Biopolymers for Drug Delivery

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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

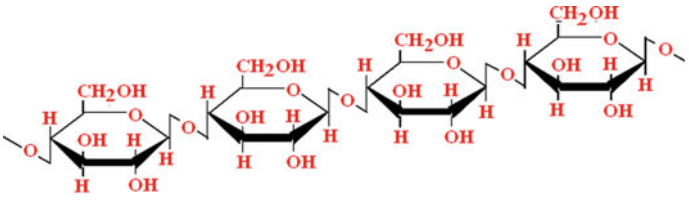

Fig. 1 Molecular structure of cellulose

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]

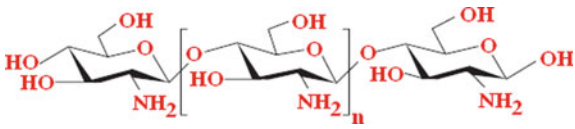

Fig. 2 Molecular structure of chitosan

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.

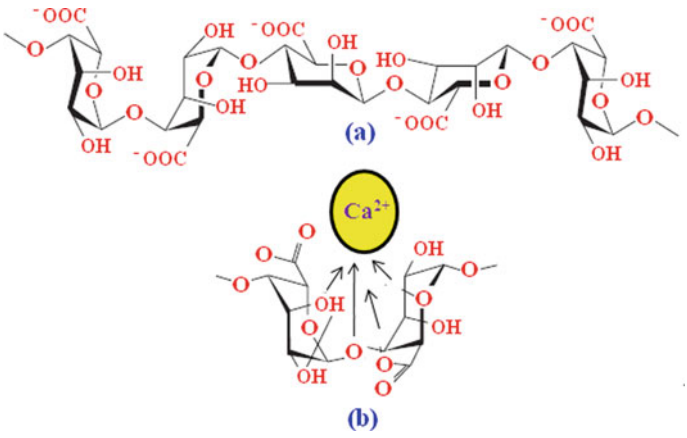

Fig. 3 **a** Molecular structure of alginate and **b** ionotropic gelation of alginate by calcium ions

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

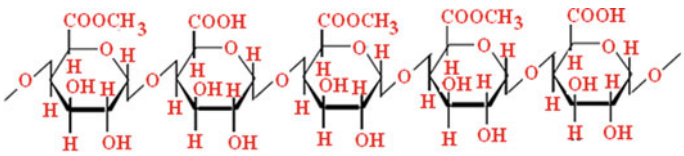

Fig. 4 Molecular structure of pectin

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,

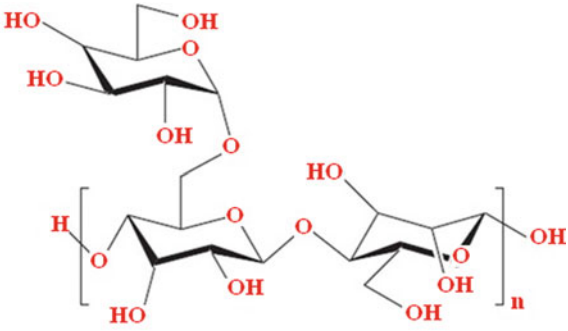

Fig. 5 Molecular structure of guar gum

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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