin into the nuclei of cancer cells as intelligent drug delivery systems in chemotherapy [32].

4.6 Pullulan

It is a neutral polysaccharide which is produced by the fermentation of fungus *Aureobasidium pullulans* [33, 34]. They are water soluble, linear, and non-toxic in nature. It has various applications due to its material properties and used in drug delivery, imaging, diagnosis, tissue engineering, etc. [35, 36]. It also reported for oral delivery due to its biodegradability nature [36] and shows anticancer activity also.

4.7 Pectin

It is structural polysaccharide which determines gelling, solubility, and its capability to form film. They can be used in drug delivery as they can protect the protein while passing through the gastrointestinal tract and then finally reaching to large intestine [37].

4.8 Xanthan Gum

It is an extracellular polysaccharide secreted by the micro-organism Xanthomonas campestris and consists of glucose, mannose, and glucuronic acid; it is a strong water-binding agent and texture modifier used in many foods. The primary structure of xanthan gum is a linear (1 → 4) linked β-d-glucose backbone with a trisaccharide side chain on every other glucose at C-3. It is manufactured by a fermentation process commercially. Xanthan gum is soluble in cold water and solutions exhibit highly pseudoplastic flow and synergistic interaction with galactomannans.

The development and advancement in the field of nanoscience and nanotechnology can improve the quality of diagnosis and care of disease in order to efficiently release antimicrobial, anti-inflammatory, and regenerative compounds and hence speeding up the endogenous healing process. The natural origin components can also overcome the drawbacks of current antibiotics and antiseptics (mainly cytotoxicity, antibiotic resistance, and allergies). Nanotechnology has been proved to be a promising approach to fulfill all the requirements needed for the next-generation technology. As the natural origin components to be used in the fabrication of polysaccharide-based biopolymeric nanoparticle that have been identified and their efficiency is validated through several clinical trials for effective delivery of insulin. Also, their combinations with other biopolymers in the fabrication of patch are also evaluated which are used as a measure of efficient characteristics for wound care. It can be concluded that for the natural occurring constituents, more clinical trials are required to reach a sufficient level of evidence as therapeutic agents for wound healing.

5 Future Prospects

For designing new materials for drug delivery, there are some factors which need to be thought of like biocompatibility, functionality, targeting, bio-distribution, stability, shelf life, and drug incorporation and its release. To fulfill this, polysaccharide-based nanocarriers are extensively studied. This will not only increase therapeutic efficacy but leaves no toxicity inside and specific target action. Polysaccharide-based carriers are promising in the field of drug delivery. Research must be carried out to enhance

the properties of the materials to make it more stable and effective. Nanotechnology and artificial intelligence could be an advanced helping tool.

Polysaccharide-based nanoformulations have also been used primarily but very few for insulin delivery. Though an invasive approach is the most widely used for insulin delivery but non-invasive routes using polysaccharide as nanoformulation could provide certain added advantages like bypassing the first-pass metabolism, relief from possible pain, and more patient compliance. Secondly, much lower doses can be used due to direct entry into systemic circulation as compared to the injection of insulin dosage forms. Researchers have to find out certain positive results polysaccharide-based nanoparticle loaded with insulin. Success in delivering insulin through polysaccharide-based nanoformulations would relieve the patients from the pain and local site morbidities associated with the injections. The success of formulating such nanoparticles using easily available biopolymers (as mentioned in this chapter) would reduce the overall cost of formulation in the future and this formulation would be very effective and safe.

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Interpenetrating Polymer Networks in Sustained Drug-Releasing

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Abstract Over the many decades, hydrogels are proven to be an effective biomaterial in various pharmacological applications. Precisely these environment-sensitive hydrogels are considered as "smart" drug delivery systems as they are capable of releasing drugs at a proper time and a site with a predetermined dosage to scale down its toxic side effects. Recently, a lot of work has been done in the field of drug delivery utilizing multicomponent hydrogels such as interpenetrating polymer networks (IPN) as well as semi-interpenetrating polymer networks (semi-IPN). IPN can be synthesized through both physical and chemical crosslinking depending upon the method of preparation. The main aim of this review is to give a detailed overview of the characteristics and applications of interpenetrating polymer networks in sustained drug delivery devices. In the first part, a detailed introduction of hydrogel is followed by the second part giving a detailed explanation of IPN and semi-IPN hydrogel. The main highlighting part of this review is the recent successful applications of IPN hydrogels in the field of drug delivery. IPN-based hydrogels are proven to be versatile and better devices for drug delivery.

Keywords Interpenetrating polymer networks · Drug delivery · Natural polymers · Synthetic polymers · Free radicals · Backbone · Future challenges

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Abbreviations

3-D	3-Dimensional
5-ASA	Mesalamine or 5-aminosalicylic acid
BSA	Bovine serum albumin
CMC	Carboxymethyl cellulose
DOX-h	Doxycyclinehyclate
FSS	Fluorescein sodium
HA	Hyaluronic acid
HEMA	2-Hydroxyethylmethacrylate
HEA	2-Hydroxyethyl acrylate
HPC	2-Hydroxypropylcellulose
IPN	Interpenetrating polymer networks
IUPAC	International Union of pure and applied chemistry
KGM	Konjac glucomannan
LCST	Lower critical solution temperature
MC	Methylcellulose
MW	Molecular weight
p(AN)	Poly(acrylonitrile)
p(AN-co-APTMACl)	Poly(acrylonitrile-co-(3-acrylamidopropyl)-trimethylammonium chloride
p(AN-co-4-VP)	Poly(acrylonitrile-co-4-viniyl pyridine)
p(AN-co-NIPAM)	Poly(acrylonitrile-co-*N*-isopropylacrylamide)
PAA	Poly(acrylic acid)
PDA	Polydopamine
PEG	Polyethylene glycol
PEGDA	Poly(ethylene glycol) diacrylate
PNIPAAm	Poly(*N*-isopropylacrylamide)
PHEMA	Poly(2-hydroxyethyl methacrylate)
pNIPAM	Poly-*N*-Isopropylacrylamide
PMA	Poly(methacrylic acid)
PNIPAM	Poly(*N*-isopropyl acrylamide)
PVA	Poly(vinyl alcohol)
RSM	Response surface methodology
SBC	Sugarcane bagasse cellulose
SGF	Simulated gastric fluid

1 Introduction

Hydrogels have become one of the most important biomaterials in the field of pharmacology for many years due to the excellent properties and high capacity to keep a large amount of water. They play an important role in various fields like tissue

engineering, biosensors, wound dressings, and drug carriers [1, 2]. Till now the major emerging area of research work with hydrogels is their applications in drug delivery because the idea of releasing the drug at a prefixed interval of time is possible by exploiting their unique properties [3–6]. Hydrogels are defined as physically or chemically crosslinked complex of 3-dimensional (3D) polymeric networks having the tendency to hold large quantities of water or any other biological fluid. These are majorly characterized by having a soft texture and rubbery consistency [7]. The capacity of retaining a large quantity of water is due to the presence of hydrophilic functional groups such as $–NH_2$, –COOH, and –OH which forms a swollen gel phase [1, 2, 8, 9]. Hydrogels are very similar to the natural body tissue due to the properties of porosity in network structure, high water holding capacity, and soft texture. They may either be stable by chemical interactions or may breakdown and dissolve due to weak interactions. A variety of natural as well as synthetic polymer-based backbones are employed for the synthesis of hydrogels as depicted in Table 1.

The most common form of categorization of hydrogels is into the following two forms: physical gels and chemical gels [11–13]. Physical hydrogels are also called reversible gels because the crosslinked networks are held together by molecular entanglements and various forces of interactions like hydrogen bonding, ionic interactions, and hydrophobic interactions. Physical hydrogels can be dissolved by altering the environmental conditions like pH, temperature, and ionic strength of the

Table 1 Commonly used backbones for the synthesis of hydrogels

S. No.	Natural polymers utilized for the synthesis of IPN hydrogels	References
1	Poly(vinyl alcohol) (PVA)	[1, 3, 10–12]
2	Alginate	[5, 6, 8, 13]
3	Chitosan	[1, 3, 6, 8, 13]
4	Pectin	[1, 8]
5	Cellulose	[1–3, 5, 7, 10]
6	Xanthum gum	[1, 3, 5, 10]
7	Gum Acacia	[1, 2, 8]
8	Gelatin	[1, 6, 8]
9	Dextran	[1, 5, 6]
10	Glucan	[1, 8]
11	Gellan	[1, 5, 8]
12	Guar Gum	[1, 5]
13	Pollulan	[1, 3, 5]
14	Poly(acrylic acid) (PAA)	[3, 8]
15	Polyethylene glycol (PEG)	[1, 10, 11, 13–16]
16	Poly(*N*-isopropylacrylamide) (PNIPAAm)	[3, 8, 10, 11, 13]
17	Poly(2-hydroxyethyl methacrylate) (PHEMA)	[3, 10, 11, 13]
18	2-Hydroxyethylmethacrylate (HEMA)	[3, 10, 13]

medium. These forms of hydrogels are not homogenous in nature due to the formation of clusters of ionically or hydrophobically associated domains or molecular entanglements [14, 15]. Chemical hydrogels, on the other hand, are called permanent gels because of the covalent interactions present between the crosslinked networks. The presence or absence of charge on gels depends on the type of functional groups on their surface. Similar to physical hydrogels, chemical hydrogels are also non-homogeneous in nature. This is due to the presence of portions of high crosslink density and less crosslink density, which are referred to as clusters. The possible reason behind their formation is the hydrophobic aggregation of agents required for crosslinking resulting in the synthesis of high crosslink density clusters [16]. Under certain circumstances, separation of phase occurs depending upon the concentration of the solvent, range of temperature, and concentration of solid used for the formation of a gel. This creates small water-filled "voids" or "macropores". The presence of free chain ends in chemical gels depicts the network defects, having no contribution towards the elasticity of the hydrogels [17]. Another unique property of hydrogels is that they do not breakdown on swelling because of the presence of crosslinking between the networks. The presence of entwined networks inside hydrogel renders them the property of not dissolving and instead of getting swollen in water, thus imparting rigidity to it. Chemically crosslinked hydrogels provide excellent crosslinking; however, the chemicals utilized for the synthesis should be removed before their implementation towards any application to avoid the toxic side effects. Comparatively, physically crosslinked hydrogels can be prepared without the utilization of any chemical reagent. Chemically crosslinked hydrogels are found to acquire more stable mechanical properties than physically crosslinked hydrogels and their immediate response to environmental stimuli such as changes in temperature, pH, and stress make them an ideal system for potential therapeutic applications [18–23]. The schematic representation of crosslinking in hydrogel and its structure in swollen as well as in collapsed state is shown in Fig. 1 [9].

Hydrogels are ideally used for a variety of applications that involve the usage of hydroxyalkyl methacrylates. The soft and rubbery texture of swollen hydrogel makes it an ideal material to be used for implants. Hydrogels have also been used as potential drug delivery systems for the optimized release of the drug under ideal conditions. Varying the concentration of the monomer is the major reason behind the diffusion and permeation characteristics of hydrogel. Manipulating the monomer concentration can be used to synthesize a variety of hydrogels, which can further be useful for loading a range of drugs into the matrix structure. Therefore, hydrogels act as novel drug delivery systems [24]. These have the tendency to protect the drug from harsh adverse environments, e.g. extremely low pH and presence of degrading enzymes in the stomach. Hydrogels control the release of drugs by changing the structure in response to environmental stimuli [25]. Hydrogel-based drug delivery systems specifically control the availability of drugs to different cells and tissues over time. These systems offer helpful therapeutic outcomes by increasing their effectiveness and decreasing their toxic side effects by controlling the dosage [26]. Another advantage of using hydrogel as a drug delivery system is that the risk of disintegration of the drug and aggregation upon interaction with organic solvents is

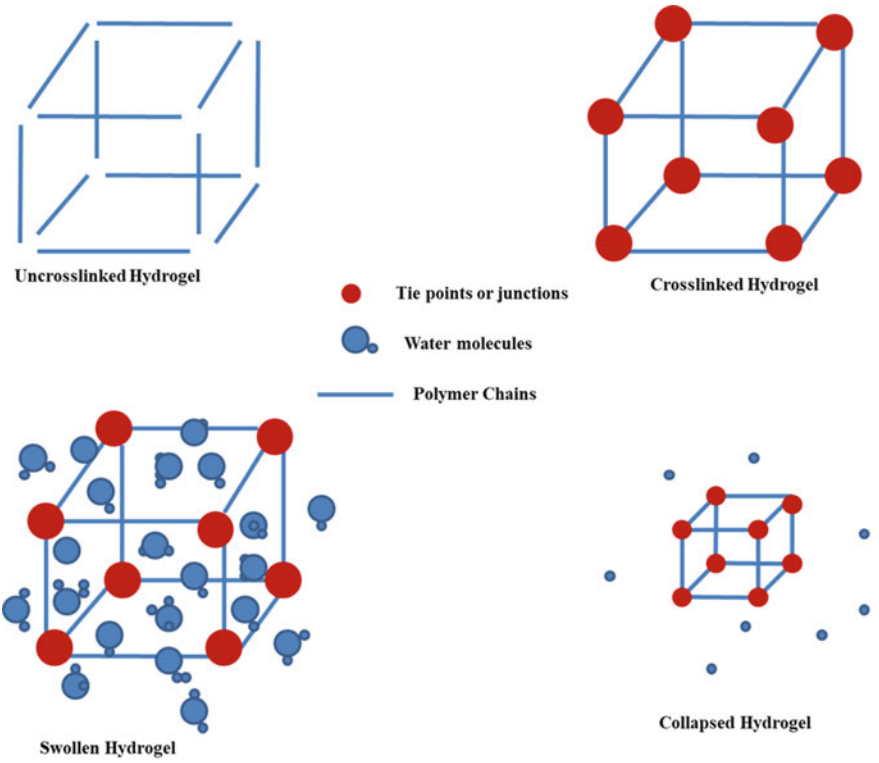

Fig. 1 Schematic representation of the structure and swelling of hydrogel

lessened due to the fact that these are typically developed in the aqueous phase [27, 28]. Hydrogels vary in size, structure, and function, and all these features together represent the functioning of hydrogels as drug delivery systems.

Designing of the porous structure of hydrogel is the major factor responsible for developing an efficient drug delivery system [29–31]. Recently, IPNs have been found as an ideal matrix for the optimized release of various drugs [32]. These come under the classification of different types of hydrogels and are prepared by crosslinking linear polymer in the presence of other crosslinked polymer with no covalent bonding. IPNs offer more strength as they cannot be separated until and unless the chemical bonds are broken [33, 34]. This combination of polymers produces an advanced multicomponent polymeric system [35]. IPN hydrogel comprises certain physico-chemical properties that impart their uniqueness in comparison with other macro-molecular components [36]. These are helpful over providing improved mechanical strength and compatibility among various polymers [37–43]. Multicomponent IPN systems also have better swelling and deswelling responses towards external stimuli. Additionally, the density of crosslinking, porosity, and stiffness can be adjusted so in IPN hydrogels making them suitable for targeted drug release [44]. The macroscopic design of IPN mainly determines the ways through which the synthesized hydrogel

can be administered inside the body. If micropores are present, they directly affect the physical properties of IPN, thereby carrying out drug transport through convection. Over a nanometre range, the crosslinked network encircles the water accommodated inside the IPN network. Networks of such type consist of open spaces, whose size is assigned as the mesh size of the hydrogel matrix. The mesh size of IPN is the most important property, determining the diffusion of drugs inside the hydrogel. Considering the molecular and atomistic scale, several chemical interactions are reported to take place between the drugs and the networks inside IPN hydrogels. The polymer chains may acquire diverse binding sites for the drugs. These sites can be manipulated according to the desired response utilizing various physical and chemical techniques. All these features consisting of mesh size and molecular and atomistic scale are important for an ideal drug release.

Further administration of these IPN hydrogels inside the body can be achieved through various means like implanting them surgically, through injection or by systemic delivery through intravenous infusion. The maximum efficiency and response of drug delivery can be obtained by using any one of the above-mentioned methods. The amount of drug released through IPN per unit time is important to meet beneficial results. After the complete release of drug from the system, the IPN hydrogel must be designed to biodegrade in the body without the necessity of employing surgical operations for its removal. In order to synchronize with tissue regeneration degradation of hydrogels is very important [29–31, 36].

This review article aims to give a detailed overview of the types, properties, and application of IPN hydrogel in the field of sustained drug delivery. The review explains the use of a variety of polymers for the synthesis of IPN hydrogel and their efficiency of drug release.

2 Interpenetrating Networks (IPNs)

Interpenetrating networks were first discovered and designed by Aylsworth in 1914 [32]. Right after that between the 1950s and 1960s, researchers begin to develop an interest in these complex structures [45]. The term “Interpenetrating polymer network” was given by Millar, who also investigated the properties of IPN [45]. According to IUPAC, the definition of IPN stands as “A polymer consisting of two or more networks partly interweaved in a molecular form not covalently to one another and is difficult to separate until the chemical bonds are fragmented. Though, a blend consists of two or more preformed polymer networks cannot be considered as an IPN” [46]. On the other hand, semi-IPN is formed when only one of the two components is crosslinked. The IUPAC definition of semi-IPN stands as “A polymer consisting of one or more networks of branched or linear chains characterized by the penetration on a molecular scale of somewhat one of the networks by at least some of the linear or branched macromolecules” [46]. The major difference between IPN and semi-IPN is that the linear or branched polymers of semi-IPN can be separated without breaking the chemical bonds as they are polymer blends, while in the case

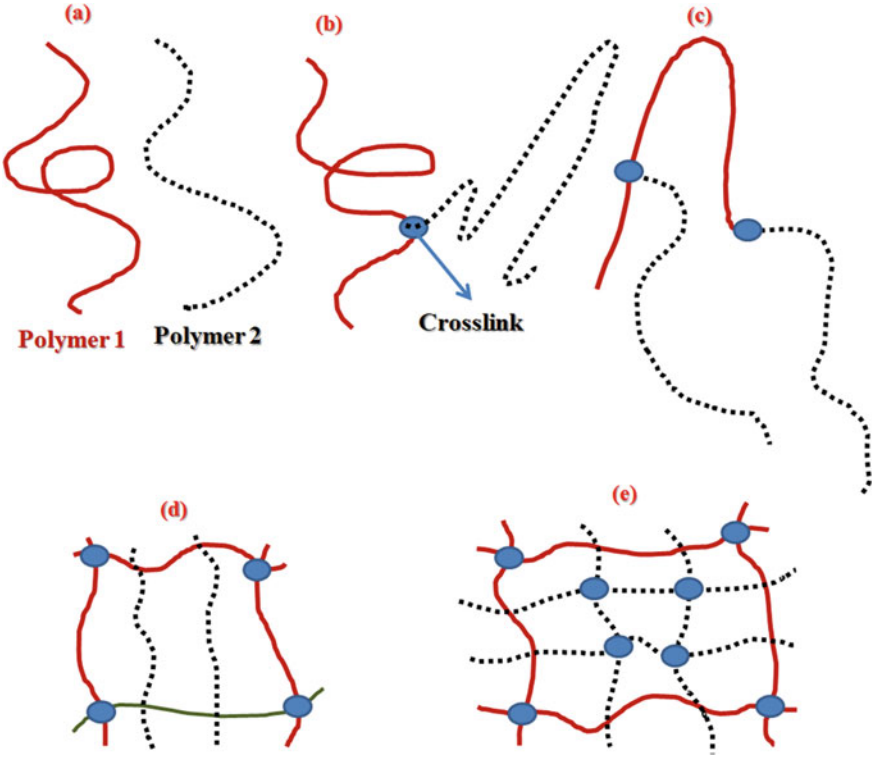

Fig. 2 Schematic representations of **a** mechanical blends, **b** graft copolymers, **c** block copolymers, **d** semi-IPN, and **e** full IPN

of IPN they cannot be separated until the chemical bonds are broken [47, 48]. A diagrammatic representation of mechanical blends, polymers, IPN, and semi IPN is displayed in Fig. 2 [49].

Most commonly employed procedure for the synthesis of IPN is through in situ preparation. In this method, the reactants are added and mixed in the solution before crosslinking as depicted in Fig. 3 [36]. The IPN hydrogel can be formed either sequentially or simultaneously on the basis of the type of crosslinking reactions taking place in both the systems [47, 48]. For the simultaneous pathway, orthogonal networks are required for the reaction in order to lower the cross-reactions, i.e. copolymer formation [50]. In the sequential formation of semi IPNs, the formation of a polymer network takes place, followed by subsequent loading of the second polymer inside the network, therefore leading to the formation of semi IPN. Further, a second network is formed by crosslinking the loaded polymer converting semi-IPN to an IPN [50].

IPN hydrogels are used successfully in biomedical applications, especially in the field of drug delivery. This is because of the fact that a combination of favourable properties of each polymer in IPN forms new systems consisting of various improved

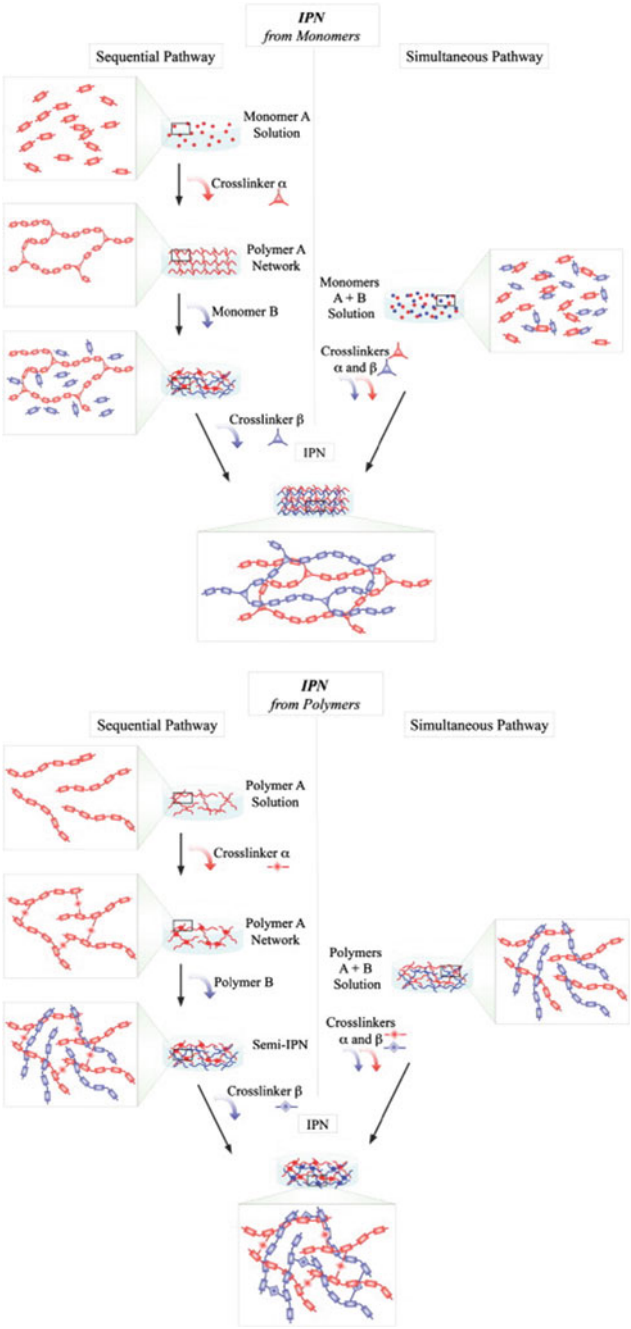

Fig. 3 Schematic representation of the semi-IPN and IPN formation. α and β are generic either chemical or physical crosslinkers [36]. Reprinted with permission from Matricardi et al. [36] Copyright © 2013 Elsevier

properties which are different from that of individual polymers. Many systems also own the property of synergism [51–53]. Therefore, this combination of various properties and synergism can be used for modifying and manipulating the material to meet the required needs. Furthermore, the broadening of the range of reachable properties of hydrogels can also be achieved through combining as well as grafting natural and synthetic polymers [7, 47, 54–56].

3 Properties of IPNs

3.1 Phase Separation

Both IPN and semi-IPN have the property of phase separation which results in the formation of a heterogeneous network structure. The reason behind this phase separation is that these are formed from chemically different structures. The overall process of phase separation occurs slowly because of the highly viscous system and entanglements present between the chains. It occurs by the following two mechanisms:

Spinodal decomposition is the commonly occurring mechanism of separation of phase. In this, the cylinders which are interconnected of the second phase are formed in the first phase matrix. The growth of these cylinders is marked by the increase in wave amplitude after which coarsening and coalescence cause the essential changes although these changes may be blocked by crosslinking, which intends to keep the domain structure small.

Nucleation and growth are characterized by the formation of spheres of the second phase in the matrix of the first phase. An increase in diameter is observed with the growth of the sphere [50, 57]. It was observed that the morphology of IPN was affected the most by phase separation. Specifically, when the process of gelation occurred before the phase separation, the formed network comprised of a small phase domain which is mainly found in sequential IPN. On the other hand, when phase separation occurred before gelation, the formed network comprised of the large size of the domain [57].

3.2 Transition Temperature

Interpenetrating network systems show two glass transition temperatures analogous to the T_g of a single polymeric compound. Alternately, IPN may possess a sharp T_g which is intermediate of the glass temperature of the components. It has also

been observed that a single transition temperature cannot be considered as proof of compatibility between two IPNs [57, 58]. In comparison with IPN, semi-IPN systems depict greater shifts in the separation of phase [59].

3.3 Mechanical Strength

IPN and semi-IPN provide improved mechanical stability and strength to hydrogels as compared to the hydrogels formed from a single polymer. Hence, a synergic effect of the components is observed in IPN and semi-IPN. On the basis of these various desirable characteristics can be obtained by choosing the appropriate starting polymer material for IPN and semi-IPN [36, 59].

3.4 Thermal Stability and Chemical Resistance

IPN and semi-IPN possess excellent stability to temperature changes and resistance to the adverse chemical effects. These can also swell without dissolving in solvents and can also creep or block the flow [58, 59].

4 Classifications

IPN systems can be classified mainly into three types on the basis of network structure, chemical bonds, and synthetic procedure. Figure 4 represents a flow chart of the types of classification of the IPNs system.

4.1 On the Basis of Network Structure

Full IPNs: These types of hydrogels comprise two networks connected to one another, producing a lot of entangled network structures. In simple terms, it consists of the intermeshing of networks. These are mostly formed through the sequential or simultaneous process [60–63].

Homo-IPNs: These types of hydrogels are considered to be a special case of interpenetrating networks comprising of two polymers forming independent networks consisting of the same structure. These are mostly sequential IPNs [60–63].

Semi- or pseudo-IPNs: These types of hydrogels consist of one linear polymer instead of having a network structure. Some of these IPNs can be excluded if the

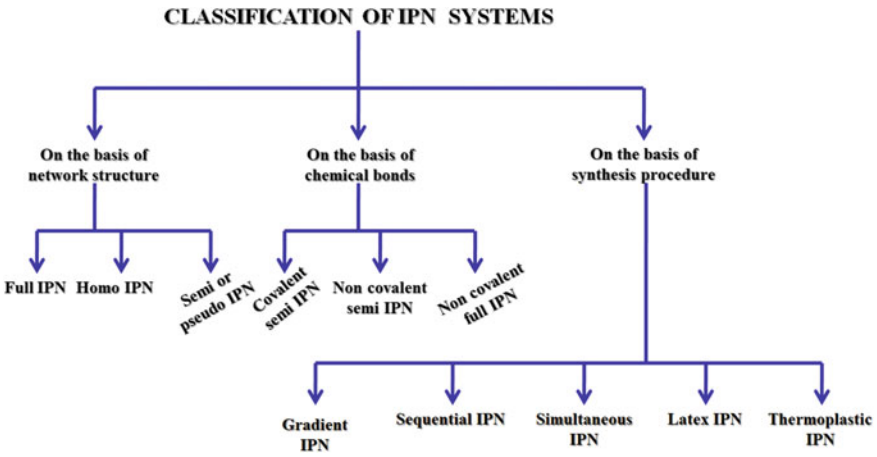

Fig. 4 Classification of different types of IPN systems

linear part is making up the majority of the material. The ones made through the sequential process are called semi-IPNs, and the ones made through the simultaneous process are called pseudo-IPNs [60–63].

4.2 On the Basis of Chemical Bonding

Covalent semi-IPN: In this, a single polymeric network is synthesized through two separate polymer systems which are crosslinked.

Non-covalent semi IPN: In this type, only one of the two polymers is crosslinked.

Non-covalent full IPN: In this type, two separate polymers are made to crosslink independently [64, 65].

4.3 According to the Procedure of Synthesis

Sequential IPN: The term "sequential" used in these types of networks simply represents the time of the order of polymerization [66]. Two polymers are required for the synthesis of sequential IPN. Firstly, polymer 1 is crosslinked, and then, it is swollen with the help of the monomer of the polymer 2. After this, polymer 2 is crosslinked in situ by a crosslinker. The only need of this method is that both the reagents, i.e. monomer 2 and co-reactants, should swell appropriately inside the polymer 1. Most elastomers are utilized for network 1 as they swell easily [65].

Latex IPN: In this system, both the polymers, networks are comprised in one latex particle, mostly through the polymerization of monomer 2 together with the crosslinking agent and activator in the existing seed latex of the first crosslinked monomer. These are generally shown as "core" and "shell" structures [65].

Simultaneous IPN: This type of IPN system is synthesized in a single-step procedure by combining and crosslinking the monomers 1 and 2 together along with their corresponding crosslinkers and activators. In comparison with sequential IPN, these are more effective; the starting mixture of monomers is greatly compatible, and therefore, a high degree of intermixing is achieved at the network [65].

Thermoplastic IPN: As the name suggests, the crosslinking among the polymers is physical in nature. Usually, three types of physical crosslinking take place in thermoplastic IPN. First is the ionomer formation in which crosslinking takes place with the help of ionic groups present on the polymer chain. In partially crystalline polymers, crosslinking takes place from the crystalline regions present inside the network, and in case of block copolymers having ABA structure, the presence of end blocks forms a discrete phase due to which crosslinking takes place from the glassy domains [66]. These types of network materials tend to flow at high temperatures; however, the presence of crosslinking renders them typical IPN behaviour at specific temperatures [64].

Gradient IPN: These types of IPN systems show a variation at a macroscopic level depending upon different locations. Formation of gradient IPN can take place by swelling polymer 1 in the network of monomer 2 followed by rapid polymerization before the equilibrium is established. In this way, the second monomer represents a concentration gradient over the first polymeric network in the resulting IPN [66, 67].

5 Application of IPNs in Sustained Drug Release

5.1 Alginate-Based IPNs for the Controlled Release of Bovine Albumin Serum and 5-Amino Salicylic Acid

Alginate is a linear polysaccharide extracted from sea algae. It comprises of homopolymeric or alternating blocks of 1-4-linked β-D-mannuronic acid (M) and α-l-glucuronic acid (G) [68, 69]. Crosslinking in alginate-based hydrogels takes place through the binding of divalent ions with glucuronic residues. Due to this property, the alginate-based hydrogel has been widely used as a biomaterial in tailoring IPN systems with natural or synthetic polymers for drug delivery applications [70]. Dipankar and co-workers synthesized a terpolymeric semi-IPN hydrogel of alginate and synthetic material 2-hydroxyethyl acrylate (HEA) and poly (ethylene glycol) diacrylate (PEGDA) through graft polymerization and crosslinking via free radical mechanism as represented in Fig. 5 [71]. The combination of alginate with HEA

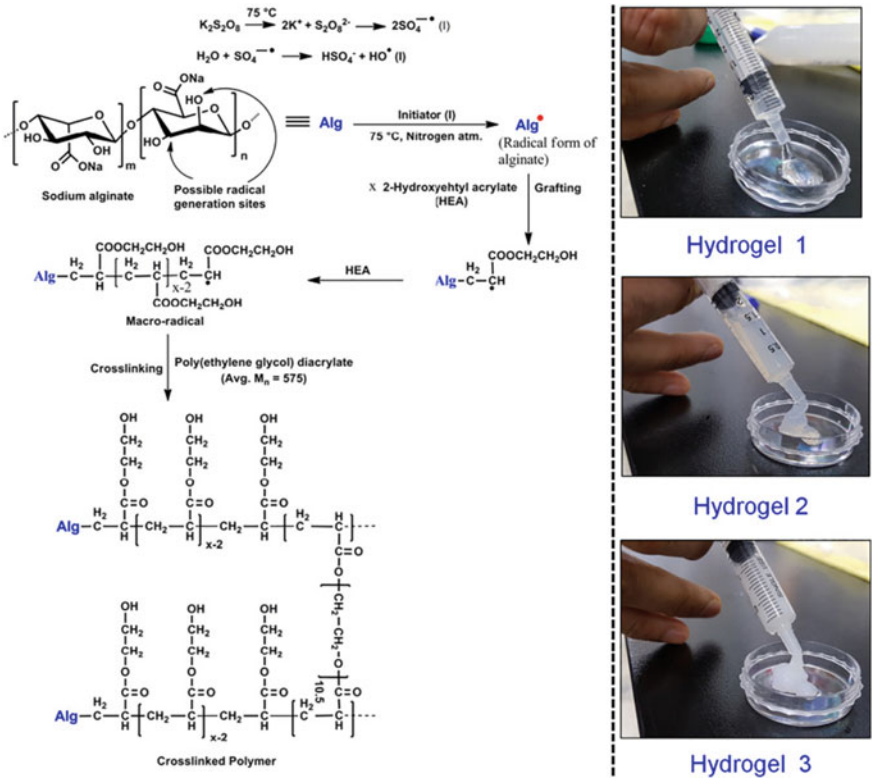

Fig. 5 Probable mechanism and digital images of alginate-, HEA-, and PEGDA-based terpolymeric semi-IPN hydrogel [71]. Reprinted with permission from Das et al. [71] 2019 Copyright © 2017 Elsevier

as a monomer and PEGDA as a crosslinker provided excellent mechanical properties, porosity, biocompatibility, and biodegradability to the IPN systems which were found to be highly suitable for drug delivery [72–77]. They also studied the effects of functional species (PEGDA) on the physical properties of IPN systems and MC3T3 cell viability and their rate of proliferation. Their major contribution was towards the in vitro release of protein bovine albumin serum (BSA) and drug 5-amino salicylic acid (5-ASA) administered for the treatment disorders of the colon, from the synthesized semi-IPN. It was observed that when the concentration of PEGDA was increased, the pore size was decreased and the mechanical properties including hardness, adhesiveness, etc., of the hydrogel were increased. Due to the presence of small pore size and excellent mechanical properties in hydrogels having high concentration of PEGDA, the rate of cell viability and proliferation of MC3T3 increased significantly in comparison with hydrogels having low PEGDA concentration. Further, these hydrogels also released both BSA and 5-ASA in a sustained way and it was observed that drug release was faster at pH 7.4 as compared to pH 2.5. The in vitro

release mechanism was carried out for 5 days, and it was concluded that the pH-responsive and biocompatible semi-IPN hydrogel could be used efficiently for the predetermined release of protein BSA and colon targeted drug 5-ASA [71].

5.2 *Sugarcane Bagasse-Based Cellulose Hydrogels for the Optimized Release of BSA*

Sugarcane bagasse is produced worldwide as a waste product by sugar and alcohol industries, especially in countries having a warmer climate. With an average, 540 million dry tons of sugarcane are produced and processed annually and about 1 ton of sugarcane produces 280 kg of bagasse [78]. Sugarcane bagasse is a by-product of the sugar industry and is a fibrous residue of the stalks left the crushing and juice extracted from sugarcane. It is often used as fuel for boilers by the sugar industries [79]. Around 40–50% of the bagasse is comprised of cellulose, which is crystalline in nature [80]. The bagasse-based cellulose has been found as an appropriate material for the synthesis of smart hydrogels [81, 82]. IPN hydrogels are more stable than single crosslinked hydrogels due to the entanglements present in the network structure. These encapsulate the drug more effective and cause its ideal release [3, 83–87]. Yuanfeng and co-workers [88] utilized the sugarcane bagasse cellulose (SBC) pulp for the synthesis of carboxymethyl cellulose (CMC)-based IPN hydrogel for the release of BSA. The resultant hydrogels (Fig. 6) formed were dual responsive gels; i.e., they responded efficiently to the changes in pH and temperature. They reported that the synthesized cellulose-based hydrogel was safe, non-toxic, and highly biocompatible. They compared the release BSA from SBC cellulose-based hydrogel and double sensitive IPN hydrogels containing poly-*N*-isopropylacrylamide (pNIPAM).

The cumulative release at 23 and 37 °C was observed, and the largest amount of drug release took place at 37 °C. In case of SBC cellulose-based hydrogels, it was found to be a 56.2% release, and in case of IPN hydrogels, it was found to be 58.1%, which clearly indicated that IPN-based hydrogels carried out the release of BSA more efficiently in comparison with cellulose-based hydrogel [89, 90]. The pH-responsive behaviour was also investigated in SBC/CMC hydrogels, and the cumulative release of BSA in PBS (pH 7.4) was lower than SGF (pH 1.35) which showed the pH-sensitive behaviour of hydrogel. It was concluded that after the polymerization and crosslinking of the IPN hydrogel depicted dual responsive behaviour. BSA was released rapidly from IPN at pH 7 and at a temperature above the lower critical solution temperature (LCST) of pNIPAM (32 °C) [91, 92]. This suggested that IPN hydrogels are better drug carriers than single crosslinked hydrogels.

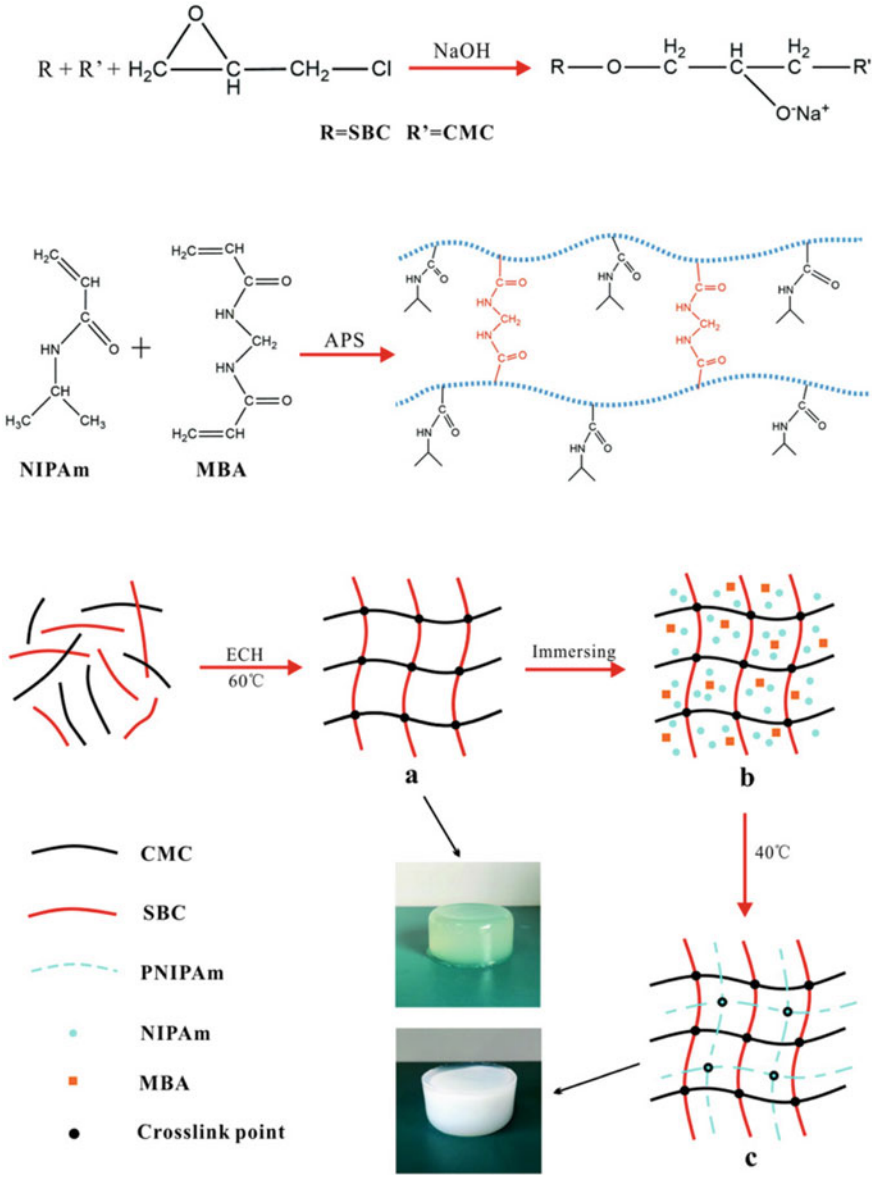

Fig. 6 Schematic of the preparation process of IPN hydrogel [88]. Reprinted with permission from Pan et al. [88] Copyright © 2017 Elsevier

5.3 *Salecan-Based Semi-IPN Hydrogel for Amoxicillin Delivery*

Salecan is a water-soluble polysaccharide derived from the strain of *Agrobacterium* sp. [93, 94]. It comprises units of glucopyronsyl linked together by glycosidic bonds as shown in Fig. 7 [95]. Salecan consists of great biological properties like non-toxic and antioxidation, which are usually required in food industries [96]. Recently, hydrogels have been synthesized using Salecan as a biomaterial which proved to be ideal candidates for applications in drug delivery [95, 97–100]. A semi-IPN hydrogels by interpenetrating Salecan chains inside the crosslinked networks of poly (*N*-(3-dimethyl aminopropyl) acrylamide-co-acrylamide) for the controlled release of amoxicillin was developed by Xiaoliang et al. [100]. In vitro release of amoxicillin as represented in Fig. 8 carried out at pH 7.4 inside artificially formed intestinal fluid and at pH 1.2 in artificially formed gastric fluid at a temperature of 37 °C. It was observed that at an acidic pH the release of amoxicillin was prohibited due to the presence of electrostatic attraction of proton transfer occurring between the –COOH groups of amoxicillin and tertiary $–NH_2$ groups of the semi-IPN [101]. At pH 7.4, drug release through semi-IPN was enhanced drastically because the de-protonation of polydopamine (PDA) chains leading to the breakage of electrostatic interactions, thereby causing maximum drug release [102]. It was also observed that the pH-sensitive release feature of Salecan was suitable for the treatment of oral infection: It could easily regulate a low amoxicillin release at the acidic pH of the stomach (pH 1.2) and enhanced release under normal physiological conditions (pH 7.4). It was concluded that the release of amoxicillin accelerated with an increase in the concentration of Salecan in the IPN hydrogel and up to 73.1% of amoxicillin was released in the medium [100].

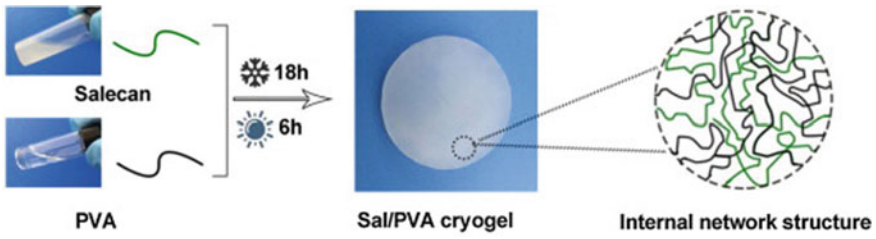

Fig. 7 Schematic representation of the formation of Sal/PVA blending hydrogels [95]. Reprinted with permission from Qi et al. [95] Copyright © 2015 Elsevier

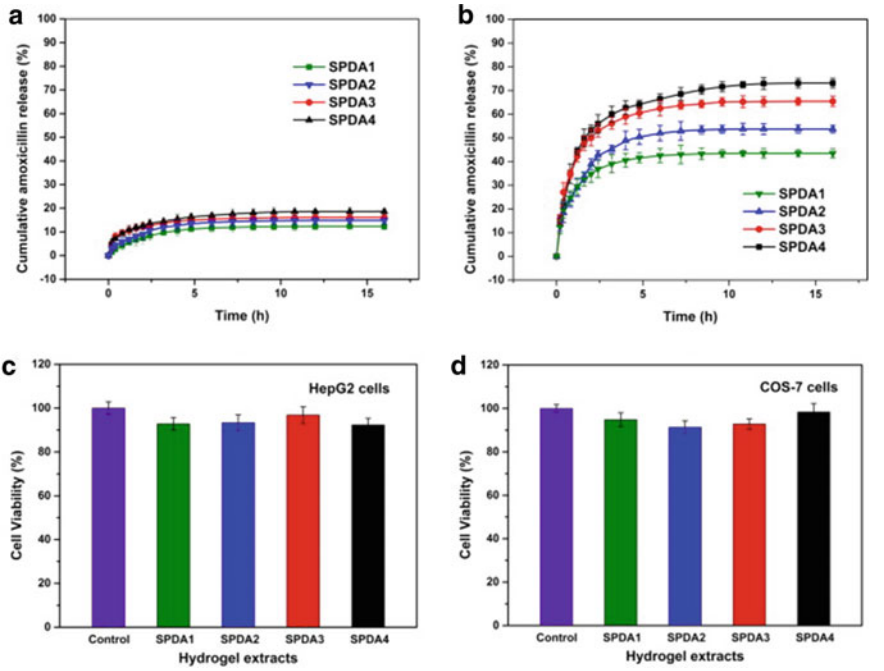

Fig. 8 Cumulative amoxicillin release profiles of the Salecan/PDA hydrogels at pH 1.2 (**a**) and pH 7.4 (**b**). Cell viability of HepG2 cells (**c**) and COS-7 cells (**d**) after treatment with hydrogel extracts [100]. Reprinted with permission from Qi et al. [100] Copyright © 2017 Elsevier

5.4 Konjac Glucomannan-Poly(acrylic acid)-Based IPN Hydrogel for the Release of Vitamin B12 Drug

Konjac glucomannan (KGM) is a water-soluble polysaccharide obtained from the tubers of the plant amorphophallus Konjac [103]. It comprises of 1, 4-linked-b-D-mannopyranose and b-D-glucopyranose units in a ratio of 1.6:1 [104]. The unique property of KGM is that it does not get hydrolyzed by digestive enzymes present in human beings because of which it is considered as an indigestible dietary fibre. It also has the ability to lower blood cholesterol and sugar level, also effective in weight loss, immune function, etc. [105, 106]. KGM is also considered as one of the traditional foods which can be deacetylated to form hydrogel [107, 108]. Previously, oral drug delivery systems for colon have been studied for the treatment of bowel diseases and other gastrointestinal-based illness [109–112]. Xian and co-workers [113] used the desirable properties of KGM to synthesize poly (acrylic acid) (PAA)-based IPN hydrogel for the treatment of bowel disease through colon-specific drug delivery of vitamin B12 drug. The colon-specific drug release studies through IPN-based hydrogels were carried out under pH 1.0 and pH 7.4 at 37 °C. The amount of drug

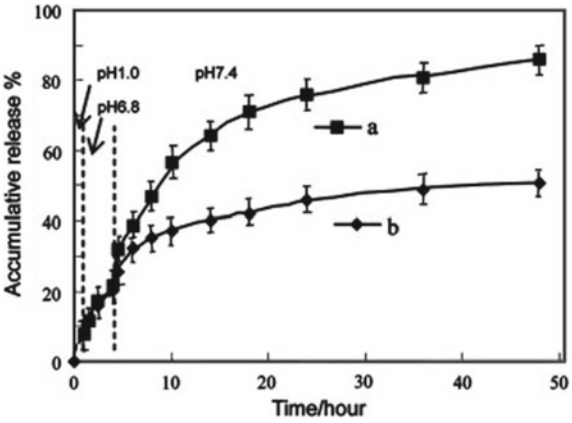

Fig. 9 In vitro release profile of VB12-loaded gels K2A1 with enzymes **a** and without enzymes **b** under different conditions: 0–1 h, pH 1.0; 1–4 h, pH 6.86; 4–60 h, pH 7.4 [113]. Reprinted with permission from Wen et al. [113] Copyright © 2009 Elsevier

release as shown in Fig. 9 was calculated as 95% at pH 7.4 and 60% at pH 1.0 clearly indicating that maximum vitamin B12 the release occurred in basic medium. Another important finding was that with an increase in the concentration of KGM during the synthesis of IPN hydrogels, there was a decrease in the amount of drug release. This concluded that the release of vitamin B12 through IPN hydrogel was controlled by both swelling and degradation. Thus, IPN hydrogels could be effectively employed as prospective carriers for colon-specific drug delivery [113].

5.5 Silk Sericin/poly(Methacrylic Acid)-Based IPN Hydrogel for the Release of BSA

Silk sericin is a naturally occurring macromolecular protein derived from silkworms that are thrown away during the process of sericulture. It is soluble in water and is a globular protein made up of 18 amino acids, and around 78% of its mol % residues contain polar side groups such as –OH, –COOH and NH_2 [114]. Silk sericin has various unique features like resistance to oxidation, antibacterial activity, resistance to UV radiations, reversible sol-gel transition, and moisture absorbability [115]. Low-molecular weight (MW) sericin hydrosylates or peptides are used efficiently in the cosmetics industry [116], and high MW is mostly utilized as biomedical materials, functional biomembranes, and degradable biomaterials [117]. The biocompatible sericin has been reported to have tremendous potential for drug delivery applications [118, 119]. Wu and co-workers [120] studied the synthesis of silk sericin poly (methacrylic acid)-based IPN hydrogel for the release of BSA. They studied the swelling behaviour of the synthesized IPN membranes at pH 7.4 and pH 2.6 and concluded that the structure of IPNs swelled more loosely in pH 7.4 as compared to pH 2.6, respectively. Therefore, it was observed that the change in pH affected the

swelling of IPN gels. The analysis of BSA permeation studies as shown in Fig. 10 showed that the permeability of BSA to IPN was higher at pH 7.4 and lower at pH 2.6 which proved it to be a desirable membrane for the optimized release of BSA.

5.6 *Hyaluronic Acid-Based pH-Sensitive IPN for the Transdermal Delivery of Luteolin*

Hyaluronic acid (HA) is a linear polysaccharide consisting of β (1-4) glycosidic linkages between *N*-acetyl-D-glucosamine and glucuronic acid. It is majorly found in the extracellular matrix of the skin and performs various physiological functions of the skin. It is hydrophilic in nature and is helpful in improvising the permeability of the skin and viscoelasticity [121]. Due to the presence of –COOH group, hyaluronic acid can ionize at pH 6–7 and cause the drug release by electrostatic repulsions. These properties can be used for developing ideal drug delivery systems [122]. A. Rang and co-workers [123] prepared a double crosslinked IPN hydrogel composed of HA and PNIPAM (N-isopropyl acrylamide) for the release of luteolin (Fig. 11) for the treatment of psoriasis. Luteolin is a flavoured component extracted from Lavandula angustifolia [124, 125] having anti-inflammatory, anticancer, antioxidant, and immunomodulatory properties [126–129]. Psoriasis causes skin lesions and increased inflammatory responses in the skin [130]. The drug encapsulation efficiency of IPN hydrogel was found to be 42.8%. The drug release was studied for 24 h at different pH (5.5 and 7.4) and temperature (25 and 37 °C) (Fig. 12). The release of luteolin from IPN hydrogel occurred maximum at a temperature of 25 °C and pH of 7.4 within 24 h. After 24 h, a total of 68% of the drug was released. The drug inhibits hyperproliferation of keratinocytes, thereby treating psoriasis. Based on the release studies, it was concluded that it was released slowly in an environment similar to psoriasis (37 °C and pH 7.4) which makes IPN hydrogel a suitable material for drug delivery [123].

5.7 *Poly(vinyl Alcohol)/Methylcellulose Blend IPN Hydrogels for the Release of Doxycyclinehyclate (DOX-h) Drug*

Doxycyclinehyclate (DOX-h) is an antibacterial drug employed for the treatment of diseases in humans and animals [131, 132]. It has a cheap price and is found to be effective in treating bacterial diseases [133]. PVA is a highly biocompatible, easy-to-prepare, biodegradable, and a water-soluble polymer which can be employed for biomedical applications [133]. On the contrary, methylcellulose (MC) is a synthetic

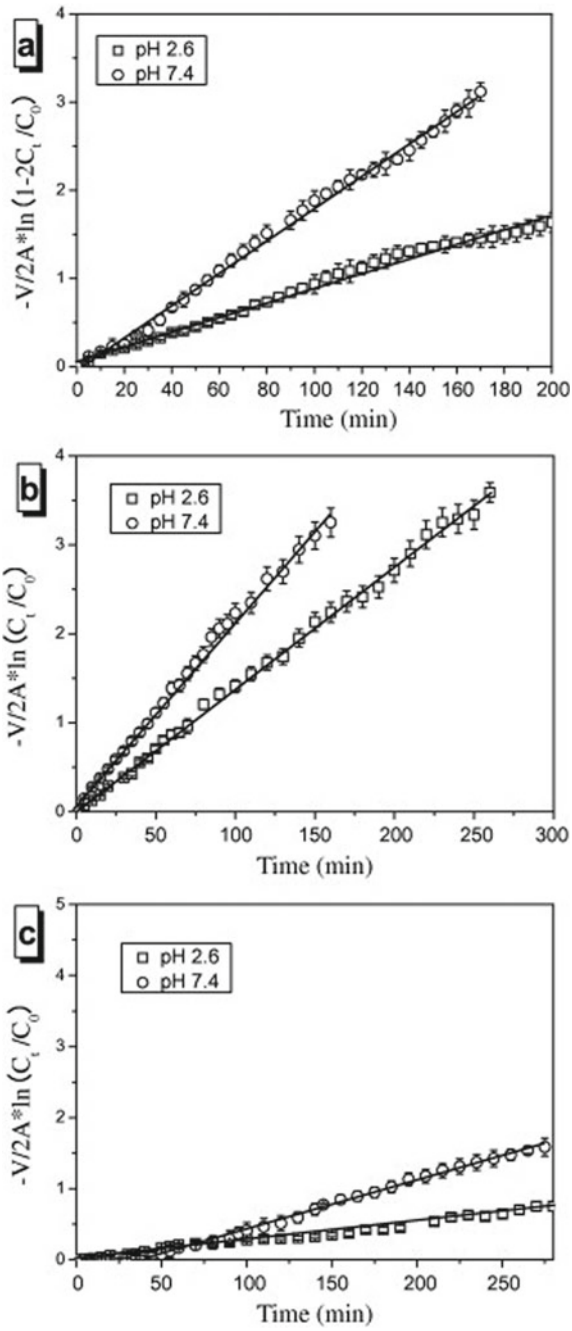

Fig. 10 Total amount of permeated BSA through SM-37 (**a**), SM-55 (**b**), and SM-73 (**c**) at pH 2.6 and 7.4 [120]. Reprinted with permission from Wu et al. [120] Copyright © 2010 Elsevier

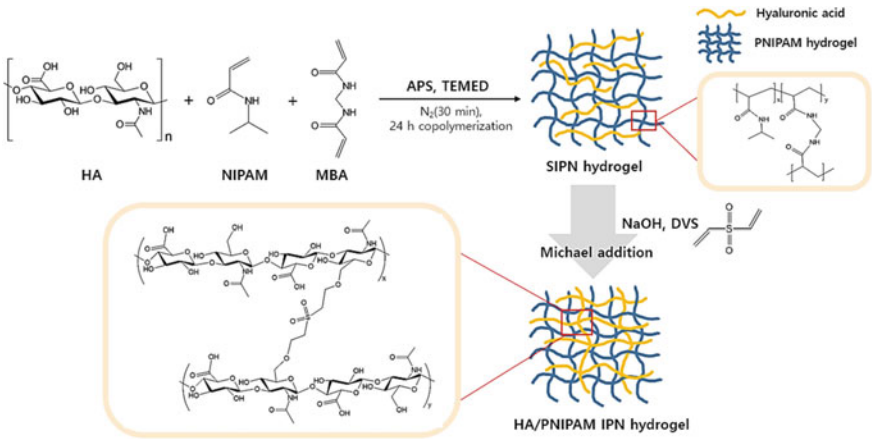

Fig. 11 Schematic representation of HA/PNIPAM IPN hydrogel formation [123]. Reprinted with permission from Kim et al. [123] Copyright © 2018 Elsevier

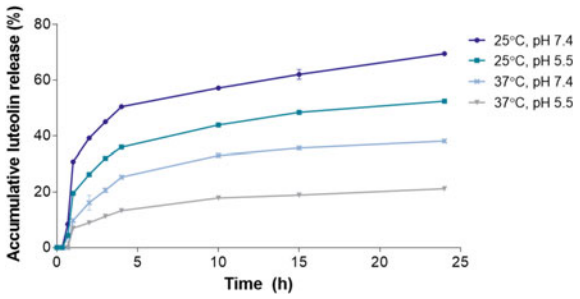

Fig. 12 In vitro drug release profiles of HA/PNIPAM IPN-3 hydrogel at different temperatures and pH [123]. Reprinted with permission from Kim et al. [123] Copyright © 2018 Elsevier

derivative of the natural carbohydrate inside which a few of the –OH groups are replaced by a methoxyl group which declines the crystallinity, thus increasing its solubility in water. PVA and MC can be joined together to form H_2 bonding with the –OH groups of the drug DOX-h. Keeping these potential benefits in mind, El-Naggar and co-workers [134] developed blended IPN hydrogels from PVA and MC through gamma irradiations for the delivery of DOX-h drug used in treatment of antibacterial infections. The amount of drug encapsulated in the synthesized IPN was calculated to be 380 mg/g of hydrogel. The release studies were carried out at pH 7 under room temperature through two forms of synthesized IPNs with varying ratios of PVA/MC. The amount of drug release as analysed increased up to 180 min, and an equilibrium state was achieved till 249 min, suggesting that the complete release of the drug had taken place. The release of DOX-h from PVA/MC (95/5%) IPN hydrogel was found to be lower than PVA/MC (90/10%) IPN hydrogel which suggested that high crosslinking restricted the drug diffusion through the matrix. The release profile also suggested that the PVA/MC IPN hydrogels were pH-sensitive and its swelling and release was affected by changes in pH values as the drug release was maximum in

the basic medium than in an acidic medium [135–138]. Therefore, PVA/MC-based IPN hydrogel was reported to be an ideal system for drug release.

5.8 *Poly (N-Isopropylacrylamide) Copolymerized Acrylic Acid (NIPAAm-Co-AAc)-Based IPN Hydrogel for the Release of Riboflavin Drug*

Poly (*N*-isopropyl acrylamide) (NIPAAm) is a thermosensitive polymer because it consists of a phase transition temperature (LCST) in the water close enough to human body temperature making it a desirable material for biomedical applications [139–141]. The crosslinked hydrogel synthesized through this polymer tends to swell below LCST and degrade above LCST making it ideal for the optimized release of drugs [142–145]. Synthesis of IPN hydrogels improves the elastic and mechanical properties of the gel in comparison with other hydrogels [146–150]. Sanogo et al. [151] synthesized NIPAAm-based IPN hydrogel through free radical polymerization. Riboflavin (vitamin B12) was chosen as a model drug, and the release profiles were investigated at different pH and temperature conditions. The modelling of drug release was done using response surface methodology (RSM) central composite design using Design Expert 10 software. They investigated the release profile of riboflavin loaded in IPN was observed to increase with the increase in temperature, which explained the presence of hydrophobic groups on the backbone of IPN hydrogel. It was noted that the maximum amount of riboflavin released was 91.47% at a temperature of 52 °C and pH 7 followed by 77.97% at 45 °C and pH 2. The ANN model was utilized to predict the drug release, and it was concluded that IPN-based hydrogel serves as an effective drug delivery device for the release of riboflavin [151].

5.9 *IPN Hydrogel Used in External Wound Dressings*

An effective wound dressing must give a moderately moist environment through transpiring excessive exudates promptly and keep the required moisture to cause tissue regeneration. It should have important properties of being non-toxic, biocompatible, and antimicrobial [152, 153]. Hydrogels possess intrinsic properties due to which they are considered to be an appropriate wound dressing material [154–159]. Their transparency is helpful in monitoring the process of healing [160, 161]. A variety of natural as well as synthetic materials have been employed in the manufacturing of wound dressing. Natural biomaterials are profoundly used over synthetic ones,

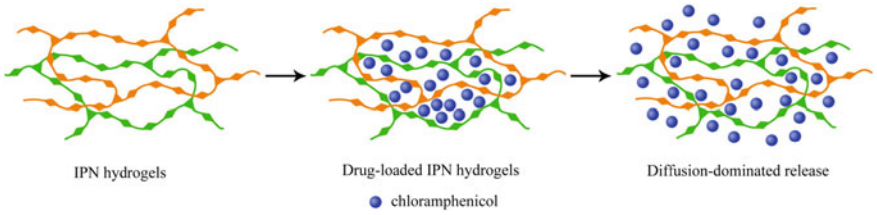

Fig. 13 Schematic diagram of drug loading and release behaviour from the IPN hydrogels [174]. Reprinted with permission from Wang et al. [174] Copyright © 2017 Elsevier

and the most commonly used biomaterials are cellulose, gelatin, chitin/chitosan, and alginate [162–167]. The process of wound healing is considered to be very complicated, and no single biomaterial can meet and fulfil all the requirements at every stage [168, 169]. To overcome this limitation, IPN hydrogels have been synthesized because they can combine properties and functions of various polymers to synthesize a multicomponent hydrogel with excellent wound healing properties [170–173]. Jingjing and co-workers [174] worked on the synthesis of IPN hydrogel based on gelatin and 2-hydroxypropylcellulose (HPC) through enzymatic and chemical crosslinking methods. They used chloramphenicol as a model drug and studied its release behaviour through the IPN hydrogel at 25 °C. The drug loading and release behaviour is shown in Fig. 13. The presence of HPC content in IPN hydrogel affected the drug release. With the increase in HPC content, the release of the drug also enhanced [175]. It was also observed that the drug release did not show any burst release suggesting the slow and efficient release of chloramphenicol from IPN in wound dressings [176]. A sustained drug release for about 22 h was observed, which suggested that these drug-loaded IPN hydrogels can be successfully utilized for the optimized release of chloramphenicol drug creating microbe-free environments, thereby limiting the side effects caused by an excessive amount of a drug otherwise acting on the target site [176].

5.10 Poly(Acrylonitrile)-Based IPN Hydrogel for the Release of Fluorescin Sodium Salt (FSS)

Acrylonitrile is a hydrophobic monomer, and the presence of cyano groups on acrylonitrile-based polymers is appropriate for the conversion into hydrophobic amidoxime groups [177]. 4-Vinylpyridine (4-VP) also consists of attractive properties like hydrophobic–hydrophilic balance and amphoteric nature [178, 179]. Coskun and co-workers [180] synthesized poly(acrylonitrile) (p(AN))-based materials such poly(acrylonitrile-co-(3-acrylamidopropyl)-trimethylammonium chloride

(p(AN-co-APTMACl)), poly(acrylonitrile-co-4-viniyl pyridine) (p(AN-co-4-VP)), and poly(acrylonitrile-co–N-isopropylacrylamide) (p(AN-co-NIPAM)) core–shell nanoparticles (Fig. 14). These developed nanoparticles were effectively used for drug delivery of fluorescein sodium (FSS) drug and antimicrobial properties. The digital camera images p(HEMA) hydrogel film, FSS-loaded p(HEMA)-p(AN-co-4-VP)$^{++}$ IPN hydrogel film, p(AAm) hydrogel films, and FSS-loaded p(AAm)-p(AN-co-4-VP)$^{++}$ film were displayed in Fig. 15. It was observed that the microgels inside the hydrogels absorb much more FSS than matrix materials (p(AAm) or p(HEMA). The drug release could also be lengthened by increasing the quantity of crosslinker in both microgel and IPN hydrogel. The drug release was studied for 200 min, and in the case of p(AAm), it was found to be 0.53 ± 0.0072 mg/g FFS, while in p(AAm)-p(AN-co-4-VP)$^{++}$ IPN composite, it was found to be 1.24 ± 0.0054 mg/g FSS. The results demonstrated that this microgel-IPN composite system has versatility and tenability in the prolonged active release of FSS drug and this can also have a high potential of applications in wound dressings and delivery of various other drugs [180, 181]. Various forms of IPN-based drug delivery systems have been summarized in Table 2.

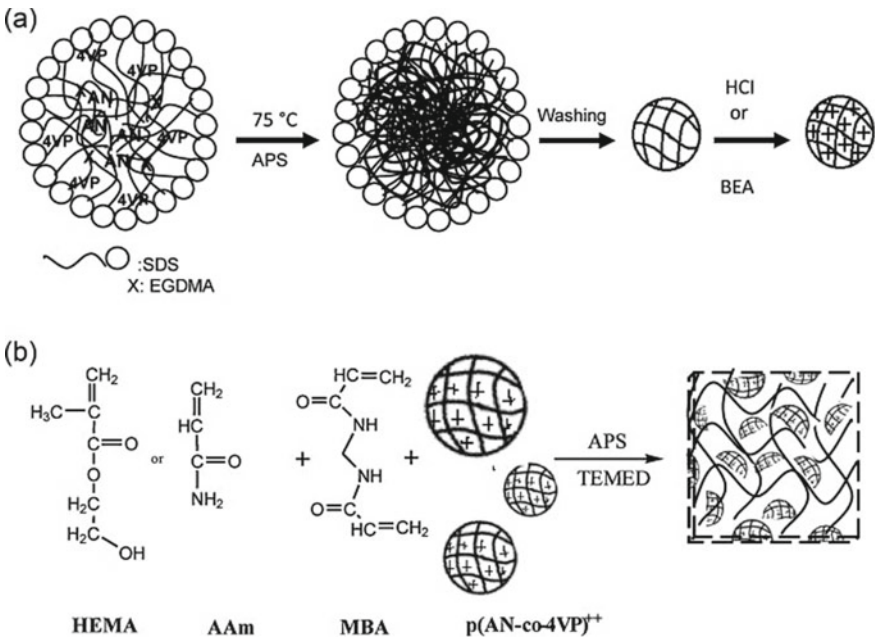

Fig. 14 Schematic representation of **a** p(AN-co-4VP) particle synthesis, and **b** hydrogel–nanogel IPN composite synthesis [180]. Reprinted with permission from Silan et al. [180] Copyright © 2012 Elsevier

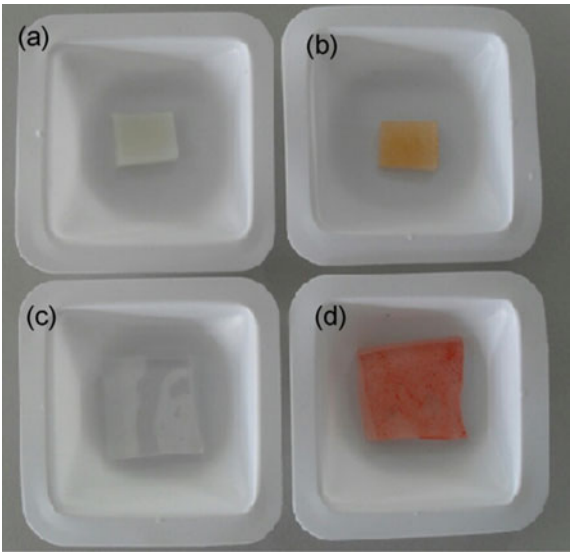

Fig. 15 Digital camera images of **a** p(HEMA), **b** FSS-loaded p(HEMA)-p(AN-co-4VP)$^{++}$, **c** p(AAm), and **d** FSS-loaded p(AAm)-p(AN-co-4VP)$^{++}$ [180]. Reprinted with permission from Silan et al. [180] Copyright © 2012 Elsevier

6 Conclusions

Interpenetrating polymer networks have received a lot of merits from the past few decades due to the improvised properties and better drug loading and release rates as compared to single network hydrogels. It has been helpful in overcoming the shortcomings of drugs which earlier could not be released through hydrogels due to poor encapsulation efficiency were improved after the development of IPN systems. Since it employs two or more polymers, multiple characteristics are imparted into one system and this property has been used for making wound dressings. It has also been stated in many works that IPN hydrogels have better drug encapsulation efficiency and faster release kinetics of various drugs which makes it an ideal system and reduces the toxic side effects of drugs caused due to unequal release at its target site. IPN hydrogels also respond to fluctuations in pH, temperature, humidity as explained in earlier works, making it suitable for the drug to release in specified target organs, thereby making it a smart gel. Therefore, it can be concluded that IPN hydrogels have all the potential benefits of being used as an efficient drug delivery device and also acts as a promising material for further research work in the future. Still, a lot more applications in the field of drug release using IPN hydrogels are yet to be discovered.

Table 2 IPN-based drug delivery systems

S. No.	IPN hydrogels	Synthesis method	Drug used	Application	References
1	Bipolymeric alginate-based IPN hydrogel	Graft polymerization and crosslinking processes by free radical polymerization technique	BSA and 5-amino salicylic acid	For the treatment of diseases related to colon like Crohn's disease and Ulcerative Colitis	[68–77]
2	Sugarcane bagasse-based cellulose IPN hydrogels	In situ free radical polymerization	BSA	Useful for fatty acid binding and prevention of cancer	[3, 78–92, 182]
3	Salecan-based IPN hydrogel	Free radical polymerization	Amoxicillin	Acts as an antibiotic for the treatment of bacterial infections	[93–102]
4	Konjac glucomannan-poly(acrylic acid)-based IPN hydrogel	Free radical polymerization	Vitamin B12 drug	For the treatment of bowel disease	[103–108, 113, 183, 184]
5	Silk sericin/poly(methacrylic acid)-based IPN hydrogel	Free radical polymerization	BSA	For the prevention of cancer	[114–120]
6	Hyaluronic acid-based pH-sensitive hydrogel	Radical polymerization	Luteolin	For the treatment of psoriasis	[121–130]
7	Poly(vinyl alcohol)/methylcellulose blend IPN hydrogels	Free radical polymerization	DOX-h drug	For the treatment of bacterial infections	[133–138]

(continued)

Table 2 (continued)

S. No.	IPN hydrogels	Synthesis method	Drug used	Application	References
8	Poly (*N*-isopropylacrylamide) copolymerized acrylic acid (NIPAAm-co-AAc)-based IPN hydrogel	Free radical polymerization	Riboflavin	Use to treat eye conditions including eye fatigue, cataracts, and glaucoma	[139–151]
9	Gelatin-based IPN hydrogel	Radical polymerization	Chloramphenicol	Wound dressings	[152–176]
10	Poly(acrylonitrile)-based IPN hydrogel	Free radical polymerization	FSS	For the treatment of antimicrobial infections	[177–181, 184]
11	Alginate-based IPN hydrogel	Free radical polymerization	Pilocarpine	For the treatment of dry mouth caused by Sjogren's syndrome	[185–190]

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Conflicts of Interest The authors declare no conflict of interest.

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Biopolymeric Nanocomposites in Drug Delivery

Zahra Shariatinia

Abstract There is a growing interest in the development of biopolymeric nanocomposite materials for application in various biomedical areas particularly in drug delivery. This is because such materials are environmentally friendly, non-toxic, biocompatible, biodegradable, and present desirable functionalities compared to the synthetic polymers. Moreover, as the ultimate goal of the drug delivery systems is their application by human beings and animals, it is very important that the designed drug delivery systems (DDSs) possess the above-mentioned characteristics. So far, a number of nanocomposites have been prepared for drug delivery purposes using diverse biopolymers and nanomaterials. The most common nanomaterials include silver, gold, ZnO, TiO_2, silica and clay nanoparticles, carbon quantum dots, carbon nanotubes, graphene, hydroxyapatite, and bioglass. Moreover, mixed nanocomposites of such nanomaterials such as core-shell, yolk-shell, and coupled/impregnated nanostructured compounds have been prepared and used as drug carriers and then they were loaded into the polymeric matrix. Furthermore, some nanocomposites are fabricated using polymers as cores and nanomaterials as a shell or vice versa. These drug delivery platforms have the capability of simultaneously carrying different pharmaceutics, vitamins, and pharmaceutical grade supplements required for the patients' treatment. This chapter offers the most recent significant researches on various biopolymeric nanocomposites in drug delivery using biomacromolecules including chitosan, carboxymethyl chitosan, alginate, hyaluronic acid, cellulose, carboxymethyl cellulose, starch, gellan gum, gum acacia/gum arabic, guar gum, gelatin, chondroitin sulfate, pectin, and collagen.

Keywords Biopolymer nanocomposites · Drug delivery · Chitosan · Carboxymethyl chitosan · Alginate · Hyaluronic acid · Cellulose · Carboxymethyl cellulose · Starch · Gellan gum · Gelatin · Gum acacia/gum arabic · Guar gum · Chondroitin sulfate · Pectin · Collagen

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1 Introduction

Nowadays, biopolymers are commonly employed as raw materials for the preparation of drug delivery systems (DDSs) because they possess exceptional properties including biodegradability, biocompatibility, non-toxicity, and biological/environmental safety [1–5]. It is notable that although synthetic polymers are also used as DDSs because they reveal light weights, high strengths, easy processing, and low costs, most of them are not biodegradable and have serious environmental problems for both the consumer and environment [6–10]; hence, numerous researchers prefer to use biodegradable polymers such as chitosan that is one of the most plentiful natural polysaccharides used as DDSs because of its antimicrobial, and mucoadhesive, biodegradability, biocompatibility, and film-forming properties [11–15].

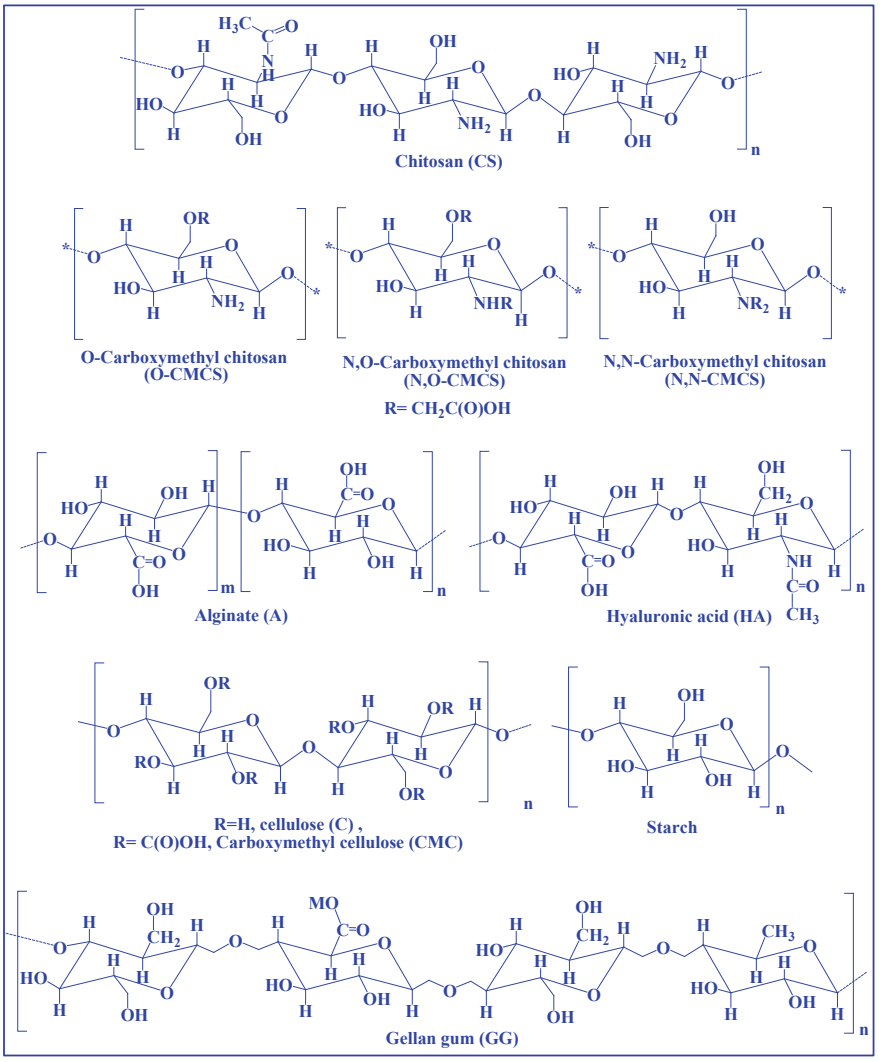
Currently, biopolymeric nanocomposites are of great interest in drug delivery as they illustrate superior biomedical characteristics [16–20]. Most biopolymeric nanocomposites are suitable drug carriers as they display highly improved properties in comparison to their related pure polymers [21–25]. Addition of nanoparticles into the biopolymeric matrix can decrease the burst drug release, enhance drug stability, and lead to slower and more sustained drug release [26–30]. For example, the drug release behaviors have been examined from a large number of biopolymeric nanocomposites containing diverse inorganic particles such as silver, gold, ZnO, TiO_2, silica, clay, carbon quantum dots, carbon nanotubes, graphene, hydroxyapatite, bioglass, core-shell, yolk-shell, and coupled/impregnated nanostructures [31–35].

The synthesis of cost-effective antibacterial nanoparticles (NPs) and their nanocomposites has been of substantial interest in numerous pharmaceutical, biomedical, cosmetics, drug delivery as well as antimicrobial applications [36–40]. NPs have extraordinary chemical, physical, and advanced medical characteristics and great potential for usage in different healthcare areas. Furthermore, polymers have shown a crucial role in the synthesis and stabilization to obtain NPs with anticipated shapes and morphologies [41–45]. Among several polymers, biopolymer stabilized NPs are very important in biomedical applications as they indicate exceptional properties like ecofriendly nature and biocompatibility [46–49]. Introducing NPs to the biopolymers matrixes can improve the properties of the prepared biopolymeric nanocomposites [50–53]. Besides, biopolymer stabilized NPs reveal significant features such as high aspect ratios, multifunctionality, and low densities which make them appropriate antimicrobial materials for application in drug delivery platforms [54–56]. It is noteworthy that biopolymers not only decrease the production costs of NPs but also they can control the morphology and size of NPs [57–59].

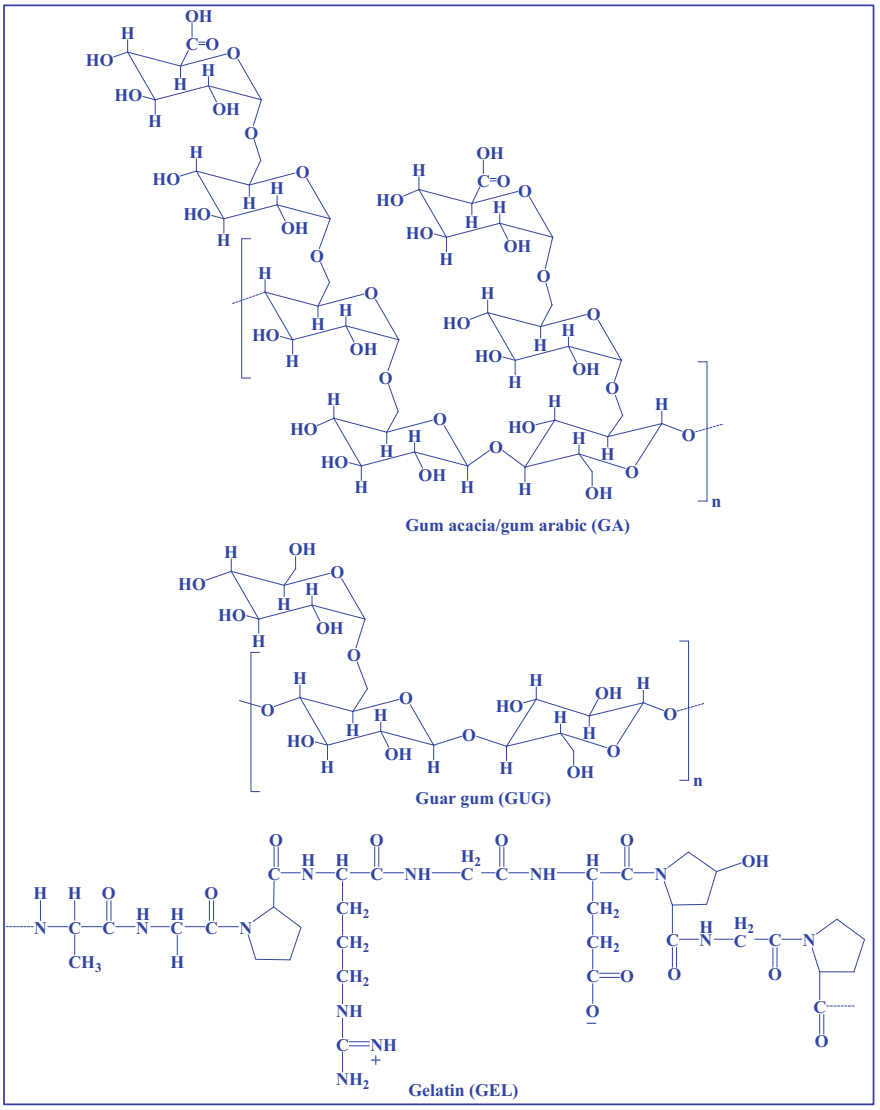
Modified drug carriers such as biopolymeric nanocomposites can improve the bioavailability of drugs and decrease side effects [60–63]. The biopolymeric nanocomposites are hybrid nanomaterials with improved features because of the synergistic effects of biopolymers (rheological/mechanical property, swelling capacity, bioadhesion, cellular uptake, and film-forming ability) and nanomaterials

(dispersion stability or ion exchange capability) [64–66]. Such optimized properties can improve the characteristics of these materials as DDSs such as enhanced drug stability, reduced burst release as well as slower and sustained drug release [67–69].

This chapter presents the drug delivery applications of diverse biopolymeric nanocomposites prepared based on biopolymers such as chitosan, alginate, hyaluronic acid, cellulose, carboxymethyl cellulose, starch, gellan gum, acacia gum, guar gum, gelatin, chondroitin sulfate, pectin, and collagen. Scheme 1 indicates the chemical structures of the biopolymers studied in this chapter.



Scheme 1 The chemical structures of the biopolymers



Scheme 1 (continued)

2 Chitosan and Carboxymethyl Chitosan Nanocomposites in Drug Delivery

Chitosan (CS) is a copolymer comprised of *N*-acetyl-D-glucosamine and D-glucosamine units containing one amino (NH_2) and two hydroxyl (OH) groups in each repeating glycosidic units [70]. At low pH values, chitosan becomes polycationic through protonation of amino groups leading to its increased solubility [3]. Chitosan is prepared from a non-toxic renewable resource and serves as a biocompatible material. The antimicrobial nature and low immunogenicity of CS together with its outstanding biodegradability and biocompatibility have resulted in its widespread biomedical applications. Other biological features of CS include in situ gelation, mucoadhesion, transfection, controlled drug delivery, permeation improvement, efflux pump inhibition, and colon targeting [6]. Also, the bioadhesiveness of CS leads to its adherence to hard/soft tissues for numerous applications like orthopaedics, ophthalmology, surgical measures, and dentistry [22]. Thus, CS has been frequently used as an excellent material in the fabrication of efficient drug delivery systems [22].

Recently, graphene oxide nanosheets loaded magnetic iron oxide NPs (mGO) were synthesized and used for the preparation of chitosan/sodium alginate (CS/SA) functionalized mGO nanocomposites through layer-by-layer self-assembly (Fig. 1) for application in targeted anticancer drug delivery as well as photothermal therapy [71].

The mGO-CS/SA nanocomposites were ~0.5 μm in diameter and 40–60 nm in thickness and exhibited superparamagnetic property (see Fig. 2).

The stability tests displayed that the agglomeration of nanocomposites was decreased but their stability in the biological medium was increased. However, nonspecific adsorption of protein was highly declined upon modification. The doxorubicin hydrochloride (DOX) was loaded onto the mGO-CS/SA nanocomposites through electrostatic and π–π stacking interactions and a large drug loading value of 137%w/w was measured. The dispersion plus pH-sensitive drug release behaviors of DOX-containing nanocomposites, mGO-CS/SA-DOX, were improved. The cellular experiments indicated magnetically targeted cellular uptake and exceptional photothermal influence of mGO-CS/SA along with concentration-dependent cytotoxicity by the mGO-CS/SA-DOX. Consequently, the mGO functionalization by CS and SA was favorable for biomedical applications. In another effort, silver NPs (AgNPs) were in situ synthesized during the preparation of physically crosslinked CS hydrogel beads by means of sodium tripolyphosphate crosslinker for application as DDSs [72]. The swelling and antibacterial properties of the CS nanocomposite beads were examined that illustrated appropriate antibacterial properties against *Staphylococcus aureus* and *Escherichia coli* microorganisms. AgNPs increased the swelling ability of the CS beads. The in vitro drug release from the nanocomposite beads (Fig. 3) proved that they had a controlled drug release behavior as controlled and prolonged drug releases happened from the CS beads containing AgNPs which was enhanced with increasing the AgNPs amount.

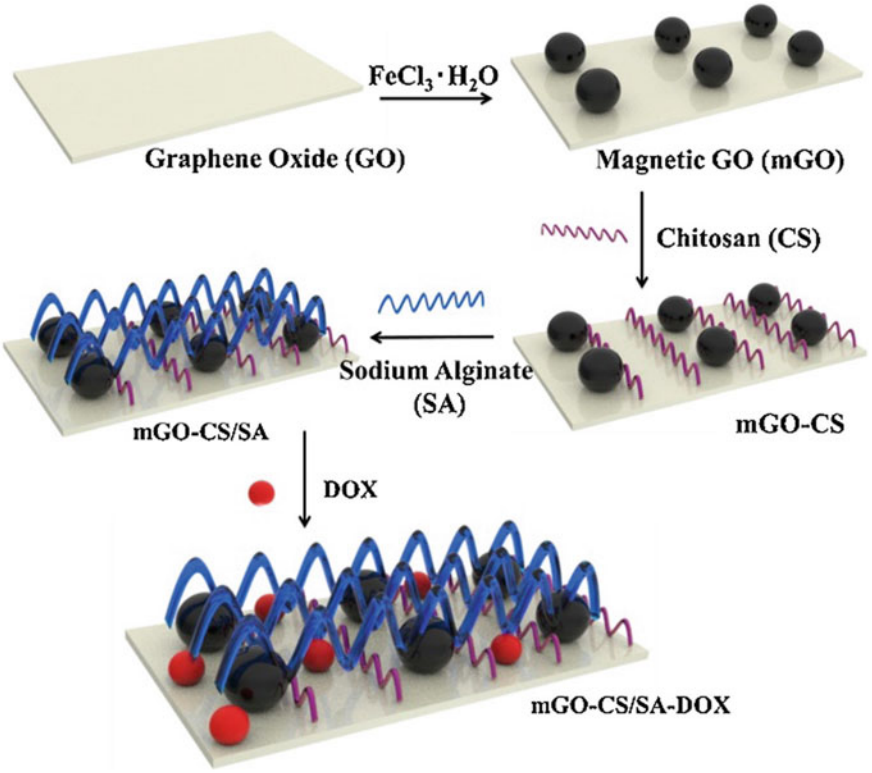


Fig. 1 Depiction of the synthesis of mGO-CS/SA and DOX loading [71] (Reprinted with permission from Xiea et al., 2019 Copyright © 2019 Elsevier)

CS supported ciprofloxacin-HCl-CS/Tween-80/tripolyphosphate (CIP@CS-TW/TPP) as DDS was prepared by the sol–gel method [73]. The CIP drug encapsulated nanocomposite interacted with bovine serum albumin (BSA) in order to carry the drug at the target site. Addition of Tween-80 to the CIP/CS-TPP boosted the loading ability of the nanocomposite and enhanced the drug release ratio to 61–78% compared to that of the pure CS (37%). The influence of surfactant concentration on the CIP–BSA interaction was evaluated through the introduction of diverse Tween-80 concentrations (1 and 2 μM). The fluorescence quenching analysis proved the CIP binding to the BSA and CIP–BSA complex formation. The thermodynamic experiments indicated that the Van der Waals forces and hydrogen bonds had significant roles in the CIP–BSA interactions (Fig. 4).

The drug–protein interactions confirmed that the CIP@CS-TW/TPP nanocomposite was a promising candidate for drug delivery purposes.

In another work, a stimuli-responsive hydrogel nanocomposite was achieved by copolymerization reaction of acrylic acid and N-isopropyl acrylamide on CS and then in situ synthesis of Fe_3O_4 magnetic NPs [74]. The hydrogel nanocomposite was used

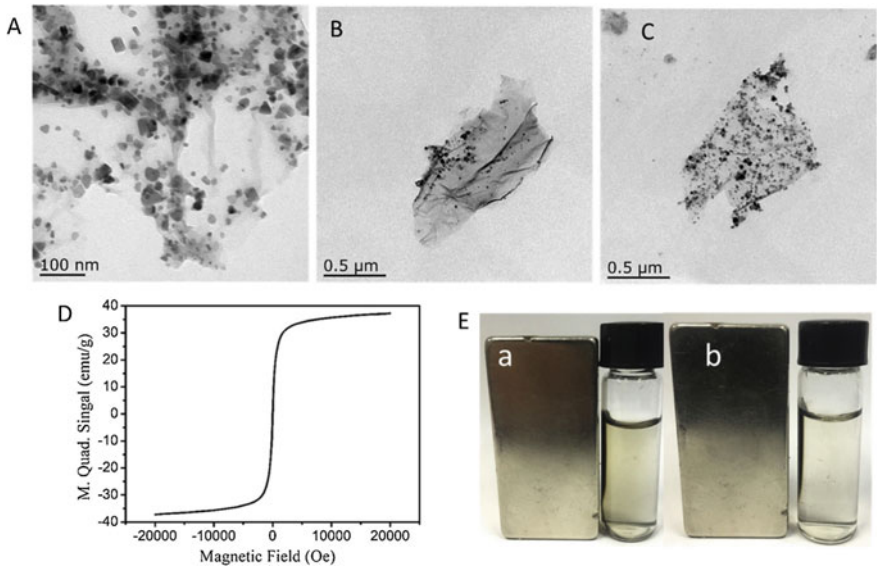


Fig. 2 TEM images of mGO (**A**), mGO-CS (**B**) and mGO-CS/SA (**C**). **D** Magnetic hysteresis loop of mGO. **E** mGO (**a**) and mGO-CS/SA (**b**) in aqueous solutions with magnets [71] (Reprinted with permission from Xiea et al., 2019 Copyright © 2019 Elsevier)

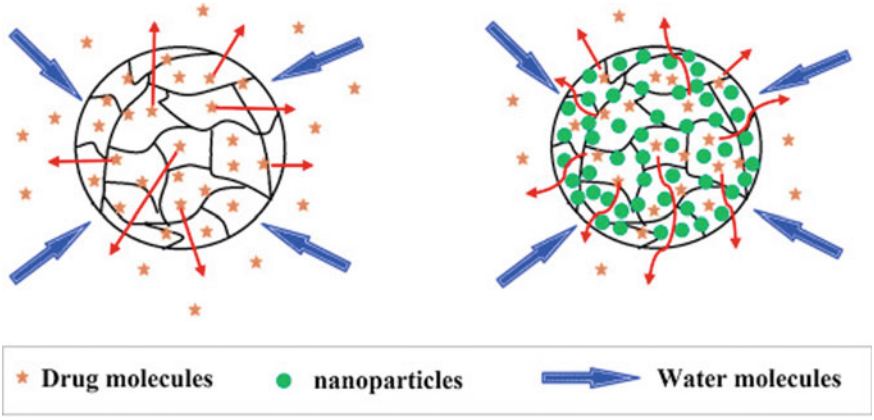


Fig. 3 Drug release mechanism from pure chitosan bead and CH/Ag nanocomposite bead [72] (Reprinted with permission from Yadollahi et al., 2015 Copyright © 2015 Elsevier)

as the DDS for the controlled release of anticancer DOX drugs. The nanocomposite revealed the maximum drug loading efficiency of 89% and the DOX was released in vitro in a sustained manner. Also, the nanocomposite illustrated dual pH and temperature responsiveness, and 82% DOX release happened from the hydrogel in 2 days (Fig. 5).

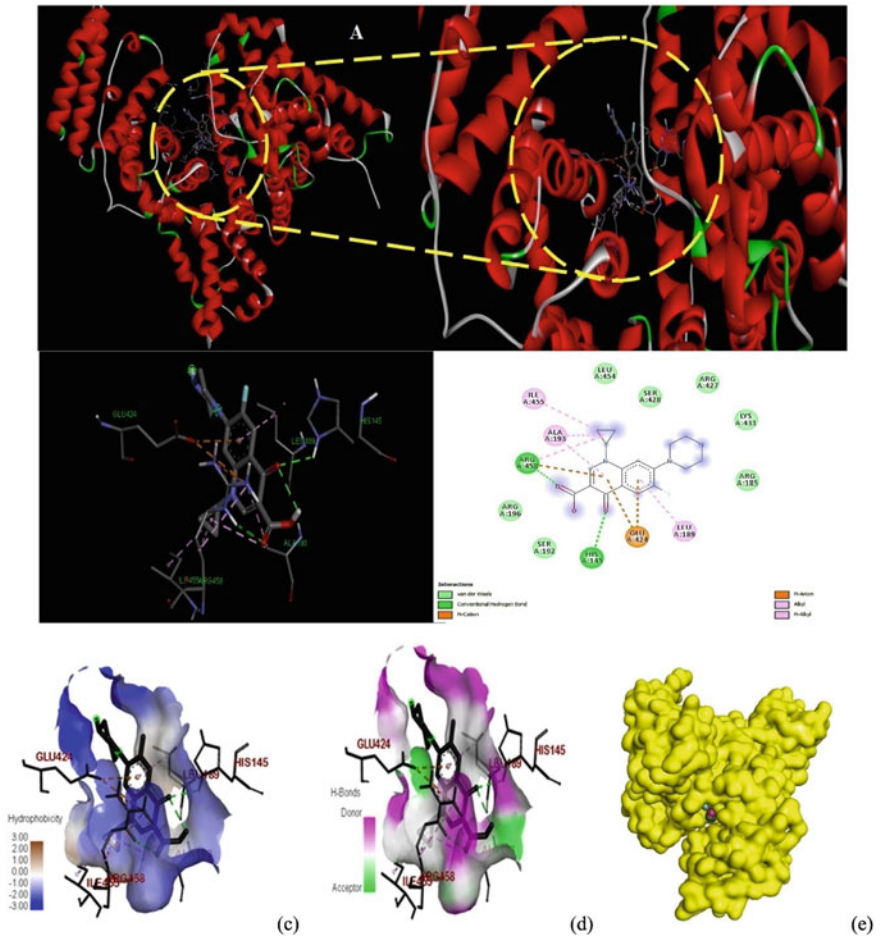


Fig. 4 **a**–**e** Interactions between ciprofloxacin and BSA using grid box size 126 Å, 126 Å, 126 Å along *x*, *y*, *z* axes covering whole protein with a grid-point spacing of 0.564 Å (**a**), The residues of BSA and the ligand structure are represented using ball and stick model (3D) and (2D) (**b**), The hydrophobic (**c**) and hydrogen bonding pocket view of binding location of BSA (**d**) interacting with ciprofloxacin shown as molecular surface structure; cluster analysis (**e**) [73] (Reprinted with permission from Manea et al., 2019 Copyright © 2019 Elsevier)

Hence, the CS-based nanocomposite could be used as an auspicious carrier for sustained and controlled drug release. Recently, Fe_3O_4 magnetic NPs were functionalized using (3-amino propyl) triethoxy silane, coated with CS and tragacanth gum (TG), and were used for encapsulation of the curcumin drug [75]. The curcumin release was tested at two diverse pH values of 7.4 and 3.4 and at two temperatures of 37 and 40 °C. The nanocomposite exhibited a greater swelling at pH 3.4 and 40 °C along with appropriate pH and thermosensitivity in vitro. It was suggested that such nanocomposite was a useful carrier for chemotherapeutic drug delivery.

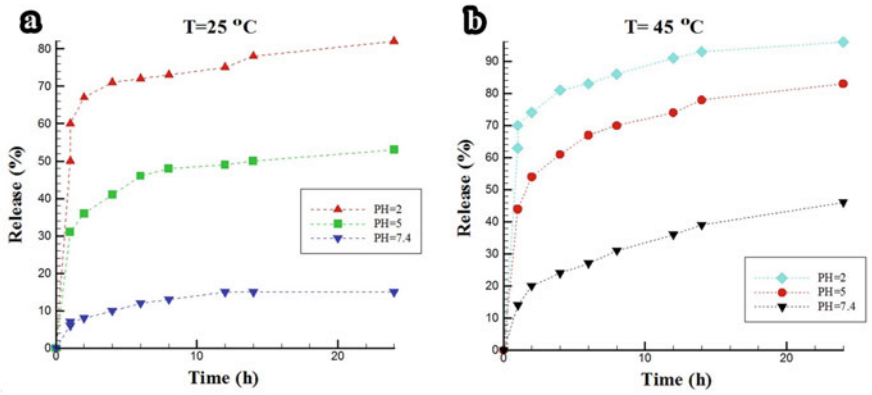


Fig. 5 Release profiles of DOX-loaded magnetic chitosan nanocomposite at **a** $T = 25$ °C and **b** $T = 45$ °C in buffer solutions with pH = 2.0, pH = 5.0, and pH = 7.4 [74] (Reprinted with permission from Hosseinzadeh et al., 2019 Copyright © 2019 Elsevier)

ZnO nanoparticles (ZnONPs) were synthesized in situ during the preparation of physically crosslinked CS hydrogel beads (in presence of sodium TPP crosslinker) for application as drug delivery platforms (Fig. 6) [76].

The scanning electron microscopy (SEM) images exhibited that the diameters of the ZnONPs dispersed in the hydrogel matrix were in the range of 10–25 nm, see Fig. 7.

The swelling of the nanocomposite hydrogels revealed a pH-sensitive trend. The ZnO containing nanocomposite hydrogels indicated higher swelling ratios in diverse aqueous solutions compared to the neat hydrogel. Controlled and sustained drug release values were measured for the ZnO NPs comprising CS beads which were enhanced with increasing the ZnO NPs quantity.

Two core-shell fibers that self-assembled the liposome were fabricated using bioadhesive carboxymethyl chitosan (CMCS) and sodium carboxymethyl cellulose (CMC-Na) [77]. The CMCS/PVA and CMC-Na/PVA (PVA is polyvinylalcohol) formed the shell layers and a mixture containing phospholipids and carvedilol (Car) was used as the core layer. It was established that the Car was nearly entirely released in 2 h which revealed a linear release profile. The permeation tests were performed using porcine TR146 cell culture and buccal mucosa which proved that both of the self-assembled liposome and bioadhesive polymers could promote drug penetration. It was also found that the TR146 cells were alive upon incubation with fibers' extraction medium with 10 mg/mL concentration. Thus, the self-assembled liposome and core-shell fiber obtained by means of a water-soluble bioadhesive polymer were suitable for the absorption of Car buccal.

To release of diclofenac sodium drug that was sensitive to the gastrointestinal environment or irritating to stomach was controlled using sodium alginate (SA) hydrogel beads containing CMCS-coated ZnO NPs (Fig. 8) as drug delivery devices [78].

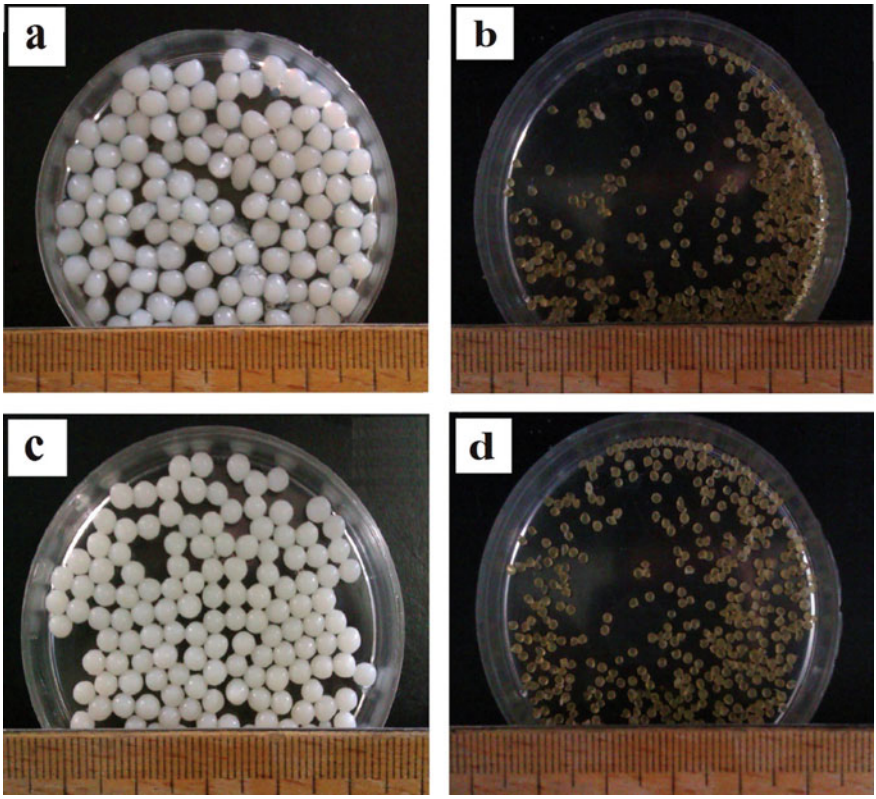


Fig. 6 Digital photo of pure chitosan hydrogel bead in **a** wet and **b** dry state: and CS/ZnO nanocomposite hydrogel bead in **c** wet and **d** dry state [76] (Reprinted with permission from Yadollahi et al., 2016 Copyright © 2016 Elsevier)

The application of CMCS-ZnO NPs led to sustained and slower drug release in vitro. The in vivo pharmacokinetics tests proved the DS bioavailability was enhanced by oral administration of the drug-loaded SA/CMCS-ZnO hydrogel beads indicating such hydrogel beads were favorable for delivery of drugs sensitive to gastrointestinal environmental or irritating to stomach. In another research, pH-sensitive fluorinated CMCS NPs were produced as DDSs using *N*-(3-aminopropyl)-imidazole pre-grafted to the CMCS to fabricate the pH-sensitive AM NPs that were then surface-modified by perfluorobutyric anhydride to achieve fluorinated (FM) NPs [79]. The cellular uptake tests confirmed that the surface fluorinated NPs enhanced cell uptake and improved cytotoxicity in diverse tumor cells without recognition between ligands and host (Fig. 9).

In addition, fluorinated NPs revealed more accumulation in tumor and longer blood circulation which led to higher antitumor efficacy and greater bioavailability of anticancer drug in vivo. Therefore, the pH-sensitive fluorinated NPs were proposed as effective drug carriers for cancer chemotherapy.

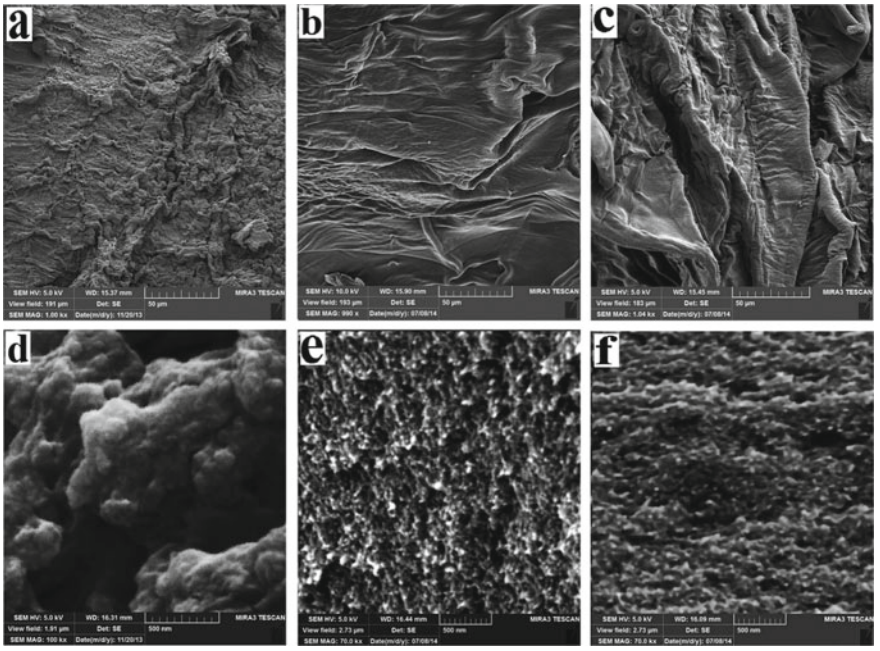


Fig. 7 SEM micrographs of pure chitosan hydrogel bead (**a**) CS/ZnO-1 (**b**) CS/ZnO-3 (**c**) at low magnification (×1000) and micrographs of pure chitosan hydrogel bead (**d**) CS/ZnO-1 (**e**) CS/ZnO-3 (**f**) at high magnification (×100,000) [76] (Reprinted with permission from Yadollahi et al., 2016 Copyright © 2016 Elsevier)

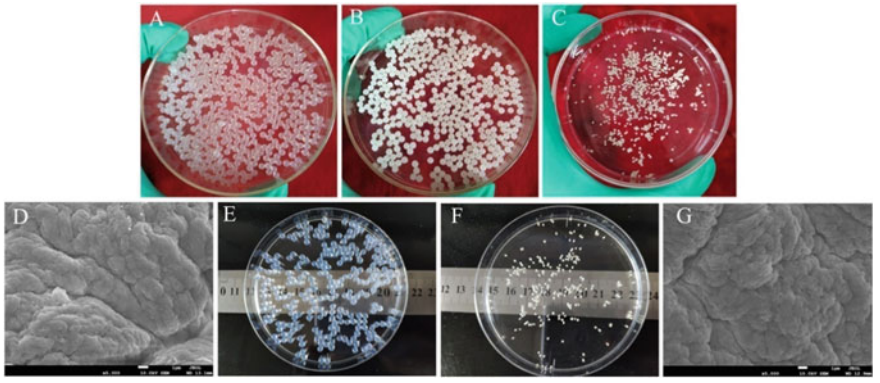


Fig. 8 Characterization of SA/CMCS-ZnO hydrogel beads. **a** Digital photo of SA hydrogel beads, **b** digital photo of SA/CMCS-ZnO-2 hydrogel beads, **c** digital photo of SA/CMCS-ZnO-2 hydrogel beads in a dry state, **d** SEM micrograph of SA/CMCS-ZnO-2 hydrogel beads in a dry state (× 5000), **e** digital photo of DS-loaded SA/CMCS-ZnO-2 hydrogel beads, **f** digital photo of DS-load SA/CMCS-ZnO-2 hydrogel beads in a dry state, **g** SEM micrograph of DS-loaded SA/CMCS-ZnO-2 hydrogel beads in a dry state (×5000) [78] (Reprinted with permission from Niu et al., 2019 Copyright © 2019 Elsevier)

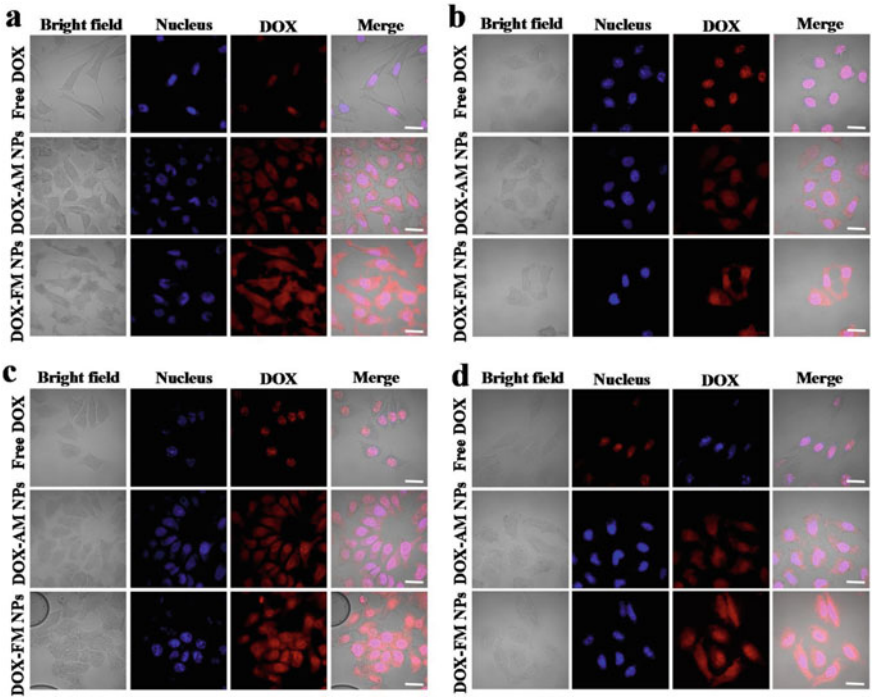


Fig. 9 The cellular uptake of DOX-loaded AM and FM NPs in SH-SY5Y cells (**a**), HepG2 cells (**b**), MCF-7 cells (**c**) and A549 cells (**d**). Scale bar = 10 μm [79] (Reprinted with permission from Cheng et al., 2019 Copyright © 2019 Elsevier)

An amphiphilic stearic acid-*O*-carboxymethyl chitosan (STA-CMC) conjugate was synthesized and self-assembled to STA-CMC NPs that revealed a hydrodynamic diameter of ~100 nm to which paclitaxel (PTX) anticancer drug was loaded [80]. The multi-hydrophobic inner core of the PTX-STA-CMC NPs led to a drug loading capacity of ~19 wt%, a biphasic drug release, and an accumulative release of 70–90% in 72 h. the PTX-STA-CMCNPs were highly accumulated at the tumor sites through passive targeting subsequent to cell endocytosis. The acid-sensitive PTX-STA-CMC NPs exhibited remarkable instability upon pH changes, thus triggered a rapid disassembly in addition to faster drug release. Accordingly, compared to the free PTX treatment, the pH-stimulus PTX-STA-CMC NPs resulted in ineffective apoptosis of cancer cells and suppressed tumors by chemotherapy.

It is known that colorectal cancer is the third main cause of death by cancer. Also, the chemotherapeutic drug 5-fluorouracil (5-FU) has limited clinical application because of its low bioavailability, non-specificity, and overdose. However, the 5-FU efficiency in colorectal cancer treatment could be improved through nano-encapsulation as well as a combinatorial method using bisdemethoxycurcumin

(BDC). Recently, a bioactive and pH-sensitive aminated mesoporous silica–alginate/folic acid-conjugated *O*-CMCS-gelatin, AMSN-A/FA-CMCS-GEL, nanocomposite was achieved that was loaded by BDC and 5-FU for application in colon cancer therapy [81]. The BDC and 5-FU loaded DDS were compatible with blood and sustained in vitro drug release was measured at pH values of 1.2 and 7.4 in 48 h, see Fig. 10. The combinatorial methodology of using BDC and 5-FU in HCT116 cells evidenced anticancer effects in addition to the intracellular drug uptake that was established with the confocal microscopy images.

3 Alginate Nanocomposites in Drug Delivery

Sodium alginate (SA) is a natural linear polysaccharide that is usually extracted from soil bacteria and brown algae. It is extensively utilized in the food industry as a thickener, in DDSs and bone tissue engineering as a result of its low cost, nontoxic, biocompatible, and biodegradable features [82]. SA can easily be prepared as microspheres with three-dimensional network structures through crosslinking by calcium ions that are more biocompatible compared to organic crosslinkers like formaldehyde and glutaraldehyde [83].

In an attempt, hydroxyapatite-sodium alginate-chitosan (HAP-SA-CS) composite microspheres were produced by an emulsion crosslinking procedure using calcium ions as the crosslinker [84]. The effect of SA concentration, the water to oil volume ratio, the HAP nanoparticles content, and rotation speed on the dispersion and morphology of the composite microspheres were examined. It was found that the encapsulation efficiency and drug loading of the HAP-SA-CS composite microspheres were very greater compared to that of the HAP NPs (Table 1).

The DOX-loaded HAP-SA-CS microspheres showed suitable pH-sensitive drug release, see Fig. 11.

The cytotoxicity and hemolysis experiments suggested that the microspheres had appropriate cell and blood compatibility. Besides, the composite microspheres displayed superior proliferation capability and cell adhesion relative to the HAP NPs and HAP-SA microspheres. Consequently, the HAP-SA-CS composite was suggested as a promising pH-sensitive controlled release DDS.

Some SA-ZnO hydrogel beads were prepared (Table 2) to improve the release of curcumin (CUR) in order to prevent the burst release observed in pure hydrogels and to decrease the fast physiological clearance of CUR and its sensitivity to ultraviolet light and alkaline solution [85].

The composite beads exhibited suitable pH sensitivity and controlled release ability which prolonged the CUR residence time within the gastrointestinal tract (Fig. 12).

Subsequent to ultraviolet radiation exposure for 6 h, the CUR-loaded beads exhibited 13.70% decrease in 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) scavenging ability but pure CUR displayed 62.04% decrease confirming the encapsulated CUR had a greater antioxidant capacity (Fig. 13).

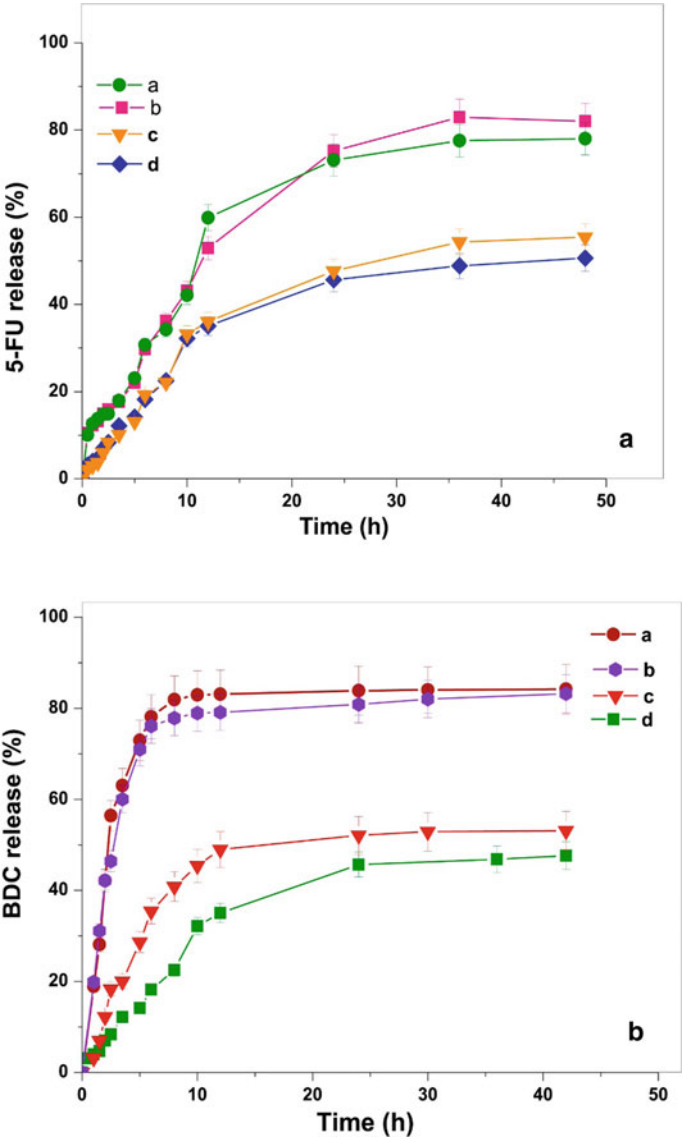


Fig. 10 Cumulative drug release percentage of 5-FU (266 nm) from 5-FU-AMSN-A (a), 5-FU-AMSN-A/FA-CMCS-GEL-BDC (b) at pH 7.4, 5-FU-AMSN-Alg (c), 5-FU-AMSN-A/FA-CMCS-GEL-BDC (d) at pH 1.2 (**A**); Release percentage of BDC (432 nm) from FA-CMCS-GEL-BDC (a), 5-FU-AMSN-A/FA-CMCS-GEL-BDC (b) at pH 7.4, FA-CMCS-GEL-BDC (c), 5-FU-AMSN-A/FA-CMCS-GEL-BDC (d) at pH 1.2 (**B**) [81] (Reprinted with permission from Anirudhan et al., 2019 Copyright © 2019 Elsevier)

Table 1 The drug loading efficiency and encapsulation efficiency of samples [84]

Samples	Drug loading efficiency (%)	Encapsulation efficiency (%)
HAP nanoparticles	5.885 ± 0.6028	11.77 ± 1.2055
HAP/SA microspheres	49.08 ± 0.1309	98.16 ± 0.2617
HAP/SA/CS microspheres	46.86 ± 0.1414	93.72 ± 0.2828

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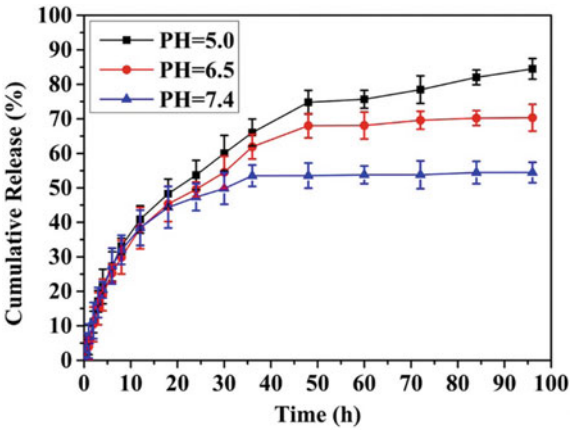

Fig. 11 The drug release curves of the DOX-loaded HA-SA-CS composite in vitro [84] (Reprinted with permission from Bi et al., 2019 Copyright © 2019 Elsevier)

Table 2 Preparation conditions of SA-CMCS-ZnO composite hydrogel beads and their drug loading [85]

Sample no.	$m_{CMCS\text{-}ZnO}/m_{SA}$ (g/g)	$CaCl_2$ conc. (wt%)	Drug loading (%)	Encapsulation efficiency (%)
SA	0	2	8.89 ± 0.31	86.12 ± 1.52
SA/CMCS-ZnO-1	0.01	2	9.01 ± 0.22	87.56 ± 2.43
SA/CMCS-ZnO-2	0.03	2	9.14 ± 0.16	88.95 ± 0.58
SA/CMCS-ZnO-3	0.05	2	9.36 ± 0.17	90.32 ± 2.41
SA/CMCS-ZnO-4	0.07	2	9.52 ± 0.23	92.44 ± 3.22
SA/CMCS-ZnO-5	0.1	2	9.78 ± 0.12	95.20 ± 2.65

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The composite hydrogel beads prevented the CUR degradation by light and thereby increased CUR antioxidant activity indicating the SA-ZnO hydrogel beads controlled the release of unstable CUR drug.

Several diclofenac sodium loaded calcium alginate films in addition to other hydrophilic polymers indicating diverse crosslinking degrees were fabricated through external gelation procedure [86]. The films obtained with the external gelation method were stronger (51.9–52.9 MPa) and thicker (0.031–0.038 mm) whereas

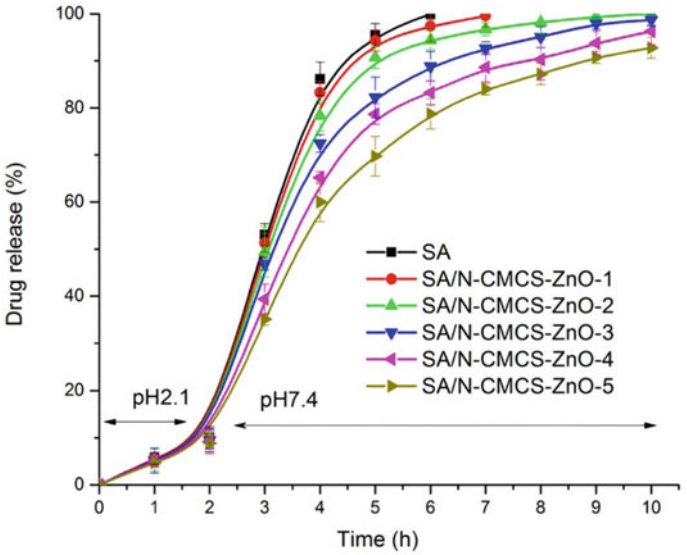

Fig. 12 Effect of ZnO content on in vitro cumulative release profiles of curcumin from the SA/CMCS-ZnO composite hydrogel beads in pH 2.1 PBS (first 2 h) and pH 7.4 PBS (for 8 h) [85] (Reprinted with permission from Wang et al., 2019 Copyright © 2019 Elsevier)

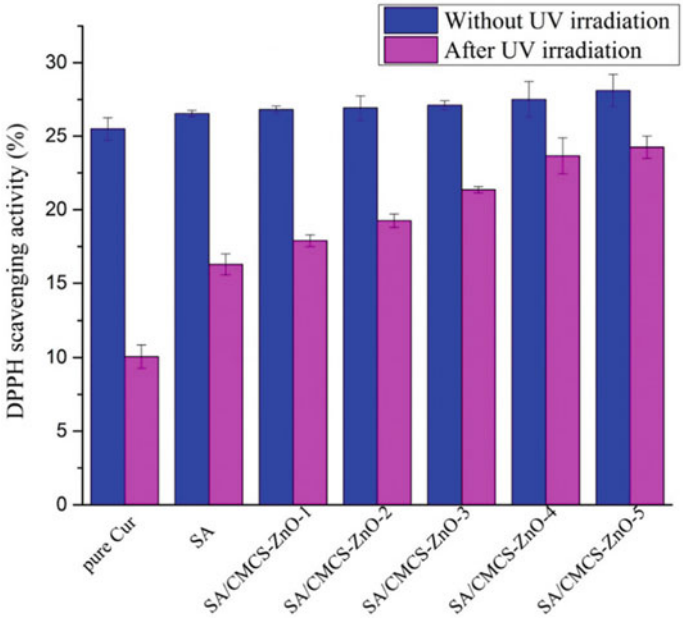

Fig. 13 DPPH scavenging activity of pure curcumin, SA, SA/CMCS-ZnO-1, SA/CMCS-ZnO-2, SA/CMCS-ZnO-3, SA/CMCS-ZnO-4, SA/CMCS-ZnO-5 composite hydrogel beads ($P < 0.05$) [85] (Reprinted with permission from Wang et al., 2019 Copyright © 2019 Elsevier)

less elastic (2.3%) compared to the non-crosslinked films (39.7 MPa, 0.029 mm, 4.4%). The films with the greatest crosslinking degree exhibited smaller water vapor permeability (WVP) values. Sustained drug release was measured for the formulated films, which was prolonged for the biocomposite films confirming the biodegradable Ca-alginate composite film could be used in clinical therapeutic applications. It was proposed that the Pickering emulsion technique could be used to interfacially assemble the amphiphilic bacterial cellulose nanocrystals (BCNs) in order to enhance the compatibility between the hydrophobic drug and alginate [87]. To achieve BCNs, the biosynthesized BC was hydrolyzed by sulfuric acid and employed as a particulate emulsifier but the drug (alfacalcidol) in CH_2Cl_2 solution was applied as the oil phase. The oil-in-water Pickering emulsions were dispersed using ultrasonic irradiation and well mixed with the alginate solution. At last, the drug-loaded composite alginate beads were obtained through external gelation. The interfacial assembled amphiphilic BCNs as well as the alginate hydrogel shells allowed the alfacalcidol drug loading and its sustained release. The drug release followed the Korsmeyer–Peppas model and the drug release mechanism from the beads was recognized as the non-Fickian transport. Furthermore, the alginate composite beads had low cytotoxicity and the desirable ability for the osteoblast differentiation.

Magnetic gelatin microspheres (MGMs) were encapsulated into self-healing CS-alginate hydrogel to prepare anticancer DDS so that the hydrogel was formed through crosslinking of carboxyethyl chitosan (CECS) as well as oxidized alginate (OAlg) by means of the Schiff-base reaction [88]. The MGMs incorporated with 5-fluorouracil (5-FU) anticancer drug was achieved via emulsion crosslinking process to increase the biological and mechanical properties of the hydrogel. It was found that adding MGMs with 30 mg/mL concentration to the composite hydrogel caused its appropriate performance and revealed exceptional self-healing capability under physiological conditions (Fig. 14).

Additionally, the composite hydrogel exhibited more sustained in vitro drug release than the control CECS-OAlg hydrogel and MGMs.

4 Hyaluronic Acid Nanocomposites in Drug Delivery

Hyaluronic acid (HA) is a natural polysaccharide which has a negative charge and exists in much amount within the extracellular matrix; thus, HA reveals favorable properties as it is biodegradable, non-toxic and biocompatible [89]. Besides, HA is able to enhance the accumulation inside the tumor sites and effectively target several tumor cells through its specific combination with CD44 receptors overexpressed over the surfaces of numerous kinds of cancer cells. As well, HA chains are broken by hyaluronidase existing in the tumor microenvironment, which allows release of the drug and cancer treatment [90].

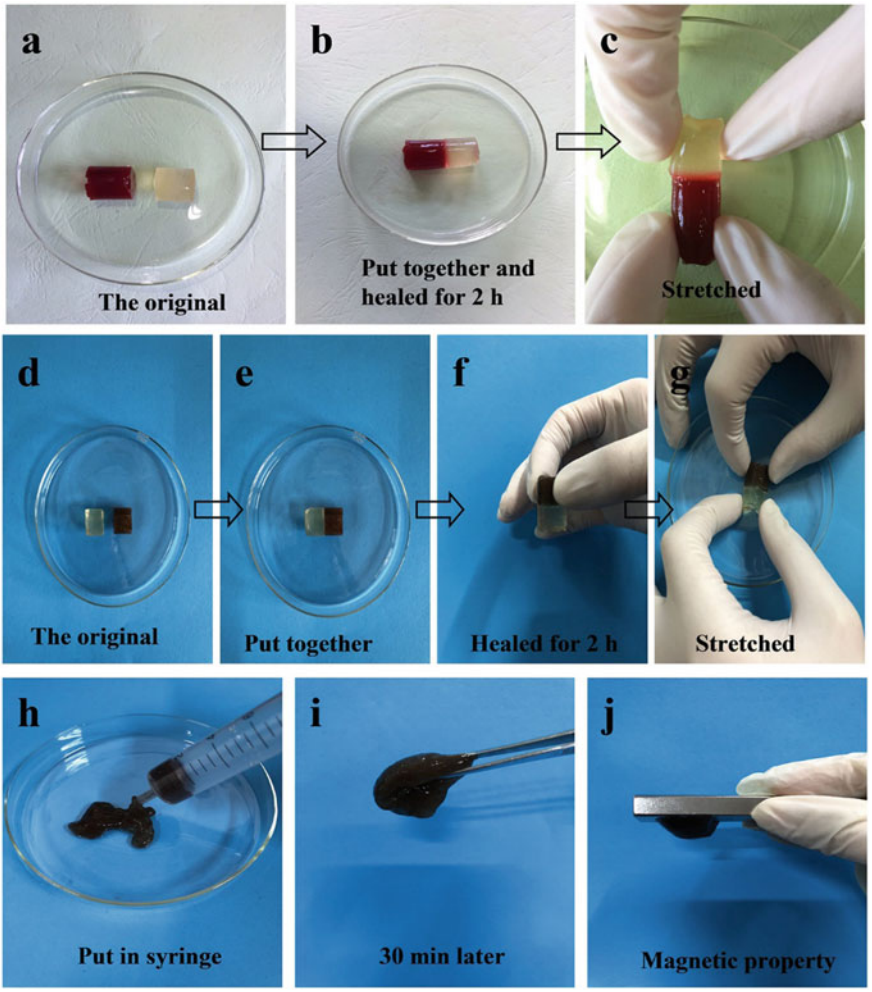

Fig. 14 **a–c** Self-healing process of blank GEL without 5-FU/MGMs. **d–g** Self-healing process of composite scaffolds. **h–j** Efficiency of composite scaffolds at 37 °C [88] (Reprinted with permission from Chen et al., 2019 Copyright © 2019 Elsevier)

Recently, the hydrophobic and unstable D-α-tocopherol succinate (α-TOS) was encapsulated in zeolitic imidazolate framework-8 (ZIF-8) that was called α-TOS@ZIF-8and then coated by hyaluronic acid (HA) shell in order to prepare HA/α-TOS@ZIF-8 nano-formulation (Fig. 15) [91].

If the α-TOS concentration was 1 mg/mL, high loading of 43.03 wt% was measured. The HA shell acted as a smart tumor-targeted "guider" and "switch" that could extend the blood circulation and enhance the tumor-specific accumulation of nano-formulation through the CD44-assisted path, see Fig. 16.

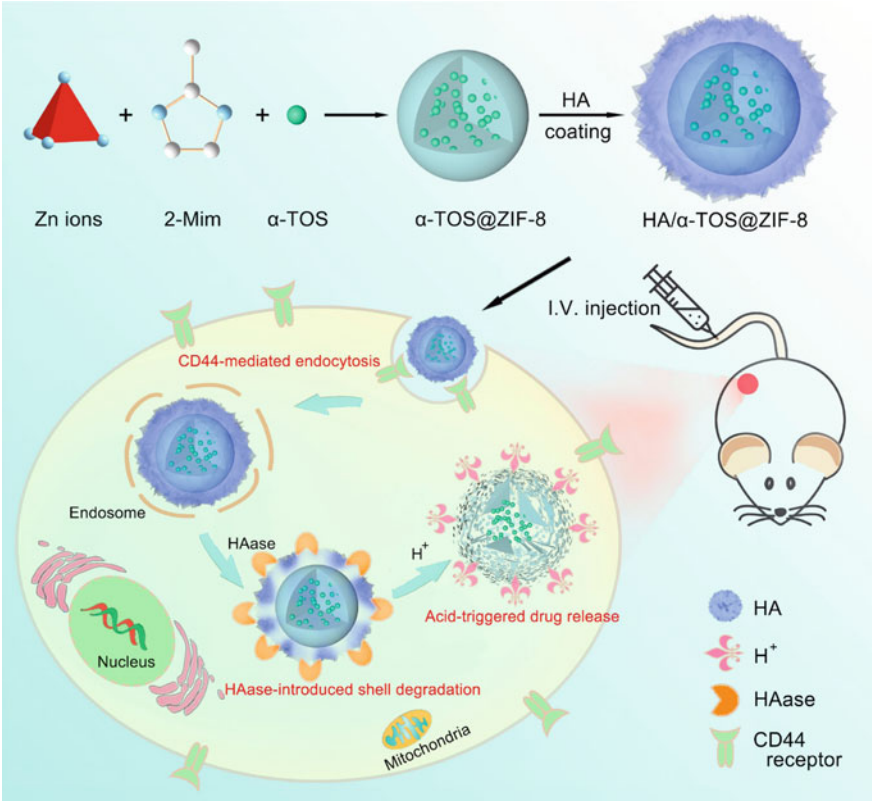

Fig. 15 Schematic illustration for the formation of HA/α-TOS@ZIF-8 nanoplatform. Schematic illustration showing the CD44 receptors-mediated pH-responsive drug delivery system for efficient antitumor therapy [91] (Reprinted with permission from Sun et al., 2019 Copyright © 2019 Elsevier)

The HA shell was damaged using the hyaluronidase enzyme presenting in the tumor microenvironment to release the wrapped α-TOS@ZIF-8which caused ZIF-8 destroying in the acidic tumor microenvironment and ultimately releasing the loaded α-TOS. Consequently, the nanoplatform HA/α-TOS@ZIF-8 was known as a non-demand tumor-specific DDS which could improve the tumor treatment effectiveness.

In another study, dual targeting (CD44 and tumor acidity) HA-coated gold nanorods (AuNRs) were prepared for combined photothermal and chemotherapy of cancer [92]. Low molecular weight HA (LMWHA) was attached to pH-sensitive groups (for the pH-induced aggregation) plus lipoic acid (to coat the AuNRs). Varying the pH-sensitive groups' using diverse pKa values changed the pH sensitivity of the modified LMWHA. Coating the modified LMWHA on the AuNRs considerably enhanced the AuNRs biocompatibility. The LMWHA-coated AuNRs were slowly aggregated under a little acidic condition, which was satisfactory for accumulation in acidic tumor sites. The surface LMWHA allowed selective uptake of the

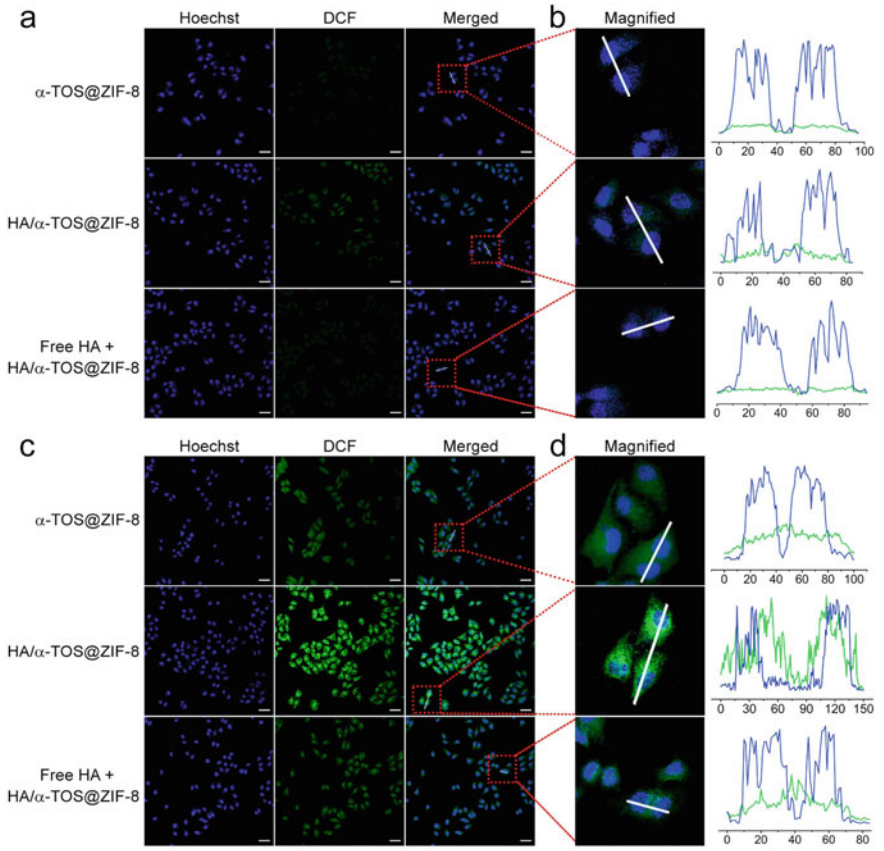

Fig. 16 CLSM images of HeLa cells incubated with α-TOS@ZIF-8, HA/α-TOS@ZIF-8 and HA/α-TOS@ZIF-8 in the presence of free HA after **a** 0.5 and **c** 3 h in the dark. Scale bars for all images are 50 μm. The magnified images from the corresponding merged (**a**) and (**c**), and the fluorescence intensity profiles along the white line crossing the cancer cells (**b**, **d**) [91] (Reprinted with permission from Sun et al., 2019 Copyright © 2019 Elsevier)

nanocomposites by the CD44 expressing cancer cells and AuNRs caused exceptional photothermal capacity of the nanocomposites. When the DOX anticancer drug was loaded, the LMWHA-coated AuNRs exhibited synergistic in vitro cancer-killing and in vivo tumor growth inhibition. Hence, such multifunctional CD44-targeting and pH-triggered aggregation nanosystem was favorable for combined photothermal and chemotherapy of cancer cells.

Polydopamine (PDA) NPs were synthesized through oxidative dopamine self-polymerization in an ethanol/water mixture and thiol-functionalized HA was obtained by crosslinking of hyaluronic acid and cysteamine (HA-Cys) by means of PDANPs [93]. The dimethyloxalylglycine (DMOG) loaded PDANPs displayed hat a sustained drug release happened during 7 days from the composite hydrogel.

The hydrogel microenvironment enabled greater endothelial migration, proliferation, and attachment of cells. Also, upon the DMOG release from the hydrogel, the cells exhibited superior in vitro capillary tube formation. Consequently, the hydrogels were suggested as efficient and valuable drug carriers. Recently, amphiphilic ferrocenium-tetradecyl (Fe-C_{14}) was synthesized to obtain cationic micelles by self-assembly in aqueous solution that was then coated with HA by electrostatic interactions which achieved HA-Fe-C_{14} micelles used for delivery of DOX drug [94]. It was found that the DOX release was rapid in a high-GSH tumor environment. The HA-Fe-C_{14}/DOX micelles were efficiently accumulated in tumor and revealed substantial in vivo and in vitro anticancer effects confirming they were useful DDSs that boosted synergistic antitumor effects.

A chemotherapeutic containing nanocomposite made from HA, fluorochrome indocyanine green, carboxyl terminated dendrimer and DOX was prepared and named HPCID which efficiently targeted metastatic cancer cells and indicated boosted therapeutic influence [95]. Such DDS was applied (both in vivo and in vitro) by the sono-chemotherapy method on the CD44 overexpressed metastatic 4T1 breast cancer cells. The HA containing DDS considerably enhanced the HPCID cell internalization and the HA shell degradation with hyaluronidase that was plentiful in 4T1 cells which caused an enzyme-responsive release of the drug. By ultrasound radiation in combination with chemotherapy, the HPCID created great amounts of reactive oxidant species that led to substantial cell apoptosis. Furthermore, the HPCID administration to 4T1 xenograft-bearing mice along with ultrasonic radiation greatly inhibited tumor growth and pulmonary metastasis without any systemic toxicity. Hence, HPCID-mediated sonodynamic therapy was a powerful approach against breast cancer metastasis and progress.

5 Cellulose Nanocomposites in Drug Delivery

Cellulose is a linear organic polysaccharide composed of β-1,4-linked anhydro-D-glucose repeating units. It is prepared from inexpensive bio-resources through acid hydrolysis [96]. The cellulose nanocrystals (CNC) are a family of nanocellulose that are also called nanocrystalline cellulose, cellulose nanoparticles, or cellulose nanowhiskers [97]. The nanocrystalline structures of CNCs can enhance/modulate the biological and physicochemical efficacy of DDSs through hydrophilic interactions and H-bond formation. CNCs have diameters of 1–100 nm and lengths of 0.025–2.00 μm depending on the cellulose sources as well as methods used for their production [98]. The exceptional hydrophilicity, high aspect ratio, nano-size dimensions, low density, high surface area, biocompatibility, non-toxicity, non-irritant nature, biodegradability, high modulus, and strength of CNCs have caused their broad applications as reinforcement filler materials in polymeric nanocomposites, edible packaging materials, scaffolds, hydrogels, DDSs, and several technical uses [99]. Further, smart features of cellulose-containing polysaccharides including, mucoadhesivity, high water affinity, and structural diversity inspire their applications

in pharmaceutical, chemical, and biomedical fields [100]. It is notable that there is worldwide attention for the biomedical application of CNCs [101].

Fe_3O_4@cellulose nanocrystal (MCNC) containing curcumin (CUR) anticancer drugs were used as magnetic-responsive drug carriers and in vitro anti-colon cancer therapy [102]. The CUR loading efficiency was 99.35% into the MCNC stabilized Pickering emulsion (MCNC-PE). It was indicated that the MCNC-PE exposure to an external magnetic field of 0.7 T caused the CUR drug release from the MCNC-PE that led to 53.30 ± 5.08% of the initial loading after 4 days. Also, the CUR-loaded MCNC-PE successfully inhibited the growth of human colon cancer cells to 18% by applying the external magnetic field (Fig. 17).

The MCNC-PE formulation decreased the volume of the multicellular HCT116 spheroids by two folds relative to that of the control (Figs. 18 and 19).

The maximum 100 μg/mL concentration of MCNC was non-toxic to brine shrimp. Overall, the palm-based MCNC-PE was an efficient colloidal DDS for magnetically triggered therapeutics release.

Triblock poloxamer copolymer (PM) is broadly applied for the delivery of several ophthalmic pharmaceuticals to achieve extended precorneal resident time and suitable drug bioavailability [103]. The CNC's effect was examined on the in situ PM gelation and in vitro pilocarpine hydrochloride release from the nanocomposites. The critical PM gelation concentration (18%wt/v) was decreased to 16.6%wt/v via adding a little CNC quantity. The CNC reinforcement characteristic within the in situ

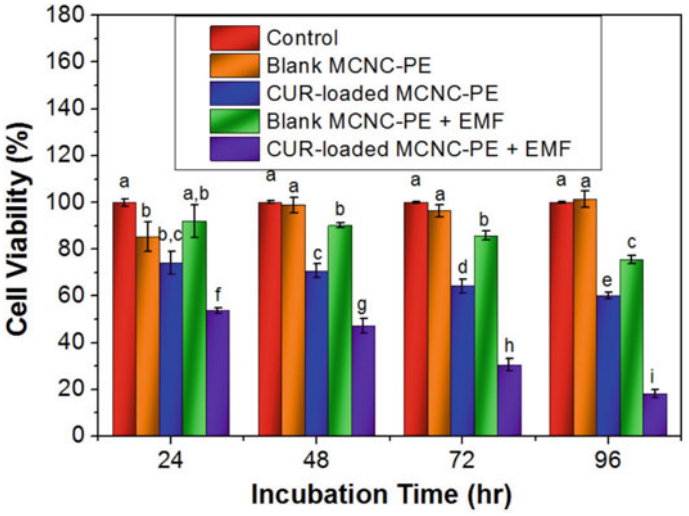

Fig. 17 Cell viability test of CUR-loaded MCNC-PE on HCT116 colon cancer cell line. The cell line analysis was performed using MCNC-PE stabilized by 0.1 wt% of MCNC composite, with emulsion content of 10 vol% and CUR content of 30 μg/mL of incubation serum (equivalent to 1 mg/mL oil basis). Error bar represents a standard error in measurement. Different alphabetic letters were significantly different at $P \leq 0.05$ by Bonferroni's Multiple Comparison Test [102] (Reprinted with permission from Low et al., 2019 Copyright © 2019 Elsevier)

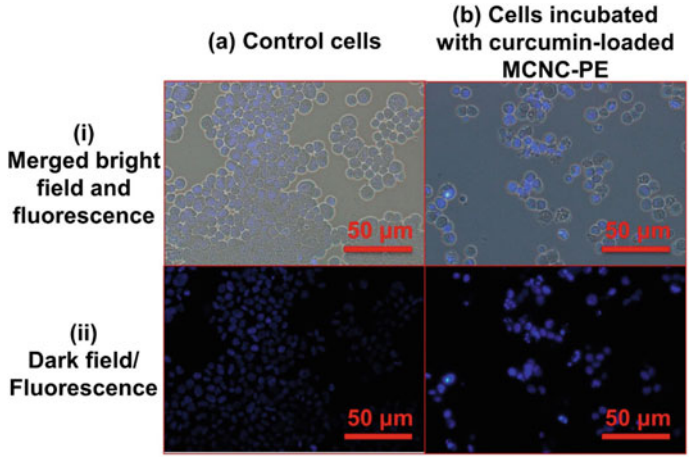

Fig. 18 Nuclear morphology changes of HCT116 cells at 24 h incubation for **a** control and **b** curcumin-loaded MCNC-PE treated samples [102] (Reprinted with permission from Low et al., 2019 Copyright © 2019 Elsevier)

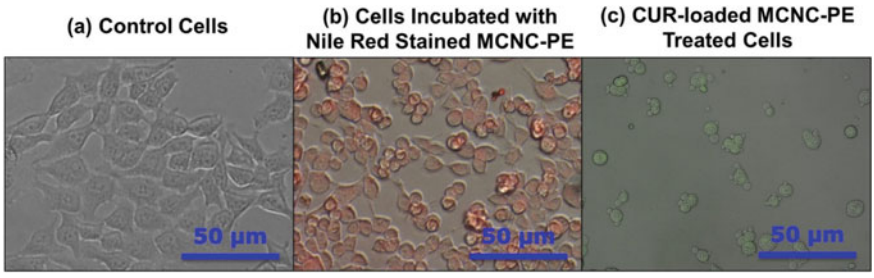

Fig. 19 Bright field-fluorescence overlay images of HCT116 cells after 2 h incubation **a** without treatment, **b** with Nile red stained MCNC-PE and **c** with CUR-loaded MCNC-PE [102] (Reprinted with permission from Low et al., 2019 Copyright © 2019 Elsevier)

nanocomposite gel increased the sustained drug release and the gel strength compared to the pure PM gel. The drug release mechanism from all formulations followed the Fickian diffusion. Porous gold NPs containing cellulose grafted polyacrylamide (PAM/C/Au) hydrogel nanocomposite was produced through in situ polymerization reaction for application in the in vitro ciprofloxacin drug release [104]. The ciprofloxacin drug release was 96.6% during 5 h. The PAM/C/Au nanocomposite hydrogels exhibited improved rheological and thermal characteristics indicating they were desirable carriers for the in vitro ciprofloxacin drug release.

It was displayed that combination of cellulose with clay afforded materials with enhanced optical, thermal, mechanical, flame resistance as well as gas and water barrier properties compared to the pristine polymer [105]. Cellulose nanofibers

(CNF) and Laponite were used to achieve composites with improved features relative to the pristine cellulose nanofibers film like higher thermal stability (45 °C for CNF/Lap 3.5/1 by mass), greater water vapor permeability (157% for CNF/Lap 1:1) and less CNF aggregation that were valuable for their application as drug carriers. The CNC was synthesized by means of high molecular weight cellulose and introduced into polycaprolactone (PCL) matrix to afford nanofibers under diverse conditions [106]. The optimum electrospinning condition was using 16% PCL polymer solution, 17 kV and 0.9 ml/h flow rate to obtain nanofibers with 233 nm average diameter. The influence of CNC amount was explored on the thermal, mechanical, and morphological properties. It was found that adding CNC to the PCL nanofibers enhanced biodegradability. The nanofibers obtained using PCL solution incorporated with 1% CNC had optimum degradation and mechanical features. The tetracycline release was decreased from the CNC-incorporated nanofibrous mats.

6 Carboxymethyl Cellulose Nanocomposites in Drug Delivery

Carboxymethyl cellulose (CMC) is a polysaccharide commonly utilized for the production of oral DDSs. It is an anionic water-soluble cellulose derivative which is prepared by introducing $–CH_2COOH$ groups onto the cellulose chains [107]. The average substitution degree of the CMC usually changes between 0.5 and 1.5. CMC forms spherical hydrogel beads in the presence of metal cations like Al^{3+} and Fe^{3+} [108]. The CMC hydrogels are pH-sensitive indicating they are appropriate for site-specific and controlled drug release purposes because pH varies at different organs and at diseased parts of the body [109]. Pure CMC polysaccharide hydrogels exhibit low mechanical strengths; therefore, several approaches are examined to enhance their mechanical strength such as the incorporation of inorganic NPs to their polymeric networks [110].

The properties of the CMC as a drug carrier were improved by the encapsulation of layered double hydroxide (LDH) [111]. The colon anticancer drug 5-FU was loaded (~87%) into the LDH(Zn/Al) and the LDH(Zn/Al)-5-FU nanohybrid encapsulated CMC was crosslinked using Fe(III) crosslinker to achieve CMC/LDH(Zn/Al)-5-FU hydrogel beads. The 5-FU drug release from the CMC/LDH(Zn/Al)-5-FU hydrogel beads was more sustained and controlled than that of the LDH(Zn/Al)-5-FU. The cytotoxicity tests confirmed that the CMC/LDH(Zn/Al)-5-FU hydrogel beads were biocompatible. The drug loading and release, swelling, and cytotoxicity assay proved that the CMC/LDH(Zn/Al)-5-FU hydrogel beads were benign oral delivery platform for the colon cancer therapy.

The surface charge, solubility, and drug loading capacity of grapheme oxide (GO) were improved by its modification using CMC and zinc-based metal-organic framework (MOF-5) in order to precisely control the drug release using the CMC/MOF-5/GO bionanocomposite [112]. The DOX anticancer drug was encapsulated into the

CMC/MOF-5/GO carrier that exhibited boosted anticancer effects. The DOX release rate was considerably higher at pH 5 in tumor microenvironment compared to that measured at pH 7.4 under physiological conditions. The cytotoxicity test revealed that the DOX@CMC/MOF-5/GO had a high cytotoxicity to K562 tumor cells approving such bionanocomposite was suitable for anticancer drug delivery. In another research, pH-sensitive magnetic hydrogels were obtained using CMC, β-cyclodextrin (β-CD), and CS and used as drug carriers for controlled release purposes [113]. Also, the influence of Fe_3O_4 NPs amount was explored on the ability of the CMC/β-CD/CS hydrogel to deliver methotrexate (MTX) drug. The CMC/β-CD/CS hydrogel illustrated somewhat greater swelling than the magnetic CMC/β-CD/CS hydrogel. The hydrogel had a pH-sensitive swelling with high water adsorption at pH = 9. The in vitro MTX release test indicated that the drug release from the CMC/β-CD/CS hydrogel was greater compared to the other hydrogel. The highest drug release for the CMC/β-CD/CS, low and high magnetic CMC/β-CD/CS hydrogels was measured to be 92.7, 80.4, and 58.3% at pH 7.4, respectively. Furthermore, the MTX release was improved by applying an external varying magnetic field indicating the hydrogel nanocomposite was sensitive to the external magnetic field stimulant.

Graft copolymers were synthesized using CMC sodium salt and diverse amounts of *N*-vinylimidazole through radical polymerization reaction [114]. The polymer coils revealed hydrodynamic radii in the range of 120–152 nm that were stable in both 0.15 M NaCl aqueous solution and physiological pH indicating they were satisfactory as targeted DDSs. The copolymer formed a complex with PTX drug through interactions of imidazole rings, O–H and C=O groups of Na-CMC-g-PVI copolymer with the aromatic rings, O–H and C=O groups of PTX drug. The in vitro PTX release was performed in neutral and acidic solutions at 38 °C and complete PTX release was achieved in 144 h. The PTX release from the copolymer followed the Korsmeyer–Peppas kinetic model that was limited via molecular diffusion.

Ecofriendly, smart, and green vehicles were developed or colon targeting drug delivery using the pH-sensitive CS and CMC biopolymers [115]. To solve the disadvantages of CMC drug carriers like poor mechanical property and burst drug release, ZnO NPs were added to the CMC beads that were coated by CS through self-assembly method to obtain core-shell polyelectrolyte complexes. The 5-FU anticancer drug was loaded to the ZnO/CMC/CS nanobiocomposite hydrogel beads. The in vitro 5-FU release and swelling tests were carried out in simulated gastrointestinal condition and the pH sensitivity of the nanocomposite beads was examined. The beads displayed a sustained drug release manner based on the ratios of CS, CMC, and ZnO NPs. Also, the hydrogel beads revealed the biodegradation capability (Fig. 20) that was beneficial for their usage as DDSs for colon-specific anticancer therapy.

7 Starch Nanocomposites in Drug Delivery

Starch is well-known as one of the most favorable natural polymers as it is inherently biodegradable, abundant, non-toxic, biocompatible, and renewable. Its backbone is

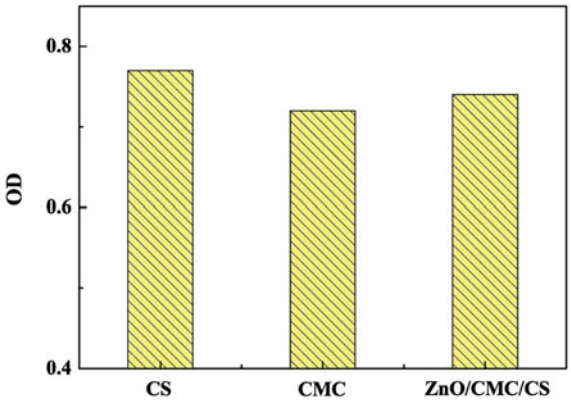

Fig. 20 Biodegradation of pure CS, CMC, and ZnO/CMC/CS bionanocomposite beads [115] (Reprinted with permission from Sun et al., 2019 Copyright © 2019 Elsevier)

made up of an extremely branched amylopectin (70–90%) and linear amylose (10–30%) [116]. In some starches, the amylose amount is more than 40%. Starches are fast degraded by microbes because microbes can degrade numerous organic/inorganic compounds including biodegradable polymers like starch, gelatin, alginate, chitosan, lignin, hemicelluloses, and cellulose. Accordingly, starch-based biopolymers are favorable biomaterials as DDSs because of their low costs, non-toxicity, and biocompatibility [117].

Biodegradable films were synthesized for recognition of sulindac (SLD) using mung bean starch, plasticizers, and PVA through UV radiation and casting technique [118]. The optimum UV radiation time was ~30 min to prepare SLD-imprinted films. The recognition tests proved that the SLD-imprinted films had binding sites for the SLD. Also, the SLD release was studied by changing the temperature and pH and it was exhibited that the SLD release at pH 10.0 was higher compared to that measured at pH 4.0. The SLD release assessment on an artificial skin confirmed that the SLD release was continued for 20 days (Fig. 21).

Recently, amphiphilic citric acid crosslinked starch (~140 nm) was used as a biodegradable, biocompatible, and efficient stabilizer to prepare Pickering emulsion with enhanced stability when the pH was increased from 3 to 5 and 7.4 (Fig. 22) [119].

The in vitro controlled curcumin drug release tests exhibited that the drug release was enhanced by increasing the pH value, see Fig. 23.

Thus, such starch stabilized pH-responsive emulsions were auspicious drug carriers for the treatment of gastrointestinal disorders through oral drug delivery.

Oxidized starch-CuO nanocomposite hydrogels were produced in situ throughout the synthesis of CuO NPs (with diameters of 39–50 nm) in swollen oxidized starch hydrogels so that the number of CuO NPs was enhanced by increasing the Cu^{2+} concentration [120]. The swelling of the nanocomposite hydrogels examined at two pH values (2.1 and 7.4) proved that they had pH-sensitive swellings relative to the neat oxidized starch hydrogel. Also, a controlled and sustained drug release was detected for the CuO NPs incorporating oxidized starch that was increased by increasing the

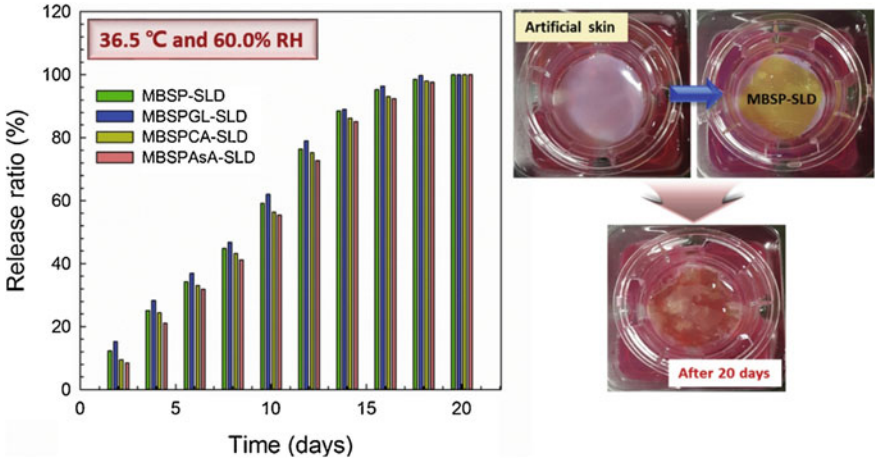

Fig. 21 SLD release ratio (%) on SLD-imprinted mung bean starch/PVA biomaterial films using artificial skin at 36.5 °C and 60.0% relative humidity [118] (Reprinted with permission from Taka et al., 2019 Copyright © 2019 Elsevier)

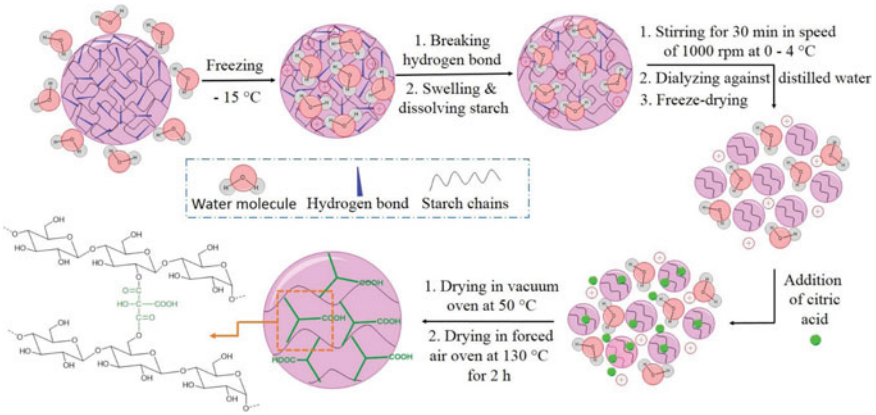

Fig. 22 Preparation of crosslinked starch nanoparticles via alkali-freezing treatment followed by crosslinking with citric acid through thermal elimination method [119] (Reprinted with permission from Sufi-Maragheha et al., 2019 Copyright © 2019 Elsevier)

CuO amount. In another study, two nanocomposite beads of St-A-E/M and St-A-E/M-Ag were synthesized as controlled release drug carriers for the methyl prednisolone drug [121]. It was found that the AgNPs within the polymeric matrix had a spherical morphology with diameters of 50–111 nm. The effects of temperature, contact time, AgNPs, and initial pH on the drug loading and release were explored. It was illustrated that the drug release values from nanocomposites with different AgNPs amounts were slightly greater than that of the bare composite. Furthermore,

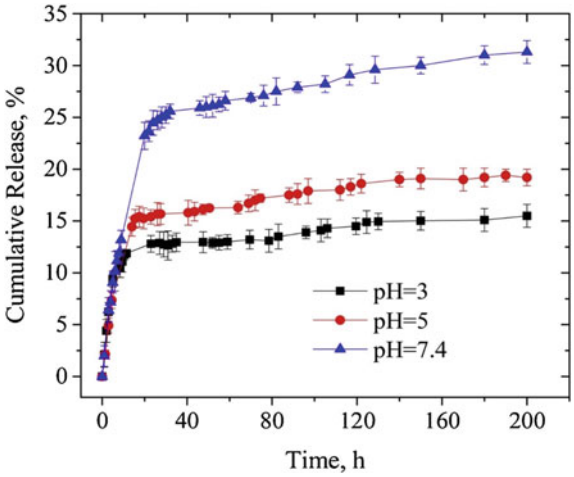

Fig. 23 In vitro release profile of curcumin from the crosslinked starch stabilized Pickering emulsion at different pHs [119] (Reprinted with permission from Sufi-Maragheha et al., 2019 Copyright © 2019 Elsevier)

the drug release was augmented by increasing the AgNPs to 3.3%v/v within the polymeric matrix but the release was reduced more than this amount of AgNPs. The highest drug release was measured at pH 7.4 in 9 h. As well, the nanocomposite demonstrated superior antibacterial property than its corresponding bare composite.

8 Gellan Gum Nanocomposites in Drug Delivery

Gellan gum (GG) is an anionic exopolysaccharide that is biosynthesized by the *Pseudomonas elodea* bacterium. It is usually mixed with other polysaccharides in order to obtain bioadhesive materials for oral therapeutics delivery [122]. It is a high molecular weight polymer that is made up of a tetrasaccharide repeating unit containing one β-D-glucuronic acid, one α-L-rhamnose, and two β-D-glucoses [123]. The pure GG has negative charges because of the existence of numerous glucuronic acid units, thus it is able to be ionotropically crosslinked in presence of divalent metal cations such as Ca^{2+} and Zn^{2+} to produce rigid composite GG-based mucoadhesive hydrogels. GG can form hydrogel depending on the temperature and it shows rapid phase transitions from the random-coil to double helix in presence of cations that protect the carboxylic groups of glucuronic acids and enhance the helices aggregation [124].

A double network nanocomposite, nDN, hydrogel drug carrier was achieved using methacrylated gellan gum (GG-MA) and different amounts (0.5–1.5%w/v) of Laponite clay as the nanofiller [125]. Also, polyethylene glycol dimethacrylate (PEG-DMA) was applied as the second elastic soft network. The Laponite® addition influenced the PEG-DMA amount that was diffused into the GG-MA network. The tough stretchable nDN indicated a greater elasticity and water swelling than the Laponite-free DN hydrogels. The double network exhibited higher ofloxacin drug

loading and a more controlled drug release than the single network hydrogel. In another work, sericin (natural protein) was used together with GG and rice bran albumin to obtain a protein polysaccharide nanocomposite drug carrier with spherical shape and average size of ~218 nm [126]. The sericin-GG-rice bran albumin nanocomposite could encapsulate a high DOX amount and effectively released the drug in the acidic tumor site (84% in 120 hat pH 4.0). The IC_{50} of the DOX-loaded nanocomposite was 5 μg/mL that was very small than that of the free DOX (9 μg/mL) in killing the MCF-7 cancer cells so that 42% of cells were alive upon treatment by the nanocomposite.

Anion-activated GG composite gel composed of amino methacrylate copolymer microparticles was prepared for the buccal delivery of aceclofenac (AC) drug [127]. Suitable buccal delivery and therapeutic efficiency in vivo were achieved in inflammation rat models. The optimal formulation had great entrapment efficiency (94.73%) and a particle size of 51.00 μm. Furthermore, sustained AC drug release, anti-arthritic response in vitro, extended, and consistent anti-inflammatory influence in vivo were established. Recently, some GG derivatives were synthesized comprising quaternary ammonium moieties and used as controlled ciprofloxacin drug release systems [128]. The quaternized GG and CS-based, QG–CS, particles were obtained to illustrate antibacterial ability due to the presence of quaternary ammonium groups (Table 3).

The in vitro transdermal ciprofloxacin release assay was done on rat skin within the phosphate buffer solution at pH = 7.43. The ciprofloxacin released for 24 h approving the quaternized gellan–CS particles were satisfactory controlled DDSs for the topical dermal therapies.

Several diethanolamine-modified olive oil-incorporated high methoxyl containing pectin (DMP)-GG hydrogel nanobiocomposites were prepared using zinc acetate crosslinker for the intragastric controlled metformin HCl (MFM) delivery [129]. Upon changing the GG:DMP mass ratios, nanofiller type (neusilin, bentonite or florite) as well as oil addition, the nanocomposites demonstrated different drug encapsulation efficiencies of 50–85% plus prolonged drug release of 69–94% in 8 h at pH 4.5 (acetate buffer). The optimal oil-entrapped nanocomposites released the MFM through case-II transport mechanism with the drug release kinetics followed the zero-order. The optimum system established outstanding gastroretentive features and significant hypoglycemic influence in streptozotocin-induced diabetic rats confirming it was suitable for the treatment of type 2 diabetes.

9 Gum Acacia/Gum Arabic Nanocomposites in Drug Delivery

Gum acacia (GA) is a natural biopolymer which is composed of β-D-galactopyranosyl (with (1 → 3) and (1 → 6) linkages) as well as β-D-glucopyranosyluronic acid (with

Table 3 Antibacterial activity of QG–CS particles (1%w/v in bi-distilled water) [128]

Sample	Diameter of inhibition area (mm)[a]						
	S. aureus ATCC 25923	*Sarcina lutea* ATCC 9341	*B. cereus* ATCC 14579	*E. coli* ATCC 25922	*E. coli* CTX-M-14	*K. pneumoniae* ATCC 53153	*P. aeruginosa* ATCC 27853
QG–CS-1/1	0	0	0	18 ± 0.38	0	17 ± 0.42	0
QG–CS-1/2	0	0	0	16 ± 0.32	0	15 ± 0.38	0
QG–CS-1/4	0	0	0	14 ± 0.42	0	13 ± 0.36	0
Ampicillin 25 μg/disk	20 ± 0.28	33 ± 0.29	0	20 ± 0.35	0	19 ± 0.41	0
Chloramphenicol 30 μg/disk	24 ± 0.46	35 ± 0.42	25 ± 0.43	26 ± 0.34	0	24 ± 0.46	0

[a]Mean of three assays ± standard deviation

(1 → 6) linkages) repeating units and its side chain has β-D-glucuronic acid, α-L-rhamnopyranose, α-L-arabinofuranosyl and β-D-galactopyranose units linked by (1 → 3), (1 → 4) and (1 → 6) glycosidic bonds [130]. GA is an environmentally benign polymer that is non-toxic, easily bioavailable, and biodegradable. GA is applied in pharmaceutics as a demulcent in wound healing [131]. It shows antibacterial property against the periodontal bacterial growth. Also, it displays anti-inflammatory ability and employed to decrease the dialysis frequency [132].

The GA effects existing in hydrogels were examined on the release of nitrogen-containing bisphosphonate at two pH values of 1.2 and 7.4 [133]. The hydrogels revealed low and high swellings at pH 1.2 and 7.4, respectively. The bisphosphonate drug release was abnormal at pH 1.2 but the release kinetic followed a zero-order mechanism at pH 7.4. The hydrogel was pH-sensitive and the bisphosphonate release was affected by the GA hydrogel crosslinking degree. The hydrogels exhibited controlled bisphosphonate delivery to the gastrointestinal area. Recently, core-shell GA–hydroxyapatite (HAP) nanocomposite was synthesized with the HAP core and the GA shell and the naringenin (N) drug was encapsulated into the HAP core via pellet press technique [134]. The GA-HAP crystallite size was diminished from 89 to 63 nm by increasing the GA concentration from 0 to 10%. The pellet samples were dipped into the simulated body fluid in order to establish their bioactivities by scanning electron micrographs. The antimicrobial, hemolytic capacity, and biocompatibility of the drug-containing core-shell composites were also assessed. Figure 24 presents the antimicrobial activities of 10% GA-HAP-N and 10% GA-HAP samples against *S. aureus* and *E. coli* bacteria.

The GA containing hydrogels were fabricated as controlled dual drug carriers for antiprotozoal drugs including curcumin and 4-aminoquinoline derivative [135]. The maximum drug release time was longer for the curcumin compared to that of the 4-aminoquinoline derivative at 37 °C which enabled the release of these active

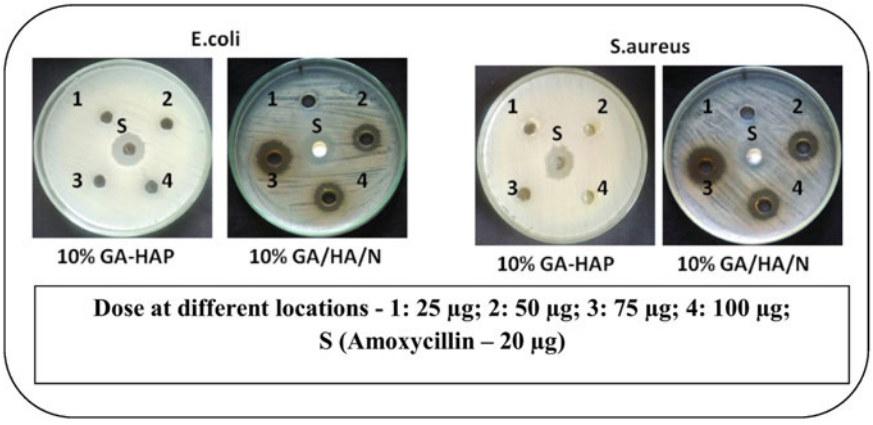

Fig. 24 Antimicrobial activity of 10% GA-HAP and 10% GA-HAP/N against *E. coli* and *S. aureus* [134] (Reprinted with permission from Padmanabhan et al., 2018 Copyright © 2018 Elsevier)

ingredients in diverse time periods. The 4-aminoquinoline derivative displayed a short release time but the curcumin demonstrated an extended and sustained release. The drug release was affected by the crosslinking degree of the GA hydrogel. The release data obeyed the Peppas kinetics model and the 4-aminoquinoline release mechanism was an anomalous transport whereas the curcumin release mechanism was a quasi-Fickian diffusion. In another attempt, nanocomposite hydrogels were produced using PVA, GA, and TiO_2NPs using gamma irradiation [136]. The hydrogels exhibited pH-sensitive swelling behaviors. The PVA/GA/TiO_2 nanocomposites were used as DDSs for the prednisone drug uptake and release and it was found that the prednisone release was pH-responsive.

Antimicrobial polyvinylimidazole, antioxidant GA, mucoadhesive and gel-forming carbopol, anesthetic lidocaine, and the antimicrobial gentamicin were used to achieve gentamicin and lidocaine loaded GA–carbopol–polyvinylimidazole hydrogel [137]. A number of hydrogels' properties were investigated such as hemostatic ability, hemolysis, water vapor transmission rate, oxygen permeability, mucoadhesion, degradation, antioxidant capacity, protein adsorption, microbial penetration, antimicrobial potency against *Pseudomonas aeruginosa* bacterium, mechanical properties (burst strength, tensile strength, relaxation, resilience, folding durability plus gel strength), histological studies and drug release. The synergistic antioxidant, antimicrobial and mucoadhesive properties of hydrogel made them appropriate materials for various biomedical applications.

10 Guar Gum Nanocomposites in Drug Delivery

Guar gum (GUG) is one of the most economical resources of galactomannan that belongs to the leguminosae family. It is prepared from the endosperm of *Cyamopsis psoraloides* and/or *Cyamopsis tetragonolobus* [138]. GUG is obtained from the guar plant and also well-known as Guaran, Glucotard, Cyamopsis, Cluster bean, Calcutta lucerne, and Cuarina. It is a high molecular weight hydrophilic polysaccharide that is odorless and indicates a white to yellowish-white color. GUGs have rod resembling polymeric structures in which the galactose side chains are attached to the mannose backbone in 1:2 average ratio. The linear D-mannose chains are joined together through β-(1–4)glycoside linkages and D-galactose units are linked in alternating mode by the (1–6)glycoside linkages. The hydroxyl groups existing in the polymeric backbone allow the preparation of different derivatives used for numerous industrial applications [139].

Some nanocomposites of neutral and cationic GUG with montmorillonite were loaded by ibuprofen drug and their abilities for the controlled in vitro drug release were investigated [140]. They displayed low initial burst release and extended sustained release for several hours at pH 7.4 (simulated intestine fluid) confirming they were satisfactory drug carriers. Recently, self-healable GUG-graft-acrylic acid, GUG-PAA, hydrogel was synthesized (Fig. 25) by means of L-alanine crosslinker in diverse concentrations from 0.4 to 1%w/v [141].

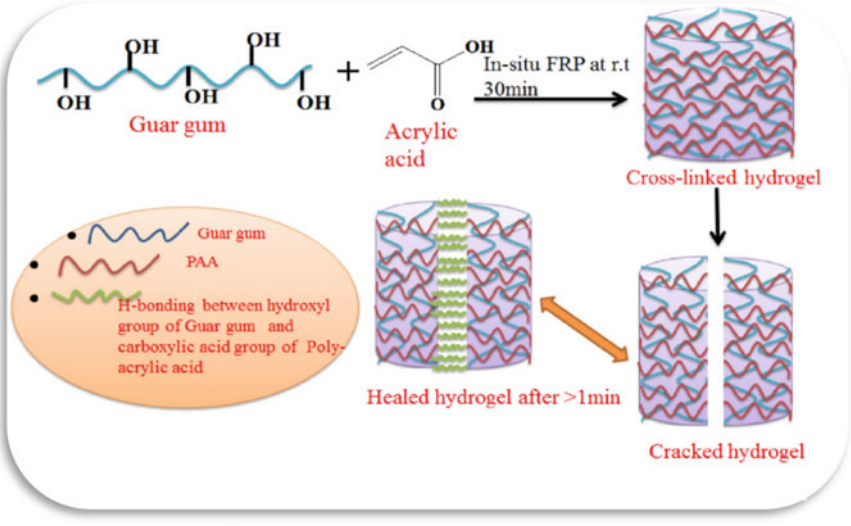

Fig. 25 Schematic illustration of synthesized crosslinked self-healing hydrogel [141] (Reprinted with permission from Sharma et al., 2019 Copyright © 2019 Elsevier)

The GUG based hydrogel showed maximum swelling of 3350% indicating its porous network, see Fig. 26.

The hydrogel revealed controlled drug delivery as it released 98% of the very water-soluble drug during 140 h.

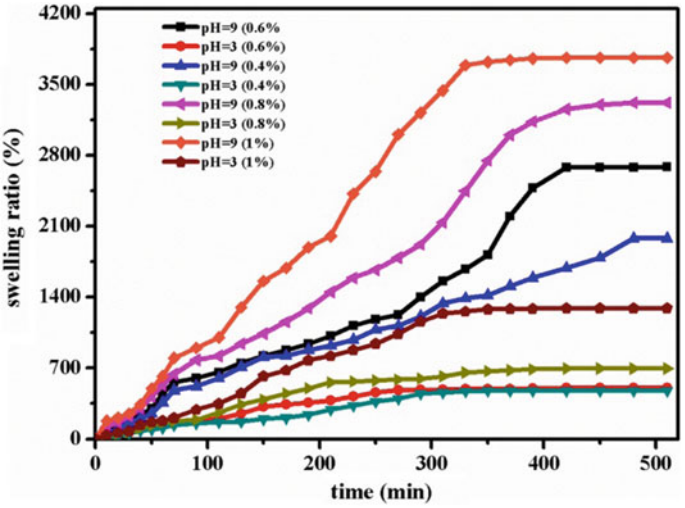

Fig. 26 The swelling ratio of GUG-PAA hydrogel series at different pH (3, 9) [141] (Reprinted with permission from Sharma et al., 2019 Copyright © 2019 Elsevier)

GUG-g-polyacrylamide was synthesized via free radical polymerization reaction by means of potassium persulphate initiator and diverse amounts of nanosilica and incorporated with diltiazem hydrochloride [142]. The water swelling and surface contact angle tests proved that the nanocomposite including 1 wt% of nanosilica had the most hydrophobic nature and the in vitro drug release tests exhibited that this nanocomposite released 8.58 and 24.76% of drug in 5 and 20 h, respectively. Besides, the nanocomposite demonstrated suitable non-irritant and cytocompatibility features which are advantageous for an effective transdermal DDS. Acrylamide-grafted-GUG (pAAm-g-GUG) was blended with CS to achieve hydrogel microspheres through the emulsion crosslinking process by means of glutaraldehyde crosslinker [143]. The 74% of ciprofloxacin (CIP) antibiotic drug was encapsulated into the microspheres and it was found that the CIP release was prolonged to 12 h. the in vitro CIP release at pH 1.2 and 7.4 revealed was dependent on the blend composition, crosslinking extent, and the initial drug loading amount. The release data followed the Korsmeyer–Peppas model signifying a non-Fickian CIP transport in the hydrogel microspheres.

Nanocomposites of carboxymethyl guar gum (CMG) and different amounts of nanosilica were fabricated and used for the transdermal delivery of diclofenac sodium drug [144]. It was indicated that the nanocomposite containing 1 wt% of nanosilica was the optimal formulation. The drug release tests displayed slower release rates from the nanocomposites compared to that of the neat CMG. The nanocomposite hydrogel with 1 wt% of nanosilica had the slowest while sustained drug release among all nanocomposites. In another effort, CMG-multiwalled carbon nanotube (MCNT) nanocomposite hydrogels were prepared using diverse MCNT quantities and applied as carriers for the diclofenac sodium drug [145]. It was found that the CMG–MCNT nanocomposites containing 0.5 and 1 wt% of MCNT had the most intermolecular interactions. The drug encapsulation was increased by the MCNT addition and the highest drug entrapment was measured for the nanocomposite including 1 wt% of MCNT (Fig. 27).

The hydrogels with 0.5, 1 and 3 wt% of MCNT presented slower transdermal drug release compared to the neat CMG. The slowest while sustained drug release was observed for the 1 wt% MCNT containing nanocomposite hydrogel.

11 Gelatin Nanocomposites in Drug Delivery

Gelatin (GEL) is a hydrophilic biopolymer and linear polypeptide composed of diverse 18 kinds of amino acids that is mostly obtained through the partial hydrolysis of collagen which is the main protein constituent existing in white connective tissues, bones, and skin [146]. It is highly heterogeneous as it consists of polypeptides with different sizes and it has a range of 15,000–250,000 molecular weights [147]. GEL is a triple-helical biopolymer that reveals unique characteristics including low cost, easily available, exceptional ability to form membranes, biodegradability, suitable adhesion, non-immunogenicity, non-toxicity, and biocompatibility which have led

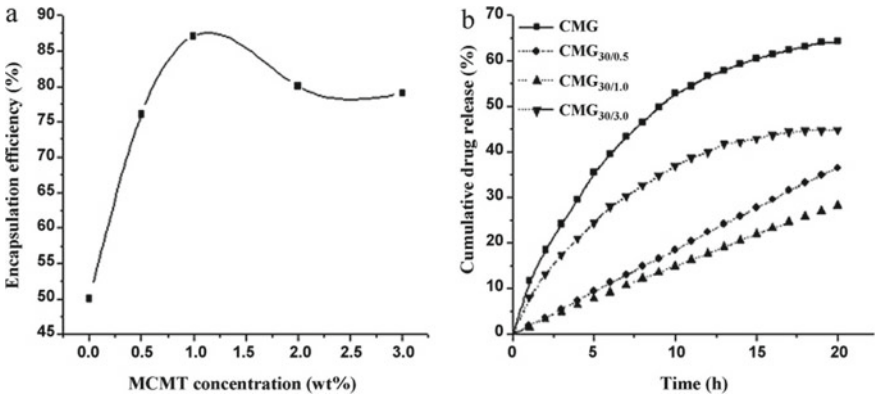

Fig. 27 Studies on **a** drug encapsulation efficiency and **b** cumulative release of diclofenac sodium of CMG–MCNT hybrid hydrogels [145] (Reprinted with permission from Giri et al., 2011 Copyright © 2011 Elsevier)

to its extensive applications in the pharmaceutical and food industries. It has film-forming capability that has resulted in its practical utilization in biomedicine like adhesive, wound dressing, plasma expander, and controlled release drug carriers [148].

Recently, fluoresce in isothiocyanate (FITC) fluorescent labeling compound and carboxyl-functionalized Pt(IV) prodrug were conjugated onto the GEL-encapsulated Fe_3O_4 NPs (Fig. 28) [149].

The Pt(IV) prodrug transporting Fe_3O_4 NPs exhibited satisfactory anticancer effects after the reduction of Pt(IV)to Pt(II) inside the intracellular medium but

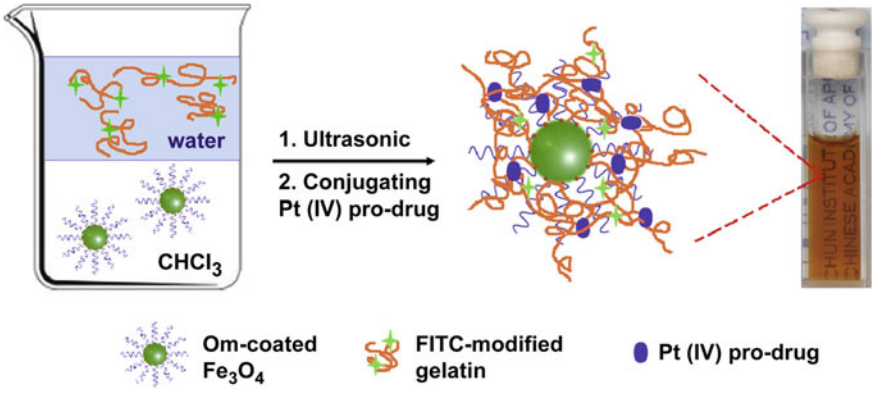

Fig. 28 Schematic illustration for transferring the hydrophobic Fe_3O_4 to water using FITC-gelatin encapsulation and covalent binding Pt(IV) prodrug. The diluted gel/Pt(IV)-NPs aqueous solution shows optical transparency [149] (Reprinted with permission from Cheng et al., 2014 Copyright © 2014 Elsevier)

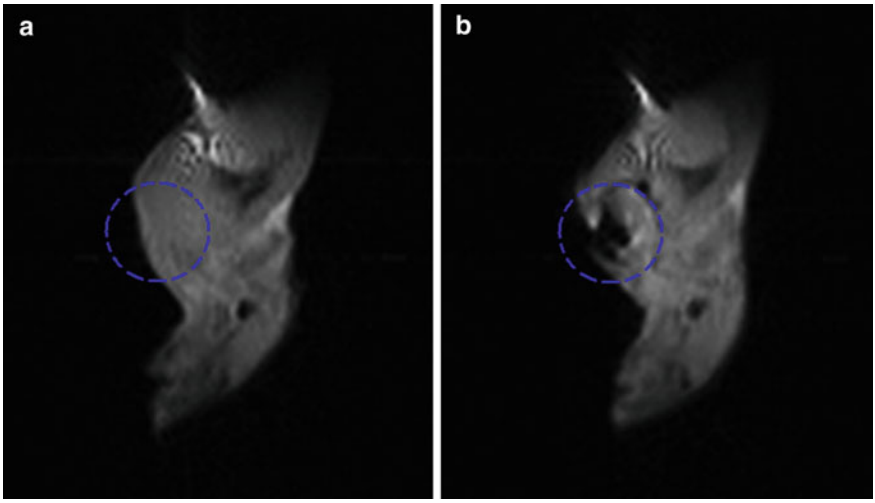

Fig. 29 In vivo T_2-weighted MR images of the xenograft tumor model on a Kunming mouse. Before (**a**) and post-injection (**b**) gelatin-encapsulated Fe_3O_4 nanoparticles in the tumor site in situ [149] (Reprinted with permission from Cheng et al., 2014 Copyright © 2014 Elsevier)

the Pt(IV) prodrug showed minor cytotoxicity to cancerous cells. The FITC fluorescence was used as a probe to monitor the drug release. Furthermore, introducing a pancreatic enzyme efficiently released the GEL from the Fe_3O_4 NPs because of the GEL degradation. High darkness was seen in the magnetic resonance image (MRI) image at the tumor site when the nanoparticles were injected in situ demonstrating the Fe_3O_4 NPs affected the tumor cells, see Fig. 29.

Some GEL/beta-tricalcium phosphate (β-TCP) nanocomposites containing zoledronic acid drug and diverse amounts of β-TCP and drug were synthesized to be used for the treatment of resected primary/metastatic bone sites [150]. It was indicated that the GEL porous structure (50–200 μm) was reinforced by the β-TCP spherical NPs (~90 nm in diameter) which was an appropriate matrix for the proliferation of the bone cells. The cytotoxicity and the osteoblast cell attachment tests proved the non-toxicity and the biocompatibility of the scaffolds. Moreover, increasing the β-TCP concentration improved the cell proliferation rate over the scaffold. The zoledronic acid drug-loaded nanocomposites illustrated enhanced cell proliferation and >75% new bone was formed in the whole defect area after 3 and 4 months using the scaffolds.

GEL-functionalized grapheme nanosheets (GEL-GNS) were prepared to ensure appropriate GNS dispersion and stability in water and several physiological media [151]. The methotrexate (MTX) was loaded into the biocompatible GEL-GNS. The pH-sensitive MTX release from the MTX@GEL-GNS was very greater in acidic solutions compared to that in neutral solutions. The cytotoxicity test proved that the MTX@GEL-GNS was remarkably toxic whereas the GEL-GNS was non-toxic

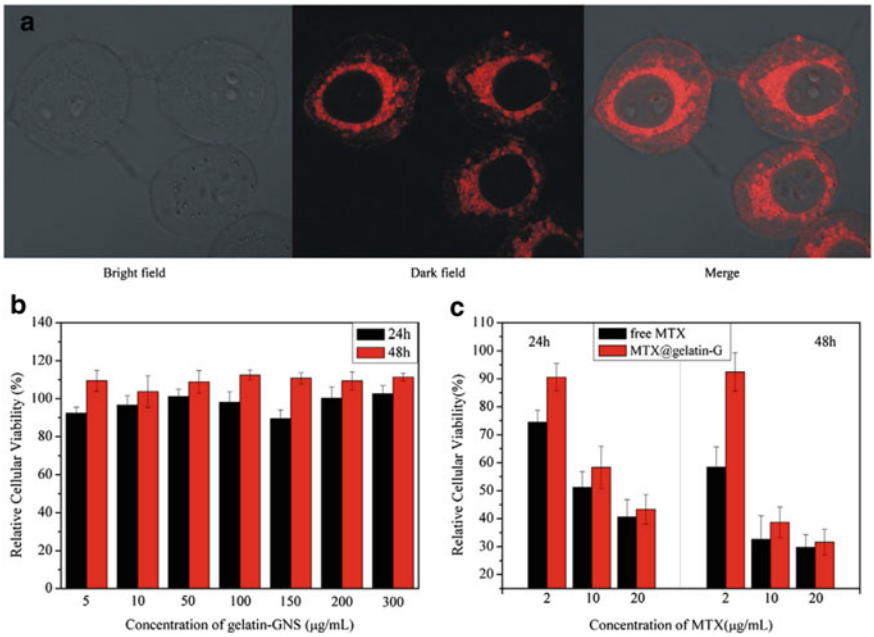

Fig. 30 **a** Confocal laser scanning microscopy images of A549 cells for incubation with R6G@gelatin-GNS for 2 h at 37 °C. **b** Relative cell viability of A549 cells treated with different concentrations of gelatin-GNS after 24 h and 48 h incubation. **c** Cytotoxicity of free MTX and MTX@gelatin-GNS to A549 cells after 24 h and 48 h incubation [151] (Reprinted with permission from An et al., 2013 Copyright © 2013 Elsevier)

in certain concentrations and both of them were taken up by the A549 cells via a nonspecific endocytosis pathway (Fig. 30).

Antibacterial CS–GEL/zinc oxide (CS–GEL/*n*ZnO) nanocomposite hydrogels were achieved by in situ synthesis of *n*ZnO and employed as naproxen drug carriers [152]. The scaffolds illustrated antibacterial, cytocompatibility, swelling, cell attachment, and biodegradation characteristics. The scaffolds exhibited high porosity (pore sizes were 50–400 μm) and *n*ZnO was suitably dispersed into the CS–GEL matrix without agglomeration. Also, then ZnO addition to the hydrogel controlled the naproxen drug release. The nanocomposite hydrogels were cytocompatible with normal human dermal HFF2 fibroblast cells.

12 Chondroitin Sulfate Nanocomposites in Drug Delivery

Chondroitin sulfate (CTS) is a naturally occurring polysaccharide biopolymer that is an essential component of the cartilage and connective tissues that can increase compressive strength of the connective tissues through regulation of their water

content. CTS has outstanding properties including biodegradability, multifunctionality, and great water adsorption that make it a promising material for biomedical applications [153]. It is a glycosaminoglycan composed of β-1,3-linked D-glucuronic acid plus (β-1,4) *N*-acetylgalactosamine (GalNac) alternating disaccharide units so that the GalNac unit has been sulfated at either 4- or 6-positions. CTS is easily dissolved in water leading to burst release of its loaded pharmaceutics. This can decrease its broad applications as drug delivery vehicles but crosslinking or its blending with other polymers like CS, poly(lactic-co-glycolic acid), hyaluronan, gelatin, and poly(vinyl alcohol), collagen can afford more stable compounds and decrease high hydrophilic nature of CTS and protect the loaded bioactive agents [154]. CTS is able to specifically bind onto the receptors that are overexpressed by cancer cells. The phagocytized species are degraded by enzymes like hyaluronidase existing in cancer cells and release the pharmaceutical drug [155].

Some covalent polysaccharide-based hydrogels were prepared by the Schiff' base reaction using oxidized chondroitin sulfate (OCTS) and water-soluble CMC [156]. Still, CS-based microspheres (CMs) loaded with bovine serum albumin (BSA) were obtained via emulsion crosslinking (diameter = 3.8–61.6 μm) that were then embedded in the CMC-OCTS hydrogels which afforded CMs/gel composite scaffold. The bioactive and mechanical features of gel scaffolds were highly increased through CMs addition because they acted as a filler and toughened the CMC-OCTS soft hydrogels. Compressive modulus 13 kPa for the composite scaffold with 20 mg/ml CMs that was greater than that of the CMs-free hydrogel. The BSA release was 30% in 2 weeks from the CMs-containing hydrogel that was very lower than those of the hydrogels and CMs (Fig. 31).

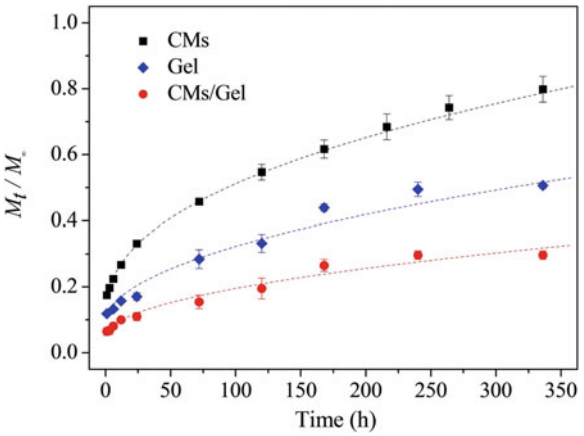

Fig. 31 Cumulative release of BSA from CMs, gel, and CMs/gel. The concentration of CMs incorporated in hydrogels was 20 mg/ml. M_t/M_∞ represents the cumulative fractional mass released at time *t*. Dashed lines indicate the fitted curves of release profiles. Values reported are an average of $n = 3$ [156] (Reprinted with permission from Fan et al., 2017 Copyright © 2017 Elsevier)

Table 4 The kinetic parameters of 7-[2-nitroxiacetyl-oxy-3-(4-acetyl-amino-phenoxy)-propyl]-8-morpholino-1,3-dimethyl-xanthine NO-donor compound release from cellulose/CS-based hydrogels according to Higuchi model [157]

Hydrogel	Half release time (min)	Time to reach maximum amount released (min)	Maximum release amount (%)	Release constant k_r 103 ($min^{-0.5}$)	R
Alkali cellulose	67	340	93	56.7	0.99
90/10	67	340	95	64.4	0.99
80/20	70	370	90	57.9	0.99
70/30	87	400	87	53.0	0.99
60/40	100	460	82	40.5	0.99
50/50	160	550	80	27.9	0.99

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Besides, the CMs/gel composite scaffold displayed slower degradation and lower swelling than those of the CMs-free hydrogel. The bovine articular chondrocytes were encapsulated in vitro into the composite hydrogel confirming its ability to be used as an injectable scaffold.

Mixed hydrogels were prepared using CTS and cellulose through crosslinking. The mixed cellulose/CTS hydrogels were loaded by 7-[2-nitroxiacetyl-oxy-3-(4-acetyl-amino-phenoxy)-propyl]-8-morpholino-1,3-dimethyl-xanthine, that was served as a nitric oxide donor agent having less toxicity and higher anti-inflammatory capacity than those of its parent drugs (theophylline and paracetamol) [157]. It was found that increasing the CTS amount in hydrogels enhanced the swelling ratios of all formulations and diminished the release of nitric oxide donor material. Also, the swelling occurred via an anomalous mechanism but the nitric oxide donor release followed a diffusion-controlled mechanism (Table 4).

Recently, synthesis of CTS-g-poly(ε-caprolactone) (CP) copolymers was accomplished by atom transfer radical addition polymerization reaction and the CP copolymers were self-assembled to micelles in water that were employed for the encapsulation of camptothecin (CPT) as a hydrophobic anticancer drug to be used for targeted tumor delivery [158]. The apoptosis-induced and cell-damaging effects of the CPT-containing micelles against CRL-5802 cells were considerably greater than CPT. The micelles were internalization in the CRL-5802 cells by clathrin and CD44 dual-assisted endocytosis pathway. The in vivo therapeutic capacities of the CPT-incorporated micelles were examined using a non-small-cell lung cancer xenograft animal model and the CPT-containing micelles exhibited suitable tumor growth inhibition in CRL-5802 tumor-bearing mice than CPT-11 commercial compound. Thus, the CP-bearing micelles were proposed as appropriate anticancer drug carriers for in vivo and in vitro lung cancer targeting.

(3-Aminomethylphenyl)boronic acid (AMPB) functionalized CTS A (CSA)–deoxycholicacid (DOCA) NPs to fabricate CSA–DOCA conjugates for targeted

tumor delivery and penetration [159]. DOX-encapsulated CSA–DOCA–AMPB NPs (diameter ≈200 nm) indicated spherical morphology, negative zeta potential, and narrow size distribution. The DOX release from the NPs was enhanced in acidic pH than in physiological pH. The CSA–DOCA–AMPB NPs exhibited enhanced cellular uptake of and penetration into A549 spheroid cells (human lung adenocarcinoma) than the CSA–DOCA NPs. The NPs were penetrated in vivo into the tumor mass core of A549 in tumor xenografted mouse. Also, intravenous injections of the DOX-containing CSA–DOCA–AMPB NPs effectively inhibited the A549 tumor growth in the xenografted mouse and increased apoptosis approving such boronic acid-containing NPs were valuable materials for cancer imaging and therapy. In another effort, CS-modified methacrylate (CSMA) was synthesized to obtain crosslinked shell polyelectrolyte complexes (PECs) with CS in order to sustain DOX release and increase its activity towards cancer cells [160]. The DOX release from the DOX-containing PECs into A549 and human cancer KB cells were detected using flow cytometry and confocal laser scanning microscopy and evaluated through capillary electrophoresis. The DOX-incorporated PEC with crosslinked shell exhibited anticancer activity for the DOX and DOX-loaded PEC.

13 Pectin Nanocomposites in Drug Delivery

Pectins (PECs) are water-soluble linear polysaccharide polymers existing in plant cell walls that are comprised of partially metoxylated poly α-(1,4)-D-galacturonic acids [161]. The esterification degrees of PECs can strongly affect the polymer characteristics. There are three kinds of low, medium, and high methoxylated PECs indicating esterification degrees of <40%, 40–60%, and >60%, respectively [162]. The medium and low methoxylated PECs have the ability to form gels using multivalent cations but high methoxylated PECs form gels only in presence of acids [163]. PECs are utilized as matrixes in drug carriers [164].

In a recent study, biopolymer nanocomposite gel beads high methoxylated PEC and guar gum alkyl amine (GUGAA) in 4:4:1 ratio including silver NPs (AgNPs) and ciprofloxacin (CIP, encapsulation efficiency of >70%) were prepared for application in the controlled release of antimicrobials [165]. The beads inhibited the degradation of AgNPs in acidic solutions as HMP had an important effect to provide hydrophobic areas. The CIP release was pH-independent and a diffusion procedure but the AgNPs release was dependent on the matrix erodibility. The beads exhibited antibacterial properties against *S. aureus*, *P. aeruginosa*, *Bacillus cereus*, and *E. coli*. Figure 32 reveals the TEM images of *P. aeruginosa* bacterium untreated and treated by the AgNPs-GUGAA for 10 min and 12 h.

Hence, the nanocomposite was a suitable DDS for the oral treatment of intestinal infections by unknown multidrug-resistant microorganisms as AgNPs and CIP both could reach to the intestine as active agents.

Starch/PEC nanocomposite films were fabricated to improve the oral bioavailability of methotrexate (MTX) drugs [166]. Improved puncture strength was

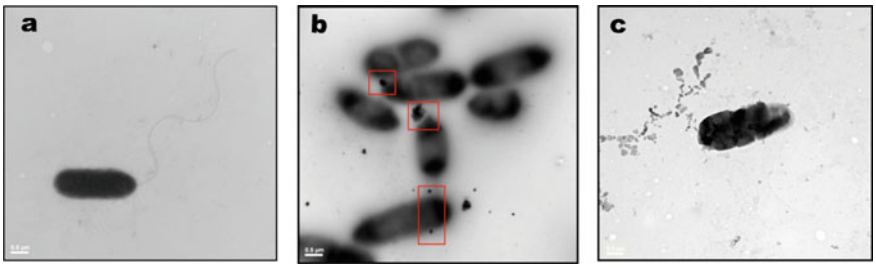

Fig. 32 TEM images of *Pseudomonas aeruginosa*: untreated (**a**); treated with AgNPs-GUGAA: for 10 min (**b**) and after 12 h (**c**). Squares are indicating the interaction zone of the AgNPs with bacterial membrane [165] (Reprinted with permission from Islan et al., 2015 Copyright © 2015 Elsevier)

measured but the barrier properties illustrated low water vapor permeability. The ex vivo bioadhesion analysis exhibited that the nanocomposites films strongly interacted with porcine gastrointestinal mucosa. The in vitro drug release test proved that the films could enhance the drug dissolution so that ~80% MTX was released in 150 min signifying such films are valuable carriers for poor solubility drugs that can enhance oral bioavailability of drugs.

Polysaccharide nanocapsules were obtained using silica templates through the layer-by-layer method and the nanocapsule shell was formed by electrostatic interactions among CS and PEC, see Fig. 33 [167].

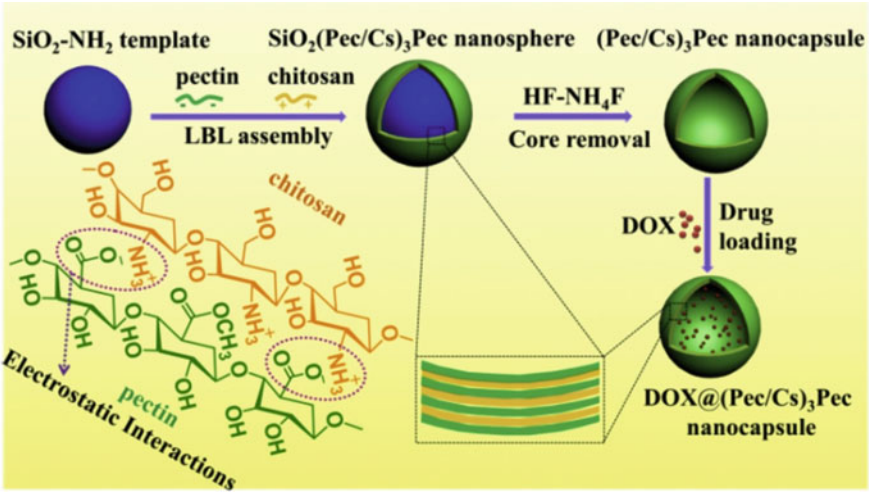

Fig. 33 Schematic illustration for the formation process of $(PEC/Cs)_3PEC$ hollow nanocapsule and DOX@$(PEC/Cs)_3PEC$ nanocapsule via layer-by-layer assembly [167] (Reprinted with permission from Ji et al., 2017 Copyright © 2017 Elsevier)

The $(PEC/Cs)_3PEC$ nanocapsules had high colloidal stability in PBS solution for 96 h and in BSA solution for 48 h. Also, the nanocapsules had a high drug loading, pH-sensitive doxorubicin hydrochloride release as well as no cytotoxicity to both L929 mouse fibroblast and HepG2 human hepatocellular carcinoma cells (Fig. 34).

Furthermore, $(PEC/Cs)_3PEC$ nanocapsules were more simply uptaken by HepG2 cells than the L929 cells. The carriers illustrated in vitro anticancer activities as they efficiently killed HepG2 cells.

Several curcumin-loaded magnetic nanocomposites were produced using magnetite NPs coated by PEC and 6-aminohexanoic acid [168]. The nanocomposite size in water was 147 nm indicating polydispersity index = 0.32 but the size of curcumin-loaded nanocomposite was 159 nm and polydispersity index = 0.34. The nanocomposite was stable in NaCl solution with a concentration of up to 0.45%w/v but they were aggregated in a solution with higher NaCl concentration. The curcumin drug release from the nanocomposite was biphasic with an initial burst release and then a slow release. Recently, a nanocomposite scaffold was achieved using chitin, PEC, and nano $CaCO_3$ by lyophilization for drug delivery and biomedical applications [169]. The composite displayed more controlled degradation and swelling than the control scaffold. The scaffold cytocompatibility test was done using L929, NIH3T3, and human dermal fibroblast cells and insignificant cytotoxicity was seen to the cells (Fig. 35).

The cell proliferation/attachment tests using these cells proved that the cells were attached to the scaffolds and proliferated after 48 h incubation, see Fig. 36.

The Fosamax bisphosphonate drug was loaded into the scaffold that was used for drug delivery.

14 Collagen Nanocomposites in Drug Delivery

Collagen (COL) is the most important naturally occurring fibrous protein existing in the extracellular matrix (ECM) of mammalians [170]. There are 28 kinds of COL so that seven types of collagens can form fibrils but nine of them form fibril-associated collagens as interrupted triple helices. The most well-known COL is Type I COL that forms fibril COL and exists in different body components like hide/skin, bone, nail, tooth, and tendon. COL fibers are typically 50–500 nm in diameter that can form the ECM scaffold of the connective tissues such as bones. The basic unit of COL fiber is the COL molecule that is a rod-like, right-handed triple-helix with 1.5 nm diameter and ~300 nm long is comprised of three chains of type II polyproline (PPII) which is composed of a several repeated three-unit amino acid sequence [171]. Accordingly, COL fibers have abundant functional groups like $–NH_2$, –COOH, and –OH. The COL fibrils reveal both in vitro and in vivo biological activities. The COL-based nanofibers are extensively employed to prepare drug delivery vehicles. As COL-based materials are rapidly degraded, crosslinking using several crosslinkers is usually accomplished to increase their stability [172].

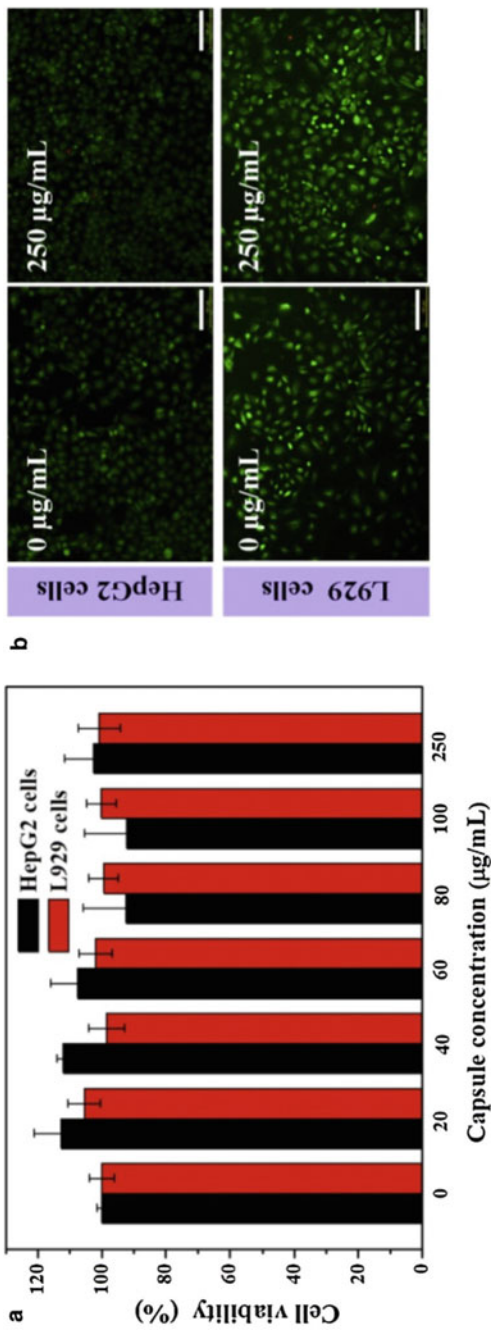

Fig. 34 Cytotoxicity evaluation of $(PEC/Cs)_3$PEC hollow nanocapsule against HepG2 cells and L929 cells. **a** Cell viabilities of HepG2 cells and L929 cells after 48 h incubation with $(PEC/Cs)_3$PEC nanocapsule at different concentrations, the data was expressed as mean ± SD, $n = 3$. **b** Fluorescence images of HepG2 cells and L929 cells stained with AO/PI assay after 48 h incubation at the concentration of 250 μg/mL (green: live cells, red: dead cells). Scale bar = 100 μm [167] (Reprinted with permission from Ji et al., 2017 Copyright © 2017 Elsevier)

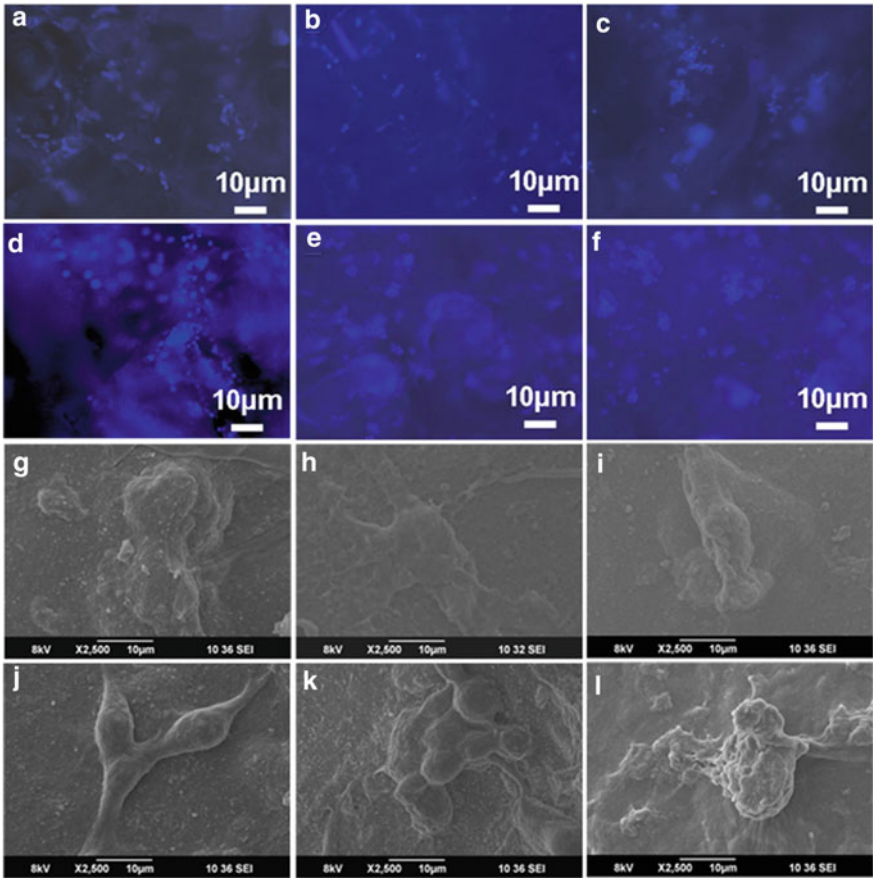

Fig. 35 DAPI staining of NIH3T3 cells **a** after 24 and **d** 48 h; L929 cells **b** after 24 and **e** 48 h; HDF cells **c** after 24 h and **f** after 48 h. **g**–**i** SEM images of NIH3T3, L929, and HDF cells attached on the scaffolds after 24 h respectively. **j**–**l** SEM images of NIH3T3, L929, and HDF cells attached on the scaffolds after 48 h, respectively [169] (Reprinted with permission from Kumar et al., 2013 Copyright © 2013 Elsevier)

Recently, a semi-conductive nanocomposite was prepared as an electrically controlled drug carrier and for this purpose, hydrolyzed COL as a naturally plentiful polypeptide was modified by polycaprolactone [173]. The in situ aniline polymerization produced conductive nanofibers inside the hydrogel matrix. The in vitro conductive-stimuli hydrocortisone drug release was observed. The conductive and non-conductive hydrogels did not show any cytotoxicity confirming the nanocomposite was a suitable externally controlled drug carrier.

It is known that gene therapy can allow protein production by transfected cells. In an attempt, nanocomposites were achieved containing complexes of DNA-polyethylenimine-silica NPs and fibroblasts in COL hydrogels [174]. By changing

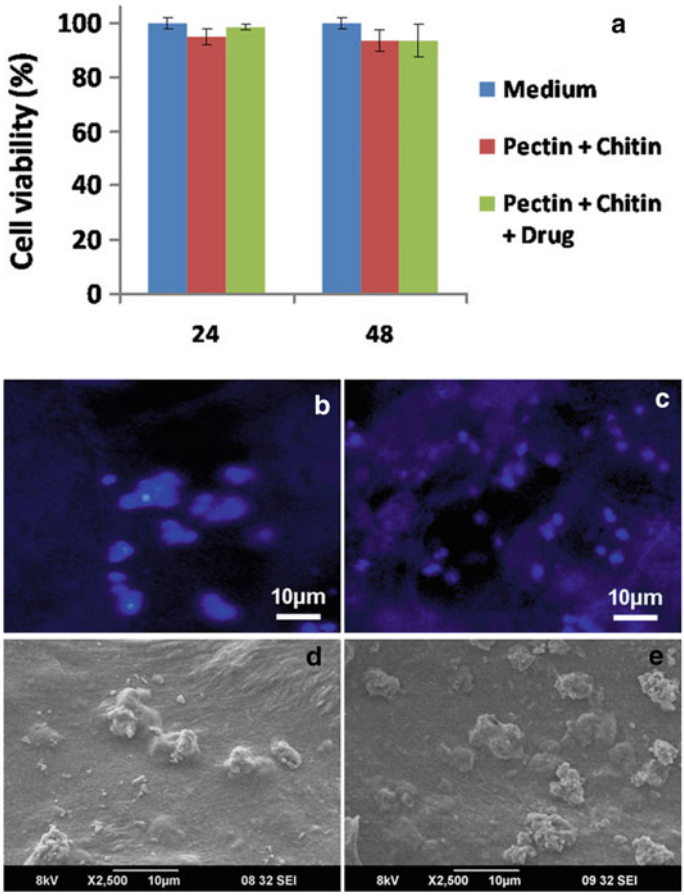

Fig. 36 **a** Cell viability study pectin–chitin/nano $CaCO_3$ composite scaffolds using MG63 cells. **b**, **c** DAPI staining of MG 63 cells attached on the scaffolds after 24 and 48 h respectively. **d**, **e** SEM images of MG 63 cells attached on the scaffolds after 24 and 48 h respectively (data shown are expressed as mean ± SD ($n = 3$)) [169] (Reprinted with permission from Kumar et al., 2013 Copyright © 2013 Elsevier)

the polyethylenimine molecular weight and particle size, "in-gel" transfection happened that led to the sustained creation of biomolecules by the hydrogels in one week. It was found that particle encapsulation limited the silica and DNA diffusion outside the hydrogels. The cell proliferation in COL hydrogels affected the transfection efficacy indicating the nanocomposites were auspicious gene delivery systems. A multifunctional COL bionanocomposite nanofiber, CFeAb*D, incorporated with iron oxide NPs, fluoresce in isothiocyanate labeled antibody plus gemcitabine anticancer drug, was prepared for targeted cancer therapy [175]. The magnetic saturation of the bionanocomposite was 54.97 emu/g and its diameter and dimension were in the range of 10–30 and 97–270 nm, respectively (Fig. 37).

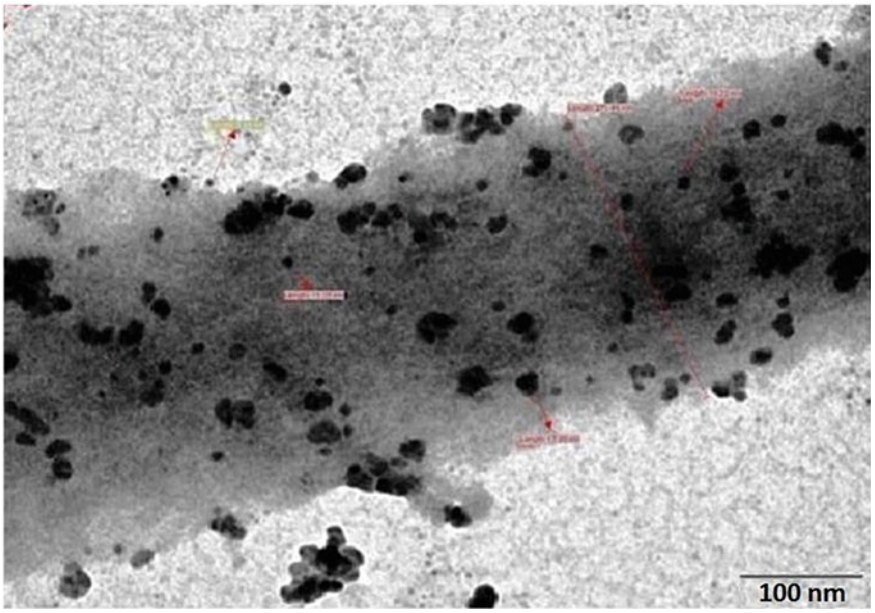

Fig. 37 TEM analysis of CFeAb*D. The whole composite is in the form of a nanofiber having a dimension of 97 nm × 270 nm and the incorporated globular FeNPs having a diameter in the range of 10–30 nm [175] (Reprinted with permission from Mandal et al., 2013 Copyright © 2013 Elsevier)

The bionanocomposite had a superparamagnetic property and was used as a magnetic resonance imaging (MRI) contrast agent. Figure 38 illustrates the MRI images of untreated and CFeAb*D treated gastric cancer cells in which the black spots signify the signal drop revealing the magnetic of the NBC internalization to the cells (the control cells do not show any signal drop).

The cytotoxicity test exhibited biocompatibility in addition to an apoptotic influence of the bionanocomposite but the phase-contrast microscopy displayed receptor-mediated endocytosis uptake. The COL nanofibers had a high penetrating ability without very cell damage, multifunctional and biocompatibility features, and could deliver multifunctional drugs.

The mesoporous hydroxyapatites (MHAP) NPs were applied to fabricate redox-responsive nanoreservoirs (LA-COL-S-S-MHAP) by means of lactobionic acid-conjugated COL (LA-COL) as cap disulfide bond as linker and MHAP as nanoreservior [176]. The lactobionic acid (LA) molecules were served as a targeting fragment to accomplish targeted drug delivery and dithiothreitol was employed as an external stimulus to induce redox-responsive drug release by the LA-COL-S-S-MHAP. The LA-COL-S-S-MHAP nanocomposite revealed a fast response and burst drug release under reduced conditions. The flow cytometry and confocal laser scanning microscopy images proved that the LA-COL-S-S-MHAP were endocytosed and

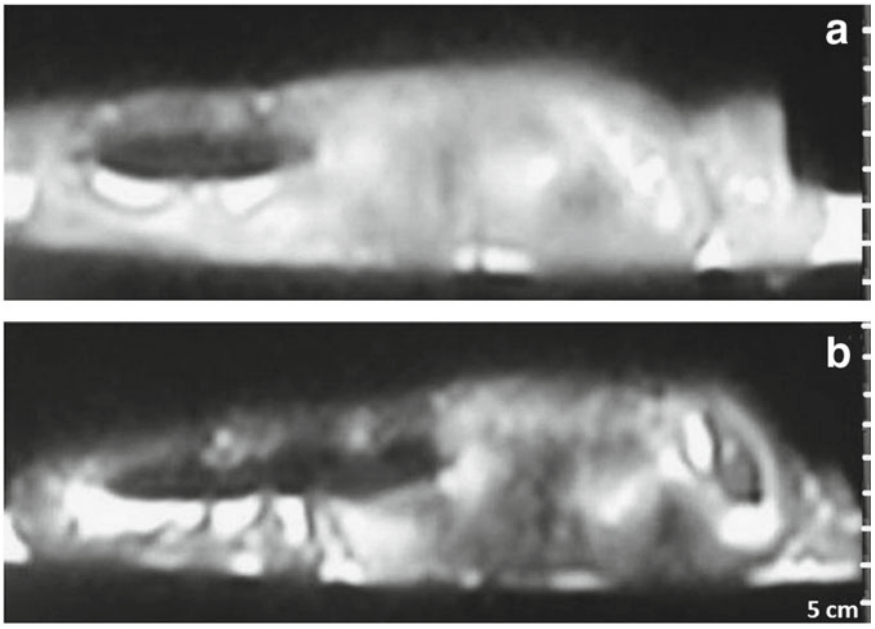

Fig. 38 MRI images of gastric cancer cell line in agarose gel: untreated cells (**a**) and CFeAb*D treated cells (**b**). The black spots seen in (**b**) denotes the drop in signal, which reveals the magnetic effect produced by the entry of NBC into cells compared to the control cells where there was no drop in signal [175] (Reprinted with permission from Mandal et al., 2013 Copyright © 2013 Elsevier)

situated within the cellular cytoplasm. Targeted redox-responsive drug delivery was done to the cells.

HAP NPs were synthesized and utilized as a DDS for the water-insoluble paclitaxel (PTX) anticancer drug [177]. The PTX-loaded HAP (PTX/HAP) demonstrated a lower activity compared to that of the free PTX due to the HAP nanoparticles were not completely dispersed in solution. Therefore, the PTX/HAP was encapsulated into the COL gel to afford the PTX/HAP incorporated COL gel (PTX/HAP/COL) exhibiting a greater activity than the PTX-loaded COL gel. The extremely metastatic MDA-MB-231 cells exhibited more sensitivity to the PTX/HAP/COL compared to the poorly metastaticMCF-7 cells. PTX/HAP/COL was a valuable DDS for the drug delivery to the metastatic cancerous cells.

15 Conclusion

Numerous researches have been accomplished using biopolymer nanocomposites in drug delivery applications. There are nearly abundant polysaccharides in nature that can be applied by humans as drug carriers including chitosan, alginate,

hyaluronic acid, cellulose, carboxymethyl cellulose, hydroxyethylcellulose, starch, gellan gum, acacia gum, guar gum, gelatin, chondroitin sulfate, pectin, and collagen. Such nanobiocomposites have exceptional characteristics such as environmentally friendly nature, biocompatibility, cost-effectiveness, non-toxicity, biodegradability, and possessing various functional groups that make them suitable for intermolecular interactions with pharmaceuticals/drugs and cell components. These properties of natural biopolymers have attracted great attention worldwide for their biomedical applications compared to synthetic polymers. It is anticipated that the DDSs fabricated using polysaccharide-based bionanocomposites will be substituted by other conventional treatment methods using synthetic and petroleum-derived polymers. Also, it is possible that the results of such investigations on biopolymer-based drug vehicles will result in the production of commercial green therapeutics with high efficiencies and very low/no side effects.

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Biopolymeric Micelles

Smriti Kumari and Kamla Pathak

Abstract Amphiphilic chemicals possess natural tendency of micelle formation in the aqueous media. Since polymers are role players in micelle formation, therefore, the carrier system developed is called polymeric micelles. The agents employed for micelles formation are of three types—di-block and tri-block copolymers and graft polymers. The polymers may be of synthetic and natural origin. Those obtained from natural sources are generally termed as "biopolymers" as they are biodegradable and biocompatible. Owing to their biological origin and nano-size range stability and safety holds significance interest, respectively. Stability aspects are focused on keeping the kinetics and thermodynamics in center, while safety issues include toxicity, bioavailability, drug leakage, etc. These biopolymers are slowly but aptly emerging as "messengers" of controlled and targeted drug delivery systems, especially in case of hydrophobic drugs. The future outlooks and thrust areas are being assessed based on stability data and targeted delivery. Therefore, molecularly imprinted polymers graft and conjugated polymers seem to hold the next-generation drug delivery in the micellar system.

Keywords Biopolymers · Polymeric micelles · Hydrophobic drugs · Targeted and controlled drug delivery · Graft polymers

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1 Introduction

Technology is ever evolving with the advancement in the current trends in all spheres. Pharmaceutical technology has always been the most sought-after science which has always set a breakthrough from the previous one. One such evolution has occurred in micellar drug delivery systems with the introduction of polymers. Basically, micellar formation is a spontaneous property of the bile acid, which is secreted into duodenum under physiological systemic process of fat digestion and its subsequent absorption in the intestine. Similarly, micellar drug formulations are an extension to the natural system inside the body. Technically, they are aggregates of few hundred *amphiphilic* molecules that contain distinct hydrophilic and hydrophobic regions. Earlier surfactants-based micellar systems were in trend which reportedly enhanced the solubility of many hydrophobic drugs [1]. Micellar drug delivery is advantageous over other drug delivery system in terms of encapsulation of macromolecules like albumin, pancreatic polypeptide with their sustained and controlled of same release, provide chemical and physical protection to these molecules, improved bioavailability, favorable tissue targeting with its distribution, low toxicity profile and easy elimination from the body through renal excretion owing to their nano-sized spherical form [2]. Micellar drug delivery has now included smart polymers in their avenues. These polymers are the ampiphillic chemicals having hydrophobic portion-oriented inwards and hydrophilic portion-oriented outwards to the aqueous milieu. The inherent automated process of micelle formation by such polymers has gained its importance in the direction of drug delivery system as earlier it was limited to physical and cosmetic sciences only. Also, the low CMC value, slow dissociation with prolonged retention and controlled drug delivery with non-selective scavenging of these carriers by the reticuloendothelial system (RES) indicates the improved stability and adaptability of the polymeric system in the body as well. These properties have put polymeric micelle ahead from the conventional one. Also, the simple preparation methods with no complications in drug loading have creamed out micelles as preferred choice of career system, especially in case of hydrophobic drugs with minimal need of any structural modification [3].

2 Description

The polymeric micelles are sub-microscopic aggregates with an average size range of 5–100 nm in most of the types [4]. Out of the several polymeric micelles reported the current shapes are star, flower-like, spherical supramolecular assemblies, worm, vesicles, toroids and helices [5]. The shape and orientation may be an outcome of different lengths of hydrophilic and hydrophobic portion and the media employed. Some of the prominent shapes with orientation and formation are summarized in Table 1.

Table 1 Morphology of the polymeric micelles [6, 7]

Hydrophobic chain	Hydrophilic chain	Media	Shape
Copolymer: Short	Long	Aqueous	Spherical
Copolymer: Long	Short	Aqueous	Rod and lamellae or polymeric vesicle (Polymersosomes)
Tri-block polymer: small	Long	Aqueous	Flower-like micelle
Copolymers: di-block: short	Long	Non-aqueous	Spherical: reverse micelles
3d uniblock polymers	N/A	N/A	Micellar aggregation (star-shaped)

In addition to the tabular presentation of morphological arrangements, given below is the pictorial presentation based on the polymeric chain length. Different morphologies are well described and depicted in the subsequent figures [7, 8].

Figure 1 represents the self-assembled form of polymeric micelles with the common orientation of hydrophobic portion and hydrophilic portion in the aqueous milieu. Micellar structure is the first obtained from unimers or unimolecular chains exhibiting three-dimensional confirmation. Generally, these are spherical in size owing to the length of the hydrophilic and hydrophobic chain. This micellar system is also known as common core–shell micellar system. Polymers commonly employed are *N*-octyl-O-sulfate chitosan (NOSC), pluronic and tetronic unimers with an intermediate PPO length (30–60 units) and low to medium HLB, monomethoxy poly (ethyleneglycol)-poly (D, L-lactic acid).

Figure 2 represents the reversal of the orientation of amphiphilic polymeric chain where the hydrophilic chain is greater in length than the hydrophobic portion resulting in spherical shape of the polymeric micelles in the non-aqueous media. Since, simple core–shell structure under complicated physiological conditions, and may burst leading to premature disintegration of the micelle and subsequently drug. Therefore, alternative structures like reverse micelles are investigated for drug delivery

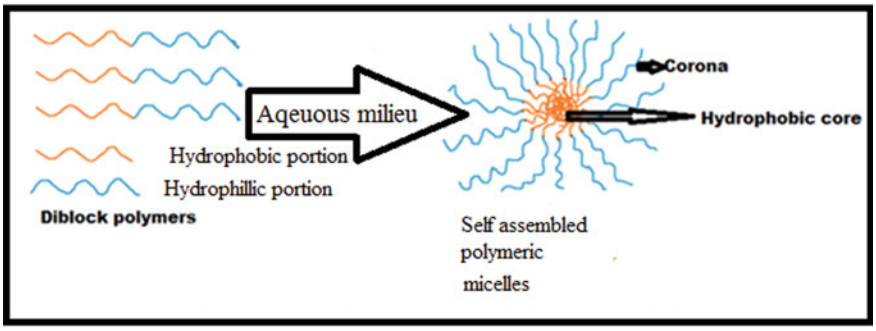

Fig. 1 Self-assembled polymeric micelles

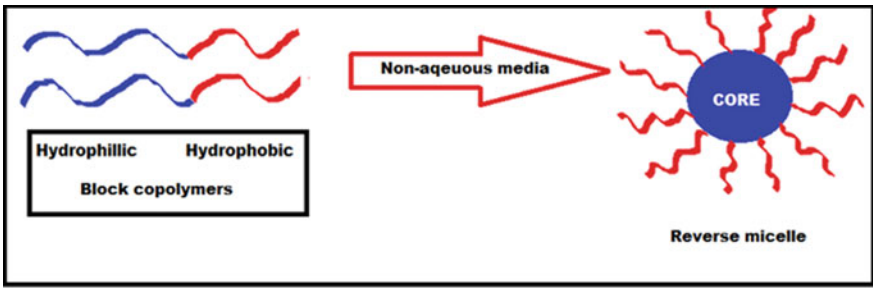

Fig. 2 Depiction of reverse micelle

and they are found to possess good biological activity. However, micellar stability is often inversely related to the water content of the formulation. Here, block polymers are used having two different polymer compositions linearly linked together through their reactive ends. The core is of hydrophilic portion of the block polymer and the corona is hydrophobic portion.

The micelle in Fig. 3 depicts rod and lamellae morphologies or polymeric vesicles (polymersomes) where copolymers with longer hydrophobic blocks and shorter hydrophilic blocks. Typically, the inner core is formed by blocks that associate via hydrophobic interactions. Micellar formation may be done by electrostatic interactions in case of charged block copolymers, also via hydrogen bonding as well as metal–ligand coordination resulting in the formation of polyion complex micelles.

The tri-block copolymers of A-B-A type make "flower-like" polymeric micelles (Fig. 4) with small hydrophobic ends marked with red color and a long hydrophilic block. These micellar structures can solubilize poorly soluble drugs in the hydrophobic core and sustain the release for long periods of time. For example.

Poly (L-lactic acid)-b-poly(oxide ethylene)-b-poly(L-lactic acid) (PLA-b-PEO-b-PLA) led to "flower-like" polymeric micelles with 7–13 nm mean diameter.

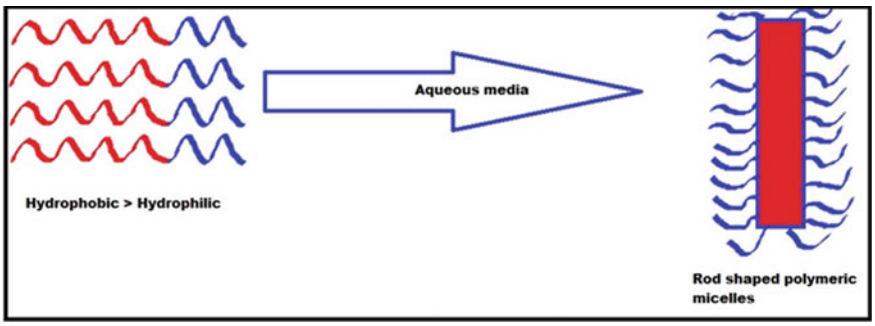

Fig. 3 Lamellar polymeric micelles

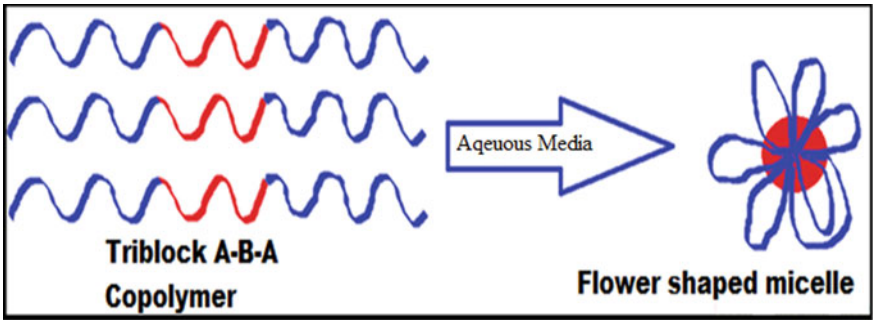

Fig. 4 Flower-shaped micelle

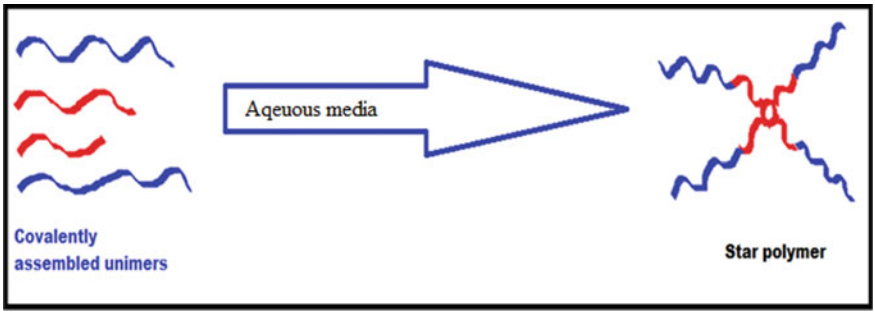

Fig. 5 Depiction of star polymer

Figure 5 represents star-shaped polymeric micelles which are covalently assembled hydrophobic or hydrophilic unimers attached to each other via covalent bonding forming a copolymer self-assembling into a star-shaped polymeric micelle. Star-shaped polymer micelles have good stability against dilution with water, therefore, have promising stability. For example, doxorubicin delivery is experimented out in a star-shaped biodegradable micelle made from poly (alpha-caprolactone)/polyethylene glycol or acrylated monomethoxy poly (ethylene glycol)-poly (alpha-caprolactone). It is a self-assembled with a core–shell structure, in water in which the double bonds at the end of the PCL blocs were conjugated together by radical polymerization [9].

The polymeric micelle in Fig. 6 represents tri-block polymeric assembly in the aqueous surrounding where the hydrophobic portion is oriented in the center with two different hydrophilic blocks. They are generally spherical in shape and stable when the assembly is not too large. Another term may be mixed micelle as it has presence of two or more copolymers having similar blocks of different length or dissimilar blocks [8].

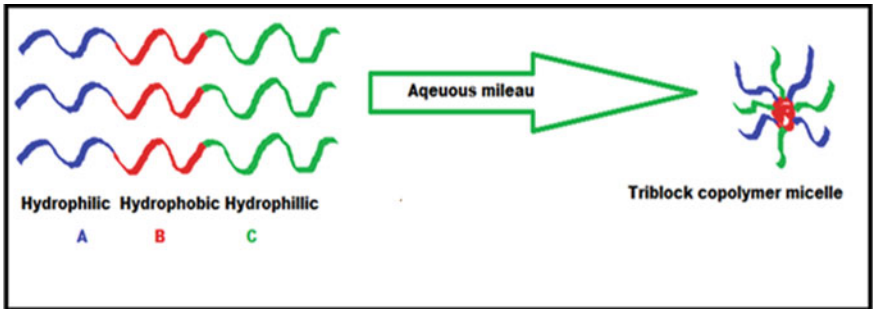

Fig. 6 Tri-block copolymer micelle

3 Types of Polymers Employed in Micellar Formation

There are three types of polymers commonly used for fabricating the micellar structure. These are,

(A) *Di-block polymers*: They consist of two types of monomers A and B. The monomers are arranged in such a way that the backbone consists of linearly arranged single block of each monomer A and B and the monomers are linked through the reactive ends. The structure can be represented in general as AAABBB. Example: block copolymers, poly (styrene)-b-poly (ethylene oxide).

(B) *Tri-block polymers*: They are the natural extension of the di-blocks such that on a di-block copolymer AB a third block C is attached to another end [10]. The general representation is AAAABBBBBAAAA or AAABBBCCC. This can be exemplified by poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) or polystyrene-block-butadiene-block-poly (methyl methacrylate) [11, 12].

(C) *Graft polymers*: Graft copolymers comprise two polymeric components, in which the second component is randomly distributed branches, which are attached to the first component serving as the backbone. Example, poly (styrene-b-[(4-vinyl phenyl-dimethyl siloxane)-g-isoprene]}. The structure can be represented as given below [9].

Grafting is done by following methods. Firstly, by grafting through, secondly grafting by, and thirdly by grafting from. Using the first grafting through technique, macro-monomers like polylactic acid, polycaprolactone and polyethylene have been grafted into polystyrene or polymethacrylate backbone. The method serves many benefits like control of functionality, copolymer composition polydispersity, backbone dimensions in terms of length, branch length and spacing. In this method, the self-assembled monolayer having polymerizable groups attached to a polymeric surface, then a suitable initiator is added to support growth, during which the integrated monomers get integrated to the polymer back resulting in fixed attachment. Grafting to is another technique by which star-shaped or loosely packed polymers are prepared. In this a covalent attachment is achieved between surface groups on a polymeric backbone with polymer chain with specific functional groups and which may be located at the end or on the side chain of the main polymeric backbone. Third technique is grafting from, which is a surface-initiated polymerization due to the growth of polymer chains from the surface attached or self-assembled moieties [13].

4 Source

The polymers may be of natural and synthetic origin. The classification with examples are categorized in Table 2.

Biopolymers from natural origin are hydrophilic natural polysaccharides which are non-toxic, biodegradable and biocompatible in their properties. These can be easily chemically modified due to plenty of hydroxyl, amine, carboxyl, sulfate and other functional groups. The tabulated polymers explored for polymeric micelles are obtained naturally from different sources plant-based polymers such as mannan, microbial derivatives such as dextran and pullulan, animal-based are chitosan and heparin. The various biopolymers and their examples as mentioned in Table 2 are discussed in detail in the preceding text.

Table 2 Sources and examples of polymers used in polymeric micelles [14]

Natural (plant, animal, marine)	Synthetic (hydrophilic + hydrophobic)
Chitosan	Poly (ethylene oxide) chains,
Dextran	Poly (ethylene glycol) blocks,
Heparin	Poly (*N*-vinyl-2-pyrrolidone),
Hyaluronan	Poly (vinyl alcohol) + hydro propylene oxide
Pullulan	Poly (L-lysine)
Polysialic acid	Poly (caprolactone) and
Mannan	K, L-lactic acid

5 Chitosan

Chitosan is a linear heteropolymer of *N*-acetyl-D-glucosamine and D-glucosamine linked by β-(1→4) glycosidic bonds. Example of chitosan-based polymeric micelles are palmitoyl chitosan, methotrexate-encapsulated polymeric nanocarriers using methoxy poly (ethylene glycol)-grafted chitosan copolymer, poly (ethylene glycol)-modified stearic acid-grafted chitosan micelles and stearic acid-g-chitosan [15]. The pharmaceutical applications of chitosan in drug delivery as polymeric micelles has been detailed in a separate subheading "*Chitosan-The lead biopolymer*" Sect. 11.

6 Dextran

Dextran is another plant polysaccharide biosynthesized from sucrose using different lactic acid bacteria like *Luconostoc mesenteroides, Lactobacillus brevis and Streptococcus mutans* with catalysts like *glucansucrases*. It has repeating units of D-glucose residues interconnected with a-(1/6) linkage along with side branches linked to the main chain via a-(1/2), a-(1/3) or a-(1/4). Examples of dextran-based polymer are dextran-PEG-C-18, dextran-PEG-C-16, dextran-cholic acid and dextran sulfate-cholic acid. Addition of fatty acids to free-OH groups of dextran resulted in production of core–shell structure or amphiphilic polymeric micelle with surface active properties. For example, palmitoyl dextran is used as a nanocarrier for delivery of hirudin [16]. Stearate-grafted dextran was been synthesized by Du et al. [17] via an esterification reaction and was used to carry doxorubicin to nude mice bearing A549 human lung adenocarcinoma. In vitro cytotoxicity experiment demonstrated substantial toxic effect against drug-sensitive tumor cells. Moreover, these micelles presented reversal activity against doxorubicin-resistant cells.

Etoposide loaded polymeric micelles of dextran stearate (coploymer had low CMC) were prepared by dialysis method. Drug-loaded copolymeric micelles could release etoposide for more than 48 h. The micelles exhibited good cellular uptake capability and were more cytotoxic than those of free drug in CT-26 cell line. The authors suggested a practical solution for drug resistance in colorectal cancer by use of a formulation of etoposide in dextran stearate micelles. Further, it was affirmed that the degree of substitution of polymer with stearic acid affected drug loading, release rate, particle size and cytotoxicity of the blank and etoposide loaded micelles [18].

The applicability of nano-sized shell cross-linked micelles based on dextran as supports for controlled release of hydrophobic drugs (nystatin, rifampicin, resveratrol and curcumin) was investigated by in vitro drug loading/release experiments. The synthesized cross-linked micelles were loaded with the drugs of various hydrophobicities and their retention/release behavior was observed. The cross-linked micelles obtained from dextran with octadecyl end groups, with or without *N*-(2- hydroxypropyl)-*N*,*N*-dimethyl-*N*-benzylammonium chloride groups attached

to the main dextran chains, could retain the drugs in amounts which increased with increasing drug hydrophobicity (water insolubility), as follows: 30–60 mg rifampicin/g, 70–100 mg nystatin/g, 120–144 mg resveratrol/g and 146–260 mg curcumin/g. The rate of drug release from the loaded micelles was dependent on the drug hydrophobicity and was always slower than the free drug recovery. Anti-oxidant activity of curcumin and resveratrol released from the loaded micelles was preserved [19]. The results highlighted the potential of the new nano-sized micelles as carriers for prolonged and controlled delivery of various hydrophobic drugs. Jeong et al. reported the use of poly (DL-lactide-co-glycolide)-grafted dextran copolymer is able to form self-assembling nanoparticles and can be used as a vehicle to carry antitumor agents. The dextran component of the copolymer forms the hydrophilic outer shell, due to its aqueous solubility, while PLGA forms the inner core of the nanoparticle [20]. Furthermore, a block copolymer composed of dextran and PLGA (DexbLG) for delivery of doxorubicin was described. The polymeric micelles were spherical and smaller than 100 nm as observed by transmission electron microscopy, with a narrow size distribution. The drug release study showed an initial burst release of the drug for 10 h, and thereafter doxorubicin was continuously released over 4 days. In an antiproliferation study, the polymeric micelles showed higher cytotoxicity to doxorubicin-resistant HuCC-T1 cells than free doxorubicin, indicating that the polymeric micelles were effectively engulfed by tumor cells, while free doxorubicin hardly penetrated the tumor cell membrane. On confocal laser scanning microscopy, free doxorubicin expressed very weak fluorescence intensity, while the polymeric micelles expressed strong red fluorescence. Furthermore, in flow cytometric analysis, fluorescence intensity of polymeric micelles was almost twice as high as with free doxorubicin [20].

Temperature-sensitive polymeric micelles were prepared from dextran grafted with poly (*N*-isopropylacrylamide) (PNIPAAm) or polyethylene glycol methyl ether (PEGMA) via controlled radical polymerization and evaluated as delivery systems of methotrexate. Temperature-responsive dextran-based copolymers exhibited self-aggregation behavior, affinity for methotrexate and high cellular internalization. In addition, some grafted polymers incorporated 2-aminoethyl methacrylate to reinforce methotrexate encapsulation in the micelles by means of ionic interactions. Dextran-based micelles were cytocompatible and had an appropriate size to be used as drug carriers. Methotrexate release was dependent on the pH and temperature. Copolymer micelles were highly internalized by tumor cells (CHO-K1) and, when loaded with methotrexate, led to enhanced cytotoxicity compared to the free drug [21].

7 Heparin

Heparin is a sulfated natural polysaccharide composed of sulfonated glucuronic acid units and glucosamine derivatives. Examples of dextran-based heparin system are deoxycholic acid-heparin micelles. Heparin is a sulfated natural polysaccharide

composed of sulfonated glucuronic acid units and glucosamine derivatives. Examples of dextran-based heparin system are deoxycholic acid-heparin micelles. Heparin conjugated amphiphilic block copolymer, Tetronic®-PCL-heparin (TCH), was developed and its polymeric micelles were prepared as an injectable vehicle for long-term delivery of bFGF, which is one of the heparin-binding growth factors. TCH PMs were fabricated by a single emulsion and solvent evaporation method. The CMC of TCH polymeric micelles was approximately 0.11 g/L. The diameter of TC micelle was approximately 25 nm and after conjugation of heparin it increased to 114 nm due to the heparin molecules on the shell of the micelle. In vitro study demonstrated controlled release of Bfgf for over two months. The results demonstrated that long-term delivery of various growth factors could be achieved by polymeric micelles [22].

Gamboic acid (GA) grafted low molecular weight heparin (GA-LMWH) was prepared and self-assembled into micelles in aqueous solution to improve the solubility and antitumor effects against hepatocellular carcinoma. The micelles had a mean size of 190.4 ± 10.8 nm, a low critical micelle concentration of 2.4 ± 0.2μg mL^{-1}, and highest area under the concentration–time curve and mean retention time in the liver compared to the heart, spleen, lung and kidney ($p < 0.05$). The targeting efficiency of micelles to the liver is 2.1 times higher than that of the gamboic acid solution. GA-LMWH micelles were administered intravenously and significantly improved liver function, decreased cell lesions in hepatic tissue, inhibited the expression of CD105 and prolonged survival time of hepatocellular carcinoma model compared with groups treated with normal saline or gamboic acid solution [23].

In an attempt to develop a drug delivery system that should be biocompatible, stimuli-responsive and multifunctional, including antitumor, anti-metastasis and anti-angiogenesis effects; a novel system of the drug doxycycline and heparin self-assembled nanoparticle via pH-sensitive hydrazone bond and hydrophobic groups, deoxycholate was designed. After systemic administration, heparin-based micelle nanoparticle showed longer half-time and enhanced accumulation of doxycycline in tumors through the enhanced permeability and retention effect, leading to more efficient antitumor effects. The micellar system exhibited significant inhibitory effect on the metastasis in melanoma animal model in C57BL/6 mouse. The additional benefit from the anti-angiogenesis effect of heparin, effectively inhibited tube formations in endothelial cells and tumor vascular density was decreased. Thus, a self-assembly nano-platform was devised such that both the drug and carrier had therapeutic effects with ideal antitumor efficacy [16].

8 Hyaluronan (Hyaluronic Acid; HA)

It is a naturally occurring glycosaminoglycan which is distributed throughout the connective, epithelial and neural tissue. It is a carbohydrate more specifically a mucopolysaccharide which heals the skin. HA has been investigated as an active

targeting agent in drug delivery for enhanced efficacy. Examples are polyethylene glycol-conjugated hyaluronic acid-ceramide self-assembled micelles, PEG was conjugated to HA-5 beta-cholanic acid, polyethylene glycol-conjugated hyaluronic acid-ceramide self-assembled micelles, etc. In an experiment titled as in vitro investigation of hyaluronan-based polymeric micelles for drug delivery into the skin: The internalization pathway, it was observed that polymeric micelles penetrated deep into the skin tissue. The mechanism was observed for the influence of the carrier composition of the drug penetration. Fluorescent Nile blue covalently linked with oleyl-hyaluronan (HAC 18:1) and hexyl-hyaluronan (HAC6) was used for tracing the course of event. HAC 18:1 carrier showed passive transport facilitated by affinity of carrier to the cell membrane, which was influenced by membrane fluidity. These carrier systems could be best employed for local transport of drug into the skin cells. Another experiment proved the similar conclusion, titled as hyaluronan polymeric micelles for topical drug delivery. In this hydrophobized hyaluronic acid were probed for topical delivery and compared with non-polymeric micelles containing same drug. In vitro skin penetration analysis proved that epidermis stored three times the drug deposition and six times larger drug deposition in dermis after 5 h treatment in Franz diffusion cells. It was confirmed by laser confocal microscopy along with increased bioactivity of loaded compound in vitro and in vivo. They were also found to be effective in cream formulations and thus they can find great opportunity for cosmetic and pharmaceutical purposes [14].

In another experiment, novel amphiphilic copolymers containing hyaluronic acid as a hydrophilic part and phophatidylethanolamine (DSPE) as a hydrophobic segment were synthesized and assessed. The spherical polymeric micelles showed high solubility of cholesterol, enhanced up to 0.25 mg/mL which is much higher than water solubility of. In vitro cytotoxic assay reveals no toxicity on human breast cancer lines (MCF-7). All these facts suggest that these polymers can be used for micellar drug delivery [24]. Yet another polymeric delivery of imatinib-loaded micelles of hyaluronic acid derivatives for potential treatment of neo-vascular ocular diseases was optimized. The novel polymeric micelles of polymers were found to cross corneal barrier with improved permeability. Various combinations, such as hyaluronic-ethyldiamine-C_{16}, hyaluronic-hexadecylamine, hyaluronic-ethyldiamine-C_{16}–PEG, hyaluronic-ethyldiamine-C_{16}-carnitine, were examined and evaluated for drug delivery into the corneal site. Among the above only three were found effective for trancorneal penetration due to their small size being lower than 300 nm and good mucoadhesive properties. The outcome suggests that imatinib via these polymeric systems would be beneficial for retinopathy [25].

9 Pullulan

Pullulan is a microbial exopolysaccharide. It is non-ionic, water-soluble carbohydrates produced by fermenting liquefied starch by non-pathogenic and non-toxigenic strains of yeast-like *Aureobasidium pullulans*. Various drug delivery systems developed using pullulan are cholesterol-bearing pullulan, pullulanacetate, poly (DL-lactide-co-glycolide)-grafted pullulan, pullulan-g-poly (L-lactide), etc. In an experiment biotin and retinoic acid-grafted polymers were used for the delivery of doxorubicin to treat the MCF-7 breast cancer line. Doxorubicin-loaded micelles were found to be more cytotoxic than freely delivered doxorubicin due to active endocytosis of doxorubicin by biotin receptors present on MCF-7 cells [26].

Pullulan-tocopherol succinate folic acid micelles were prepared to target Hela and MCF-7 cell lines by delivering epirubicin. It was assessed for cytotoxic effects to improve the anti-cancer activity. The particle size was found to be 149.5 nm with a zeta potential of −49 mV and polydispersity index of 0.259 ± 0.07. MTT assay revealed that pullulan-tocopherol succinate folic acid micelles depicted more cytotoxic effect than the free drug [21].

In another experiment, pullulan-stearic acid-based polymeric self-assembled micelles in aqueous media were used for delivery of doxorubicin [27]. The in vitro IC-50 test showed that doxorubicin-loaded pullulan-stearic acid micelles had lower activity than doxorubicin-loaded micelles without reduction sensitivity against HEPG2 and MFC-7 cells. These polymeric micelles were found effective for intracellular delivery of doxorubicin [14].

Other biopolymers

Other polymers include polysialic acid (PSA), which is a non-toxic polysaccharide that protects and increase body circulation of therapeutics in the form of micelles to inflamed tissue. Example includes polycaprolactone modified PSA. Mannan-based micellar system with high stability was developed by grafting cholesterol or hexdecanethiol (C16) to mannan. All the polysaccharidic micelles are expected to exhibit better properties and functions. The above-discussed polymers obtained from different sources are employed in the formation of different polymeric systems. These different polymeric systems have been diversely used in various drug delivery routes which have almost made them versatile carrier systems [28].

10 Versatility of Polymeric Systems in Different Drug Delivery Routes

The routes employed for drug delivery by polymeric micelles are oral, topical, ocular and brain. The still in exploration route is parenteral to detect their efficacy against other dosage forms like liposomes. The oral delivery route is the most sought out routes for anti-cancer and antitumor drugs. Most of these drugs are hydrophobic in

nature which involves polymeric micelles as vehicle for effective drug delivery. The studies reveal that these drugs loaded on polymeric micelles have given an improved performance like anti-cancer drug like paclitaxel loaded onto NOSC: *N*-octyl-O-sulfate chitosan polymer has shown increased accumulation in the intestine [29]. As discussed above, polymeric micelles have gained their importance in various aspects of improvisation in hydrophobic drug delivery via enhanced solubilization and targeted delivery. The drug targeting is mainly employed for antitumor drugs and gene delivery enrouted by two approaches, i.e., active and passive. Passive targeting utilizes two conditions. Firstly, the anatomical and pathophysiological condition of the tumor and the enhanced permeability and retention effect of polymer in the tumor. Another approach is active targeting, which is done by two methods, namely ligand coupled and stimuli responsive. Folic acid, tripolyphosphate, proteins like transferring, peptides-like aptides, antibody fragments like F(ab)/2 and nucleic acid-based ligands such as the A10 aptamer are some examples of ligand coupled method-based drug delivery. Folic acid coupled polymeric micelles have strong affinity for cancer cells which possess over expressed proteins which binds the polymeric micelles as receptor site. Hyaluronic acid conjugated with polyethylene glycol polymer efficiently delivered multi-drug resistant siRNA to the ovarian cancer cell resulting in down regulation of multi-drug resistant gene [5].

Targeting with polymeric micelles serves three purpose, (i) affords **c**ontrolled release of drug over a prolonged period of time, (ii) the block copolymer displays pharmacological function in addition to the active, e.g., poly (propylene oxide)-b-polyethylene oxide exerts inhibitory effect on P-glycoprotein, and (iii) solubilization of water-insoluble drug, e.g., doxorubicin, cyclosporine, ketoconazole, etc. [7].

Although polymeric micelle system possesses many advantages, yet it has some difficulties which pose them on disadvantageous side. First problem arises out of their complex chemical synthesis as high levels of polymer chemistry are critical for the synthesis of the controlled chemical structures and chain lengths. Second obstruction arises out of non-uniform drug entrapment method which is non-scalable to the large scale manufacturing and is limited to laboratory experiments only [18].

11 Chitosan-The Lead Biopolymer

Chitosan is the naturally obtained biopolymer which has gained wide importance in the polymeric micellar system. It is a non-toxic, semi-crystalline marine polymer extracted from the exoskeleton of crustaceans such as crabs, lobsters and shrimps. Chemically, it is a linear polysaccharide of randomly distributed *N*-acetyl glucosamine and glucosamine units, or it may be expressed as α-(1-4)-2-amino-2-deoxy-β-D-glucose as given in the structure below.

It possesses excellent biocompatible, biodegradable and antibacterial properties. It is the preferable choice for the drug delivery as it is biodegraded by enzymes such as lysozymes, some lipases and proteases. Owing to the biocompatible nature,

chitosan has been used in delivery of hydrophobic drugs. Also, due to its antibacterial property decreases the risk of using it in the pharmaceutical drug delivery. However, due to its solubility problems in water and other organic solvents grafting has been done to improve its performance such as mechanical strength, chemical stability, polymer elasticity, hydrophobicity which allow their use as viscosity modifiers, compatibilizer of polymeric blend. In an experiment, it was found that by grafting catechin onto chitosan, the chitosan showed improved anti-oxidant and anti-diabetic activities. Also, a versatile polymeric micelle was developed by grafting oleic acid into chitosan, which proved to an effective carrier for antibiotic. Apart from the above drug the processability of chitosan and several derivatives allow obtaining different types of systems to be covered by chitosan. Presence of reactive amine group gives chitosan a wide opportunity for chemical adaptability for modification and functionalization. Since it is a cationic mucoadhesive polymer its functionality was improved by chemical modification like thiolation as it was proved after intratracheal administration in rats that nanoparticles composed of thioglycolic acid-glycol chitosan showed enhanced mucoadhesion than non-thiolated one. This property made chitosan an effective pulmonary drug delivery polymer [15]. Various drugs delivered via chitosan-based polymers are summarized in Table 3.

The values in the featured Table 3 are characteristic indications of polymeric drug delivery systems like CAC and CMC. The CAC value is critical aggregation concentration which denotes stability of the chitosan polymeric system. Aggregation number is the number of polymer chains that assemble to form a micelle [31]. In its simplest form, the aggregation number (Nag) is given by the equation:

Table 3 Chitosan-based polymeric micelles with formulation features [13, 30]

Polymeric micelle	Features
Amphiphilic palmitoyl chitosan	**CAC**—2.0×10^{-3} to 37.2×10^{-3} mg/mL
Methotrexate-encapsulated polymeric nanocarriers using methoxy poly (ethylene glycol)-grafted chitosan copolymer	**Size**: 50–300 nm
Poly (ethylene glycol) modified stearic acid-grafted chitosan micelles coupled with RGD peptide	
1. PEG-CS-SA	**CAC**—25.9 ± 1.2 μg/mL
2. RGD-PEG-CSSA	**CAC**—23.5 ± 0.5 μg/mL
Drug: Doxorubicin	Increased drug concentration in cancer cells Prolonged release for 9 days
Stearic acid-g-chitosan	**CAC** value: 0.16–0.25 mg/mL **Size range**: Between 33.4 and130.9 nm
Itraconazole loaded chitosan	**CMC** value 1.58×10^{-2} mg/mL
n-benzyl-*n*,o-succinyl chitosan alpha tocopherol	**CMC** value 0.0385 mg/mL
Prednisone acetate loaded *N*-phthaloyl chitosan-g-polyvinyl pyrrolidone	Low CMC of 0.83 mg/L with controlled release [31]

$$\text{Nag} = M/M_0 \tag{1}$$

where M = molecular weight of one micelle and M_0 = molecular weight of the polymer backbone. Likewise, CMC value also indicates the micellar properties of the system. Although been reported in thousands; aggregation number for micelles usually varies from tens to hundreds. The lower the CAC value the higher the stability of the micelles in the biofluids. The mentioned chitosan-based polymers are mainly employed for oral drug delivery. These polymers were found to show high in vivo physical stability and resistance in the harsh conditions of gastrointestinal tract owing to the low CAC and CMC value [28].

Chitosan derivative polymeric micelles for co-delivery of paclitaxel and α-tocopherol succinate were developed for improving therapeutic efficacy and reduce side effects**.** In this study, amphiphilic tocopherol succinate-grafted chitosan oligosaccharide was synthesized and physically loaded with paclitaxel and α-tocopherol succinate. The grafted polymeric micelles were synthesized via the reaction of activated carboxyl group of α-tocopherol succinate with amine group of chitosan in the presence of dicyclohexylcarbodiimide and *N*-hydroxysuccinimide. The drug was loaded into the polymeric micelles by three methods, namely dialysis, evaporation and emulsion. The CMC value of the copolymer was found to be 7.63103 mg/mL in deionized water that suggested stability of α-tocopherol succinate even after dilution in blood stream and their structure preservation without dissociation. The amount of α-tocopherol succinate was kept constant in all the cases of paclitaxel loading. In the micellar solution obtained by emulsion, the entrapment efficiency of paclitaxel was found to be highest 74.6–54.8%, in comparison with other methods like dialysis which had entrapment efficiency of 67–42 and 50–30% for evaporation method. However, the highest entrapment efficiency of α-tocopherol succinate was 76.5% using dialysis method while the other values were 65.2% and 49.6% for evaporation and emulsion methods, respectively. α-tocopherol was physically incorporated into the micelles which improved the micelles stability, by increasing the hydrophobic interaction between paclitaxel and micelles core. This process also resulted in size reduction of micelles and sustained release of paclitaxel form its micelles core. This was proved by in vitro release pattern of paclitaxel with and without α-tocopherol succinate loaded with it. The release of paclitaxel was fast without α-tocopherol succinate–chitosan and with α-tocopherol succinate–chitosan it extended and sustained up to 9 days. Stability studies reported no change in paclitaxel content and micelle size in both lyophilized powder and solution of α-tocopherol succinate/paclitaxel loaded micelles and they could be stored at 4 °C for at least three months. It was observed that the freeze-dried α-tocopherol succinate/paclitaxel loaded micelles were more readily dissolved in water compared to paclitaxel loaded micelles after three months storage at 4 °C [26].

Yet another experiment tilted as “evaluation of micellar architecture based on functionalized chitosan for the in vitro release of an antibiotic” stated the versatility of chitosan in delivery of different drugs. The chitosan polymer was grafted with oleic acid which is a monounsaturated omega-9-fatty acid, rendered chitosan a great change in solubility and configuration. In this polymeric micelle, cefixime trihydrate

is used which is loaded into the core formed by hydrophobic methyl groups of oleic acid and whose shell is formed by relatively water-soluble amino and hydroxyl group of chitosan. The drug was loaded by physical entrapment by stirring in water and ethanol and incubated for 72 h at pH 5.5. The polymeric micelles were of 520 nm in size, zeta potential as +42 Mv. The in vitro drug release studies showed 52% of total release in first 24 h of incubation and were enhanced to 83% in next 72 h in the simulated intestinal basic fluid, which is more than present bioavailability status of 40%. The antimicrobial activity proved that they are effective as the drug-loaded polymeric micelles showed shrinkage in zone size, indicating effective drug encapsulation. Thus, chitosan-based polymeric micelles have been found useful and exploring in the field of drug delivery [32].

12 Drug Loading, Release and Characterization

Polymeric micelles are loaded onto the polymers via two mechanisms which are physical entrapment and secondly chemical conjugations. Physical entrapment methods include following methods, namely stirring, heating/emulsification, ultrasonic treatment, solvent evaporation and dialysis. Chemical cross-linking includes cross-linking of hydrophilic shell and cross-linking of hydrophobic core [8]. Physical methods can be represented as.

12.1 Stirring

The polymer's aqueous solution is ultrasonicated for 2–24 h to form micelles. It is a simple dispersion system with water-soluble copolymers with various drug encapsulated in this system. Few examples are adriamycin, naphthalene and nystatin.

12.2 Heating

In this, drug is added with copolymer and organic solvents under nitrogen atmosphere or by rotary evaporator under vacuum with addition of water at 40–60 °C leading to micelle formation. This process is also called emulsification. It is suitable for hydrophobic drugs and copolymers soluble in organic solvents. Drug encapsulated are diazepam, docetaxel, genistein and indomethacin.

12.3 Ultrasonication

This process includes addition of drug in aqueous solution of copolymer which undergoes ultrasonicated for 1 s to 1 h resulting in micelle formation. It has high drug loading capacity along with small size of micelles. Various drugs encapsulated are doxorubicin and curcumin.

12.4 Solvent evaporation

In this method, drug is added with aqueous miscible organic solvent with aqueous solution of copolymer between 25 and 40 °C resulting in micelle formation on stirring. It is known for its high drug loading and encapsulation efficiency. The various drugs encapsulated are diazepam, docetaxel, genistein and indomethacin.

12.5 Dialysis

This method includes a water-miscible solvent with water-miscible solvent which undergoes dialysis against buffer solution resulting in micelle formation. It is most suitable for hydrophobic drugs and copolymers soluble in organic solvents. They are suitable for hydrophobic drugs and copolymers soluble in organic solvents. Various drugs encapsulated are amphotericin B, dexamethasone, griseofulvin and paclitaxel.

12.6 Lyophilization

Drug is added in water or tert-butanol where lyophilization of the solvents is done. Then, freeze-dried polymer–drug cake is reconstituted in an injectable vehicle, resulting in spontaneous drug-loaded micelles formation. The various drug encapsulated are docetaxel, gliclazide and naproxen.

12.7 Chemical Cross-Linking [9, 14]

12.7.1 Cross-Linking of the Hydrophilic Shell

This method includes use of cross-linked hydrophilic polymer which is cross-linked after micelle formation, using polymeric chemistry. Example includes glutaraldehyde as cross-linking agent in the chitosan-grafted stearic acid loaded with paclitaxel.

12.7.2 Cross-Linking of the Hydrophobic Core

The core is cross-linked which form a matrix for controlled and sustained release of the drug from the center after micelle formation. Example includes a 2, 2-azoisobutyronitrile which cross-links the polymer PEG-b-PLA with 5-methyl-5-allyloxycarbonyl-1,3-dioxane-2-1 as polymerizable group. Cross-linking has its own patterns of effect in the polymeric preparation. In the cross-linking of hydrophilic shell toxic chemicals are often employed for cross-linking. However, the brighter side holds for a sustained release of drug from the core.

12.8 Release kinetics

Generally, the drug takes two pathways to follow for its release namely dissociation of the micellar system followed by separation and drug-polymer bond breakage followed by drug diffusion. The nature and mechanism of release are expressed by Pappas's equation which is represented as follows:

$$\frac{Mt}{M\infty} = kt^n \tag{2}$$

$$\text{Log}\frac{Mt}{M\infty} = n \log t + \log k \tag{3}$$

where Mt is absolute cumulative amount of drug released at time t, $M\infty$ is absolute cumulative amount of drug released at time infinite time, k is rate constant and n is release exponent which indicates the mechanism of the drug release. If is $n = 0.45$ the mechanism of drug release is diffusion controlled, when $n = 0.89$, it is swelling controlled release and when $n = 0.45$ and ≤ 0.89, the drug release mechanism is of anomalous transport type [8].

12.9 Characterization

12.9.1 Critical Micelle Concentration

Critical micelle concentration's characterization involves many techniques such as surface tension measurements, chromatography, light scattering, small-angle neutron scattering, small-angle X-ray scattering, differential scanning calorimetry, viscometry and utilization of fluorescent probes**.** Critical micelle concentration is an important parameter in the stability determination. Practically, critical micelle concentration is obtained from plots of the surface tension as a function of the logarithm of

the concentration. In surface tension measurements, critical micelle concentration is said to be attained when the surface tension stop declining and reaches a plateau or constant value.

12.9.2 Size and Shape

Polydispersity index is an important parameter in determining size distribution. Monodisperse micelles are good micellar preparation when they produce blue color from light scattering, as white color is shown by micellar aggregates. The prepared structures are obtained by careful observation of the micellar solution with quasielastic light scattering technique. Size of polymeric micelles usually falls in the colloidal range. For the direct visualization, size and shape determination of block copolymer micelles Scanning electron microscopy and transmission electron microscopy (TEM) techniques have been widely used. For characterization of block copolymer micelles in aqueous medium, a more recent technique called cryo-TEM has increasingly started gaining importance. If chemically attached micelles to surfaces are presented, atomic force microscopy reveals information regarding size distribution. Also, this technique facilitates direct visualization of block copolymer micelles either in the dried state or directly in situ within a liquid. Photon correlation spectroscopy reveals the hydrodynamic diameters and polydispersity indices of micelles. Some recent technique such as asymmetrical flow field flow fractionation is being explored for size characterization for drug-loaded polymeric micelles and small-angle neutron scattering determines structure of polymeric assemblies [33].

13 Stability: In Sync with the Different Dosage Form

Stability of micelles is an important study for its effective delivery and targeting to the main site. Upon parenteral administration via intravenous route, they go through a number of environmental changes including changed pH and salts of the body fluids and contact with numerous proteins and cells leading to significant dilution. For use as drug delivery vehicles, micelles must remain intact to prevent premature drug release from the polymeric system before reaching the target site of the cells. Micelles should be intact during formulation and administration in case of local drug delivery or solubilization. The stability of micelles is discussed under two categories, namely thermodynamic and kinetic stability. Thermodynamic stability describes how the micellar systems are formed and reach equilibrium. Kinetic stability deals with the behavior of the system over time and details the micellar disassembly with rate of polymer exchange [28].

13.1 Thermodynamic stability

Polymeric micelles are featured by lower CMC values than surfactants having low molar mass micelles because the polymer chains possess multiple points of interaction than small molecules. Lower values indicate greater thermodynamic stability, as this property is related to thermal energy, kBT and the effective interaction energy between polymers and the bulk solution, εh. It is expressed in the equation,

$$\text{CMC} = \exp(-n\varepsilon h / kBT) \tag{4}$$

In another equation, CMC is shown as a direct function of free energy [7],

$$G_{\text{mic}} = RT \ \ln(\text{CMC}) \tag{5}$$

where G_{mic} is free energy of micellization. Thus, lower the free energy lower is the critical micelle concentration. It is also affected by hydrophobic bonding, as by increasing the hydrophobicity of the copolymer cohesiveness increases which results in small CMC [9]. Stability for micelles used in drug delivery is also affected by the drug–core interaction, as encapsulated hydrophobic drug poses additional hydrophobic interactions between the core and the drug. Micellar thermodynamics is also influenced by the interactions between polymer chains in the hydrophobic zone with each other along with the aqueous environment. Yet another factor is temperature which has impact on the inter-micelle chain movement, since increase in temperature increases the micelle size.

13.2 Kinetic Stability

Characterization of the kinetic stability of micelles is performed to ensure mature delivery of the encapsulated drug. Therefore, it comes as an essential parameter for stability determination. At equilibrium, the relation between concentrations of individual polymer chains (A) with respect to the concentration of micelles is shown below:

$$\text{KM} = [\text{A}]n/[\text{micelle}] \tag{6}$$

where KM = micelle dissociation constant and n is aggregation number of the micelle.

Kinetic stability is an extension of the polymer chain exchange system between the micelles. The number and rate of transitions are directly related to aggregate number and kinetic stability.

Environmental factors also contribute to destabilization of the micelles such as composition and concentration of disrupting agents in solution [34]. Hydrophobic

core of micelles is protected from the aqueous environment by the hydrophilic corona because if water interacts with hydrophobic layer it may disrupt the micellar organization or lose its integrity [18].

14 Proprietary and Pipeline Products

While there is a lot of noise in the research on polymeric micelles, biopolymers need to be explored more. Nevertheless certain patents are documented in literature that in fact asserts the significance of biopolymeric micelles. Table 4 enlists the proprietary products.

Table 4 Cross section of proprietary products on biopolymeric micelles

Patent number	Patent title	Drug	Polymers used
CN102397236A [35]	Method for preparing shell-sheddable polymeric micelle drug carrier	Doxorubicin, paclitaxel, camptothecin	Dextran-SS-poly(ε-caprolactone)
EP2051998A1 [14]	Polymeric micellar system including chitosan clusters and their uses in formulating drugs	N/A	Chitosan
EP2934592B1 [7]	C6-c18-Acylated derivative of hyaluronic acid method of preparation thereof, nanomicellar composition in its basis, method of preparation thereof and method of preparation stabilized nanomicellar composition and use thereof	N/A	Hyaluronic acid
PAT-CN188708 [36]	Surface modified hydrophobically modified drug-carrier chitosan polymer micelle and method for preparing same	N/A	Grafting chitosan with 1.5–51 kdD of average molecular weight and aliphatic acid of chain length C10-C22
CN102139113B [37]	Novel pharmaceutical solubilization carrier and preparation method and application thereof	Anti-cancer drug	Carrier is a hydrophobic graft chain of vit E or a derivative thereof in the skeleton

15 Future Trends

In the series of nanocarriers, polymeric micelles have emerged as an important drug carrier in pharmaceutical arena. Despite many synthetic polymers, biopolymer was employed as a bio-suitable option for delivery systems. But being from natural origin, various disadvantages of biopolymers in the polymeric micelle system are related to the physicochemical properties. They are prone to microbial contamination, drop in viscosity occurs with slight change in temperature and uncontrolled hydration, while synthetic polymers have poor shear-resistant properties as per Kaity and Ghosh. Although many advantages, like biodegradability, non-cytotoxicity and biocompatibility along with their rigid backbones, have attracted significant attention in the research community to investigate in the field of drug delivery systems like grafting which has requisite for the above properties. Grafting holds the future of biopolymers in polymeric drug delivery system [18]. Grafting solves for targeted drug delivery by utilizing biopolymers and architecturing their structure with new polymers for formulating a more stable product. Common method employed are chemically induced grafting, radiation-induced grafting, photochemical-induced grafting, plasma-induced grafting and enzymatic grafting.

Apart from graft polymers, much need-based modifications have been added to the neo-trend in the polymeric applications. However, grafting is change in the polymeric architecture leading to delivery of RNA and DNA. Other spatial changes in the structure are steric stabilization which has opened doors for non-parenteral, oral, needleless delivery of peptides and proteins.

The change in the polymeric structure has evolved the way for image guided and stimuli-responsive polymers in drug delivery. Numerous polymers have been evolved so as to cater the needs of technology demands. In the field of controlled and self-regulated drug delivery, the concept of stimuli responsive such as smart, intelligent or environmental sensitive polymers have evolved as potential commercials in the coming medicinal systems. These stimuli can be classified into two divisions (1) physical stimuli, which includes temperature, ultrasound, light, and magnetic and electrical fields (2) chemical stimuli, which includes pH, redox potential, ionic strength and different chemical agents. Temperature and pH are two major stimulants which are taken into consideration while targeting and controlling the polymeric drug delivery [13].

Based on temperature responsiveness, polymers are of two types: (1) polymers having lower critical solution temperature that are insoluble at increased temperature (2) polymers having upper critical solution temperature that become soluble upon heating [38]. Another chemical stimulus in body physiology is pH, to which pH-responsive polymers are activated for site-targeted drug delivery. Molecular imprints polymers are another subject to be experimented in the polymer field where it micellar delivery is yet to be explored in terms of drug delivery. Molecular imprinting technology is based on the formation of a complex between an analyte (template) and a functional monomer which in presence of a cross-linking agent forms a three-dimensional network. After the polymerization process, the template is removed

from the polymer leaving specific recognition sites which is complementary to the template molecule. This technology is versatile and is used for both biological and chemical molecules. Due to designing of new polymers new fabrication techniques, new clinical trial designs, adapted regulatory guidelines and modified analytical methods have been experimented out and established as an extension to the present studies [13].

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Liposomes for Advanced Drug Delivery

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Abstract Liposomes are sphere-shaped vesicles consisting of one or more phospholipid bilayers. The liposomal drug delivery systems were utilized for delivery of compounds for different diseases. These systems improve the stability as well as cellular uptake of drugs. Site-specific delivery to the target site reduced the site effects. This chapter summarizes the recent advances in liposomal drug delivery systems (i) therapeutic applications-based chemotherapy; (ii) chemotherapy in combination to gene therapy and immunotherapy; (iii) theranostic applications for precise detection and simultaneous treatment of critical diseases and heavy metal toxicity; (iv) stimuli-triggered liposomes. This chapter gives a detailed account on aforementioned applications which might be beneficial to pharmaceutical scientists and industries to develop safe and effective liposomal systems.

Keywords Liposomes · Delivery system · Gene therapy · Theranostic · Stimuli

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1 Introduction

Liposomes are lipoidal carriers constituted of an aqueous core which is surrounded by lipid bilayers. Numerous therapeutic applications of liposomes have been manifested in clinical practices. They range from diagnostic and therapeutic applications to recently employed theranostic applications [1]. The first ever clinical applications of liposomes were the delivery of chemotherapeutic moieties to the diseased sites. Conventional techniques employed for the liposomal formulation lead to inadequate drug delivery to the target sites and lead to side effects thereby obtruding few limitations on the drug dose and frequency. To surmount these hurdles, attempts have been made to develop safe and effective liposomes. Subsequent to their approval as carriers for small molecule therapeutics (i.e., chemotherapeutic drugs), they were inquired with respect to their capability to administer macromolecules like nucleic-acid-based molecules (plasmid DNA, antisense oligonucleotides, and small interfering RNA) to diseased organs. These macromolecules are hydrophilic, high-molecular weight, highly charged molecules which do not have the ability to cross the cell membranes via passive diffusion. Besides, degradation by the enzymes and systemic clearance, non-specificity for the diseased tissues, and inadequate cellular uptake substantially restrict the clinical applicability. Due to these restrictions, it has always been a challenge to deliver nucleic-acid-based agents using liposomes as carrier system. Cationic lipids like 1,2-bis(oleoyloxy)-3-(trimethylammonio) propane (DOTAP) and 3β[N′,N′-dimethylamino-ethane]-carbomoyl] cholesterol (DC-CHOL) have been used for the development of cationic liposomes. The interaction between these cationic liposomes and anionic nucleic-acid-based agents leads to the formation of "lipoplex." These lipoplexes fuse with the plasma membrane, thereby entering the cell and release the nucleic acids from endosomes followed by internalization [2]. Liposomes have evidenced effective immunological adjuvants for protein and peptide antigens [3]. Both humoral and cellular responses are evoked by them for many diseases including cancers. Surface of liposomes can be functionalized by anchoring ligands or antibodies with an aim to attain specific delivery to the diseased site. Likewise, chemical groups could be anchored to the liposomal surface which will be responsive to different stimuli. On the basis of their physiological properties, these smart liposomes could lead to trigger the drug release. The stimuli are of two types: (a) Internal stimuli, e.g., enzymatic activity, pH alterations, or presence of reductants and (b) external stimuli, ultrasound, light, alterations in temperature, or presence of magnetic field. The drug release from liposomes which is triggered by external stimuli renders an enhanced accuracy pertaining to the site of release and hence a better regulation on the drug dose and its delivery [4, 5]. The development of pH-sensitive liposomes endues liposomes with added benefits in comparison with the conventional adjuvants by allowing the evasion of the peptide antigen from endosomes into the cytoplasm and therefore permits the linkage of antigen with MHC-I complex (i.e., major histocompatibility complex), that hastens a cytotoxic T-lymphocyte response. Besides encapsulation, direct modification of liposomes with

an antigen can evoke an immunologic activity. The capability of liposomes to encapsulate a broad range of diagnostic and therapeutic materials has grabbed the attention of researchers in employing them as nano-delivery systems of theranostic applicability. Diagnostic and therapeutic compounds exert a major function in the early detection and treatment of diseases like cancer, diabetes, Parkinson's, and gastrointestinal disorders. This novel strategy integrates both agents (i.e., diagnostic and therapeutic) into one system with an aim to concurrently detect and treat a disease. To attain these objectives, stable and effective theranostic systems are necessitated to be formulated with targetability and free from any encumbrance between the therapeutic and imaging compounds which are used in the developed system. Amidst the various types of nanosystems inquired till date, liposomes persist as one of the most potential carriers because of their high carrying capability and the good encapsulation abilities to entrap both diagnostic and therapeutic agents for clinical utilities [6, 7]. The application potential of liposomes is summarized in Fig. 1.

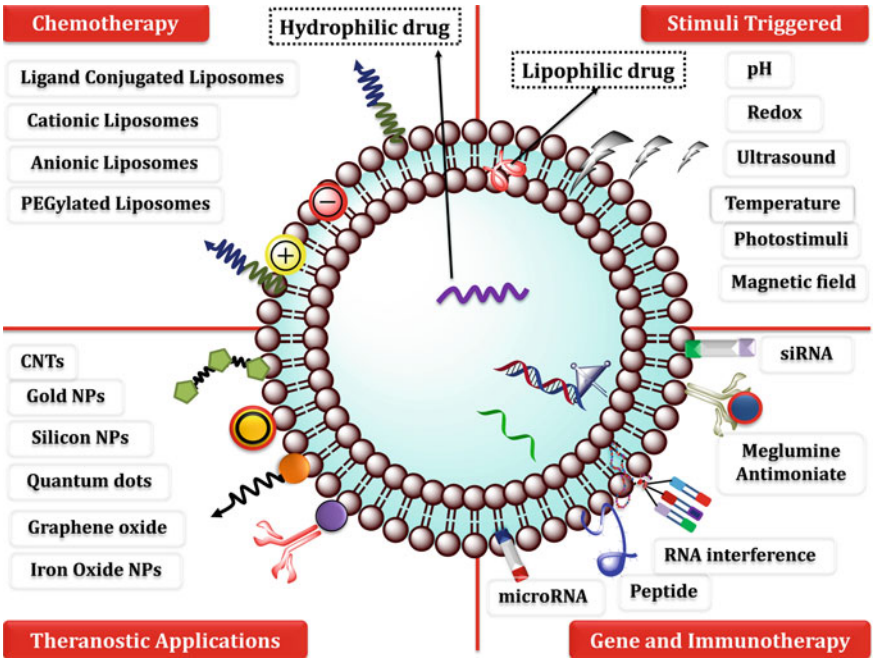

Fig. 1 Application potential of liposomes

2 Applications of Liposomes in Chemotherapy

2.1 In Cancer

Cancer is a deadly disease caused by an uncontrolled cell division and loss of cell growth; these abnormal cells are termed as tumor cells. Cancer can develop in almost every site of the body and affects the normal functions of the body. Chemotherapy is one of the conventional approaches for the treatment of cancer. It helps in improving survival of cancer patients, but there are number of adverse effects noticed in conventional therapeutic approaches. Moreover, cancer patients also face mental and physical disturbances during or after the course of chemotherapy [8]. Chemotherapy leads to adverse effects such as destroying of rapidly dividing normal cells, i.e., bone marrow cells, hair follicle cells, as well as cell linings of the gastrointestinal tract. It can also cause fatigue, nausea, constipation, diarrhea, mouth sores, decreased appetite, and skin and nail problems [9]. To overcome these problems, the chemotherapy requires the selection of suitable chemotherapeutic agents, understanding of tumor patient characteristics and treatment cycles [10]. Chemotherapy is becoming advance, specifically using target drug delivery systems which destroy the tumor cells selectively without affecting the normal cells. This revolution in cancer treatment offers improved efficacy and tolerability for better outcomes [11, 12].

2.1.1 Colon Cancer

Liposomes of 5 Fluorouracil (5FU) were prepared, where folic acid (FA) was used as targeting ligand for colorectal cancer [13]. In vitro cytotoxicity and in vivo tumor inhibition studies were performed to evaluate the 5FU loaded liposomes. The outcomes from these studies showed that collapsing membrane potential increases the cytochrome c activity as well as caspases activity. The molecular-targeted therapy (MTT) studies were performed which exhibited higher cytotoxicity activity as compared to the free drug with liposomal formulation [14]. The developed FA conjugated liposomes were observed to trigger necrosis in HT-29 cells, but in case of HeLa cells, FA-liposomes stimulated the apoptotic pathway by collapse of membrane potential. The in vivo results exhibited that targeted liposomes decreased the tumor volume more efficiently as compared to free drug therapy. From these results, it can be concluded that folic-acid-targeted liposomes is a potential drug delivery system for the treatment of colorectal cancer [15, 16]. The Eudragit S-100 encapsulated chitosan-coated liposomes containing prednisolone were formulated for targeting colon cancer. The liposomes were prepared by lipid film hydration technique using soya phosphatidylcholine (PC) and cholesterol in optimum ratio. The coated and uncoated liposomes were evaluated for in-vitro, ex vivo, and in vivo studies. The in vitro drug release study was carried out using the pH gradient technique. The ex vivo study was performed using excised tissues from male albino rats. In vivo

characterization was done for the comparative study of histopathology and myeloperoxidase (MPO) activity. The ex vivo studies displayed higher tissue-drug entrapment in cancer cells as compared to the normal cells of the colon. The in vivo histopathological studies exhibited a remarkable reduction in colonic inflammation using Eudragit-encapsulated chitosan-coated liposomes (ECLs) in rats. The reduction in healing process was further confirmed using MPO assay in ECLs treated groups. Further, a site-specific release was noticed along with a higher accumulation of drug-encapsulated formulations in colon cancer tissues [17].

2.1.2 Breast Cancer

Matrix metalloproteinases (MMPs) is a potential target for breast cancer. The liposomal system was prepared by conjugating a MMP inhibitor, epigallocatechin gallate (EGCG) and paclitaxel (PTX). In this system, PTX exhibited higher entrapment as compared to EGCG. The in vitro efficacy was assessed by inducing the apoptosis process and reduced cell invasion. The cytotoxicity and caspase 3 activity express the apoptosis process. The MMP-2 and 9 invasion assays revealed cell invasion. The co-loaded liposomal formulation showed better results than the free drug. However, this synergistic outcome of co-loaded liposomes of PTX/EGCG combination was a potential carrier for the treatment of breast cancer [18]. The pH-sensitive folate-coated DOX-loaded liposomes (SpHL-DOX-Fol) were formulated for delivery of doxorubicin (DOX) to breast cancer. The formulation assessed for antitumor activity using both in vitro and in vivo *studies* in a 4T1 breast cancer model system. A higher tumor uptake was showed using radiolabelled SpHL-Fol (99mTc-SpHL-Fol) as compared to the non-folate-coated liposomes (99mTc-SpHL). The antitumor activity of formulations arrests the cellular growth and reduces pulmonary metastasis. Thus, pH-sensitive liposomal system can be considered as a novel drug delivery system to increase the DOX tumor delivery as well as reduce the dose-limiting toxicity [19].

2.1.3 Prostate Cancer (PCa)

The mitomycin C lipophilic prodrug (MLP)-based product Promitil® was explored in clinical trials. The folate-conjugated liposomes was prepared using doxorubicin, and MLP and their antitumor potential were investigated in PSMA-expressing human prostate cancer cell line (LNCaP). It has been revealed that the folate-targeted liposomes displayed more interaction with PSMA over-expressing cells as compared to simple liposomes. The folate-modified liposomes enhanced the cytotoxicity in PCa [20]. It has been investigated that combination of two drugs/agents is beneficial as compared to single drug/agent for chemotherapy. The combination of paclitaxel and imatinib increased the cytotoxic and antiangiogenic potential synergistically. Both drugs were loaded into folate-targeted liposomes, and anticancer activity was determined using the PC-3 cells. The viability of PC-3 cells and VEGF gene expression was found to decrease as compared to the non-targeted liposomes and free paclitaxel [21, 22].

2.1.4 Brain Cancer

A dual-functionalized liposomal system was prepared for the efficient transport across BBB for targeting of brain cancer [23, 24]. The surface of liposomes was modified with transferrin (Tf), which used as receptor for targeting. Translocation of doxorubicin (Dox) and erlotinib (Erlo) was improved into glioblastoma cells of brain using cell-penetrating peptide PFVYLI. The liposomes were evaluated for in-vitro cytotoxicity and haemolytic studies. The cellular uptake studies assessed effective internalization of drug in U87 brain endothelial and glial cells of brain. The dual-functionalized liposomes displayed higher apoptosis in U87 cells of brain [25]. The paclitaxel (PTX)-loaded liposomal system were developed. The liposomes were modified with microenvironment acid-cleavable folic acid (FA) and cell penetration peptide dNP2 for the delivery in glioma cells. The in vitro BBB model significantly increases transmission across BBB by the modification of peptide in liposomal system. The acid-cleavable folate-conjugated liposomes showed a pH-sensitive cleavage of FA at pH 6.8. It leads to an improvement of cellular uptake by the glioma cells of brain. The liposomal system enhanced the antitumor effect and improved accumulation of drug in glioma cells in mice as compared to free drug [26].

2.1.5 Lung Cancer

A novel co-delivery system (L-PTX-PSur) of paclitaxel (PTX) and survivin siRNA (Sur) was developed which specifically delivered the drug to lung cancer cells. Protamine was selected to condense siRNA into the “core” of the delivery system. Furthermore, carbamate-linked cationic lipid was entrapped into the core of drug delivery system. The liposomes with this protamine facilitated the entry of Sur into the NCI-H460 cells and displayed a better encapsulation efficiency. The in vitro studies on the NCI-H460 lung cancer cells exhibited that L-PTX-P Sur has more advantages over the control groups. It demonstrated highest cellular uptake, lowest cell viability, and apoptosis. The expression of surviving protein was reduced substantially by the liposomal formulations in NCI-H460 cells using western blot. The down-regulation of survivin protein could lower the growth of cancer cells and provide PTX more effective with low doses [27]. The docetaxel (DTX) liposome system was prepared by surface modification with CD133 aptamers and intended to target lung cancer. The liposomes were prepared by the thin-film hydration method. The in-vitro study displayed a slower drug release profile. In cytotoxicity study, CD133 aptamers-modified DTX LP significantly reduced the cell proliferation and increased the therapeutic efficiency. The in vivo antitumor activity indicated that the CD133-DTX LP exhibits a higher antitumor activity in A549 tumor mice and reduces the systemic toxicity [28].

2.2 Applications in Other Diseases

2.2.1 Tuberculosis

Liposomes are potential vehicles for the delivery of anti-tuberculosis drugs. The pH-dependent liposomes of isoniazid from isonicotinic acid (4-hydroxybenzylidene) hydrazide were developed. The liposomes were prepared by thin-film hydration method. The in vitro release studies of drug from liposomes were assessed in media of different pH using a dialysis method. It can be concluded that pH-dependent release characteristics of liposomal carrier was used to minimize the leakage of drug from liposomes which might be a potential target drug delivery in tuberculosis [29].

2.2.2 Antifungal

The itraconazole (ITZ)-loaded deformable liposomes (DL) were developed using hydroxypropyl-β-cyclodexterin (HPβCD) (DL-CD) to enhance antifungal activity. These liposomes were reported as realistic vesicles for the delivery of drug into the different skin layers. The liposomal carrier was exhibited higher concentration of ITZ in stratum corneum as well as deeper skin layers as compared to conventional liposomes. It can be concluded that deformable liposomal system in the presence of HPβCD was emerging carrier for effective cutaneous delivery of ITZ for antifungal action [30].

3 Chemotherapy in Combination to Gene Therapy and Immunotherapy

Gene therapy is widely used as an innovative treatment strategy in many diseases including the deadly disease of cancer to prevent the overall deaths. It introduces new genes into a cancer cell and thus reduces the cancer growths or kills the cancer cells. In immunotherapy, genetically modified cells are used along with the viral particles to stimulate the immune system and target the cancer cells. Immunotherapy has been employed to prevent metastatic growth of cancer by improving antigen-specific immune responses. Combination therapy of chemotherapeutic drugs and/or other biomolecules signifies a promising approach that may progress the anticancer effects by synergistic activities. It helps not only in the treatment of cancer but also in many other diseases [31–34]. Sun et al. demonstrated that the combination therapy of anticancer agent and siRNA improves the anticancer effects synergistically in hepatocellular carcinoma (HCC). They developed PEI-modified liposomal system by thin-film hydration method and co-delivery of both sorafenib (SF) and siRNA to target antiapoptotic gene, i.e., GPC3 gene (siGPC3) and cyclin D1 gene, respectively, in HCC

[35]. Another study investigated the pH-sensitive carboxymethyl chitosan-modified liposomes (CMCS-SiSf-CL) assembled with sorafenib (Sf) and Cy3-siRNA. The results demonstrated the co-delivery and penetration into two-dimensional cultured HepG2 cells, three-dimensional cultured HepG2 tumor spheroids and tumor regions of H22 tumor-bearing mice. These liposomes displayed higher vascular endothelial growth factor down regulating effect and trigger apoptosis. Therefore, the CMCS-SiSf-CL system may be a novel co-delivery system and offer an emerging platform for HCC therapy [36]. Zuo et al. prepared novel liposomes which delivered the combination of 7-O-geranylquercetin (GQ) and survivin siRNA or interleukin-10 siRNA (siIL-10) and enhanced the anti-proliferation and pro-apoptosis effects in MCF-7 cells. Further, it decreased the level of survivin and increased the level of caspase-7. This combination gene therapy not only inhibited cancer growth but also down-regulated the expression of survivin and up-regulated the expression of caspase-7 in cancer cells. Moreover, the combination of GQ and siIL-10 slowed down the cancer growth, reduced the level of IL-10, and elevated the level of TNF-α. These results displayed a fruitful effect of the combination therapy to enhance the pro-apoptosis action for the treatment of breast cancer [37]. A topoisomerase inhibitor, i.e., SN38 (prodrug), was combined with a survivin siRNA and co-delivered by transferring-targeted liposomes (Tf)-L-SN38/P/siRNA. It was conjugated with the help of a cell penetrating peptide TAT through a polyethylene glycol (PEG) linker to prepare TAT-PEG-SN38. This prepared TAT-PEG-SN38 was amphiphilic in nature and enhanced the cellular uptake of the liposomes. Moreover, protamine was comprised in the core of the liposomal system to form an electrostatic complex with siRNA. This liposomal combination system was evaluated as a promising therapeutic approach for cancer targeting [38]. Yan et al., demonstrated that the DESI2 (recombinant plasmid/pro-apoptotic gene) and endostatin (antiangiogenic inhibitor) was encapsulated with cholesterol cationic liposomes, and this combined gene therapy more significantly inhibited the cancer growth as compared to the mono therapy. It improved the anticancer activity by inducing apoptosis, inhibiting angiogenesis, and act as a DNA lesions accumulator [39]. A cationic liposomal co-delivery of XY-4 (Aurora-A kinase inhibitor) and Bcl-xl targeted siRNA was developed as an injectable for melanoma cancer therapy. The anticancer ability and mechanisms of these formulations were studied both in vitro and in vivo and it displayed an enhanced anticancer effect on B16 melanoma cells by the activation of mitochondrial apoptosis pathway. Moreover, the intratumoral injection of this liposomal system significantly reduced the cancer growth that was observed in B16 melanoma in vivo xenograft model. The results suggested these formulations as a potential combination strategy for melanoma therapy [40]. Xu et al., prepared dual-therapeutic-loaded GE11 peptide-conjugated liposomes to improve the therapeutic efficacies for the treatment of laryngeal cancer. GE11 is an EGFR-targeting ligand used in the liposomal formulations containing docetaxel and siRNA against the ABCG2 gene that regulates multidrug resistance in many cancers [41]. Liposome-encapsulated DTX/ABCG2-siRNA was targeted against the Hep-2 laryngeal cancer cells. It improved the antitumor and apoptotic effects and may be effective for the treatment laryngeal cancer [42]. Thermal-responsive liposomes (TRL) were prepared using the combination of indocyanine

Table 1 Chemotherapy in combination to gene and immune therapy for cancer and other diseases

Drugs/Biomolecules/Therapeutic agents/	Immune agents/Genetic materials	Diseases	References
Docetaxel	Small interfering RNA (siRNA)	Glioblastoma	[45]
Pemetrexed	RNA interference	Malignant pleural mesothelioma	[46]
X-396 (anaplastic lymphoma kinase inhibitor)	siRNA	Neuroblastoma	[47]
Camptothecin	Anticancer siRNA (siPlk1)	Cancer	[48]
Allopurinol	Meglumine antimoniate	Canine visceral leishmaniasis	[49]
SiRNA	Peptide derived from rabies virus glycoprotein	Neurodegenerative protein misfolding diseases	[50]

green (ICG) and polyinosinic:polycytidylic acid (poly I:C). Poly I:C is a water-soluble immune stimulatory agent used to provide immune response. This novel system is not only intended to provide primary treatment to cancer but also for the prevention of cancer metastasis. The poly I:C- and ICG-containing TRLs (piTRLs) analyzed both in vitro and in vivo and the results showed the potential application of a piTRL with laser irradiation for immuno-photothermal therapy against the metastatic cancers [43]. Yang et al. developed liposome-based nanocapsules with surface endoglin aptamer and encapsulated it using an interferon-inducible protein-10. They tried to target vascular endothelial cells in tumor vasculature of the mouse and observed the significant action against cytotoxic T lymphocytes in melanoma cancer immune therapy [44] (Table 1).

4 Theranostic Applications

"Theranostics" is a new approach merging both diagnosis and treatment in a single delivery system like liposomes. These theranostic liposomes (TLs) contain both drug and diagnosis agents and precisely monitor the treatment efficiency along with the treatment. These systems were utilized for various diseases such as cancer, tuberculosis, and Parkinson's [51]. TLs were developed for the effective management of mycobacterial infections. These targeted TLs improved the therapeutic efficacy of drugs by site-specific delivery to the target and decreased the adverse effects. Folate-modified PEGylated liposomes encapsulating rifampicin and ofloxacin were prepared for in vivo imaging and treatment of mycobacterial infections. The formulation was evaluated for various parameters like physicochemical properties, in vitro

drug release, mycobacterial activity, in vivo blood-kinetics, bio-distribution, and bio-efficacy and stability. The vesicle size was found to be 160.6 nm with excellent anti-mycobacterial activity and considerable colloidal stability (up to 120 days). Entrapment efficiency was found to be 66.89 (±10.9)% and 40.61 (±8.7)% for rifampicin and ofloxacin, respectively. The in vitro drug release studies showed a slow biphasic pattern with longer terminal half-life of 19.13 h. The results of bio-distribution studies revealed higher localization of drugs in organs like spleen, liver, and kidneys one hour post-injection. The cellular uptake of TLs was assessed using scintigraphic in murine model of TB infection. Results demonstrated higher uptake at 2 h [52]. The TLs integrated with superparamagnetic iron oxide nanoparticles (SPIONs) and quantum dots (QDs) as well as cilengitide in a single system were developed for guiding surgical resection of glioma using magnetic targeting (MT). Encapsulation of SPIONs and QDs into TLs was detected by TEM and X-ray photoelectron spectroscopy. The size, zeta potential, and entrapment efficiency of cilengitide were found to be 100 ± 1.24 nm, −17.10 ± 0.11 mV, and ∼88.9%, respectively. In vitro drug release studies revealed a biphasic release pattern (initially rapid followed by sustained). Moreover, uptake of TLs is significantly increased by C6 cells under MT. The in vivo dual-imaging displayed negative-contrast enhancement effect on glioma [53]. Resveratrol (herbal neuroprotective agent) plays crucial roles in the treatment of Parkinson's disease (PD). However, the use of resveratrol is limited due to their poor penetration across the blood–brain barrier (BBB). Differential diagnosis of PD is also one of challenges in neurology. Herein, liposomes modified with a Fe_3O_4 (magnetic targeting) was developed for treatment of PD. The factional anisotropy (FA) values and T2 relaxation time of formulation were observed by magnetic resonance imaging in rats which showed good therapeutic effects. The formulation showed sustained and slow drug release and better stability. The results of in vivo studies displayed higher drug accumulation in target under the external magnetic field. Therefore, the Fe_3O_4 modified liposomal system offers a potential platform for the treatment of cerebral disease due to better penetration of drug across the BBB [54]. In another study, doxorubicin and grapheme nanosheets containing liposomes were developed using thin-film hydration method for the treatment of cancer. The GNSs have good optical properties, like photoluminescence which helps in tracking of the formulation, high absorption in ultraviolet region which can be utilized in photothermal therapy. The formulation was characterized for various parameters such as in vitro drug release, cytotoxicity, and cellular uptake. MCF-7 cells were utilized for cytotoxicity and cellular uptake studies. The formulation demonstrated higher cytotoxicity as compared to free forms of both [55]. Stimuli-responsive drug delivery systems selectively delivered the drug to the target site in presence of stimuli (external or internal). Theranostic liposomal systems were developed for simultaneous diagnosis and treatment. Reactive oxygen species (ROS)-responsive liposomes were developed which release drug upon ROS treatment. These liposomes showed sustained drug release in response to higher H_2O_2 concentration as well as displayed higher cytotoxicity as compared to unmodified counterpart [56]. Prostate-specific membrane antigen (PSMA) is a potential bio-marker for prostate cancer. Lipopolymer-modified liposomes were developed for theranostic delivery to

PSMA-expressing ($PSMA^+$) LNCaP cells. Lipopolymer was prepared using PSMA ligand, polyethylene glycol, and palmitate. Surface of preformed liposomes was modified with lipopolymer by post-insertion technique [57]. Doxorubicin and radiolabelled with ^{99m}Tc radionuclide were loaded into liposomes. Formulation of ^{99m}Tc-labeled lipopolymer-modified liposomal formulation increased the cellular uptake more than threefold in LNCaP cells compared to ^{99m}Tc-labeled plain liposomes. The results of cytotoxicity assay demonstrated that lipopolymer-modified formulation was more cytotoxic to LNCaP cells ($p < 0.05$), but not effective to PSMA-negative PC3 cells. The IC_{50} values of these liposomes were decreased upto ~five fold in case of LNCaP as compared to plain drug-loaded liposomes. These results suggested that PSMA ligand-based theranostic liposomes offer a potential platform for prostate cancer [58]. The folate-conjugated doxorubicin (Dox) and poly(9,9-dioctylfluorene-2,7-diyl-co-benzothiadiazole) (PFBT) as a fluorescent probe-loaded TLs were prepared and characterized. Liposomes were developed by thin-film hydration method using the active loading technique. The size and zeta potential of TLs were found to be 127.30 ± 3.20 (nm) and -25.00 ± 2.00 (mV), respectively. This carrier system showed extended drug release at 24 h under the mild hyperthermia as compared to Dox-Lip-FA. The IC50 value was reduced from 28.3 ± 3.7 (μg/mL) [in case of Dox-Lip-FA (37 °C)] to 16.8 ± 4.5 (μg/mL) in case of PFBT-Dox-Lip-FA. The results of cellular uptake study demonstrated higher drug accumulation inside the target. In vivo studies supported that distribution of PFBT-Dox-Lip-FA properly detected by PFBT. The growth of tumor-bearing mice was also reduced by PFBT-Dox-Lip-FA [59]. The theranostic applications of liposomes are summarized in Table 2.

5 Stimuli-Triggered Liposomes

Stimuli-sensitive drug delivery system (SSDDS) is a type of drug delivery system, which has a wide range of applications in drug delivery and cancer therapy. SSDDS can promote the effective localization of drug to the tumor site and avoid the side effects [69–71]. Traditional chemotherapeutic drugs are associated with several limitations such as systematic toxicity, low concentration of drug in tumor site, and short half-life. So, there is a need of SSDDS, which can deliver the anticancer drug to tumor site and reduce the side effects. The stimuli-sensitive drug delivery system could be fabricated to stimulate the response of living organ by assembling stimuli-sensitive carrier system to identify the dynamic process of body's biochemical reactions and changes of microenvironment, which leads to sustained or controlled release of drugs. Several reactions such as polymerization, isomerization, protonation, and hydrolysis are responsible for changing the behavior of stimuli-sensitive nanocarriers. It is based on the specific intracellular and extracellular physicochemical environment, which leads to accelerate the release of active components in special physiological environment [72]. In this approach, drug can be incorporated into the liposomes (either in core or in bilayer) by physical encapsulation or chemical bonding. It is a

Table 2 Theranostic application of liposomes

Drugs	Diagnosis agents	Ligands	Disease/Application	References
Doxorubicin hydrochloride	Graphene oxide flake under NIR light irradiation	Folic acid	Phototriggered tissue visualization and tumor regression	[60]
Anticancer siRNA	Quantum dots	Anti-EGF receptor aptamer	Theranostics of triple-negative breast cancer	[61]
Apomorphine	Quantum dots		Brain targeting and bio-imaging (disease like Parkinson)	[62]
Docetaxel (DTX)	Quantum dots	RGD-TPGS	Brain cancer imaging and therapy	[63]
Coenzyme Q10 (CoQ10)	Ultrasound-targeted microbubbles destruction (UTMD)		Diabetic nephropathy	[64]
Paclitaxel (PTX)	Superparamagnetic iron oxide nanoparticles (SPIO NPs)	pH-responsive peptide H7K(R2)2	Cancer	[65]
Indocyanine green	NIR dye [indocyanine green (ICG) and perfluorooctyl bromide (PFOB)]		Cancer	[66]
Doxorubicin	Gold nanorods (near-infrared laser light-activated)		Tumor in lymph nodes	[67]
Rapamycin and indocyanine green	Indocyanine green plus NIR laser	Folate	Cancer	[68]

unique strategy to achieve precise drug delivery in which carrier can show response, depending on the various environmental changes or stimuli. There are two types of stimuli, i.e., endogenous stimuli, which will stimulate on change in pH and redox potential, while exogenous stimuli are those which will be stimulated by changing temperature, magnetic field, light, and ultrasound [73]. The applications of different types of SSDDS are discussed as follows.

5.1 Endogenous Stimuli-Sensitive Drug Delivery Systems

The SSDDS are subtle to particular endogenous stimuli, such as pH of different tissue and organ [74–76], and change in redox potential of cell [77–80]. The main strategy of SSDDS is to deliver the drug directly into the endosome or to escape from lysosome

to cytoplasm while in tissue-level studies, endogenous SSDDS can utilize the change of tumor's microenvironment or pathological conditions like inflammation, infection, and hypoxia to achieve targeted release of drug [81, 82].

5.1.1 pH-Sensitive Drug Delivery System

The pH-sensitive drug delivery system is used to achieve targeted drug release. The change in pH is utilized to control the delivery of drug especially to the body organs such as gastrointestinal tract or tumor tissue and intracellular compartment such as lysosomes and endosomes as well as triggers the release of the drug. These stimuli-responsive nanocarriers could be triggered to environmental changes which are associated with pathological conditions, like inflammation or cancer. Various anticancer drug delivery systems have utilized the slight difference in pH which are existing between normal tissues (about 7.4) and the extracellular environment of solid tumors (about 5.5–7.2). This is mainly due to the irregular angiogenesis in fast-growing tumors, which will lead to the deficiency of both oxygen and nutrients subsequent to the production of acidic metabolites in the tumor interstitial. An important strategy is in which, cell-penetrating peptide on the surface of nanocarrier that can act upon the change in pH and leads to cell internalization. Surface-charge reversal of pH-responsive systems from negative or neutral to positive could promote cell internalization [83]. The pH-sensitive liposomes consisted of 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) or 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine experience a transition from a lamellar phase to a fusogenic hexagonal phase at acidic pH. Sawant and Torchilin [84] reported the significant delivery of gene and siRNA via conjugation of DOPE to low-molecular-weight PEI due their fusogenic and buffering properties. The positively charged PEGylated liposomes potentially interact with the endosomal membrane, which facilitates the delivery of bioactives. On the other hand, the pH sensitivity can be considered using anchored polymer chain, causing deterioration of lipid membrane through phase transition in lysosomal acidic environments, which leads to release of payload [84].

5.1.2 Redox-Sensitive Drug Delivery System

These are the systems which use electron-transfer reactions to trigger the drug release. Redox-sensitive liposomal vehicles could be destabilized either by changes in charge or hydrophilicity of the amphiphile with chemical reducing agents. It is also disrupted due to elimination of cross-links to initiate the transition of lipid phase. Redox potential is an activating stimulus for both intracellular drug delivery and tumor targeting. These activating stimuli were generated through the high potential differences between the reducing environment of intracellular space and the more oxidative extracellular environment. Powerful thiolytic reducing agents, like dithiothreitol (DTT), are commonly used for the disruption of disulfide linkages within an

amphiphile, which involve in the activation of redox system. The critical micelles concentration (CMC) of the thiolytically cleaved amphiphile byproduct is usually increased, due to reduction reaction [85]. Fu et al. [86] prepared TAT modified paclitaxel liposomes comprising redox-responsive poly(ethylene glycol). At physiological conditions, and the TAT was protected by PEG which makes liposomes as long circulating. Glutathione was used as exogenous reducing agent which facilitates the detachment of PEG at tumor site. After detachment of PEG, TAT was exposed and shown to improve the cell internalization. It was concluded that the system increased tumor localization both in vitro and in vivo with increased tumor inhibition [83, 86].

5.2 Exogenous Stimuli-Sensitive Drug Delivery Systems

5.2.1 Temperature-Sensitive Drug Delivery System

Temperature-sensitive liposomes can regulate the release of drug and also expresses their function in response to local heating of desired tissues, which are used to accomplish target-selective drug delivery [83]. In case of liposomes, the dipalmitoylphosphatidylcholine (DPPC) displays the gel-to-liquid crystalline transition at about 41 °C, the temperature at which the permeability of the bilayer increases. Distinctive temperature-sensitive liposomes consist of DPPC which was used to achieve targeted release of drug. Drug release occurs at temperature higher than that of gel-to-liquid crystalline transition temperature [87]. Temperature-sensitive liposomes are utilizing the property of polymers which are known to change their water solubility in response to temperature. The lower critical solution temperature (LCST) is the specific temperature at which the temperature-sensitive polymers become water insoluble or experience phase separation. It has wide application in the field of drug delivery system. Temperature-sensitive polymers were used to produce temperature-sensitive liposomes. Liposome surface was modified using poly(*N*-isopropylacrylamide) (pNIPAM) and its copolymer. These polymers are decorated on surface of liposomes, which helps in triggering release of drug in response to temperature higher than LCST. It demonstrated that the destabilization of liposomal membrane occurs when polymer chain becomes hydrophobic at temperatures higher than LCST [88, 89]. Temperature-sensitive functions of liposomes are affected by the physical characteristics of temperature-sensitive polymers and their modification methods. Poly[(2-ethoxy)ethyl vinylether] (pEOEVE) shows LCST at around 40 °C. It comprises similar structure on the side chain as that of biocompatible PEG [90]. pEOEVE polymer forms highly hydrophobic domain which offers temperature sensitivity after liposome modification [91]. PEG-decorated liposomes were modified using block copolymer containing a pEOEOVE chain as a thermosensitive block and octadecylvinylether block. Kono et al. [91] prepared doxorubicin (DOX) containing liposomes, which leads to the triggered release of drugs within few minutes at 45 °C. Intravenous liposomal injection to the colon 26 tumor-bearing

mice with local heating of tumor lesion at 45 °C for 10 min leads to suppression of tumor growth [90, 91].

5.2.2 Magnetic-Field-Sensitive Drug Delivery Systems

Magnetic field is an external stimulus, a non-invasive energy source, which shows an important role in sustained release of drugs from magnetic-field-sensitive nanocarriers [92]. Magnetically sensitive liposomes can incorporate both type of drugs (hydrophilic and hydrophobic) using active targeting approaches for the treatment of several diseases. Magnetic field facilitates the delivery of drugs to target sites and maintain its concentration in blood upto its complete absorption [93].

5.2.3 Light-Sensitive Drug Delivery Systems

In light-sensitive drug delivery system, light is used as a physical stimulus to initiate the drug release. For the initiation of release process, light is used as a trigger to activate the photons. Light having 600–900 nm wavelength range is transmissible deep into biological tissues due to small absorption coefficient and low scattering [94]. Photodynamic therapy (PDT) involves the use of photosensitizing agents that can be stimulated by different intensities, wavelengths, or pulse durations to attain direct cell death or selective release of drug from a carrier systems [95, 96]. Photosensitizer (PS) absorbs light that can act as an energy transducer like energy transfer to molecular oxygen which leads to the formation of reactive oxygen species (ROS) that can consequently react with the liposomes to stimulate drug release or directly act on target tissues to activate apoptotic and necrotic cellular responses [97]. Most of the PSs are hydrophobic, and nanocarriers like liposomes and micelles are extensively used for improving the stabilization and tumor targeting of these agents. PDT was clinically approved modality, which can provide diagnostic evidence, specific targeting, and used in combination with other therapies. In case of light-sensitive liposomes, photo-polymerizable phospholipids like DC8,9PC (1,2-bis(tricosa-10,12-diynoyl)-sn-glycero-3-phospho choline) are widely used [97–99]. The major factors for the determination of photo-sensitive drug release are to determine the lateral phase separation and packing properties of polymerizable lipids in the liposome.

5.2.4 Ultrasound-Sensitive Drug Delivery Systems

Ultrasound (US) triggered drug delivery is used to deliver bioactive to the targeted site. The ultrasound can activate the delivery of drugs through several mechanisms such as microbubble activation, cavitation, increased cell membrane permeability, etc. [100–102]. Local heating was achieved via propagation of longitudinal pressure wave on the tissues and a part of its energy is absorbed by the tissue or drug carrier which increases the temperature of tissue viz drug carrier to release the drug [103].

Furthermore, free radicles are obtained from insonation of certain drugs, which can disrupt the cell membrane and enhance the transmembrane transport [104]. Low-frequency US (20–100 kHz) can be utilized in sonophoresis and transient cavitation-induced drug release from the liposomal drug delivery system [105, 106]. At high intensities, high-frequency US (>1 MHz) can lead to the thermal damage to cells and tissues [106]. Awad et al. [107] developed ultrasound-triggered albumin-conjugated liposomes for breast cancer therapy. In this study, human serum albumin (HAS) has been conjugated to PEGylated liposomes to explore the drug delivery (calcein) to breast cancer cells. Fluorescent microscopy displayed the calcein uptake by two breast cancer cell lines (MDA-MB-231 and MCF-7) which were considerably higher with the HAS-PEG liposomes as compared to non-targeted control liposomes [107].

6 Conclusion

The development of liposomes as carriers for therapeutic molecules is an ever-growing research area. The possibility of manipulating the inherent characteristics of these nanocarriers makes them versatile carriers for a wide range of materials (drugs, proteins, peptides, nucleic acids, and so on) and widens their potential use in many clinical settings. In the field of drug delivery, the liposomes have numerous applications due to their versatile nature. It has ability to encapsulate any type of drugs and other therapeutic agents. This vesicular drug delivery system can be administered by different routes which make them potential tool for the delivery of drug. Due to their unique components, they have ability to deliver the drug at target site. Nowadays, liposomes are showing many applications in the field of diagnosis and even in theranostic areas. Furthermore, the ability of liposomes to co-encapsulate both therapeutic and diagnostic agents paves the way for a novel application of liposomes as theranostic platforms. However, a rational design approach to achieve therapeutic objectives might represent the rate-determining step in the development of more sophisticated lipid-based therapeutics in the future.

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Dendrimers for Advanced Drug Delivery

Shiv Kumar Prajapati and Aakanchha Jain

Abstract Dendrimers are 3D hyperbranched nanoscopic compounds in which active molecule is loaded non-covalently or covalently coupled on the surface for the drug delivery applications. The potential of linking or entrapping bioactive molecule or drug into dendrimer improves solubility, bioavailability, and biological properties. These are known for their size, shape, monodispersity, drug protection, cellular internalization, and controlled drug release. The biological and physicochemical properties can be modified during their synthesis. The chemical modification of dendrimers enhances its functionality to couple the ligand for targeting and enhances biocompatibility. Dendrimers obviously have potential to use it as drug carrier or gene carrier. Non-biodegradability is the main concern about the dendrimers which causes toxicity in cells or tissues due to the accumulation of synthetic polymers. Thus, biodegradable dendrimers have been developed with unique architecture, plentiful cavities, and surface functionalities. The cytotoxicity of dendrimers can be reduced by modifying with carbohydrates, polyethylene glycol, ligands, or other compounds which do not affect cell and parallelly improve other properties. The emphasis of this chapter is to cover recent advances in dendrimer technology, applications in drug delivery, cytotoxicity.

Keywords Dendrimers · Drug delivery · Targeting · Toxicity

1 Introduction

Dendrimers are nanosized globular-layered architecture composed of several perfectly branched monomers that show aptitude in several drug delivery applications and commonly referred to as arborols [1]. The dendrimers derive their name

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from Greek word *dendra* (tree-like structure) and comprise three domains (A) a central core, (B) repetitive branching units, and (C) terminal groups (a corona) with peripheral reactive functional groups [2]. First, the core encapsulates several chemical moieties that show surpassing properties owing to the distinct nano-environment encircled by widespread dendritic branching. Then, repeating units "interior layers" endue a stretchy space created inside the cavities of dendritic building blocks and are able to hold many active molecules (Fig. 1). Finally, the repeating units' conserves abundance of functional groups which helps to interact with the external environment. Compared to lower generation, the higher generation dendrimers are larger, highly branched with the more end group functionality at the periphery [3, 4]. Dendrimers show distinct characteristics such as easy synthesis, high structure control, well-defined architecture, high drug loading, monodispersity, highly branched, surface functionality, electrostatic interactions, covalent conjugations, low glass transition temperature, and stability [5]. The possibility of control in architecture of dendrimers attracts them for various applications ranging from solubility enhancement to the advanced drug delivery. Drugs can be encapsulated in internal voids and/or bound to the periphery via electrostatic or hydrophobic interactions or can be covalently attached to the terminal groups [6]. Besides the targeted delivery, dendrimers have been explored for imaging by delivering the diagnostic agent.

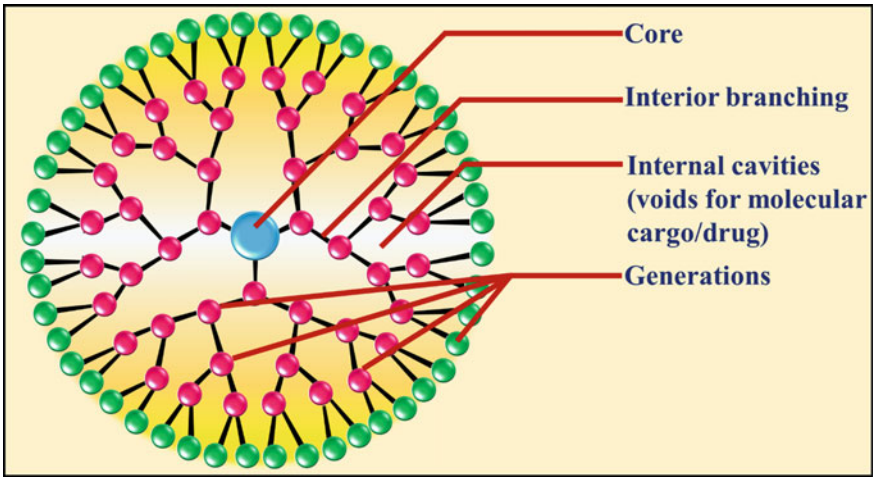

Fig. 1 Structure of dendrimer

2 Properties of Dendrimer

Monodispersity is important factors to project dendrimers to its applications in drug delivery, and for such applications, monodispersity allows for the investigation of structure activity relationships. This is a powerful tool for drug and medical device development. Though the question arises whether monodispersity is necessary for drug delivery/clinical applications, polydispersity cannot be assumed a limiting factor for its application. If monodispersity controls the consistency and accuracy of dendrimer formulation for drug delivery purposes, "why have linear polymeric delivery agents continued to enter into clinical trials over dendrimers?" [7]. The dendrimers for its dispersity profile can be confirmed by various techniques such as mass spectroscopy, transmission electron microscopy (TEM), gel electrophoresis, size exclusion chromatography [8].

Pharmacokinetic is the most considerable facet that is essential for the efficacious application of dendrimers for drug delivery. Dendrimers have various peripheral functional group that represents potential which manages the pharmacokinetics by surface modifications [9, 10]. The significant role of dendrimer's ADME properties to describe the pharmacokinetics of the drug, the pharmacodynamics, and toxicokinetics enlighten comprehensive investigation of dendrimer pharmacokinetics is justified [11].

Surface charge and polyvalency, the surface modification of dendrimers with different charges either positive, negative, or neutral charge is critical in the formulation development for their bioactivity and therapeutic applications [12]. The positively charged dendrimers enable their interaction with negatively charged bio-membranes thereupon enhances intracellular drug delivery. Various functional groups present on the dendrimer surface make it polyvalent, and the polyvalency of dendrimers also leads to the toxicities (cytotoxicity, hemolysis, etc.) [13]. Such toxicities can be reduced or diminished by modifying the peripheral versatile functional groups by polymer cross-linking, anchoring of ligands, development of drug—dendrimer complex, antibody—dendrimer, targeting agent—dendrimer, imaging agents—dendrimer, carbohydrates, PEGylation, etc., conjugates, or complexes [14–16]. Polyvalency is tremendously significant for various interactions with biological receptor sites.

Size and Shape, nanosized dendrimers have somewhat similar dimensions to biobuilding blocks like proteins and DNA. The molecular mass can be controlled during synthesis compared to the linear polymer. The optimum size and shape attract it for drug delivery applications because it can easily permeate the cell membrane and prevents it from clearance. The increase in the size can be seen with the increase in generation number.

Self-assembling, dendrimers itself precisely get self-assembled into vesicles, micelles, worm-like structures, etc., by specific interdependent intermolecular forces. The driving force to form self-assembled designs is depending on the hydrophilic and hydrophobic segments [17]. Amphiphilic Janus dendrimers with hydrophilic and

hydrophobic groups prepared that have the tendency to self-assemble into vesicles, dendrimersomes, disks, helical ribbons, tubular vesicles, and cubosomes [18].

Biocompatibility, dendrimers, as they are smart carrier should be devoid of toxicity and immunogenicity. Both the toxicity and biocompatibility of dendrimers depend on end group present on its surface. Generally, the amine group of dendrimers interacts with negative charge of cell membranes [19]. These electrostatic interactions knowingly impact the stability and permeability of membranes. Generally, amine-terminated PAMAM and PPI dendrimers showed concentration-dependent toxicity and hemolysis [20, 21], while neutral or anionic groups at the end surface of dendrimers showed relatively less toxicity and hemolysis [22]. Nonetheless, it would not be correct to say that the dendrimers are compatible for drug delivery without being tested for its toxicity profile.

Stability, the dendrimeric structure is highly stable at chemical and physical stimuli. Functionalization and conjugation of dendrimer enhance the stability of complex formed.

3 Method of Synthesis

Generally, two methods divergent and convergent methods are used for synthesis, and apart from them, some other methods are used such as branched method, double exponential, and mixed growth methods.

3.1 Divergent Method

This method was firstly developed by Tomalia and Newkome. In the divergent method, the dendrimer grows around the core, and firstly, the surface functional group activates and then sequentially the branching monomer joins containing one reactive and two dormant groups lead to the formation of first-generation group. In this approach, the core is reacted with two or more molecules of reagent containing at least two protecting/branching sites, followed by removal of the protecting groups. This will lead to the formation of first-generation dendrimer [9]. This process continues until the desired size 3D dendrimer architecture is not formed. As the branching increases, the increase in generation, molecular weight, and surface functional group can be seen (Fig. 2). The advantage of divergent approach is that the end group at the periphery layer can easily be changed to modify the surface. Complications arise from side reactions and incomplete reactions of the end groups that lead to structure defects. To prevent side reactions and to force reactions to completion, large excess of reagents is required [23]. It causes some difficulties in the purification of the final product.

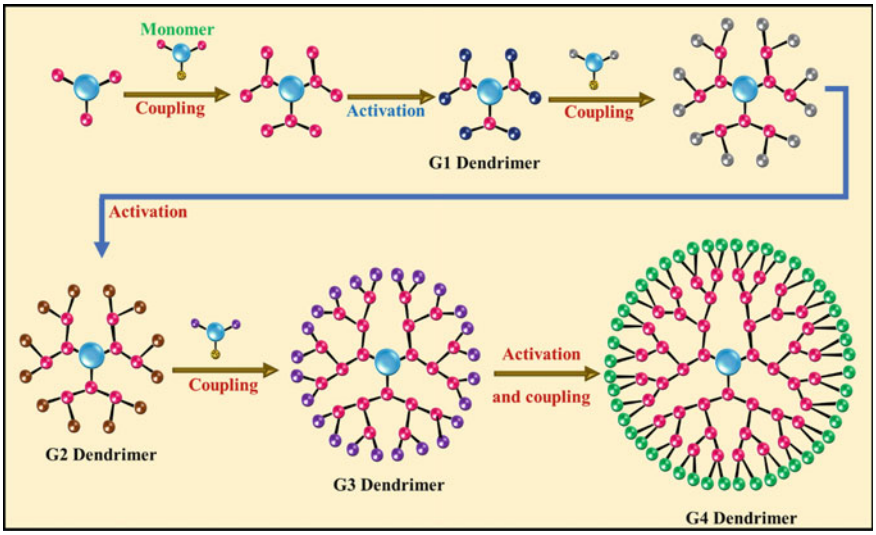

Fig. 2 Divergent method for dendrimer synthesis

3.2 Convergent Method

The convergent method is firstly introduced, and it is developed in response to the weaknesses of the divergent synthesis [24]. In this, the process starts from the end group and continues inwardly. The convergent method comprises two steps: first a coupling of branch to produce a central point functionalized dendron and second a divergent core attaching to produce dendrimers (Fig. 3). The growing dendrons

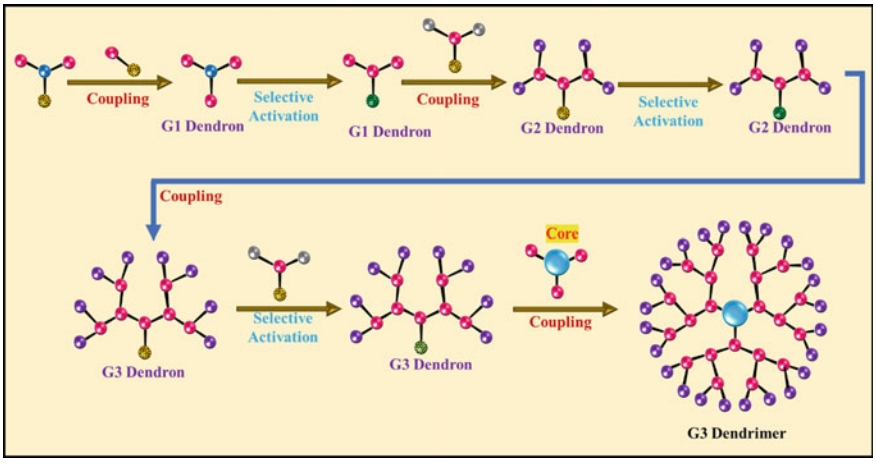

Fig. 3 Convergent method for dendrimer synthesis

are large enough, and they are attached to the multifunctional core molecule. The advantage of this method is that the dendrimer produced can easily be purified, and defects can be minimized. It becomes possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecule. The convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule [25].

3.3 Double Exponential Method

It is the advanced and rapid method where both divergent and convergent approaches are used to form "Dendrimer." This method necessitates an AB_2 monomer with A and B functional groups, which have focal and surface functionalities. The monomer can activate selectively, which results to form two activated monomers. The second-generation dendron forms by joining of the monomer having reactive B-functionalities with two equivalents of the monomers that having the reactive A-functionality. Reiteration of second-generation dendron occurs with selective activation, and coupling leads to dendron formation of the fourth generation [26, 27]. The growth of dendron continues joins to the core to form the dendrimers (Fig. 4).

3.4 Hypercores and Branched Monomers

In this method, the synthesis of dendrimers occurs in few phases by the joining of oligomers after their pre-assembly. Hypercore is constructed by divergent growth of core in single step. The hypercore and the branched monomers are pre-branched analogous of core and dendron, and the surface units are linked to branched monomer with the activation of focal point results in the synthesis of blocks [13, 20]. These are then coupled to the hypercore to produce higher generation dendrimer (Fig. 5).

3.5 Lego Chemistry

Lego chemistry has been exploited in the preparation of phosphorus dendrimers by the use of highly functional monomers and groups. The end groups are fabricated of phosphines and hydrazines. This method also covers the advantage of employing minimum volume of solvent, permitting easy purification process with nature-friendly by-products like water and nitrogen [8].

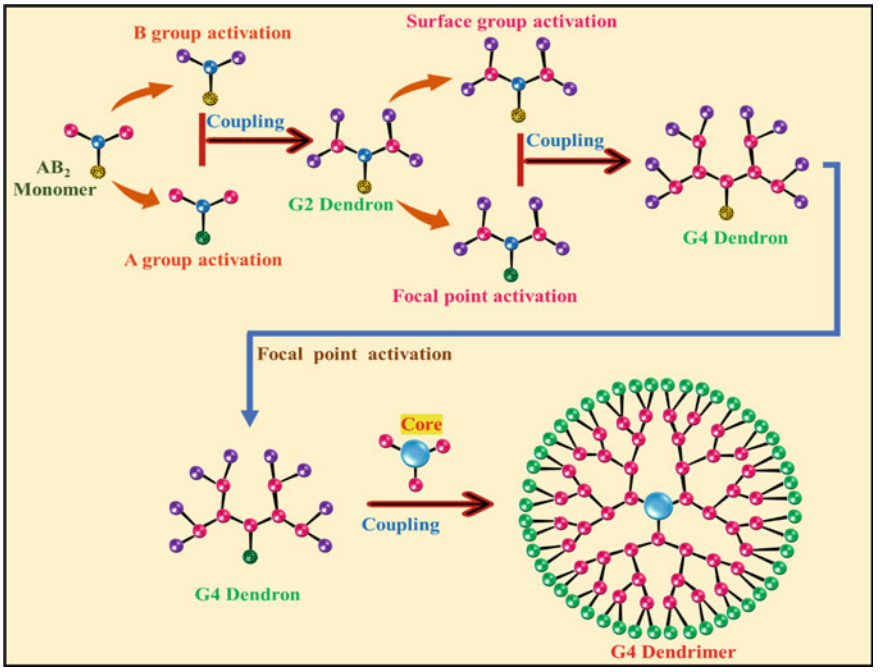

Fig. 4 Double exponential method for dendrimer synthesis

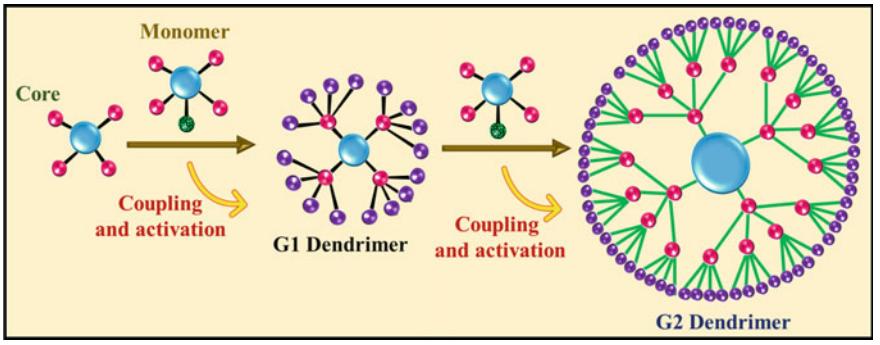

Fig. 5 Double exponential method for dendrimer synthesis

3.6 Click Chemistry

In click chemistry method, smaller units are joined together by way of heteroatom. Distinctive reactions applied are 1,3-dipolar cycloadditions, nucleophilic substitutions for ring-opening of strained electrophilic heterocycles, and accompaniments to carbon–carbon multiple bonds, e.g., epoxidation. Click chemistry strategy produces highly pure dendrimers with various surface groups and outstanding yield.

4 Types of Dendrimers

4.1 Carbosilane Dendrimers (CBS)

A sequence of carbosilane dendritic molecules grown up from four directions of a tetrahedral Si central core has been synthesized and characterized. The plus point of utilizing silicon chemistry to develop dendrimers is that the nucleophilic molecule can easily access electrophilic silicon (Si+). They have a hydrophobic internal skeleton, but these can be changed into water-soluble compounds by surface functionalization with cationic or anionic group. These are the most imperative amid the heteroatom-based dendrimers attribute to the flexibility of the synthetic route and to their chemical stability which consents further functionalization. Reactive peripheral groups, such as Si–Cl, Si–H, Si–CH=CH_2, and Si–CH_2CH=CH_2, provide the prospect through proper chemistry to acquaint with many other suitable inorganic, organic, and organometallic substituents and enhances their application in drug delivery field [28, 29].

4.2 Glycodendrimers

The combination of glycobiology and nanotechnology has prompted a rapid growth of research activities to design the novel functional nanomaterials, i.e., glyconanotechnology [30]. Dendrimers incorporating sugar moieties (glucose, mannose, galactose) and/or disaccharide into their structure are termed as glycodendrimers. Their vast majority comprises saccharide residues on the surface, but there is sugar unit in the core of glycodendrimers, from which the branches derive. Glycodendrimers are classified into three categories: (i) carbohydrate-centered; (ii) carbohydrate-coated dendrimers; and (iii) carbohydrate-based [31]. Glycodendrimers have received extensive attention for site-specific drug delivery to the lectin-rich organs, imaging, therapeutics and in biodiagnostic devices. These dendrimers were expected to show the improved association with lectins conjugated systems as compared to monocarbohydrate anchored systems [13]. Glycodendrimers for drug delivery permit to avoid naturally occurring drug resistance because of reduced transporter activity. Glycodendrimers have been widely studied for interactions with both therapeutic and natural nucleosides and nucleotides, showing stable complex formation. These have the ability to protect the triphosphates from enzymatic degradation and to facilitate their delivery into resistant cancer cells [32].

4.3 Polyamidoamine Dendrimer

Polyamidoamine (PAMAM) is a noble class of polymer was introduced in 1985, by Donald A. Tomalia, it is also known as "starburst polymers." PAMAM was the first dendrimer that was synthesized and commercialized, and it is the most well-studied and well-characterized class of dendrimers. The core of PAMAM dendrimer encompasses linear chain molecules with primary amines [33]. The PAMAM dendrimer core can be composed of linear chain molecules containing primary amines. The most commonly used compounds are ethylenediamine, ammonia, or cystamine. To grow the further generation of PAMAM dendrimer, it is essential to come by an thorough, repetitive, two-step process involving (i) Michael addition reactions with an alkyl acrylate, which creates half-generations (i.e., G0.5, G1.5, etc.), composed of terminal ester groups, and (ii) to obtain full dendrimer generation, ester amidation with an additional ethylenediamine must be applied. The cavities that are fundamentally present in the globular shapes of high PAMAM generations make dendrimer appropriate for encapsulating and adsorbing bioactive molecules. PAMAM has distinguished potential for applications not only for drug delivery but also in electronics, nanolithography, photonics, and chemical catalysis due to their ability to form complex and encapsulate numerous molecules with nanoscopic topological precision [34]. PAMAM dendrimers can trigger the immune response and are mainly affected by size, charge, and antigen loading [35]. The positively charged dendrimers can be used as a carrier for vaccine delivery, attributable to their aptitude to rise cytokine production [36]. Concerning PAMAM immunogenicity, the dendrimer was not immunogenic by itself, as it did not induce production against dendrimer-specific antibodies [37]. PAMAM dendrimers have internal cavities, and surface functionality can be modified to encapsulate drugs or other cargos. Moreover, non-immunogenicity, water solubility, spherical structure, biodegradation, biocompatibility, minimal nonspecific blood-protein binding, and controlled drug release that makes them distinct vehicle to deliver drugs and genes [38]. PAMAM dendrimers were used as a potential nanocarrier for water-insoluble antimicrobial quinolones like nadifloxacin and prulifloxacin. The encapsulation of these molecules into dendrimers not only increased their antimicrobial activity but also increased their aqueous solubility [39].

4.4 Peptide Dendrimers

These are branched polymeric macromolecules that consist of peptidyl branching attached to the core covalently linked functional units over surface [40]. "Peptide dendrimers are less compact than proteins but are more tightly packed than conventional linear polymers" [41]. The definite composition and ease of production make peptide dendrimer well matched for various biotechnological, biochemical, and drug delivery applications. These are generally used in various areas for immunological

applications, protein mimetics [42], in de novo design of artificial protein [43], anti-cancer drug delivery, central nervous system (CNS) disorder, antiviral agent delivery, vaccines and gene delivery carrier and as theranostic. Peptide dendrimers differ from low molecular weight of 2 kDa to large protein-like molecules 100 kDa. The size and complexity depend on number generation number and the terminal functional group (peptides or proteins of large size). Peptide dendrimers can be classified into three types. (i) First, the grafted peptide (largest in size) and (ii) second type of peptide dendrimers are essentially branching polyamino acids (smallest in size); (iii) the third type is generally peptides traditionally termed as peptide dendrimers [44].

4.5 Tecto Dendrimers

The core–shell dendrimers are generally termed as tectodendrimer. Tectodendrimers are highly ordered polymeric architectural structure composed of a core dendrimer molecule and surrounded by many dendrimers attached to its periphery by covalent linkages between dendrimer building blocks [45, 46] which implements definite function for smart therapeutic drug delivery, diagnosis, and recognizes diseased cells [47]. These can be characterized by their total mass, the generation of growth of the dendritic units, and the peripheral dendrimers linked to the central core. Besides, the tectounits on the surface do not require to be the similar of central dendrimer generation of growth [48]. The active drug molecule or cargo generally arranged layer-by-layer, and it may or may not be in the structure of dendrimer [20]. Core–shell dendrimers grasp a capacity to deliver multiple drugs and environmental remediation applications [48]. The bioavailability can be managed by increasing or reducing the tectounits.

4.6 Poly(propyleneimine) (PPI) Dendrimers

PPI dendrimers are generally polyalkyl amines having primary amines as an end group and designates the propylamine spacer moieties. The core of PPI dendrimer involves plentiful tertiary tris-propylene amines and available up to fifth generation. Furthermore, these dendrimers sometimes termed as “DAB-dendrimers” in which DAB is diamino butane present in the core structure [49]. The amino groups in PPI dendrimer were known to improve the aqueous solubility and enabling it to enhance the solubility of hydrophobic drug by entrapping in cavities of PPI dendrimer. Beside advantages, these are positively destabilizing cell membrane, low drug loading capacity, and less stable when complexed with drug. To overcome such issues, the PPI dendrimers are PEGylated or acylated to stabilize and to improve its

permeation [45, 46]. The modification of PPI dendrimers by Maltotriose significantly diminishes the toxicity [50]. A branch of PPI dendrimers "polyethyleneimine (PEI) dendrimers" is holding diaminoethane or diamino propane functional groups in the central core [49].

5 Applications of Dendrimer

An idyllic carrier for drug delivery must be non-toxic and biochemically inert and must shield the drug up until it reaches the target site. Dendrimers easily cross biological barriers due to their size in nanometers, high surface functionality, and narrow polydispersity index. It is also known that dendrimers cause toxicity; however, it can be reduced by conjugation of dendrimer or by altering the surface functional groups. Availability of multiple internal cavities and end groups makes it suitable for variety of therapeutic and biomedical applications (Table 1). Dendrimers frequently used in drug delivery are primarily modified in the following manner: (i) PEGylation, (ii) modification with targeting agents, and (iii) modification with stimuli-sensitive groups [51].

5.1 CNS Drug Delivery

Drug delivery to brain is very challenging due to multiple barriers, and the effectiveness of noninvasive technique is limited. The conventional strategies are not good enough to treat CNS related disorder due to solubility bioavailability concerns of various therapeutically active molecules. Thereby, various nanocarriers (nanoliposomes, nanoparticles, carbon nanotubes, nanosponges, micelles, etc.) are being used for CNS drug delivery. Among these carriers, dendrimers have received much attention because of its plenteous characteristics, i.e., enhances drug solubility, increases half-life and bioavailability, improves the membrane permeation, reduces macrophage uptake, targeting ability, and facile passage by transcytosis, etc. [52]. Crossing the blood–brain barrier (BBB) or brain cells necessitates that the drug-loaded dendrimer attaches to cell membranes. If the dendrimer has conjugated with ligand, then it would enter via receptor-mediated endocytosis, or else, cells will use adsorptive endocytosis for uptake [53]. Santos et al. developed PAMAM dendrimers and functionalized with poly(ethylene glycol) (PEG) to enhance the circulation and to minimize the cytotoxicity. After persuading focal brain ischemia, the formulation was intravenously administered. PEGylation of dendrimers showed the improvement in biocompatibility. The integrity in vitro BBB model did not affect by the PEGylated

Table 1 Applications potential of dendrimers

Dendrimer	Therapeutic compound	Route of administration	Remark	References
PAMAM	Camptothecin	Oral	Enhance oral bioavailability	[69]
PPI	Albendazole	Oral	Significantly increased mean residence time (MRT) and increased the pharmacokinetic properties of Albendazole	[80]
PAMAM	Doxorubicin	Oral	Increased bioavailability 200-fold higher than free doxorubicin	[70]
PAMAM	Insulin, Calcitonin	Nasal	G3 dendrimer improves nasal absorption without any membrane damage to the nasal tissues	[81]
PAMAM	Methylprednisolone	Nasal	Significantly improved drug residence time in the lung and treating inflammatory disorder such as asthma	[82]
PAMAM	–	Oral	Significantly decreased the transepithelial transport,	[83]
PAMAM	Ketoprofen, Diflunisal	Transdermal	Bioavailability of Ketoprofen–PAMAM dendrimer complex 2.73 times higher and 2.48 times higher for the diflunisal–PAMAM than pure drug suspension. Effectively facilitate skin penetration	[84]
PAMAM	Pilocarpine nitrate, tropicamide	Ocular	Significantly enhanced drug residence time for the ophthalmic route	[58]
PAMAM	–	Ocular	Modification with penetration and co-modified with cyclic arginine–glycine–aspartate (RGD) hexapeptide improved penetration of the nanocarriers and highly distributed in the cornea and retina	[85]

(continued)

Table 1 (continued)

Dendrimer	Therapeutic compound	Route of administration	Remark	References
PAMAM	Dithranol	Topical	Microsponge gel showed prolonged penetration and efficacy in the treatment like psoriasis	[86]
PAMAM	Diclofenac	Transdermal	PAMAM dendrimer coupled with sonophoresis to enhanced potential permeation of diclofenac through the skin	[87]
Polyanionic carbosilane	Tenofovir and raltegravir	Topical	inhibited cell-to-cell HIV-2 transmission and showed synergistic interactions	[88]
Janus	Protein	Intravenous	In vivo release of insulin was controlled along with improvement in the blood sugar	[89]
PAMAM	Camptothecin	Oral	Study revealed that improve bioavailability of drug	[90]
PPI	Methotrexate	–	Improvement in anticancer potential was observed	[91]
PPI	Cytarabine		Cellular uptake and cytotoxicity was found to be increased toward 1301 cells	[92]
PPI	Lamivudine		Enhanced cellular uptake, antiretroviral study showed improved HIV activity at low drug concentration	[93]

Rhodamine B isothiocyanate (RITC) modified dendrimers. The PEGylation mitigated the interaction and uptake of formulation signifying that the transport across BBB due to focal brain ischemia would be facilitated. PEGylated dendrimers reduced the blood clotting. It was observed that the dendrimers were reached to the brain and crossed the BBB and detected in neurons indicating that PAMAM can reach bEnd.3 cells and rat primary astrocytes in the ischemic brain [54]. Patel et al. developed PPI dendrimers for delivery of paclitaxel (PTX) to the brain. Three different ligands, i.e., sialic acid, glucosamine, and concanavalin A were engineered with PPI dendrimers to compare their targeting potential. The biodistribution and pharmacokinetic studies revealed a greater retention of PTX in brain compared to free drug and reduced the deposition of drug in excretory organs. The sialic-anchored PPI dendrimers (SPPI) showed greater targeting potential compared to glycosamine and concanavalin A anchored. The outcomes of investigation also revealed that, the anchoring of ligand

may block of P-gp efflux system to exert the highest therapeutic effect of anticancer drug to tumor cells [55]. For the delivery of carbamazepine (CBZ), Igartúa et al. developed PAMAM dendrimers for the delivery of neurodegenerative disease. The developed CBZ and dendrimer complex were found to stable up to 90 days, and the release of drug was noticed in a controlled manner. The findings of nanotoxicity had not shown any in vivo hemolytic toxicity. The complex of CBZ with PAMAM dendrimers with carboxylate terminal groups (DG4.5-CBZ) significantly diminished the toxicity compared to delivering the drug independently. The zebrafish model did not show any type of neurotoxicity, cardiotoxicity, or malformation revealing that the formulation is biocompatible [56].

5.2 Ocular Drug Delivery

The anatomical and physiological barriers are the key obstacles in ocular drug delivery. To attain the ideal therapeutic activity, drug molecules should circumvent the barriers without permanent tissue damage. Dendrimers are appropriate carrier for ophthalmic delivery of drug because they have tendency to solubilize lipophilic and hydrophilic drugs in their core and the surface modification provide sustained drug release [57]. It has been reported that the carboxylic and hydroxyl groups of PAMAM dendrimers have the ability to enhance the residence time in the eye and so the bioavailability of pilocarpine [58]. The PEGylation of dendrimers creates hydrogel which helps to seal ophthalmic injuries and production of cartilage tissue [59–61]. Holden et al. formulated brimonidine and timolol maleate loaded dendrimer hydrogel by PEGylation of polyamidoamine dendrimers. The dendrimer hydrogel did not cause any toxicity to human corneal epithelial cells. The solubility of brimonidine was found to be increased by 77.6%. The formulation showed considerably higher corneal transport of both drug and human corneal epithelial cells uptake. The greater uptake of dendrimer hydrogel formulation was due to the disruption of the corneal epithelial cell layer tight junctions [62]. Lin et al. developed dexamethasone-loaded dendrimers (D-Dex) for the treatment of dry eyes. The formulation administered subconjunctival route showed improved clinical results. Downregulation of inflammatory cytokines and less inflammatory cell infiltration was observed in the D-Dex treatment group lead to partial recovery of LG function. The dendrimer formulation showed pathology-dependent biodistribution in the inflamed LGs [63].

5.3 Transdermal Drug Delivery

The transdermal route has a great importance to avoid the maximum GI and renal-sided effects. The biocompatible and water-soluble dendrimers improve the plasma circulation and solubility when administered transdermally [6, 49]. Manikkath et al. developed PAMAM dendrimer and studied the dermal permeation of ketoprofen.

The ultrasound combined with PAMAM dendrimer showed an increase in permeation along with plasma drug concentration compared to orally administered formulation [64]. In another attempt, Manikkath et al. studied the combined transdermal permeation of ketoprofen by using arginine peptide dendrimers of low-frequency ultrasound. It was observed that the permeation from skin was enhanced and gave the synergistic effect. Compared to the passive diffusion, the formulation showed significant improvement in plasma drug concentration and did show considerable dermal toxicity [65].

5.4 Oral Drug Delivery

Patient compliance must be considered while designing the dosage form. The oral route is generally economic for anticancer drug delivery and enables the use of chronic treatment administrations. Oral routes provide flexible and controlled dosing regimens and suitable for long-lasting therapy, though poor aqueous solubility of drug and their permeability from biological membrane limit its intake through oral route [66]. A major challenge is the design and development of linker chemistries that are stable in the GIT and the blood after oral delivery, but then amenable to cleavage at the target site [67]. The parameters such as hydrophobicity, surface charge, dendrimer chemistry may affect the permeation, hence the bioavailability of drug delivery. The permeability after oral delivery can be enhanced by enhancing the lipophilicity or receptor-mediated endocytosis by ligand conjugation on dendrimers [68]. Camptothecin exhibits low bioavailability and GIT toxicities. Sadekar et al. studied to improve their potential by developing PAMAM dendrimer encaging camptothecin. In their study, PAMAM dendrimer shows their potential not only as drug carrier but also as drug solubilizer and permeation enhancer. The developed formulation after oral administration showed twofold–threefold increase in the solubilization of camptothecin in simulated gastric fluid. Due to the surface electrostatic interaction, there was not a significant difference in solubilization. PAMAM dendrimers were effective in enhancing the oral absorption of camptothecin [69]. Ke et al. worked for the enhancement of oral bioavailability of doxorubicin (DOX) by developing complex with PAMAM dendrimer. Interestingly, the bioavailability after oral administration was increased by 200 folds compared to the drug administered individually. The cellular uptake of DOX in Caco-2 cells treated with the DOX–PAMAM complex was found to be increased significantly with an increase in concentration and time [70]. For the treatment of neurological disorder of pediatric, Yellepeddi et al. developed complex of dendrimer (D) and *N*-acetyl-L-cysteine (NAC). For the poisoning of acetaminophen, NAC is used as antidot. D-NAC containing glycerol monocaprylate (capmul) "a permeability enhancer" showed nine folds increase in apparent permeability. The area under the curve was found to significantly increase by 47% with on oral administration of D-NAC with capmul compared to D-NAC administered individually showing their potential in neuroinflammation treatment [71].

5.5 Dendrimers in Cardiac Disorder

An ideal carrier for drug delivery to the heart must not be toxic. The toxicity can be altered by various surface modification techniques. Dendrimers have explored for prevention and treatment of cardiac diseases. Dendrimer-based formulations have developed for various heart diseases such as myocardial infarction, hepatic ischemia, hypertension, and angina. The dendrimers not only explored for drug delivery to heart but also for diagnosis. Katsumi et al. developed PEGylated lysine dendrimer for reperfusion injury. The dendrimer with thiol group showed prolonged retention in plasma. Raise in alanine aminotransferase activity assists as an imperative indication for reperfusion injury [72]. Kulhari et al. developed Simvastatin (SVM) and PAMAM dendrimer complexes and measured their potential for the in vitro improvement of water solubility and controlled release. They also evaluated in vivo enhancement of the oral absorption of the drug. The outcomes of pharmacodynamic exhibited that the augmented percentage of plasma cholesterol was lower when SVM-PAMAM dendrimer formulations were given compared to SMV given individually [73].

5.6 Anticancer Drug Delivery

Currently, most of the researches are being done for a successful delivery of anticancer drug. Dendrimers have shown their potential for the theragnostic applications and/or for anticancer drug delivery. The anticancer drug delivery based on dendrimer depends on rational designing of system and in-depth sightedness of biological processes [5]. There are multiple functional groups in dendrimers for conjugation and encapsulation of drug molecule. It can be complexed with ligands and/or diagnostic probe for imaging. Dendrimer and anticancer drug complexes have shown their aptitude to evade efflux transporter, intracellular delivery of drug, and for bioavailability enhancement [74]. Dendrimers have also revealed potential for diagnostic and theragnostic applications in cancer treatment apart from targeted delivery of antineoplastic drugs [75, 76]. The characteristics of dendrimers help in the delivery of anticancer agents include their exceptional uptake by cells, high density, surface functionality, and their aptitude to encage or conjugate the drug. Additionally, dendrimer nanocarriers also enable the passive targeting of drugs to tumor tissues through an enhanced permeation and retention effect [77]. Liu et al. developed PAMAM dendrimer encapsulating DOX for the treatment of triple-negative breast cancer. The PAMAM dendrimers were conjugated with EBP-1 and the cell-penetrating peptid. The formulation showed the antiproliferative effect against breast cancer MDA-MB-231 cells when compared with free drug given individually. In vivo results showed accumulation of drug in tumor, and their inhibition due to conjugation of h EBP-1 and TAT peptides is showing the potential of ligand toward EGFR for targeted

drug delivery [78]. Uram et al. developed PAMAM third-generational dendrimer and biotinylated them for delivery of celecoxib (COX-2 inhibitor) and/or Fmoc-L-Leucine (proliferator-activated receptor γ agonist). The results were investigated on multiple cancer cell line and normal cells. The outcomes of the investigation showed significant cytotoxicity of dendrimer complex with both drugs compared to drug given individually or conjugate of single drug. The results revealed that biotinylated PAMAM may be a good candidate for local therapy of glioblastoma [79].

6 Conclusion

These days, nanotechnology-based drug delivery systems are extensively being explored. Various nanocarriers (nanoparticles, micelles, carbon nanotubes, nanosponges, liposomes, etc.) have been developed for drug delivery. But there are some shortcomings in the use of each nanocarriers which have observed. Dendrimers out of them are potential carrier with distinguished properties. Although dendrimers have known for its toxicities due to complex structure and high chemical functionality, this problem can be easily overcome by modifying dendrimer by PEGylation, conjugation of polymer biomolecules, ligand anchoring or by altering the surface functional groups. They provide a podium for complexation or encapsulation of drugs or genes and release them through numerous mechanisms. Poor solubility of drug, permeability, biocompatibility, bioavailability, and toxicity can be overcome by using dendrimers. For various applications in nasal, cardiovascular, oral, transdermal, ophthalmic, and cancer therapy, dendrimers have shown their distinguished potential here we discussed in this chapter. Even though dendrimer necessitates attention to design them in a way, they can be considered for acceptable successful biological responses.

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Nanofibers for Filtration Applications

El-Refaie Kenawy and Md Saquib Hasnain

Abstract Due to their interconnected nanoscale pore structures, highly specific surface areas, fine diameters, and porous structure as well as their ability to incorporate active chemistry on nanoscale surface, electrospun fibers are becoming a promising versatile platform for filtration. In the current chapter, we will focus on nanofibers by electrospinning method. Special attention will be focused on antimicrobial nano-fibrous membranes as antimicrobial filters, fibers for oil spill cleanup, fibers for nanoparticles removal from aqueous solution. Also, examples for antimicrobial nano-fibrous membranes developed from electrospun polymers and applications will be discussed.

Keywords Nanoscale · Nanofibers · Electrospun · Nanoparticles

1 Introduction

Electrospinning technology is a simple but effective solution-based method used to prepare nanofiber membranes, which could be applicable to separation operations [1, 2]. A schematic description of electrospinning is shown in Fig. 1 [3]. The fibers are derived by charging a liquid typically to 5–30 kV vs. a ground a short distance away, which leads to charge injection into the liquid from the electrode.

Basically, the electrospinning apparatus is made of three major parts: a high-voltage power supply, a capillary tube containing polymer solution/melt connected to a needle, and a metallic grounded collector.

Electrospinning is a relatively simple method to produce submicron fibers from solutions of different polymers and polymer blends. In general, fibers with

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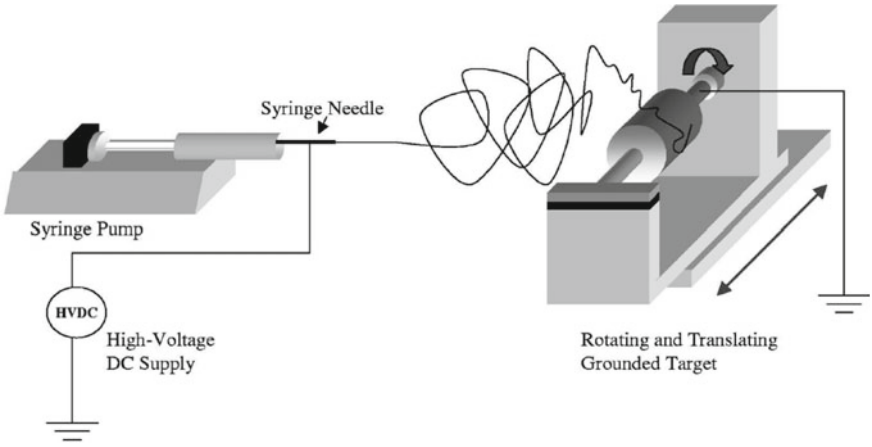


Fig. 1 Diagram of electrospinning system [3] (Reprinted with permission from Kenawy et al. [3]. Copyright © 2002 WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim)

diameter less than 1000 nm are called nanofibers in electrospinning. Electrospinning nanofibers are of interest in many applications [2]. These include filter media, composite materials, biomedical applications (tissue engineering, scaffolds, bandages, and drug release systems), protective clothing, optoelectronic devices, photonic crystals, and flexible photocells.

Filtration is necessary in many engineering fields. Fibrous materials used for filter media provide advantages of high filtration efficiency and low air resistance. Filtration fineness is one of the most important concerns for the filter media performance. Since the channels and structural elements of a filter must be matched to the scale (as small as 0.3 m) of the particles or droplets that are to be captured in the filter, one direct way of developing high efficient and effective filter media is by using nanometer-sized fibers in the filter structure [4].

In general, because of the very high surface area to volume ratio resulting high surface cohesion, tiny particle can easily trapped in electrospun nanofibrous structured filters and hence, the filtration efficiency can be improved. The filters of nanofibrous membranes with antimicrobial functionality have attracted growing attentions due to the concerns about qualities of purified water and/or filtered air as well as the processing costs. Water and air filters (especially those operating in the dark and damp conditions) are constantly subject to attacks from microorganisms. For example, bacteria can be readily captured by the filters grown rapidly and cause the formation of biofilms. Consequently, the buildups of microorganisms on the filter surfaces deteriorate the qualities of purified water and/or filtered air; additionally, they also have the unfavorable effects on the flow of water and/or air. Moreover, the contaminated filters with biofilms are difficult to clean; usually, high pressure is required during the operation. This in turn increases the costs. Electrospun PAN nano-fibrous membranes with antimicrobial functionality was reported. Methods are generally used to incorporate antimicrobial agents (such as N-halamine and silver

ions/nanoparticles) directly into spin dopes, and thus, the molecules/particles of antimicrobial agents are distributed throughout the nanofibers. This direct-spinning approach, however, often leads to low antimicrobial efficacy primarily because the high content of antimicrobial agents can seriously affect the process of electrospinning and/or deteriorate the properties of the resulting nanofibers. It was hypothesized that a potential solution to these problems was to introduce antimicrobial functionality onto nanofiber surfaces after the nanofibers were produced. Another way is to start with high functionality polymers or in another way to increase the weight efficiency of polymer before electrospinning.

2 Nanofibers as Antimicrobial Filters

2.1 Antimicrobial Polymers

Contamination by microorganisms is of great concern in a variety of areas, such as medical devices, healthcare products, water purification systems, hospitals, dental office equipment, food packaging, food storage, household sanitation [5]. Bacterial contaminations of biomedical devices, antimicrobial agents are those materials capable of killing pathogenic microorganisms [6].

Antimicrobial agents of low molecular weight are used for the sterilization of water, as antimicrobial drugs, as food preservatives, and for soil sterilization [7]. However, they can have the limitation of residual toxicity even when suitable amounts of the agent are added. The antibacterial treatment of fibers started with the antibacterial treatment of fabric for protecting mummies in Egypt 4000 years ago. Recently, new antibacterial reagents and a mechanism for antibacterial activity on bacteria have been reported [8–10].

The use of antimicrobial polymers offers promise for enhancing the efficacy of some existing antimicrobial agents and minimizing the environmental problems accompanying conventional antimicrobial agents by reducing the residual toxicity of the agents, increasing their efficiency and selectivity, and prolonging the lifetime of the antimicrobial agents [5]. Self-sterilizing antimicrobial polymers are environmentally friendly in that potentially toxic chemicals are not incorporated and hence cannot leach out. Furthermore, they are easily incorporated into fibers, extruded to fibers or electrospun into nanofibers and prevent adhesion of microorganisms to their surface. Antimicrobial polymers are synthesized by covalent binding of biocidal functional groups in a post-polymerization modification, providing antimicrobial or antiseptic properties. Modification is either to the bulk polymer or selectively to the surface via available reactive moieties. Another form of synthesis is the chemical modification of a biocidal molecule into a polymerizable compound that can subsequently by polymerized or co-polymerized with another monomer. Both these approaches have been valuable in establishing feasibility for the concept of non-leaching antimicrobial polymeric materials.

The incorporation of antimicrobial agents such as silver with nanofiber is known to exhibit antimicrobial properties to the filters. Yu et al. reported antimicrobial (*Escherichia coli* and *P. aeruginosa*) activity for poly(vinyl chloride) PVC, cellulose acetate (CA), and polyacrylonitrile (PAN) nanofiber membranes containing Ag nanoparticles [11].

Electrospun polyacrylonitrile nanofiber membranes (PAN ENMs) upon treatment with hydroxylamine led to the formation of $–C(NH_2)N–OH$ groups, which were subjected for the coordination of Ag^+ ions followed by Ag nanoparticles formation by Zhang et al. [12].

Zhang et al. reported processing of polyacrylonitrile (PAN) nano-fibrous membranes with fiber diameters of ~450 nm by the technique of electrospinning; amidoxime nano-fibrous membranes were then prepared through treatment of PAN nano-fibrous membranes in hydroxylamine (NH_2OH) aqueous solution. The –C = N groups on the surface of PAN nanofibers reacted with NH_2OH molecules and led to the formation of $–C(NH_2)$ N–OH groups, which were used for coordination of Ag^+ ions. Subsequently, the coordinated Ag^+ ions were converted into silver nanoparticles (AgNP) with sizes being tens of nanometers. Morphologies, structures, and antimicrobial efficacies (against *Staphylococcus aureus* and *E. coli*) of the membranes of electrospun PAN (ESPAN) nanofibers, ESPAN surface functionalized with amidoxime groups (ASFPAN), ASFPAN coordinated with silver ions (ASFPAN–Ag^+), and ASFPAN attached with silver nanoparticles (ASFPAN–AgNP) were investigated. The study revealed that, with treatment of ESPAN membranes in 1 M NH_2OH aqueous solution for 5 min, the resulting ASFPAN membranes became antimicrobial without distinguishable morphological variations; further treatment of ASFPAN membranes in 0.1 M $AgNO_3$ aqueous solution for 1 h and the subsequent treatment in 0.01 M KBr aqueous solution for 2 h followed by photo-decomposition made the respective membranes of ASFPAN–Ag^+ and ASFPAN–Ag NP highly antimicrobial, which were capable of killing the tested microorganisms in 30 min. The water permeability test indicated that these membranes possessed adequate transport properties for filtration applications. This study demonstrated a convenient and cost-effective approach to develop antimicrobial nanofibers.

2.2 *Antimicrobial Nano-Fibrous Membranes Developed from Electrospun Polyacrylonitrile Nanofibers*

Son et al. [8] prepared Chitosan/poly(vinyl alcohol) (PVA) nanofibers with antibacterial activity by the electrospinning of a chitosan/PVA solution with a small amount of silver nitrate ($AgNO_3$) and titanium dioxide (TiO_2) (Fig. 2). Nanofibers with diameters of 270–360 nm were obtained. The yield of low-viscosity chitosan (LCS)/PVA nanofibers was higher than that of high-viscosity chitosan (HCS)/PVA. The nanofibers developed in this study exhibited antibacterial activities of 99 and 98% against *Staphylococcus aureus* and *E. coli*, respectively [13–16].

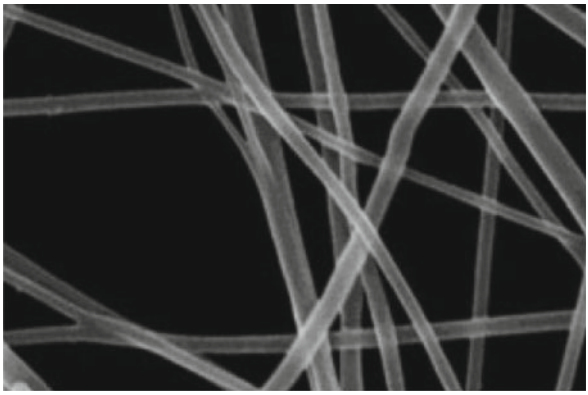


Fig. 2 SEM photographs of the AgNO3/HCS/PVA [8] (Reprinted with permission from Son et al. [8]. Copyright 2008 © Wiley Periodicals, Inc.)

3 Electrospun Nanofibers Membrane for Air Filtration

Nanofibers can improve the performance of filter media's ability to remove particulates from air streams. This improvement can be seen in air intake streams of vehicles, computer disk drive ventilation, and high-efficiency filtration. In the case of cabin air filters, removing the particulate matter improves the comfort and health of the passengers. Nanofibers offer enhanced filtration performance in both mobile and stationary engines and industrial filtration applications [17].

Concerning the engines, gas turbines, and combustion furnaces, it is important to remove particulate material from the air stream supply that can cause substantial damage to the internal components. In other instances, production gases or off-gases from combustion engines and industrial processes may contain damaging particulate material. The removal of this particulate is desirable to protect downstream equipment and minimize pollution discharge to the environment.

This new, durable nanofiber coating can also be used in self-cleaning or pulse-cleaning filter applications. The dust cake formed on the upstream side of the filter media can be removed by back pulsing air through the media to rejuvenate it. As great force is exerted on the surface during the back pulse; nanofiber with poor adhesion to substrates or comprised of delicate nanofibers can delaminate as the shock wave moves from the interior of a filter through the substrate to the nano-fibrous layer. The new nanofiber technology provides excellent adhesion to the substrate as well as durable structural stability of the nanofibers themselves enabling longer life and improved efficiencies in pulse-cleaning applications because of the greater particle collection and overall energy expended during the cleaning process.

A much finer surface structure with decreased pore size is formed with the addition of a nanofiber coating, in comparison to a typical cellulose surface. An electrospun nanofiber coating is also very fine, but so fine that the fibers offer little strength and have little depth. The depth of the nanofiber coating illustrates that a nanofiber coating serves not only as a surface filter, but also has a depth filtration aspect that an electrospun coating lacks. The plurality of the nanofiber layers also provides superior durability.

Many air filtration technologies have been developed. Air filtration using electrospun fibers that intercept fine particles/volatile organic gases/bacterium is a relatively new, but highly promising, technique. Due to their interconnected nanoscale pore structures, highly specific surface areas, fine diameters, and porous structure as well as their ability to incorporate active chemistry on nanoscale surface, electrospun fibers are becoming a promising versatile platform for air filtration.

Polymeric nanofibers can be produced by electrospinning. Electrospining is a simple and cost-effective process to prepare polymeric nanofibers. It uses an electrical field to draw a polymer solution from the tip of a capillary to a collector, during which a high voltage is applied to polymer solution. This causes a polymer jet to be drawn toward a grounded collector. By choosing a suitable polymer and solvent system, nanofibers with diameters ranging from tens of nanometers to a few microns can be obtained. One apparent advantage of nanofibers is the huge increase in the surface area-to-volume and mass ratio compared to larger fiber dimensions, which enables such nano-fibrous scaffolds to have many biomedical and industrial applications [17].

However, there are critical factors that influence the ability of a polymer to form fibers by electrospinning. Suitable solution viscosity and high enough polymer molecular weight are among the critical parameters for successful electrospinning to occur. To date, a large number of polymers have been successfully electrospun, which found applications in industrial consumer and defense filtrations for more than twenty years. With the increased academic research on the fabrication of various polymer systems into nanofibers, significant progress has been achieved in different fields such as protective textiles, advanced composites high-performance filters, sensors, photovoltaic cells, wound dressing and as scaffolds in tissue engineering. However, very limited studies have been published on fabrication of nanofibers having inherent or permanent antimicrobial properties, yet the research in this area is growing rapidly, where the development of new antimicrobial materials is of continuous interest.

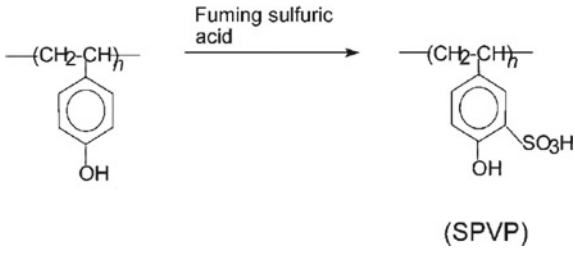
It is expected that antimicrobial ultrafine fibers will exhibit much stronger antimicrobial activity than conventional microfibers because of their high surface area-to-volume ratio. Yang et al., first prepared ultrafine polyacrylonitrile (PAN) fibers containing silver nanoparticles by electrospinning [9]. The average diameters of the PAN fibers and silver nanoparticles were 400 and 100 nm, respectively. It was recently reported that silver nanoparticles also had very strong antimicrobial activity [8, 10, 11]. In this study, antimicrobial ultrafine cellulose acetate (CA) fibers with silver nanoparticles were prepared by electrospinning of a CA solution with small amounts of silver nitrate ($AgNO_3$) followed by slow and fast photoreduction. The study showed a feasible method for the preparation of antimicrobial ultrafine fibers with silver nanoparticles was developed by direct electrospinning of a cellulose acetate (CA) solution with small amounts of silver nitrate followed by photoreduction. Silver nanoparticles in ultrafine CA fibers were stabilized by interactions with carbonyl oxygen atoms in CA. Ultrafine CA fibers with silver nanoparticles showed very strong antimicrobial activity. However, there are critical factors that influence the ability of a polymer to form fibers electrospinning. Suitable solution viscosity and high enough polymer molecular weight are among the critical parameters for successful electrospinning to occur. To date, a large number of polymers have

been successfully electrospun, which found applications in industrial, consumer and defense filtrations for more than twenty years. With the increased academic research on the fabrication of various polymer systems into nanofibers, significant progress has been achieved in different fields such as protective textiles, advanced composites, high performance filters, sensors, photovoltaic cells, wound dressing, and as scaffolds in tissue engineering. However, very limited studies have been published.

Kenawy et al. [3], prepared sulfonated derivatives of (Mw 20 k and 100 k) polyvinyl phenol (Scheme 1),

The polymeric materials were electrospun into microfiber mats and were characterized by SEM (Fig. 3).

The prepared derivatives were evaluated for antimicrobial activity in both powder and fiber forms against a range of organisms including Gram negative (*E. coli* and *Salmonella choleraesius*), as well as Gram positive (*B. subtilis* and *S. aureus*) species.



Scheme 1 Sulfonation of poly(vinyl phenol [3] (Reprinted with permission from Kenawy et al. [3]. Copyright © 2002 WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim)

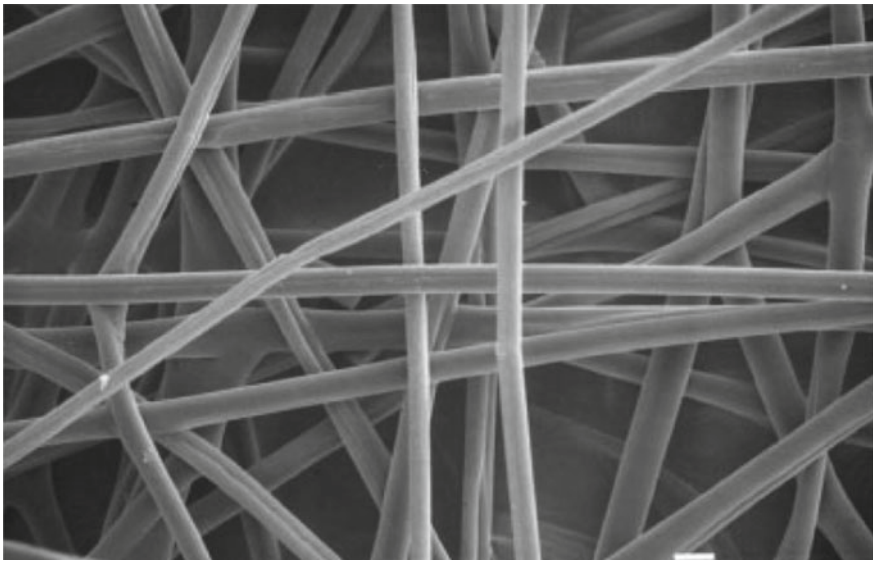


Fig. 3 SEM micrograph of electrospun PVPh 100 k [3] (Reprinted with permission from Kenawy et al. [3]. Copyright © 2002 WILEY–VCH Verlag GmbH & Co. KGaA, Weinheim)

It was also tested for fungicidal activity against *Aspergillus niger*, *T. rubrum* and *Candida albicans.*

All electrospun fibers showed good antimicrobial activity. In general, the SPVP had the strongest antibacterial activity. The bacterial growth inhibition effect became stronger in the order *B. subtilis* < *S. choleraesuis* < *S. aureus* < *E. coli.* However, it did not have an effect on the fungi. On the other hand, the lithium salt-based fibers were able to inhibit fungal growth in the order *A. niger* < *C. albicans* and had an inhibitory effect on bacteria in the order *B. subtilis* < *S. choleraesuis*. It was also demonstrated that the electrospun PVP fibers were active against *B. subtilis*, whereas no effect was observed for the same polymer in powder form [3].

4 Examples for Antimicrobial Nano-Fibrous Membranes Developed from Electrospunpolymers and Applications [18–20]

Silver ions and silver compounds have been widely used in various biomedical fields, such as wound dressing materials, body wall repairs, augmentation devices, tissue scaffolds, and antimicrobial filters [1–8]. Positively charged silver ions attracted to electronegative bacterial cells are bonded to their membrane or bacterial DNA with sulfhydryl groups, resulting in the prevention of proliferation of bacteria and blockage of biofilm production. Microorganisms with resistance to the antimicrobial activity of silver are exceedingly rare.

Antibacterial material was developed using surface modification of electrospun polyurethane (PU) fibrous membranes, employing a process which involved plasma pretreatment, UV-induced graft copolymerization of 4-vinylpyridine (4VP), and quaternization of the grafted pyridine groups with hexylbromide.

The success of modification with poly(4-vinyl-*N*-hexyl pyridinium bromide) groups on these was ascertained by X-ray photoelectron spectroscopy (XPS). The morphologies and mechanical properties were investigated by scanning electron microscopy (SEM) and tensile test, respectively [18–20].

Quaternized chitosan derivative (QCh) N-butyl-N,N-dimethyl chitosan iodide was prepared according to known procedure [18] (Fig. 4).

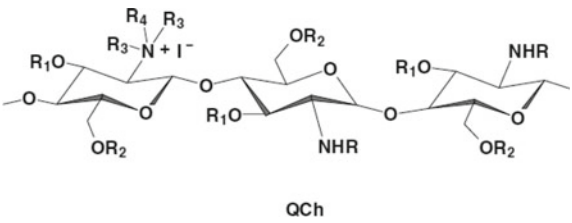


Fig. 4 Chitosan nanofibers with quaternary salts [18] (Reprinted with permission from Ignatova et al. [18]. Copyright © 2007 Elsevier Ltd.)

4.1 Nanoporous Polystyrene Fibers for Oil Spill Cleanup

Oil is one of the most important energy sources for human beings living in the developed world. However, oil spill accidents often take place during the oil utilization process, resulting in energy loss as well as threats to the environment [21].

Oil accidents, such as the Exxon Valdez oil spill in 1989 and the Gulf of Mexico oil spill in 2010, caused serious environmental damage, which highlighted the importance of oil spill prevention and oil spill cleanup. More recently, an oil spill accident by an American company, ConocoPhillips, occurred in the Bohai Bay in China and greatly affected the local aquaculture and people's homes. Therefore, it is imperative that the cleanup of oil and petroleum products that are spilled at sea be addressed.

Nonwoven polypropylene (PP) fibrous mats, as synthetic fibers, have been widely used in oil spill cleanup because of their oleophilic–hydrophobic properties, good oil/water selectivity, high buoyancy, and scalable fabrication. However, they suffer from a low oil sorption capacity, approximately 15–30 g/g [22–24].

These are made of solid fiber having large diameters. It is believed that the oil sorption capacity will be increased if the fibrous sorbent has the capability of driving the oil not only into the voids between fibers but also into its material matrix, which is a porous structure [25].

Oil pollution is one of the environmental concerns that are currently becoming a major issue in the petroleum industry [25].

4.2 Nano-Fibrous Membrane for Nanoparticles Removal from Aqueous Solution

Air pollution becomes more and more serious especially haze pollution [1, 2]. Haze is caused by fine particles that scatter and absorb light before it reaches the observer [4]. In particular, airborne fine particulate matters especially PM 2.5 (defined as particulate matters with an aerodynamic diameter 2.5 μm) are one of the most serious sources of fine particles. PM 2.5 and its extracts can induce many human diseases [5–8]. So, there is a great need for the development of filtration technologies to prevent harmful nanoparticles affecting human health. One of the most valid methods of removing particles from a gas stream is via fibrous filters [26].

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Marine Polysaccharides Systems for Drug Delivery Applications

Pandurang Appana Dalavi, Jayachandran Venkatesan, V. Rani, and Sukumaran Anil

Abstract Drug delivery system (DDS) has the ability to enhance the efficiency of the conventional drugs which are commonly suffers in lower bioavailability in human body. Recently, marine polysaccharides such as alginate and chitosan are gaining much attention in DDS due to their unique properties such as biocompatible, biodegradable, non-toxic, pH sensitivite, good thermal stability, and pore-forming ability. These polysaccharides can be tailored in different forms like microspheres, beads, films, hydrogels, tablets, and micelles to enhance the drug delivery in specific places. Chemical and physical modifications of these polysaccharides can provide sustainable drug-releasing phenomena with higher therapeutic applications. In the current chapter, we have discussed alginate and chitosan and their modified derivatives in the utilization of ocular and oral drug delivery applications. Hence, these polysaccharides can be utilized in several pharmaceutical industries for the development of tablets and medicines.

Keywords Alginate · Chitosan · Drug delivery · Polysaccharides

1 Introduction

Development of drug delivery system (DDS) is a technique in which the formulation can be developed through the combination of pharmaceutically active ingredients with lipids, polymers, and ceramics for a better enhancement of drugs. It has been found that a controlled releasing profile, better absorption with proper distribution

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of DDS can enhance the efficacy of the drug. The material can be used for the DDS if it possesses some properties like biocompatibility, better blood circulation, and also selectively target the disease sites. The advantages of while utilizing the DDS, minimum amount of drugs will be utilized with the lesser side effects and sustainable drug releases. Some drugs having poor soluble which can dissolve and form precipitation in aqueous water while in DDS can be developed which having hydrophobic and hydrophilic nature can help to reduce extravasation of the drug [1]. Several polymeric substances have been extensively studied for DDS from synthetic polymers and natural-based polymeric systems. Both polymeric systems have advantages and disadvantages. The utilization of natural-based polymeric systems is having advantages in terms of abundant, inexpensive, biocompatible, and biodegradable properties. In addition to this, natural biopolymers are bio-adhesive with minimal toxicity and having lesser side effects. Natural polymers can be obtained from various sources including microorganisms, plants, and animals. Some of the well-known natural polymers are cellulose, alginate, chitosan, carrageenan, fucoidan, pectin, agar, etc. Natural biopolymers from marine resources, such as alginate, chitosan, fucoidan, are being extensively studied in DDS. Natural polymer substances can be blended with synthetic polymers to get the required property and also increases the synergistic effect in DDS. However, natural polymers have some disadvantages for the usage in the drug delivery system like a lack of thermal stability, so that during fabrications sometimes they need to use plasticizers. Besides natural polymers having lesser shelf life than synthetic polymers [2, 3]. Recently, marine-based polysaccharides (polymers) have gained much attention in DDS due to its unique properties. Seeli et al. developed pH-sensitive beads from the sodium alginate and guar gum succinate [4]. Chitosan is an important class of marine polysaccharides substances with several applications [5–7]. Chitosan is pH sensitive and can be utilized in targeted DDS. Gnanadhas et al. have reported the use of nanocapsules containing chitosan and dextran sulfate. This system has potential applications in the treatment of *salmonella* infections [8]. Figure 1 shows the different kinds of systems utilized in DDS.

2 Role of Alginate in Drug Delivery System (DDS)

Alginate is a polysaccharide which contains a complex chemical composition of 1 → 4 linked β-D-mannuronic (M) and α-L-guluronic acid (G) (Fig. 2). Sodium alginate is the mostly used alginate form. Alginate has an enormous source of nature, and it can be extracted from the marine brown algae. Alginate can be extracted from bacterial species such as *Pseudomonas* species [9]. Alginate properties can be varied which depends on the *M* and *G* ratio.

Alginate is having the capacity to form homogeneous gel due to the electrostatic interaction between the cationic solutions; therefore, alginate can be molded in various forms including microsphere beads, fibers, sponges, films, hydrogels, membrane, and matrix. Moreover, biochemical, physical, and gel strength properties are dependent on the chemical structure of the alginate. Also, molecular variability

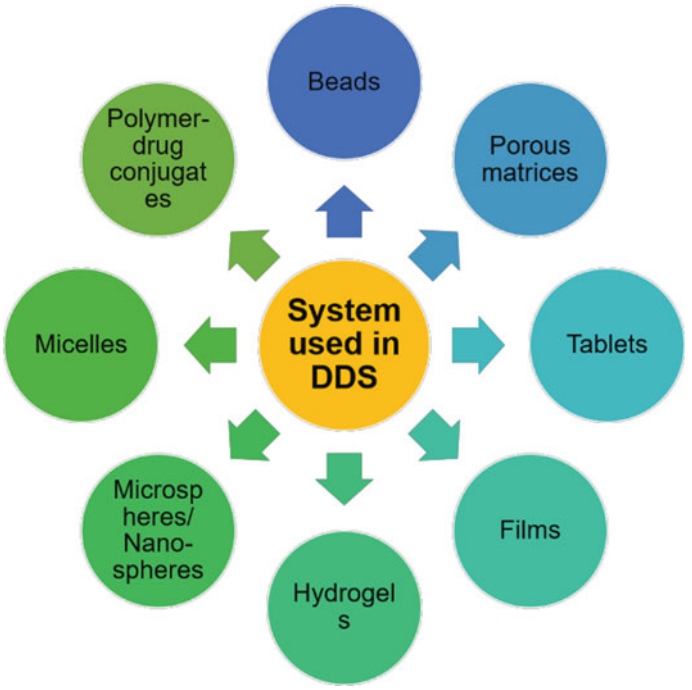

Fig. 1 Different types of systems used in DDS

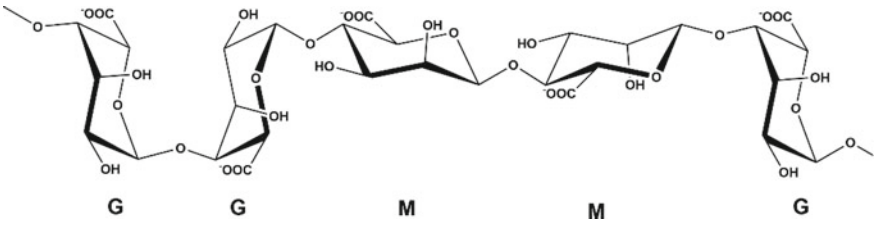

Fig. 2 Chemical structure of alginate, here G = α-L-guluronic acid and M = β-D-mannuronic acid

depends on the source from which alginate has been extracted. Alginate is having the ability to form a stable bond with divalent or multivalent cations. The gel-forming capacity of the alginate is dependent on the ion-binding capacity of the cations used. Besides, to get a homogeneous solution there must be a controlled addition of cations containing solutions. For the fabrications of various forms of the alginate calcium-containing cations can be the first choice due to its properties like cost-effective and clinically safe.

One of the important properties of alginate polymer is non-toxic. Besides alginate is biocompatible, non-immunogenic, and biodegradable. Alginate is having hydroxyl and carboxylic groups in their chemical structures, and these functional groups can be

modified for better physical, chemical and biological properties. Since the decades, alginate has been used as food, in beverage industries, pharmaceutical, biomedical products, and dentistry. Alginate is playing an important role in wound dressing, and tissue engineering applications. Alginate in DDS can be a potential material for the controlled release of the drug [10, 11].

2.1 Alginate-Based Hydrogel

Alginate can easily form a hydrogel with divalent cation. Alginate-based hydrogels are having good mechanical strength and porous structure. Mechanical strength and porosity depends on the concentrations of β-D-mannuronic (M) and α-L-guluronic acid (G), and the type of cross-linking agents is used for the synthesis. Incorporation of enzymes, protein, and active ingredients is possible in alginate-based hydrogels; due to these facts, these materials are promising materials in biomedical applications including drug delivery and bioprocessing [11].

Alginate biopolymer is widely used for the development of microgels. Moreover, microgels are having a cross-linking system with a higher content of water. Microgels are useful in various biomedical fields including bone tissue engineering and drug delivery systems due to their excellent biocompatibility. Generally, researchers use the ionic cross-linking system to develop microgels but it has some disadvantages like uncertainty in degradation rate and difficulty in controlling the non-spherical shape of microgels with monodispersive nature. However, due to this unpredictable property of microgels, it has some complications when we use in biomedical applications. Wang et al. have developed the easiest in situ microfluidic synthetic route to synthesize non-spherical, monodispersive oxidized *methacrylated* alginate (OMA) microgels with photocross-linking system by using UV light to solve the problems like biodegradation. Also while synthesis, they use (VA-086) photoinitiator. Further, these microgels are showing better curability and cytocompatibility. Finally, they concluded that these material potential applications in chondrocyte encapsulation and DDS [12].

2.2 Alginate Tablets and Matrixes

Alginate-containing tablets can be synthesized by using the combination of sodium alginate and other co-polymers. Drug release from the tablets is independent of the ratio of the concentration of co-polymers. Shilpa et al. have explained the role of alginate matrix for the controlled DDS. Microspheres beads, films, tablets, and membranes can be incorporated into the alginate matrix [9]. Polymeric matrices like a hydrophilic matrix can swell in aqueous medium and form gel type of layers. Drug-releasing phenomena of this gel layers can happen in two ways, the water-soluble drug releases through gel layers or erosion of gel layers. Alginate-based

matrix tablets for the DDS can be developed by various methods including direct compression, compression coating, spray coating [10, 11], wet granulation method [13], and ion-exchange method [14].

Liew et al. have explained the role of sodium alginate in a matrix tablet for DDS. Water-soluble drugs can be released easily from the sodium alginate. Also when the particle size of the alginate reduced, drug releasing capacity were also lowered significantly. It has been observed that highly viscous alginate can release a higher quantity of the drug. Further, the concentration of the sodium alginate will also play an important role in the drug-releasing capacity of the drug, and also, alginate is a pH sensitive so that while targeting specific organ tissue [10, 11]. Togcu-Demiroz et al. have developed sodium alginate-containing site-specific matrix tablets for DDS. They impregnated Mesalazine drug in alginate, and they checked the efficiency of Mesalazine-alginate matrix tablet system in acidic media. In vitro study, they observed that the Mesalazine-alginate matrix tablet system can release drugs faster than the conventional system. Furthermore, they found that this system having the ability to release the drug in both smaller and larger intestines [15]. Ghosal et al. have developed matrices for the site-specific DDS by using the ion-exchange technique. They used sodium alginate, hydroxypropyl methylcellulose (HPMC), and diclofenac potassium (DP) for the synthesis of matrices. In vitro studies, they found that these systems can provide a sustainable drug-releasing profile up to 10 h [14]. Lesser half-life time is the biggest problem when utilizing the antihyperglycemic repaglinide (RG) drug. Due to a shorter lifetime, therapeutic applications may be less. He et al. have developed hydrophilic matrix tablets containing HPMC, sodium alginate, and ethyl cellulose by using direct compression method to resolve these types of problems. In vivo trials on dog reveal that these systems can provide prolong and sustainable drug-releasing profile. Therefore, this system has potential applications to use in the treatment of type 2 diabetes patients [16]. Kanjanabat et al. have used a direct compression method to develop a matrix tablet of nicotine (NCT)–magnesium aluminum silicate (MAS) complex loaded with sodium alginate (SA) for the use of buccal drug delivery. MAS will provide thermal stability to the NCT-MAS complex structure. Furthermore, due to the chemical interaction between MAS and SA, sustainable release of NCT was achieved. Also, the mucoadhesive properties of the matrix tablets can be enhanced by SA [17]. Zheng has developed matrix to achieve 24 h drug-releasing profile which contains sodium alginate with xanthan gum and zinc acetate composition. They have used ranitidine HCL drugs as a standard to check the drug-releasing efficiency of this system. They have performed the in vitro study in simulated intestinal fluid (SIF), and this system can provide sustainable drug release of drugs up to 24 h while composition without zinc acetate giving only 12 h of drug-releasing profile [18]. Mandal et al. have developed matrix tablets by using wet granulation synthetic route. They used sodium alginate (SA) with calcium gluconate (CG) as a precursor to prepare matrix tablets. Furthermore, they used diltiazem hydrochloride (DTZ) as a standard drug to check the efficiency of this system [13].

2.3 Alginate-Based Floating Drug Delivery System

Oral drug delivery has some disadvantages including lower content of drug released and stomach or small intestine may absorb preponderance amount of drug. To overcome these limitations, researchers are developing floating drug delivery systems (FDDS). FDDS must and should have a lower density than gastric fluid present in the stomach. Microporous polymers like alginate can be a better option because they are having low density with porous structure. A material is produced from the alginate which can float in the stomach content, and this type of drug-releasing process is called as the floating system. Gaviscon tablets having a content of calcium carbonate are the best example of a floating system used for treatment. Choi et al. have reported floating alginate beads for FDDS by using gas-forming agents like calcium carbonate and sodium bicarbonate compounds. They used a simple dropping method for the development of beads. Sodium alginate containing gas-forming agents were dropped in a 1% $CaCl_2$ and 10% acetic acid-containing solution. The main purpose of using acetic acid is that acetic acid can react with calcium carbonate or sodium bicarbonate, and it produces carbon dioxide gas. Furthermore, the evaporation of these gas from the materials will create porosity. They found that the floating capacity of the material is dependent on the concentration of gas-forming agents used. Floating capacity can increase with the increasing concentration of gas-forming agents. Riboflavin drug were used to check the drug-releasing capacity of the developed beads and they found that beads synthesized from sodium bicarbonate as a gas-forming agent showing superior results than beads synthesized from calcium carbonate as a gas-forming agent [10, 19]. Zhang et al. have developed alginate containing floating beads to target a gastric mucosa. While synthesis, they incorporate berberine and octodecanol. Octodecanol has low density; therefore, it can enhance the floating capacity of the beads. In experimental in vitro studies, they observed that the drug-releasing profile and floating time of these beads were high in gastric media of rats [20]. Gupta et al. have reported alginate containing floating beads for the delivery of 5-Fluorouracil (5-FU). They used calcium carbonate to disperse 5-FU in alginate and hydroxypropyl methylcellulose. For the development of beads, they used calcium chloride as a cross-linking agent. During synthesis, carbon dioxide formed due to inotropic gelation of calcium and which one creates porosity in the beads and increases the floating capacity of the system. They checked the efficiency of these systems on stomach tumors of female mice, and they found that alginate containing floating beads showing better results than conventional dosage systems [21]. Fursule et al. did research on oil implicated floating gel beads. For synthesis, they used alginate as a gel-forming agent. They developed floating gel beads of amoxicillin trihydrate by using the emulsifying gelation technique [22]. Gadad et al. have reported floating beads derived from sodium alginate to deliver a cefpodoxime proxetil antibiotic drug. Floating beads of sodium alginate were developed by using precipitation method. Furthermore, they used calcium carbonate compound to generate gas into the system and HPMC to achieve swelling properties. From in vitro studies, it is clear that these beads having sustainable drug-releasing profile [23]. Peter Dios et al.

have checked potential applications of metronidazole containing a floating system to eliminate the *Helicobacter pyroli*. To develop beads, they used HPMC, sodium bicarbonate, and sodium alginate precursors. In vitro studies, they found that this system can withstand 8 h in a gastric environment [24]. Jadupati Malakar et al. have used the emulsion–gelation technique to fabricate liquid paraffin implicated with alginate containing a floating system to check its potential applications in gastric fluid. In this system, they have used cloxcillin antibiotic drug and they found that this system can provide a sustainable drug-releasing profile upto 8 h [25]. Baljit singh et al. have reported the use of barium ions as a cross-linking agent to develop an alginate-based floating system. They used alginate with sterculia gum to fabricate these beads. Pantoprozole drug was used to check the potential applications of these beads as anti-ulcer treatment [26].

3 Role of Chitosan in a Drug Delivery System

Chitosan is a cationic polymeric polysaccharide that having a β (1 → 4) linkage of 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-acetamido-2-deoxy-D-glucose (*N*-acetyl-D-glucosamine) chemical complex structural repeating units (Fig. 3). Chitosan mostly derived from the deacetylation of chitin, which having abundant sources in crustacean's shells. Chitosan is the second most abundantly occurring natural polymeric polysaccharide after cellulose [27]. Chitosan is having the chelating property, and it forms precipitation with multivalent anion-containing solutions and in alkaline solution. Due to the high swelling properties of chitosan, the drugs may release rapidly from the chitosan matrix. Therefore, chemical modification is possible in chitosan and can be tailored physicochemical properties of the chitosan. Moreover, chitosan properties depend on the viscosity and molecular weight of the materials used. Also, chitosan's properties depend on the degree of deacetylation. It has been observed that solubility and hydrophobicity can affect by the degree of deacetylation. Chitosan is having excellent biocompatibility, biodegradability, and non-toxic. Another important property of chitosan polymer is bio-adhesion with hard and soft tissues; due to these properties, chitosan is useful in dentistry and ophthalmology.

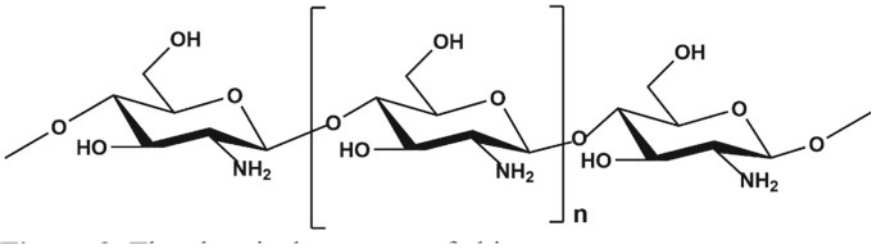

Fig. 3 Chemical structure of chitosan

Chitosan is having fungistatic properties. Also, chitosan is having antibacterial property; due to this, chitosan is mostly used in the wound-healing treatment. Chitosan is having biocompatibility with human tissues, and it can support cell adhesion and cell proliferation due to these properties [27]. Chitosan is useful in DDS for several reasons including biocompatibility with human cells, non-toxicity, and porous structure. Chitosan can enhance pharmacokinetic properties of the drug, and in DDS first aim is to achieve a controlled release of drug and then comes to target a specific disease tissue called "targeted drug delivery system." Chitosan is a promising material for the target-specific diseased tissue [27].

In DDS, chitosan polymer has a limitation in utilizing in DDS such as low solubility, and it is soluble in acidic aqueous media like formic acid and citric acid. To overcome this type of problems, researchers are trying several synthetic and chemical modifications on chitosan to tailor the physicochemical properties [27].

Chitosan-based microparticles and nanoparticles are having potential applications in DDS. Nowadays, researchers are trying to develop chitosan-based nanoparticles as drug carriers for different therapeutic agents in DDS. The mucoadhesive nature of chitosan can help in the absorption of the drug; further, it can enhance the bioavailability of the drug. Also, chitosan nanoparticles possess a high surface to volume ratio, and this one can increase the drug efficacy and reduces the side effects. Chitosan-based nanoparticles are having good stability, lower toxicity, permeable and can be prepared by easier synthetic routes. While developing a chitosan-based microparticle or nanoparticles, degree of acetylation and the molecular weight of the material can firmly alter the properties of the chitosan [27, 28].

3.1 Chitosan-Based Material in Oral DDS

The oral drug delivery is the oldest and most widely used DDS. One of the major complications in oral drug delivery is that it requires multiple dosages; therefore, there is a requirement to use a drug that has higher solubility and better bioavailability. Polysaccharide-based polymers like starch, cellulose, and chitosan are useful in oral drug delivery as a drug carrier or as a protecting agent [29]. Chitosan derivatives like a trimethyl chitosan chloride (TMC) and mono-carboxymethylated chitosan (MCC) can increase the solubility of the material and absorption in drug in oral drug delivery [30]. Chitosan is a pH-sensitive material; therefore, chitosan-based DDS is useful to deliver a drug to the gastrointestinal tract [30]. Saboktakin et al. have reported the usage of a chitosan-based pH-responsive gel system for the delivery of insulin [31]. Makhlof et al. have developed chitosan-based pH-responsive nanoparticles for insulin delivery [32]. Fabrication of chitosan with hydrophilic polymers has promising applications in oral DDS like a gingival delivery via the oral route [33]. Chandy et al. have used the chitosan matrix for oral DDS. In vitro studies, they used ampicillin as a standard drug to check the efficiency of the system [34]. A chitosan-based gel is a promising material to deliver a peptide drug in the oral mucosa [35]. Chitosan with sodium alginate-based adhesive tablets has potential applications

in oral DDS. In vitro studies on diltiazem drugs showing 69% of bioavailability by using these tablets which is higher than conventional drug delivery [36]. Lin and his colleagues have prepared hydrogels by using *N*,*O*-carboxymethyl chitosan and alginate. These systems are pH-sensitive and can be used for protein delivery via the oral route [37]. Gel beads composed of alginate and chitosan and prepared by the double cross-linking process which helps to achieve specific targeted oral drug delivery [38]. Chandy et al. have developed chitosan with polyethylene glycol (PEG) and alginate polyelectrolyte complex containing microcapsules for the use of oral DDS. This system showing a sustainable drug release of hirudin drugs [39]. Nanocapsules composed of chitosan, and PEG has potential application as a drug carrier in oral DDS. There are some reports available on the use of these nanocapsules for peptide delivery [40].

Chtiosan with liposome system has been developed and potentially utilized for delivery different kind of drugs. Liposome compounds in the oral drug delivery system can be used in the encapsulation of drugs or as a drug carrier. From experimental results, it has been proved that encapsulation of liposome on the drug can enhance the bioavailability of the drug by protecting the drug from degradation in gastrointestinal (GI) tract circumstances. One of the major problems of using liposomes in oral DDS is that internal chemicals and enzymes present in the GI tract environment can make liposome unstable. This one leads to the reduced bioavailability of the drug. Therefore to resolve, this problem surface modification on liposome is needed. Therefore, polymers coating on liposome may be one of the choice because it has hydrophilic and hydrophobic groups; therefore, interface with other materials can be easier. Besides polymers can survive for a longer time in the intestine, and polymer coating increases the stability of the liposome. For example, the coating of chitosan on liposome enhances its stability, solubility, mucoadhesive property, cellular uptake, and bioavailability. Some reports are available on the combination of chitosan and thioglycolic acid bio-composition for the coating of the liposome. Another route to enhance stability and survival time of liposome in the GI tract is that by using multi-layered surface modifications. For example, chitosan and anionic charged alginate biocomposite developed via self-assembly route is used for the coating on liposome. Moreover, multivesicular carriers like chitosan containing bioactive β-glycerophosphate as a coating material can enhance the stability of the liposome in the GI tract environment. Besides mucoadhesive properties on liposome can be enhanced by using different polymers like chitosan, thiomer, pectin [41]. Huang et al. have reported usage of coated *N*-trimethyl chitosan on liposome to use as drug carriers in oral DDS. This system showed longer residential time. Therefore, these systems can be used to deliver peptide or protein drugs [42]. Besides *N*-trimethyl chitosan chloride can be used for the coating of liposomes. Chen et al. have reported the use of this system for the delivery of curcumin [43]. Microspheres of the chitosan-coated liposome can play a vital role in the delivery of a colonic drug [44].

3.2 Chitosan-Based Material in Ocular DDS

Since the decade's researchers are trying to increase the applications of eye-drops by using different DDS containing nanoparticles, microparticle, hydrogels, etc., to enhance bioavailability and longer retention time of the drug. Eyes treatment using eye-drops is the most extensively used technique in ocular treatment because it is easy to use and giving better results. One main complication in using eye-drops is that tear fluid drains out active ingredients of the dosage and instant clearance of drug which leads to lesser therapeutic effects. There are several reports available on the use of hydrogels in ophthalmic treatment to increase the retention time of the drug and to enhance the efficacy of the drug. Moreover, researchers have done work on the use of chitosan-gelatin-based hydrogels developed by using cross-linking agents in the ophthalmic treatment. Besides chitosan-based scaffold systems are mostly used in ophthalmic DDS. Genipin is a cross-linking agent which one having excellent biocompatibility and minimum cytotoxicity compared to other aldehydes and epoxy-based cross-linking agents. Song et al. have developed a chitosan–gelatin-based hydrogels by using double co-cross-linking agents for the use of ocular treatments. They used genipin and β-glycerophosphate disodium salt hydrate (β-GD) as a co-cross-linking agent. Further, they found that rapid gel formation is taking place at 37 °C. Chinese hamster fibroblast V 79 cell lines were used to check the cytotoxicity, and hydrogel is found to be non-toxic to these cell lines. Timolol maleate drug was used to check the drug-releasing profile from the hydrogel. From the experimental observations on the rabbit's eyes, they found that rapid formation of gel in eyes and gel protected drugs from the tears and drug-releasing profiles were high. Also, efficient intraocular pressure reducing the capacity of hydrogel was more compared to conventional drug delivery systems. Furthermore, they found that there is no irritation in the rabbit's eyes after the dosage of the drug by using this hydrogel system indicates that hydrogel developed from the double cross-linking agents has potential applications in ocular DDS [45]. Hydrogel system composed of chitosan, gelatin, and glycerol phosphate has potential applications to use in the prevention of ocular hypertension [46]. Swati Gupta and her co-workers have used chitosan with carbopol to develop a gel. They used timolol maleate drugs to check the efficiency of this in situ gelling systems. This gelling system has longer residential time and having the capacity to release drugs constantly [47].

Age-related macular degeneration (AMD) is a type of senile disease which one leads to vision loss of eyes. When the degradation of retinal epithelium and macular happens, this one can reduce and ruin a central vision of eyes. Since the year's ophthalmologist is using several clinical trials like drug delivery, radiotherapy, and photodynamic therapy for the treatment of AMD. Naringenin (Nag) is a naturally occurring flavanone compound in which one has much more importance in the ocular drug delivery system. Nag compound has antioxidant properties. Moreover, the low solubility of Nag is the main disadvantage to use in ocular drug delivery. Zhang et al. have developed a complex bio-composition of sulfobutylether-β-cyclodextrin (SBE-β) and chitosan (CD) containing nanoparticles by using ionic gelation method

for the loading of Nag for the treatment of AMD. Furthermore, they found that SBE-β-CD having average particle size is 446 nm; therefore, it enhances the efficacy of the drug and target specificity can be achieved in ocular treatment. Finally, they have performed in vivo studies on rabbit eyes to check the efficacy of the Nag loaded on SBE-β-CD material and they found higher bioavailability and longer drug-releasing profiles. Besides, they observed that there is no irritation in the rabbit's eyes after the dosage of drugs indicating that Nag loaded in SBE-β-CD has potential applications in ocular treatment [48]. Furthermore, chitosan-based films have potential applications for the treatment of AMD [49].

4 Conclusion

From the last two decades, natural polysaccharides are gaining much attention in DDS due to their unique properties, such as biocompatibility, and acts as a non-toxic carrier. Alginte and chitosan can be formulated in different forms such as hydrogel, microsphere, fibers as per DDS requirement. The polysaccharides' system in the form of DDS can be useful for the sustainable release, enhance the pharmacodynamics, and increase the bioavailability of the drugs for therapeutic applications. Therefore, these polysaccharides in DDS can specifically target the size with lesser amount of drug usage which significantly reduces the cost for treatment. In addition to this, stability of drugs (compounds, proteins, peptides etc) can be improved in multifold time with the combination of these polysaccharide systems. Hence, alginate and chitosan in the form of DDS are having potential application in the pharmaceutical industries.

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