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Biodegradable Polysaccharides for Controlled Drug Delivery

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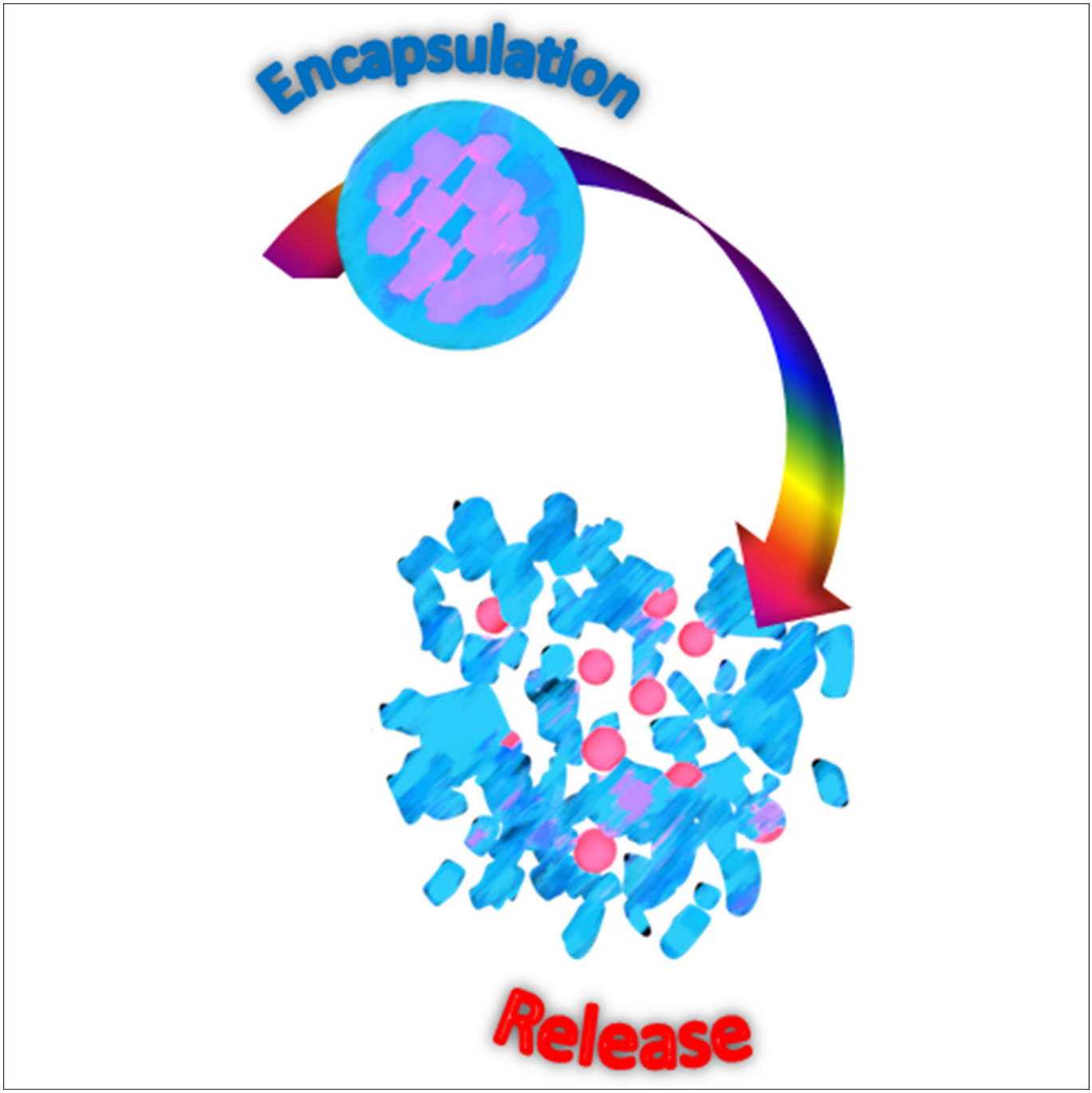

Polysaccharides are ideal candidates for drug delivery and biomedical applications as they are easily obtained from natural sources. Furthermore, they can be subjected to a wide range of chemical and enzymatic reactions, they have biocompatible and biodegradable properties and have inherently low immunogenicity. Polysaccharides are potentially the materials of choice for the development of "smart" delivery systems, which are capable of releasing, at the appropriate time and site of action, an encapsulated drug. This Review examines various aspects of the crosslinking of polysaccharides, either for a single polysaccharide or mixtures, and also natural–synthetic hybrids. The Review focuses on the strategies for using these biodegradable polymers for controlled drug delivery, and examines in particular polysaccharide–drug conjugates, the encapsulation of drugs in hydrogels and aerogels, and the self-assembly of polysaccharide drug-loaded nanoparticles.

Introduction

Biodegradable polymers are polymers that break down after their planned use. The degradation of these polymers results in the formation of natural byproducts such as carbon dioxide, water, small organic molecules and biomass. The biodegradable polymers typically studied can be both naturally and synthetically derived. Their backbone can possess ester, amide, and ether functional groups. The manner of their degradation, as well as their properties, is determined by their structure. There is a wide range of examples and applications of biodegradable polymers, which can be polyesters, polyamides, polyanhydrides, polycarbonates and polysaccharides.[1] Polysaccharides are biodegradable polymers that are found in all living organisms. These polymers are polymeric carbohydrate molecules composed of long chains of monosaccharide units covalently bound together by glycosidic linkages and which, upon hydrolysis, give the constituent monosaccharides or oligosaccharides. Their structures range from linear to highly branched structures.

Examples of polysaccharides of plant origin include starch, cellulose, hemicellulose, hyaluronic acids, alginate and guar gums, whereas polysaccharides that originate from animals include chitin and chondroitin sulfate. Polysaccharides have many roles in nature, which include energy storage (starch and glycogen),[2] structural support for plants (cellulose),[3] interphase adhesion in the cell walls of plants (hemicellulose),[4] structural roles for aggrecan assemblies and extracellular components (hyaluronic acid),[5] structural support in arthropods (chitin),[6] cell wall constituents (alginate),[7] components in plant cell walls and middle lamellae (pectin),[8] anionic extracellular cell wall constituents (gellan gum),[9] and components in seed husk (psyllium husk).[10]

Slight variations in the molecular structures of the polysaccharides can give rise to a significant difference in their properties. For example, starch and cellulose differ only in their stereochemistry, but play significantly different roles in nature. These polysaccharides are rich in functional groups such as carboxyl, hydroxy, amide or other hydrophilic functional groups that can be used to modify the properties of the polymers to suit the desired applications. Atom transfer radical polymerization and click chemistry have been used to graft various polymers onto cellulose backbones.[11] Polysaccharide-based materials have been proposed for drug and gene delivery applications.[12]

Polysaccharides are mostly considered to be amorphous polymers. These green polysaccharides have been of recent research interest due to their abundance, renewability, good biocompatibility, nontoxicity, biodegradability, good photostability and capability of enhancing absorption capacity. Regarding their biodegradability, polysaccharides are useful for ingestion and subsequent elimination from the body. For example, the human intestine possesses at least 500 bacterial species, making up an extraordinary microbial ecology in this organ. The microbiota needs to maintain its capacity to perform a basic set of biochemical reactions, including degradation of carbohydrates, synthesis of vitamins and fermentation. In particular, the degradation of polysaccharides takes place in the intestines.[13] The majority of work on alkaline degradation of polysaccharides has focused on temperatures of 100 °C or less to investigate the degradation mechanisms, termination of reaction, and structure–property relationships.[14] At low temperatures, there is little conversion of polysaccharides to acids. Starch and cellulose can both be thermochemically degraded in alkaline solution to water-soluble compounds of lower molecular weight.[15] The alkaline degradation products of starch and cellulose were found to be similar. Based on chromatographic methods, small organic compounds such as formic acid, acetic acid, glycolic acid, lactic acid, 2-hydroxybutyric acid, and 2-hydroxyvaleric acid were identified. Starch and cellulose degradation in alkaline solution can be described by second-order kinetics with the reaction activation energy according to the Arrhenius equation calculated to be 165 kJ mol^{-1}.[15] The thermal degradation of the polysaccharides sodium alginate, carrageenan and carboxymethyl cellulose (CMC) has been obtained from the time dependence of the viscosity at high temperatures measured using a slit vis-

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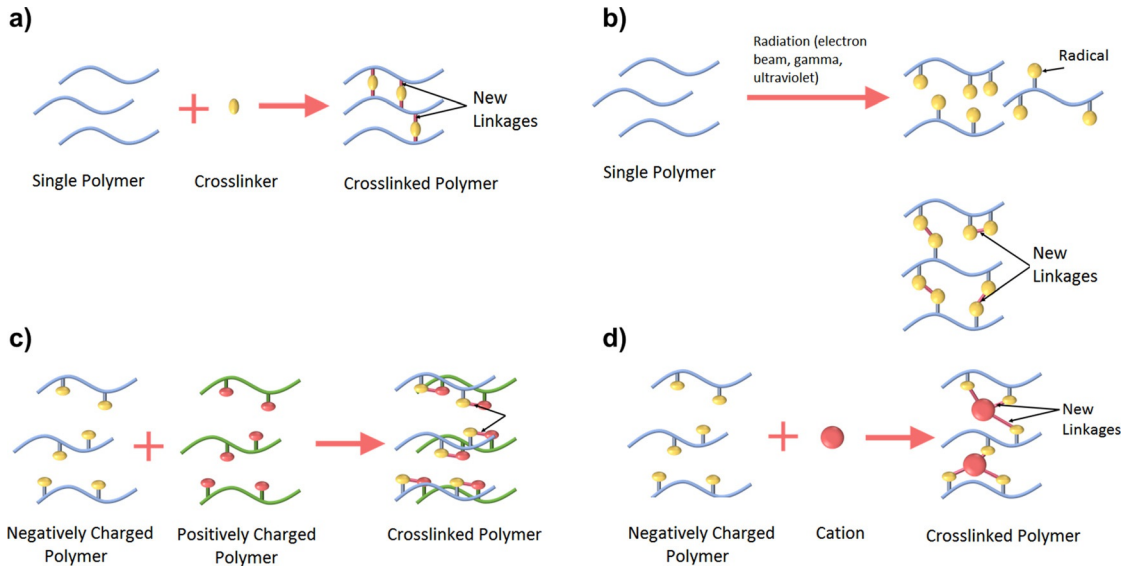

Figure 1. Crosslinking can be achieved by using a) chemical or natural crosslinking reagents, b) radiation, c) complex coacervation, and d) ionic moieties.

cometer. It is found that alginate is much less stable than CMC and carrageenan.[16] The activation energy for carrageenan was found to be 104 kJ mol^{-1}, and 50.7 kJ mol^{-1} for alginate and 79.9 kJ mol^{-1} for CMC. Indeed, the study of the different modes of polysaccharide degradation is a vast and complicated topic and is beyond the scope of this Review. The interested reader is referred to a detailed resource on this topic.[17]

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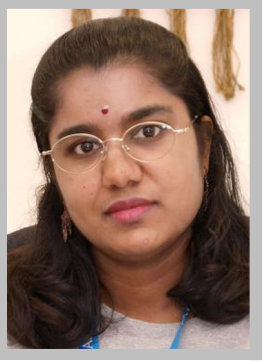
Dr. Janarthanan Pushpamalar is a Senior Lecturer at Monash University Malaysia. Her research interest is in developing new biodegradable polymers using plant waste and currently focusing on preparing low cross-link CMC hydrogel to be used as control release device for anticancer drug and slow release device for application of fertilizer in agriculture.



Crosslinking in single polysaccharides

In polysaccharides, the presence of the hydrophilic functional groups in amorphous states allows for crosslinking reactions to take place by various means, such as those shown in Figure 1. Chemical crosslinking can be achieved through the use of chemical or natural crosslinkers (Figure 1 a), radiation (Figure 1 b), complex coacervation (Figure 1 c) and ionic crosslinking (Figure 1 d). Crosslinking can take place with a single type of polysaccharide. Chemical crosslinking can be achieved through the use of crosslinkers such as epichlorohydrin for cellulose and CMC,[18] itaconic acid for starch,[19] tripolyphosphate and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) for chitosan,[20] and glutaraldehyde[21] and 1,2,3,4-butanetetracarboxylic dianhydride[22] for guar gum. Ionic crosslinking can be achieved by using solutions of cations such as Al^{3+}, Fe^{2+} or Ca^{2+} that crosslink the anionic polymers; these crosslinks are stabilized by electrostatic interactions. Ionic crosslinking of a single type of polysaccharide include examples such as CMC with Al^{3+},[23] and gellan gum, alginate and pectin with Ca^{2+}.[1i,24] Radiation crosslinking has been achieved by using an electron beam or gamma radiation for CMC,[25] starch,[26] chitosan[27] and alginate.[27a] Use of any of these crosslinking methods for a single type of polysaccharide will result in the production of a crosslinked polymer with improved physical and chemical properties such as solubility, crosslinking density, swelling behavior, mechanical strength, thermal stability and sensitivity to the environment such as changes in pH and temperature that widen their applicability.[28] Recently, a chemoenzymatic methodology was reported for the multivalent functionalization of cellulose surfaces by regioselective oxidation of hetero-polysaccharides with galactose 6-oxidase.[29] This is a useful step for designing cellulose-based materials for diagnostic applications.

Crosslinking in polysaccharide mixtures

These crosslinking methods can also be used on polysaccharide mixtures to enhance and to achieve desired properties. Polysaccharides obtained from various sources can, through various chemical modifications, lead to polysaccharides with different chemical compositions, molecular weights and structures. The polysaccharides possess various physicochemical properties including gelation, solubility, low osmotic effect, and surface properties depending on their composition and architecture. Chemical crosslinking of two polymers can be performed using reagents such as EDC for CMC–chitosan[30] and chitosan–hyaluronan,[31] sodium tripolyphosphate for chitosan–gelatin[32] and genipin for kappa-carrageenan–CMC.[33] Ionic crosslinking of two polymers such as alginate/chitosan with Ca^{2+} has also been reported.[34]

Examples of radiation crosslinking of two polymers through the use of gamma, electron beam or UV radiation include CMC–chitosan,[35,36] chitosan–alginate,[34] pectin,[37] chitosan–dextran[38] and alginate.[39] Another crosslinking method for a mixture of polysaccharides is called complex coacervation. Complex coacervation is achieved by adding two oppositely charged polymers, allowing for the formation of crosslinking due to the attraction of the opposite charges. Chitosan-based composite particles have been used to encapsulate enhanced green fluorescent protein plasmid (pEGFP) by the complex coacervation method (Figure 2).[35] Other combinations include anionic modified starch–cationic chitosan, pectin–chitosan and carboxymethyl sago pulp–gelatin,[40] which are mixed and stirred to form micro/nanoparticles. These crosslinking methods for single polysaccharides or polysaccharide mixtures lead to the formation of hydrogels,[25c,d,40,41] microcapsules, microgels,[30] nanocomposites,[34,42] nanoparticles,[43] and nanogels,[44] resulting in many products that are being exploited in areas such as the pharmaceutical, medical, cosmetics, and food industries.[45] The combination of various polysaccharides with different properties and different crosslinking methods is important and interesting because it has opened a new research area that allows for the production of polymers with altered properties such as enhanced mechanical strength, thermal stability, miscibility, absorption and swelling capacity.

Crosslinking in polysaccharides and synthetic biodegradable polymers

Polysaccharides have been added to other synthetic biodegradable polymers in order to impart desired properties such as improved mechanical strength, swelling capability with retention of shape, endowment of pH sensitivity and enhancement of biodegradability. Superabsorbent hydrogels with favorable swelling and mechanical properties were obtained by crosslinking various polysaccharides and polysaccharide–synthetic mixtures such as tara gum–acrylic acid,[46] bacterial cellulose–acrylic acid,[47] dextran–poly(ε-caprolactone),[48] chitosan–poly(ethylene glycol),[49] chitosan–cyclodextrin,[50] modified hemicellulose–*N*-isopropylacrylamide,[51] CMC–poly(acrylic acid),[52] modified chitosan–carbopol,[53] alginate–poly(*N*-vinyl-2-pyrrolidone),[54] alginate–polyacrylamide,[55] chitosan–chondroitin-6-sulfate,[56] psyllium–acrylamide and 2-acrylamido-2-methylpropanesulfonic acid,[57] psyllium–acrylic acid,[58] xanthan–poly(acrylic acid)–poly(vinyl alcohol)[59] and chitosan–gelatin,[60] chitosan–poly(vinyl alcohol).[61] These semisynthetic hydrogels have a wide variety of biomedical applications, such as controlled release drug delivery,[47,57,61–62] wound dressings,[61,63] tissue engineering[36,64] and gene therapy.[65] The use of polysaccharide mixtures or chemically modified forms of polysaccharides has eradicated the weaknesses associated with single natural polysaccharides.

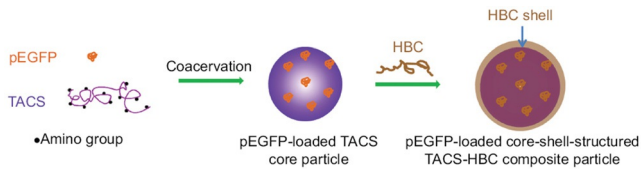


Figure 2. Synthesis of pEGFP-loaded core–shell-structured TACS–HBC composite particles. Abbreviations: pEGFP, enhanced green fluorescent protein plasmid; TACS, thiolated N-alkylated chitosan; HBC, hydroxybutyl chitosan. Reproduced with permission from Ref. [35], Dove Press, 2014.

Biodegradable polymers for controlled drug delivery

Interest in using biodegradable polymers as drug carriers for drug delivery systems is increasing. These natural biodegradable polymers are being used as binders in tablets and as viscosity enhancers in liquids or emulsions. Polymers are also being used as coating agents to eliminate the unpleasant taste of a drug, improve drug stability and to modify the amount and release rate of the drug. The short half-life of a drug results in the need for multiple doses, which has the tendency to increase the side effects and cost of the treatment. Multiple dosing is also problematic in the event of poor patient compliance. To overcome these problems, there have been attempts to improve the method of drug delivery to patients by using biodegradable polymers for the encapsulation of drugs. The drug encapsulated in the crosslinked biodegradable polymer can then be released in a sustained or controlled manner, as shown in Figure 3.

The rate of drug release is dependent upon the crosslinking density of the polymer—denser crosslinking affords slower drug release. The drug can be loaded into a hydrogel such as a CMC hydrogel, which consists of many pores and can be shaped into beads/tablets that disintegrate through hydrolysis or other forms of degradation, resulting in the release of the drug.[40] Many types of polysaccharide are being used as carriers for drug delivery in the biomedical field. Intensive research has been focused on conjugating the polysaccharide and drug in order to reduce the side effects of the commonly used synthetic polymers, as well as to prevent over dosage of the administered drug. The formulation of the drug carriers and the loading of the drug are achieved by four different strategies. The four methods are: use of polysaccharide–drug conjugates, entrapment of the drug in hydrogels or in aerogels, and forma-

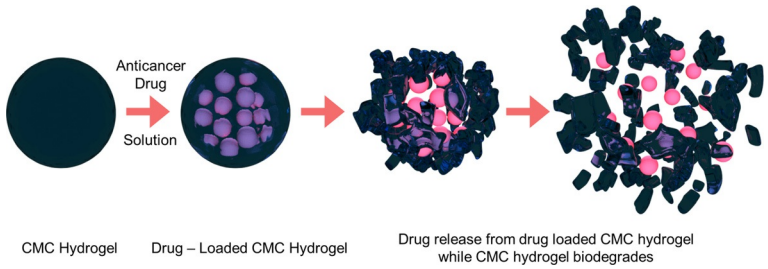


Figure 3. Drug release from the crosslinked polysaccharide by biodegradation.

tion of polysaccharide drug-loaded nanoparticles by self-assembly.

Nanocelluloses are important candidate materials for controlled drug delivery.[66] Huang et al. reported using bacterial cellulose membranes as vectors for the sustained release of berberine hydrochloride and berberine sulfate.[67] The drug carriers were also shown to have good sustained transdermal delivery. Muller et al. demonstrated the use of bacterial nanocellulose as a drug delivery system, showing the loading and release using the model protein albumin.[68] The encapsulation and release of indomethacin in self-assembled nanocellulose structures has also been reported.[69]

Polysaccharide–drug conjugates

The concept of polymer–drug conjugates was first proposed more than three decades ago.[70] Many natural and synthetic water-soluble polymers have been conjugated directly or indirectly using a chemical linkage, to develop a prodrug.[70] Pharmacokinetics studies of drug-conjugated polysaccharides have demonstrated the advantage of using the natural polymers. Although synthetic, water-soluble polymers have been widely utilized, natural polymers such as chitosan, dextran, cellulose, and hyaluronic acid are also used because of their remarkable potential as drug carriers.[51,71] For example, doxorubicin (DOX) prodrug nanoparticles with pH-sensitive drug release properties and antitumor activity were designed and synthesized by conjugating the hydrophobic DOX with chitosan through an acid-cleavable hydrazone (hz) bond.[72] Chitosan-hz–DOX nanoparticles were stable at neutral pH and disassembled at pH 5.0, resulting in the burst release of DOX in HeLa cells treated with the nanoparticles. The prodrug nanoparticles could be quickly internalized, leading to a significant DOX accumulation in the cells, demonstrating the potential for application in tumor-targeted drug delivery.

Polysaccharides of simple sugars, such as dextran, are widely used for drug conjugation.[73] Dextran is produced by strains of bacteria such as *Leuconostoc* and *Streptococcus*.[74] The primary and secondary hydroxy groups in dextran provide potential sites for drug conjugation by different methods. Initially, dextrans were used as plasma expanders[75] and were further developed by conjugating drugs to them, resulting in products that have entered clinical trials. Dextran has been an attractive biopolymer for drug delivery due to its physicochemical characteristics and low cost.[76]

Hyaluronan (HA) is an anionic disaccharide composed of repeating D-glucuronic acid and D-*N*-acetylglucosamine, which are linked with β-1,4- and β-1,3-glycosidic bonds.[77] The biocompatibility, biodegradability and non-immunogenicity of HA have facilitated the development of various drug delivery applications. The hyaluronate backbone comprises of hydroxy and carboxyl groups that can be involved in drug conjugation. Both direct and indirect conjugation of the drug can be achieved. However, direct conjugation might be less favored due to steric hindrance and the low reactivity of the carboxyl group.[78] HA derivatives that provide reactive functional groups (e.g., hydrazine, NH_2—NH_2) will increase reactivity and make forming drug conjugates more efficient. HA derivatives that allow substitution and functionalization of the carboxylic acids have exhibited greater drug loading with minimal polymer modification.[79] Paclitaxel (PTX) conjugates with HA–deoxycholic acid linked with bio-reducible cystamine showed high loading and limited toxicity of the drug compared to free PTX.[80] It was also observed that a high degree of substitution did not affect the targeting properties of the drug. In order to address the poor solubility of HA in typical organic solvents, which hinders conjugation reactions with cytotoxic drugs, several approaches have been utilized.[81] These methods involve the use of a combination of polar solvents and water, nanocomplexation by polyethylene glycol dimethyl ether and ion-pair complexes with long-chain aliphatic cations.[82] A study on using HA–drug conjugate design to specifically target over-expressed CD44 was performed.[83] The HA–drug conjugates, such as HA–mitomycin C, HA–epirubicin, HA–butyrate and HA–paclitaxel, were well studied.[84] HA–butyrate, a histone deacetylase inhibitor[84] showed increased apoptosis activity, which resulted in a decreased tumor burden in vivo and inhibition of cell growth in vitro.

Polymeric nanoparticles have been produced by modifying sucrose molecules as biomimetics in carbohydrate-mediated biological processes that assist drug delivery. The modification of sucrose and poly(D,L-lactic-co-glycolic acid) (PLGA) was made by crosslinking using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and cholic acid derivatives by esterification and conjugation.[85] This represents promising work toward a controlled drug delivery system for drugs with poor solubility in water.[86] Different applications of various pure and composite hydrogels based on cellulose, chitin, or chitosan include applications as controlled and targeted drug delivery systems, improved tissue engineering scaffolds, wound dressings and water purification

sorbents.[87] Chitin polymers can be made into spherical nanogels and conjugated with the dye rhodamine 123 for drug delivery and tissue engineering.[44b,88] Other types of polysaccharides, such as CMC, can be conjugated with folate and fluorescent molecules in order to increase drug loading and release that drug in a sustained manner to specifically targeted sites such as cancer cells, and potentially, could also be used for gene therapy.[89]

In recent years, pectin has been combined with cellulose and micro-fibrillated cellulose for wound healing materials. It was used to create a scaffold for wound healing in rats to study skin regeneration. The results were promising on rats but further animal studies will need to be performed before putting the sample through clinical trials.[64a,90] Pectin is also used as a drug carrier in nasal sprays for drug delivery. The nasal spray drug incorporated is fentanyl, which relieves cancer pains and aids in providing a more comfortable chemotherapeutic treatment.[91]

Entrapment of drugs in hydrogels and aerogel matrices

Three-dimensional, hydrophilic, polymeric networks that can retain large volumes of water or biological fluids are called hydrogels.[92] By contrast, aerogels are highly porous, have large internal surface areas and exhibit outstanding performance in drug delivery.[93] These are mostly rigid and brittle but if polysaccharides are incorporated to form a xerogel, they have a tendency to form transparent hydrogels, forming randomly interconnected polymeric networks.[94] The structural and physical characteristics depend solely on the density of the aerogel formed. Hydrophilic polysaccharides and their precursors are used to prepare hydrogels and aerogels for drug delivery that are chemically stable.[95] "Ionotropic" hydrogels are formed by the interaction between a polyelectrolyte and an oppositely charged multivalent ion using a technique called complex coacervation.[96] Hydrogels can be sensitive to various environmental influences, such as ionic strength, pH, and temperature, which affect their properties and morphology.[97] In some cases, the application of nanofibrillar cellulose as a matrix-forming material allows for long-lasting release of up to three months for sustained drug delivery applications.[98] Similar materials have also been fabricated into particles for sustained release applications.[99] Permanent changes can be made by forming covalent crosslinks in these hydrogels, which are also known as smart hydrogels.[28e,100] Single networks within the hydrogel decreases the mechanical strength and, in order to enhance the mechanical strength and swelling–deswelling properties of the polymer, interpenetrating polymer networks (IPNs) have been designed. The IPNs are formed by crosslinking two different polysaccharides to form the interpenetrating polymer network shown in Figure 4. In this example, injectable conductive IPN hydrogels with enhanced mechanical properties were prepared from gelatin-graft-polyaniline and carboxymethyl chitosan, which were crosslinked with oxidized dextran through a Schiff base at physiological conditions.[101] The hydrogels were electroactive, cytocompatible and tested to be biocompatible in vivo, thus showing great potential for drug delivery and tissue engineering. These natural polysaccharides are often used alone or with synthetic polymers with hydrophilic functional groups such as COOH, OH, $CONH_2$, SO_3H, amines and ethers.[102] Advanced multicomponent IPN systems can be designed and generally classified as simultaneous IPNs and sequential IPNs. This classification of IPNs based on the synthesis method of the IPNs[102,103] on how these two polymers are cross-linked within the hydrogel. A composite system of nanoparticles in an aerogel matrix was also developed for sustained drug release.[104]

Alginate, which is refined from brown seaweed, is a charged biopolymer made of repeating disaccharide units composed of 1-4-linked β-D-mannuronic acid and α-L-guluronic acid,[105] arranged in individual blocks or alternating blocks at different ratios. The ability to form a gel rapidly with alginate using ionic and covalent conjugation methods has drawn researchers to make extensive studies into developing improved systems for the delivery of chemotherapeutic drugs. Hydrogels and nano-gels are formed using the redox-responsive alginate by EDC crosslinking.[106] The gels formed using redox-degradable polymer networks degrade to release the therapeutic drug. Temperature- and pH-sensitive hydrogels could be synthesized using poly(diallyldimethylammonium chloride) (PDADMAC) and alginate.[107] The pH response of these hydrogels indicates a maximum swelling at pH 4,[108] which is caused by electrostatic repulsion due to ionization of COOH groups on alginate.

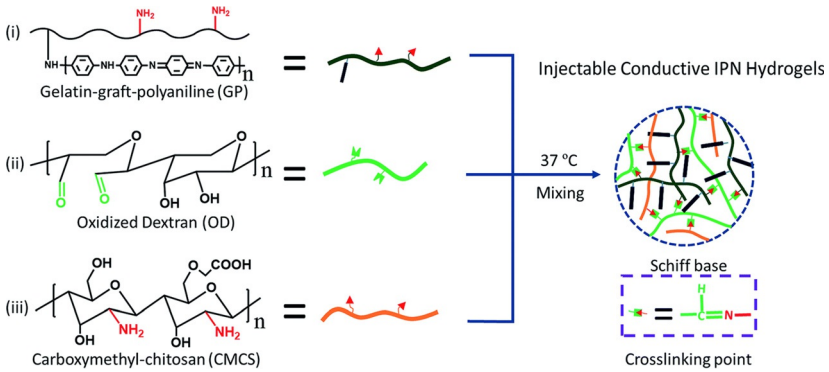


Figure 4. Preparation of an injectable conductive IPN hydrogel based on gelatin-graft-polyaniline (GP), oxidized dextran (OD) and carboxymethyl chitosan (CMCS). Reproduced with permission from Ref. [101], Royal Society of Chemistry, 2015.

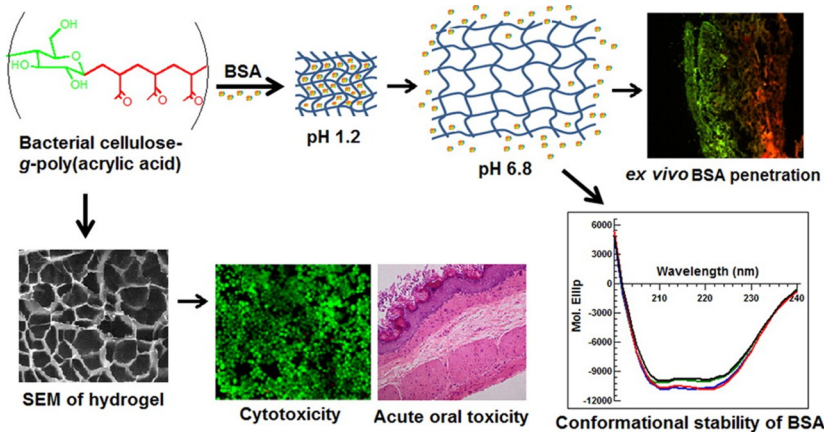


Figure 5. Schematic of cellulose-grafted-poly(acrylic acid) hydrogel used to encapsulate BSA. Reproduced with permission from Ref. [110], American Chemical Society, 2014.

By contrast, PDADMAC co-existing with ionized COOH forms polyelectrolyte complexes resulting in decreasing swelling ratio.[109] Along with the swelling property, other properties such as super-porosity and electrical sensitivity help researchers to create a system for drug controlled release. Another attempt has been made by using ionic crosslinking for *O*-carboxymethyl chitosan and carbopol with Ca^{2+} solution to deliver rabeprazole sodium to the colonic area in which the usage of the biodegradable polymers has prolonged the residence time due to its muco-adhesive properties.[53] A hydrogel from bacterial cellulose and acrylic acid was irradiated with electron beam radiation and loaded with bovine serum albumin by a diffusion method. The hydrogel was thermo-sensitive and could be exploited for temperature-controlled protein-based drugs (Figure 5).[110] Another temperature-sensitive hydrogel obtained by UV radiation from modified hemicellulose and *N*-isopropylacrylamide might be useful materials for biomedical applications.[111]

A carboxymethyl sago pulp (CMSP) hydrogel was prepared via ionic (Al^{3+}) crosslinking for colon-targeted drug delivery. A 5-aminosalicylic acid (5-ASA)-loaded CMSP hydrogel released low amounts of 5-ASA at stomach pH and sustained the drug release at colonic pH. As this formulation was produced from industrial waste, an added benefit was that it would reduce pollution as well as the cost of formulation.[40] Locust bean gum was crosslinked with poly(vinyl alcohol) using glutaraldehyde to control the release of buflomedil hydrochloride.[112] It was found that this formulation was suitable for controlling the release rate for drugs with short half-lives and high water solubility. Recently, alginate was used as a medium to which hydrophilic fluorescein- (FL, a model chemotherapeutic agent) loaded gelatin microbeads were added and crosslinked to entrap the FL-loaded gelatin into the crosslinked matrices of the alginate.[113] Other modified polysaccharides commonly used are the psyllium-based polymers. Psyllium–poly(vinyl alcohol) loaded with rabeprazole sodium and the drug release was found to most efficient in buffer at pH 7.4. A thrombogenicity study and calculation of the hemolytic index confirmed that the hydrogels had hemocompatibility indicating that these hydrogels might have applications in drug delivery systems for treating bleeding ulcers.[114]

Self-assembling polysaccharide drug-loaded nanoparticles

Hydrophilic polysaccharide backbones, if introduced to hydrophobic moieties, form self-assembled structures such as nanoparticles,[115] "missiles",[116] liposomes and niosomes.[117] Hydrophobic moieties such as cholesterol, carboxyl groups (steroid acids), deoxycholic acid, and hydrophobic polymers are used to form nanoparticles by minimizing the interfacial free energy through the optimization of the molar ratio of the chosen polymers.[118] The self-assembly of hydrophilic polysaccharide backbones and hydrophobic polymers is shown in Figure 6. Hydroxy, amino or carboxyl groups of the hydrophilic polysaccharides backbones can be used to graft with hydrophobic

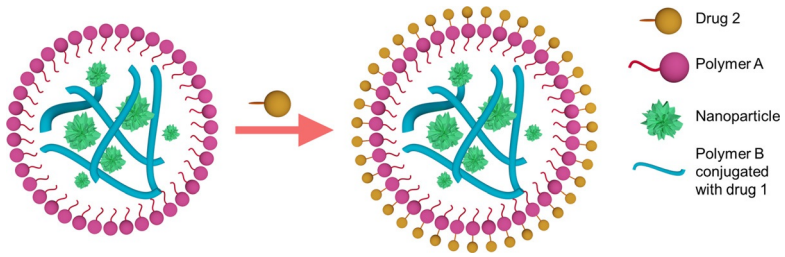


Figure 6. Self-assembling polysaccharide drug-loaded nanoparticles.

segments to create amphiphilic macromolecules by intra- and/or intermolecular interactions, which form nanoparticles.[63d] This allows the water-insoluble drugs to be encapsulated in the hydrophobic region and hydrophilic shell to solubilize the drug,[119] which is released with stimuli such as changes in pH, temperature and ionic strength.

Recently, interest in self-aggregated nanoparticles for drug delivery systems consisting of hydrophilic polysaccharides, such as amylose, guar gum, pectin, chitosan, dextrans, and locust bean gum, has grown.[120] These polysaccharides are suitable for colon-targeted drug delivery because they are stable within the physiological environment of the stomach and intestine, and bacteria in the colon cause degradation of the polysaccharide and subsequent release of the drug into the colon.[121] Polysaccharide-based nanoparticles, such as chitosan nanoparticles loaded with drugs such as paclitaxel, ibuprofen and the amphiphilic DOX, have been synthesized.[115] The amino groups on chitosan were chemically modified by grafting hydrophobic groups, by acylation with the acyl chloride or acid anhydride, and then further crosslinked with deoxycholic acid. Transfection of plasmid DNA using deoxycholic acid-grafted chitosan nanoparticles (160 nm) in COS-1 cells has been reported.[122] Another biopolymer, dextran, is also a candidate for use as a self-assembled nanosized drug carrier. Various biomolecular moieties such as bile acids, natural amphiphilic steroids, or lauryl chains have been grafted onto dextran.[123] Chemically modified, azido-bearing dextran nanoparticles have been conjugated with mannose groups and exhibited enhanced antigen response due to internalization and activation of antigen-presenting cells.[124] Acrylic acid was grafted onto dextran to produce pH-sensitive nanoparticles ranging in size from 40 to 140 nm. Inter-polymer nanocomplexes were prepared using poly(acrylic acid) by forming hydrogen bonds between carboxyl groups and glucose units.[125] Modified dextran was shown to successfully increase the uptake of DOX, and this material could become a promising carrier for DOX.[126] Modified cellulose, hydroxypropyl and hydroxyethyl celluloses were also used to create similar kinds of nanoparticles.[127] Non-viral gene delivery was performed using comb-shaped poly[(2-dimethylamino)ethyl methacrylate], which is cationic, and dextran backbone through atom transfer radical polymerization.[65a] A dextrin nanogel loaded with DOX was formed by chemical crosslinking using glyoxal and ultrasonication. The DOX-loaded dextrin nanogel could significantly reduce DOX toxicity towards normal cells, which reduces the side effects.[128] Similar to dextran and chitosan, HA was chemically modified with 5-β-cholanic acid to form nanoparticles ranging in size between 200–400 nm, and showed more specific targeting of passive tumors expressing CD44.[129] HA, if conjugated with poly(γ-benzyl L-glutamate)-block, forms amphiphilic block copolymers.[130] These particles, loaded with DOX, formed a self-targeting drug carrier to CD44 over-expressing glycoprotein cells in the cancer tumors.[131] Some negatively charged polysaccharides, such as heparin, which is also a good anticoagulant, have been reported to form nanoparticles.[132] Folate conjugated with chemically modified poly(β-benzyl L-aspartate)–heparin was loaded with paclitaxel and proposed for targeted site-specific drug delivery.[133] These nanoparticles not only exhibited high uptake in cells through endocytosis, but also enhanced drug toxicity in KB cells.[134] Heparin was also modified with deoxycholic acid to produce nanoparticles for drug delivery.[135] Starch- and cellulose-based nanoparticles have also been widely studied; these are the most abundant natural polysaccharides found in all biomass. Starch mainly consists of amylose and amylopectin,[136] whereas cellulose consists of β-glucose units.[137] Chemical modifications like addition of hydroxy and carboxyl groups to these polymers have increased their solubility in organic solvents, which helps increase drug loading efficiency. In another attempt to deliver poorly water-soluble drugs, a carrier for hydrocortisone (HC).[138] The hydrocortisone nanocarrier was made from chitosan and modified β-cyclodextrin by ionotropic gelation. The β-cyclodextrin was used because of the lipophilic nature of the cavity in which a lipophilic drug such as hydrocortisone could be loaded; this formulation allows for pH-controlled drug release. A similar hydrogel formed from chitosan and modified β-cyclodextrin using crosslinking reagent EDC showed promise for the delivery of anticancer drugs such as paclitaxel in a controlled manner.[139] Alginate and chitosan were crosslinked by coacervation to provide a controlled β-lapachone delivery system. The resulting crosslinked beads were resistant to the acidic medium and might be an alternative for the β-lapachone therapy of colorectal cancer.[140]

Summary and Outlook

A significant limitation to the administration of conventional drugs is related to their known toxicity to the body. Toxicity can also depend on the presence of molecules introduced to a formulation to improve the poor aqueous solubility of many small-molecule organic drugs during pharmaceutical preparation. Hence, it is important to develop optimal delivery materials to greatly improve their therapeutic efficacy. Additionally, the use of appropriate delivery materials might allow the combined administration of conventional drugs, possibly potentiating their therapeutic effects. Polysaccharides have been reported as potential rheological modifiers, opening up the possibility of controlling the release of a drug by tuning the viscosity of the formulation.[141]

Among the delivery materials studied so far, polysaccharides represent ideal candidates for drug delivery and biomedical applications as they are easily obtained from natural sources. Furthermore they can be subjected to a wide range of chemical and enzymatic reactions, have biocompatible and biodegradable properties and have inherently low immunogenicity. Polysaccharides could be the materials of choice for the development of "smart" delivery systems capable of releasing, at the appropriate time and site of action, their encapsulated drugs. However, the development of such delivery systems needs to take into account several aspects. First, the polysaccharide–drug interaction must be optimized, and this is a variable that is heavily dependent on the physicochemical properties of both the polysaccharide and the drug. Second, the optimization of the pharmacokinetics and pharmacodynamics has

to be performed with careful consideration of absorption, distribution, metabolism, and excretion (ADME) principles. Third, the conjugation of a targeting moiety to the polysaccharide will be useful to limit the off-target impact on healthy tissue. Finally, the applications requiring a gel must be carefully studied in terms of the mechanisms of drug release from the gel. Taken together, these considerations show explicitly that only a multidisciplinary approach can successfully address the challenging task of selecting delivery materials that are optimal for the drug and application of interest. If an ideal delivery system is not yet available, the examples reported in this Review indicate that many interesting options, based on the use of polysaccharides, are emerging. Thus, whereas additional research is required, the promising results obtained thus far in this field fully justify further efforts in terms of both economic support and investigations.

Keywords: chemical modification · drug delivery · natural products · polysaccharides · polysaccharide–drug conjugates

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