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Review Article

Natural Polymers and their Application in Drug Delivery and Biomedical Field

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Abstract

Biodegradable polymers are widely being studied as a potential carrier material for site specific drug delivery because of its non-toxic, biocompatible in nature. Natural polysaccharides have been investigated for drug delivery applications as well as in biomedical fields. Modified polymer has found its application as a support material for gene delivery, cell culture, and tissue engineering. Now a day, the polymer is being modified to obtain novel biomaterial for controlled drug delivery applications. This review provides an overview of the different modified polymer derivatives and their applications with special attention being put on controlled drug delivery and biomedical engineering.

Keywords: Polysaccharide, modified biopolymers, biodegradation, drug delivery

Introduction

Biopolymers have received attention as tissue engineering (TE) substrates in the past with several studies examining materials, such as alginate, chitosan, and gelatin as cell scaffolds for both two-dimensional (2D) and three-dimensional (3D) cell culture.[1-4] Carbohydrate polymers are extensively used in recent years in biomedical and pharmaceutical applications due to their biocompatibility and biodegradability.[5,6] The polysaccharides represent one of the most abundant industrial raw materials and have been the subject of intensive research due to their sustainability, biodegradability and bio-safety. We review here a selection of the most important polysaccharides that have been studied and exploited in several fields related to drug delivery, biomedical, gene delivery and tissue engineering.

Biopolymers and their Applications

Alginate

Alginate is a water-soluble linear polysaccharide extracted from brown seaweed and is composed of alternating blocks of 1–4 linked α-L-guluronic and α-D-mannuronic acid residues. Fig. 1 shows the structures of mannuronic and guluronic acid residues and the binding between these residues in alginate. Because of the particular shapes of themonomers and theirmodes of linkage in the polymer, the geometries of the G-block regions, M-block regions, and alternating regions are substantially different.

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Specifically, the G-blocks are buckled while the M-blocks have a shape referred to as an extended ribbon. If two G-block regions are aligned side by side, a diamond shaped hole results. This hole has dimensions that are ideal for the cooperative binding of calcium ions. The homopolymeric regions of β-D-mannuronic acid blocks and β-L-guluronic acid blocks are interdispersed with regions of alternating structure (β-D-mannuronic acid–β-L-guluronic acid blocks). [7,8]

Some modifications of alginate for drug delivery are Alginate combined with chitosan,[9] thiolated alginate-albumin nanoparticles,[10] Alginate–poloxamer microparticles,[11] Hydrated thiolated alginate,[12] alginate-poly (lactic-co-glycolic acid) nano/micro hydrogel matrices,[13] chitosan-Ca-alginate microspheres,[14] alginate modified by microenvironmental interaction with calcium ion,[15] polyethylene glycol–anthracene modified alginate,[16] photocrosslinked heparin-alginate hydrogels,[17] alginate–guargumhydrogel,[18] Micelles/sodium-alginate composite gel beads,[19] scleroglucan/alginate/borax gels,[20] dual crosslinked alginate/N-α-glutaric acid chitosan.[21]

Demiro¨z et al (2007) prepared alginate based mesalazine tablets for intestinal drug delivery.[22] Moebus et al (2009) used hydrogel-forming polymers (e.g., alginates and poloxamers) as encapsulation materials for controlled drug delivery to mucosal tissue.[23] Pinhas et al (2009) prepared mucoadhesive drug delivery systems based on hydrated thiolated alginate .Extensive studies have shown that dry, un-crosslinked, compressed tablets made from thiolated polymers adhere better to the mucus layer compared to the native polymers.[24] Mennini et al (2011) developed chitosan-Ca-alginate

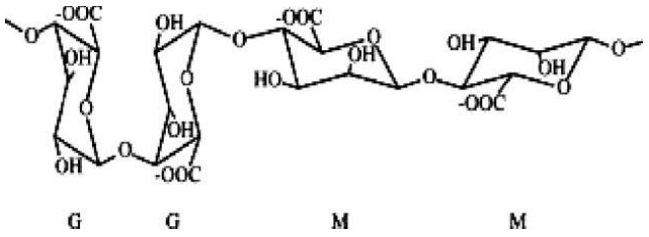

Fig. 1: Chemical structure of Alginate

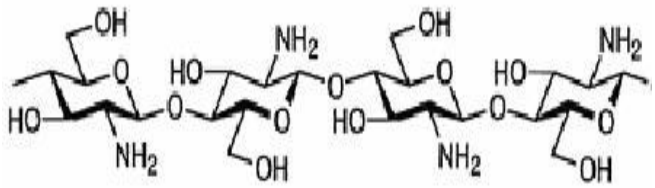

Fig. 2: Chemical structure of a chitosan polymer chain

microspheres for colon delivery of celecoxib-hydroxypropyl-beta-cyclodextrin-PVP complex.[25] Ciofani et al (2008) developed alginate-based drug delivery system for neurological applications, specifically, by considering the target application of neural regeneration and neuroprotection.[26]

Chitosan

Chitosan is a linear polysaccharide composed of α-1, 4-linked 2-amino-2-deoxy-α-D-glucose (N-acetyl gluco- samine). It is obtained from the N-deacetylation of chitin with a strong alkali (Fig. 2).[27-28] Its structure is basically constituted of D-glucosamine units, with contents of N-acetyl-D-glucosamine in the range of 0-50%.[3-4] It is a FDA GRAS (Generally Recognized as Safe) material and has been widely utilized in many fields including pharmaceutics, tissue engineering, and food technology. It contains high amino (pK_a 6.2–7.0) groups and is water-soluble in aqueous acids. However, it is insoluble at high pH conditions. Chitosan itself is nontoxic,[29] biodegradable, [30-31] and biocompatible. [32] However, the applications of chitosan are limited by its poor aqueous solubility. Chemical modifications of chitosan are widely used to obtain its derivatives. Many chitosan derivatives are water soluble in a wide pH range and show unique biological activities and physicochemical properties. It has been used as an excipient for direct tabletting of pharmaceuticals to enhance the dissolution properties of some less soluble drugs and to prepare the sustained release products.[33-36] Therefore, modified chitosan is being used in the fabrication of different drug delivery devices such as inhalable powders, [37] matrix tablet, [38] transdermal film/patches,[39-40] microparticles /nano-particles.[41-44]

Some modification of chitosan are carboxymethylation,[45-46] carboxyethylation,[47] reductive amination with phosphorylcholine glyceraldehydes, [48] sulfation,[49] N- or O-acylation [50-53] alkylation,[54] quaternarization.[55-57] , thiolated chitosan [58] phosphorylated chitosan [59-60] grafted chitosan. [61]

Ubaidulla et al (2009) described chitosan succinate and chitosan phthalate microspheres for oral delivery of insulin. The chitosan succinate is more hydrophilic than chitosan phthalate. The relative pharmacological efficacy for chitosan phthalate and chitosan succinate microspheres was almost three-fold higher than the efficacy of the oral insulin administration.[62] The surface modified chitosan-TBA conjugate PLGA nanoparticles have the potential to be used as mucoadhesive drug delivery system. The modified-surface PLGA nanoparticles represent a promising transmucosal drug delivery device.[63] Self-aggregated nanoparticles of cholesterol-modified chitosan conjugate as a novel carrier of epirubicin.[64] Methoxy poly(ethylene glycol)-grafted-chitosan (mPEG-g-CS) conjugates by formaldehyde linking method mono- disperse nanoparticles in aqueous media and showed a potential as a sustained release carrier of methotrexate (MTX). Low molecular weight (LMW) alkylated chitosans has potential interesting properties as nonviral vectors for gene therapy.[65] The polyelectrolyte complexes of chitosan and pectin showed a pH-sensitive swelling ability on the release behavior of vancomycin for colon-specific delivery.[66] Hydrogels of oxidized dextran (Odex) and N-carboxyethyl chitosan (CEC) without any extraneous crosslinking agent can be used for wound dressing purpose.[67] Novel polyampholyte hydrogels based on carboxymethyl chitosans (CMC) can be used in oral delivery system for protein drugs.[68] Chitosan–TBA (chitosan-4-thiobutylamidine) conjugates can be considered as a vehicle for nasal peptide drug delivery.[69] Some mucoadhesive vaginal gels were prepared using hydroxyethylcellulose (HEC) mixed with chitosan (CS) or its derivative namely 5-methyl pyrroli- dinone-chitosan (MPCS) loaded with the model antibacterial drug metronidazole (MET).[70] Membrane of chitosan was developed

by Dureja et al (2001) using a model drug of diclofenac sodium [71]. According to Wen et al (2008) N-trimethyl chitosan can be used as a transdermal drug delivery of chitosan.[72] Paulino et al (2009) prepared chitosan (CS), acrylic acid (AAc), and N, N'-methylenebisacrylamide (MBA) hydro- gels in the presence of citrate-covered-γ-Fe_2O_3 nanoparticules.[73] Methylated N-(4-N,N-dimethyl amino benzyl) chitosan, used as an absorption enhancer and it showed good para- cellular permeability through Caco-2 cell.[74] γ-poly(glutamic acid) (γ-PGA), a hydrophilic and biodegradable polymer, was chosen to modify chitosan matrices to produce a γ-PGA/chitosan composite biomaterial. This has hydrophilic, cytocompatible, and mechanical properties, and are very promising biomaterials for tissue engineering applications.[75] Chitosan/glycerol phosphate salt (GP) hydrogels scaffolds have been reported for neural tissue engineering.[76]

Carrageenan

Carrageenans are a family of sulfated polysaccharides extracted from red marine algae and that are widely utilized in the industry because they can form reasonably stiff and thermoreversible gels in the presence of so-called gel-promoting salts at room temperature.[77] These polysaccharides are linear polymers consisting of chains of (1→3)-linked ß-D-galactose and (1→4)-linked α-D-galactose units which are variously substituted and modified to the 3, 6-anhydro derivative, depending on the source and extraction conditions.[78] Three major types of carrageenan are recognized on the basis of their patterns of sulfate esterification: κ (kappa), ι (iota), and λ (lambda). All carrageenans are highly flexible molecules, which, at higher concentrations, wind around each other to form double-helical

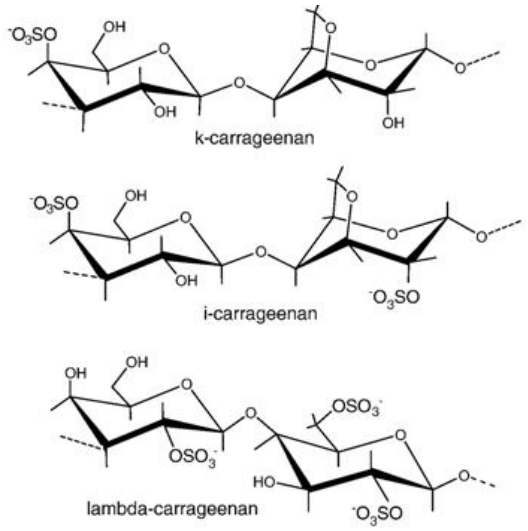

Fig. 3: Chemical structure of carrageenan

structures. A particular advantage is that they are thixotropic.[79]Due to the strong ionic nature, these carrageenans exhibit a high degree of protein reactivity. These materials have been used in the field of drug delivery, which creates the potential for their use as drug delivery systems. Some modified forms of carrageenan for drug delivery are iota-carrageenan combined with locust bean gum[80], carrageenan combined with gellan gum,[81] chitosan/carrageenan nanoparticles [82],agarose–carrageenan hydrogels [83],κ-carrageenan-AZT conjugates [84], carrageenan/ Eudragit RLPO polymer mixture [85],λ-carrageenan–gelatin mucoadhesive systems [86], κ-carrageenan grafted acrylic acid-co-2-acrylamido-2-methylpropanesulfonic acid.[87] Suzuki et al (1994) prepared microencapsules with carrageenan-locust bean gum mixture in a multiphase emulsification technique for sustained drug release of gentamycin sulphate.[88] Ghanam et al (2011) observed the suitability of κ-carrageenan pellets for the formulation of multiparticulate tablets with modified release. Sufficient prolonged release properties were obtained with κ--carrageenan pellets containing theophylline as a model drug and coated with Kollicoat® SR 30 D.[89] Bonferoni et al (2004) prepared carrageenan–gelatin mucoadhesive systems for ion-exchange based ophthalmic delivery. As a model drug, an alkaline anti-glaucoma drug, timolol maleate, was chosen.[90] Vlieghe et al (2002) prepared covalently bound kappa-carrageenan-AZT conjugates with improved anti-HIV activities.[91] Piyakulawat et al (2007) prepared chitosan/carrageenan beads for controlled release of sodium diclofenac.[92] Sankalia et al (2006) improved stability of alpha-amylase by entrapping in kappa-carrageenan beads.[93]

Gellan Gum

Gellan gum is a bacterial exopolysaccharide commercially prepared by aerobic submerged fermentation of *Sphingomonas elodea*. Gellan gum is a linear tetrasaccharide built up by (α-1→ 4)- L-rhamnopyranosyl-(α-1→ 3)-D-glucopyranosyl-(ß-1→ 4)-Dglucuronopyranosyl-(ß-1→ 4)-D-glucopyranosyl-(ß-1→ with O(2) L-glyceryl and O(6) acetyl substituents on the 3-linked glucose (Fig. 1D). It consists of about 50,000 residues and it is normally de-esterified by alkali treatment before use. Gellan gum forms a 3-fold double helix from two left-handed chains with the acetate residues on the periphery, and glyceryl groups and hydrogen-bonds stabilizing the inter chain associations.[94]

Some modified forms of gellan gum for drug delivery are deacetylated gellan gum [95], methacrylated gellan gum hydrogel [96],gellan gum-poly(vinyl alcohol) hydrogel. [97], Gellan gum films with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, [98] Al^{+3} ion cross-linked gellan hydrogel,[99] branched polyethylenimine

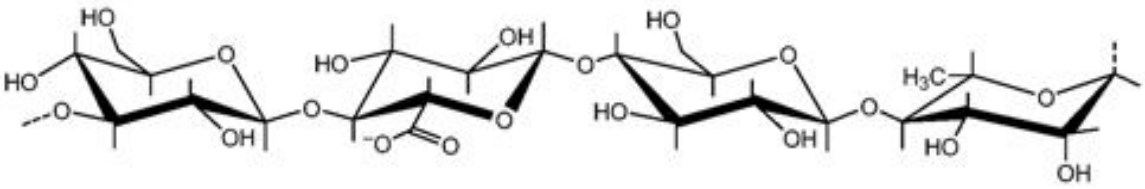

Fig. 4: Structure of gellan gum

blended with gellan gum.

Goyal et al (2011) prepared gellan gum blended PEI nanocomposites as gene delivery agents.[100] Agnihotri et al (2006) prepared gellan gum beads containing cephalexin by extruding the dispersion of cephalexin and gellan gum into a solution containing a mixture of calcium and zinc ions (counterions) for controlled release of drug.[101]

Agnihotri et al (2005) prepared gellan gum-poly(vinyl alcohol) hydrogel microspheres for the controlled release of carvedilol.[102] Sanzgiri et al (1993) developed gellan-based systems for ophthalmic delivery of methylprednisolone.[103] Fujii et al (2005) prepared Alkaline phosphatase encapsulated in gellan–chitosan hybrid capsules.[104] Kubo et al (2003) prepared oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulations.[105]

Gelatin

Gelatin is a translucent, colorless, brittle (when dry), flavorless solid substance, derived from the collagen inside animals skin and bones. It is commonly used as a gelling agent in food and pharmaceuticals.[106] Gelatin is produced by partial hydrolysis of collagen extracted from the boiled bones, connective tissues, organs and some intestines of animals such as domesticated cattle, and pigs. The approximate amino acid composition of gelatin is glycine 21%, proline 12%, hydroxyproline 12%, glutamic acid 10%, alanine 9%, arginine 8%, aspartic acid 6%, lysine 4%, serine 4%, leucine 3%, valine 2%, phenylalanine 2%, threonine 2%, isoleucine 1%, hydroxylysine 1%, methionine and histidine < 1% and tyrosine < 0.5%.[107]

Some modifications of gelatin for drug delivery are PEGylated-gelatin nanoparticles[108], fluoride anion-modified gelatin nanogel system for ultrasound-triggered drug release,[109]antibody modified gelatin nanoparticles as drug carrier system for uptake in lymphocytes,[110] agar modified gelatin A and gelatin B,[111] thiol-modified gelatin nanoparticles for intracellular DNA delivery[112], hydrophobic hexanoyl anhydrides grafting to the amino groups of primitive gelatin[113],cationised gelatin ,DNA-loaded gelatin nanoparticles[114] ,modified gelatin microspheres impregnated collagen scaffold[115].

Kaul et al (2002) prepared PEG-modified gelatin nanoparticles for long-circulating intracellular delivery of DNA.[116] Daocheng et al (2008) prepared Adriamycin gelatin nanogel, modified with fluoride anion by co-precipitation method with fluoride anion and Sodium sulfate targeted and controlled drug release delivery system for cancer and other diseases.[117] Balthasar et al (2005) used gelatin nanoparticles for the attachment of biotinylated anti-CD3 antibodies by avidin-biotin-complex formation. These antibody modified nanoparticles represent a promising carrier system for the specific drug targeting to T-lymphocytes.[118] Saxena et al (2011) prepared agar-gelatin compositions& tablets made of agar, gelatin A, gelatin B and their blends agar-gelatin A, agar-gelatin B, gelatin A-gelatin B in 1:1 ratio. Salbutamol is the model drug.[119]

Guar gum

Guar gum, also called guaran, is a galactomannan. It is primarily the ground endosperm of guar beans. The guar seeds are dehusked, milled and screened to obtain the guar gum.

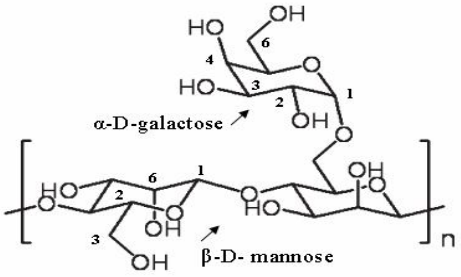

Fig. 5: Structure of Guar gum

Chemically (Fig. 5), guar gum is natural polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of ß-1, 4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side-branches.

Several modifications of guar gum for drug delivery are graft copolymers of N-Vinyl-2-Pyrrolidone onto guar gum for sorption of Fe^{2+} and Cr^{6+} ions.[120] Graft copolymer of partially carboxymethylated guar gum-g-N-vinyl-2-pyrrolidone[121], Cross-linking of alginate guar gum with glutaraldehyde[122], carboxymethyl guar films for the formulation of transdermal

therapeutic systems[123], graft copolymer H-partially carboxymethylated guar gum-g-methacrylic acid[124], Complexation of cupric ion-guargum-graft-acrylamide[125],yttrium crosslinked guargum-g-acrylamide gel systems[126], Phosphated cross linked guar gum[127], polyester-guar gum/hydroxypropyl guar gum.[128]

Nayak et al (2009) designed pulsatile release capsule of valsartan for chronotherapeutic drug delivery for early morning surge in boold pressure by using guar gum and sodium alginate, responsible for delaying the release.[129] Poly-acrylamide-grafted guar gum (pAAm-g-GG) hydrogel microspheres for controlling the release of calcium channel blockers like verapamil hydrochloride and nifedipine were prepared by Soppirnath et al. (2000) as well as by Soppirnath and Aminabhavi (2002).[130] Momin (2004) observed that matrix tablets containing 50%, w/w guar gum were suitable for targeting of sennosides for local action in the colon. These results were complementary to studies conducted by Ji et al (2007), which suggested pellets prepared with 44%, w/w guar gum and coated with Eudragit FS 30D to be suitable for colonic drug delivery.Krishnaiah et al (2003) prepared guar gum based matrix tablets of 5-FU and investigated the tablets for in vivo study in humans. These tablets showed delayed T_{max}, absorption time, decreased C_{max} and absorption rate constant compared to immediate release tablets.[131-33] Mundargi et al (2007) prepared tablets of metronidazole by using various polysaccharides or by graft copolymerisation using methacrylic acid (MAA) with guar gum.[134] Kabir et al (2000) prepared hydrocortisone hydrogels by using guar gum Crosslinked with tri sodium trimetaphosphate.[135] Murthy et al prepared carboxymethyl guar , an anionic semisynthetic guar gum for use in transdermal drug-delivery systems. Terbutaline sulphate was used as a model drug.[136]

Pectin

Pectin is a natural, non-toxic and anionic polysaccharide extracted from cell walls of most plants. Pectin consists mainly of linearly connected α-(1-4)-D-galacturonic acid residues partially esterified with methanol. The degree of methoxylation (DM) is used to classify the pectins as high methoxyl pectins (DM > 50) and low methoxyl pectins (DM < 50).[137, 138] The composition of pectin varies depending on plant origin. Citrus pectins appear to contain less neutral sugars and have smaller molecular size than apple pectins. [139] Functional properties of pectin are derived from their molecular weight distribution and from the degree of methoxylation of carboxyl groups. [140]

To achieve better drug delivery, certain modifications of pectin are done. These are polyelectrolyte complex (PEC) film between pectin as an anionic polyelectrolyte and chitosan as a cationic species,[141] self-assembling pectin–liposome nanocomplexes,[142] novel pectin–4-aminothiophenole conjugate microparticles,[143] pectin/HPMC polymer mixture,[144] Pectin-NH_2 was prepared by modifying the galacturonic acids carboxyl groups with primary amine groups and further modified to generate pectin-T ($T = N^+H(CH_3)_2$) and pectin-NH_2-Q ($Q = N^+(CH_3)_3$),[145]amidated pectin derivatives with n-propyl-,3-aminopropyl-,3-propanol- or7-aminoheptyl-substituents,[146] thiolatedpectin[147] pectin/poly(lactide-co-glycolide) composite matrices[148],mixed pectin/ethylcellulose films,[149] calcium cross-linked pectinate.[150,151]

Ghaffari et al (2007) prepared mixed-film formulation containing pectin/chitosan/Eudragit RS for sigmoidal drug delivery with an initial, controllable slow release followed by a burst release immediately after the change in pH. The burst drug permeation might possibly be due to change in film's porosity.[152] Perera et al (2010) prepared metronidazole-containing microparticles based on a pectin–4-aminothiophenol conjugate for colon-specific drug delivery.[153] Nisin containing pectin/HPMC compression coated tablets were prepared by Ugurlu et al (2007) and their in vitro behavior tested for colonicdelivery.[154] Maestrelli et al (2008) prepared enteric-coated calcium pectinate microspheres (MS) for colon drug delivery, by using theophylline as a model drug.[155]

Sandolo et al (2011) designed an oral vaccine against *Clostridium difficile* infection. The virulent factor Cwp84, that is a cystein protease highly immunogenic in patients with C. difficile-associated disease, was entrapped within pectin beads. Beads encapsulating Cwp84 were shown to be stable in the simulated intestinal medium.[156] Katav et al (2008) studied modified Pectin with various amine groups was for non-viral gene delivery carrier. Based on the attractive characteristics of the pectin molecule and on other polysaccharide-based gene delivery systems , they assumed that cationic pectin will be able to interact with DNA to form compact transportable unit that will also be biocompatible and biodegradable.[157] Thirawong et al(2008) prepared self-assembling pectin–liposome nanocomplexes by a simple mixing of cationic liposomes with pectin solution, in order to improve intestinal absorption of drugs. Calcitonin was the model drug.[158]

Xanthan gum

Xanthan is an extracellular heteropolysaccharide produced by fermentation of the bacterium *Xanthomonas campestris*. The primary structure (Fig. 7) of this naturally produced cellulose derivative contains a cellulose backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose- β -D-gluronic acid –α-D-mannose attached with alternate glucose residues of the main chain.[159]

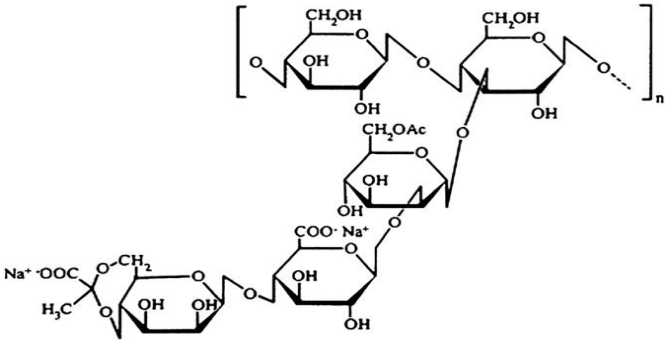

Fig. 6: Structure of Xanthan[160]

It is a hydrophilic polymer, which until recently had been limited for use in thickening, suspending, and emulsifying water-based systems It appears to be gaining appreciation for the fabrication of matrices with uniform drug release characteristics.[161,162]

Some modifications of xanthan for drug delivery are gelatinized starch–xanthan gum hydrogel system,[163] acrylamide-grafted-xanthan gum,[164] Graft copolymerization of ethylacrylate onto xanthan gum,[165]xanthan combined with Konjac glucomannan,[166] xanthan combined with boswellia gum (3:1),[167] xanthan gum combined with guar gum (10:20),[168] xanthan gum combined with locust bean gum in 1:1 ratio.[169]

Jiangyang et al. (2008) combined xanthan gum with Konjac glucomannan to produce matrix tablets of Cimetidine.[170] Sinha et al (2004) prepared rapidly disintegrating core tablets coated with a mixture of xanthan gum and guar gum. It was found that the xanthan gum:guar gum mixture (10:20) coated tablets were able to deliver the drug to the colon. 5-FU was used as model drug.[171] Sinha et al (2007) prepared 5-FU Compressed coated tablets with a mixture of xanthum gum and boswellia gum (3:1) and studies also showed that XG play a major role in retardation of drug release.[172] Mundargi et al (2007) investigate the utilization of xanthan-grafted copolymer of acrylamide as a controlled release matrix for antihypertensive drugs such as atenolol and carvedilol.[173] Bose et al (2011) prepared sustained release floating tablets of diltiazem HCl using xanthan gum for the treatment of angina and hypertension.[174] Gohel et al(2009) prepared modified Release Tablet Formulation of Metoprolol Succinate using hydroxypropyl methylcellulose and Xanthan Gum.[175] Ahmed et al(2010) developed a constant rate delivery formulation of diclofenac sodium to release the drug in intestine. Matrix tablets and triple-layer matrix tablets were formulated by using locust bean gum (LG), xanthan gum (XG) and a mixture LG: XG in 1:1 ratio as matrix forming agent, and anionic SCMC were compressed on both the surfaces of the matrix core.[176] Venkataraju et al (2007) prepared controlled delivery system for propranolol hydrochloride using the synergistic activity of locust bean gum and xanthan gum to avoid first pass effect.[177]

Conclusions

Natural biodegradable polymers have received much more attention in the last decades due to their applications in the fields related to environmental protection and the maintenance of physical health. To improve the properties of them, a number of methods have been developed, such as random and block copolymerization or grafting. These improve both the biodegradation rate and the mechanical properties of the final products. To provide added value to biodegradable polymers, some advanced technologies have been applied such as active packaging technology and natural fibre reinforcements. From the discussion, it can be concluded that natural polymers and their modified derivatives are very promising candidates for the mucosal, colonic and different targeted protein/peptide, gene/vaccine, and anticancer drug delivery. This review is based on several research reports and their outcomes have been cited here in a concise manner. We hope this article will contribute to the new researchers for further investigations.

Acknowledgement

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