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REVIEW ARTICLE

Natural Gums and Modified Natural Gums as Sustained-Release Carriers

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ABSTRACT

Although natural gums and their derivatives are used widely in pharmaceutical dosage forms, their use as biodegradable polymeric materials to deliver bioactive agents has been hampered by the synthetic materials. These natural polysaccharides do hold advantages over the synthetic polymers, generally because they are nontoxic, less expensive, and freely available. Natural gums can also be modified to have tailor-made materials for drug delivery systems and thus can compete with the synthetic biodegradable excipients available in the market. In this review, recent developments in the area of natural gums and their derivatives as carriers in the sustained release of drugs are explored.

Key Words: *Biodegradable natural polysaccharides; Natural gums; Sustained-release carriers.*

INTRODUCTION

Natural polysaccharides and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. Various kinds of natural gums are used in the food industry and are regarded as safe for human consumption. These polysaccharides are obtained usually as plant exudates containing various sugars other than glucose and having significant quantities of oxidized groups in adjunct to their normal polyhydroxy format. In many cases, water-soluble polysaccharides generally similar to the exudates are components of land and marine plants and their seeds. These materials result from normal metabolic processes, and many times, they represent the reserve carbohydrate in that system.

It is established that the hydrophilic polymers release freely soluble drugs at a fairly constant rate (1). Various synthetic polymers (e.g., cellulose ethers, polyalkylmethacrylates, etc.) used for this purpose have been reviewed (2–5). These polymers, when in contact with water, are hydrated and form a gel. Natural gums (like agar in the form of beads and konjac in the form of cylinders) have

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also been examined as matrices for the sustained release of drugs (6,7). When natural gums in the form of compressed tablets are placed in water, they are expected to absorb water from the medium and form a gel before they dissolve in the medium. If a drug is contained in the tablet, it is expected to be released through the gel layer, and sustained release may be achieved.

Natural gums are often preferred to synthetic materials due to their nontoxicity, low cost, and free availability. It should be noted that many ''old'' materials compete successfully today after almost a century of efforts to replace them. It is the usual balance of economics and performance that determines the commercial realities. Natural gums have been modified to overcome certain drawbacks, like uncontrolled rate of hydration, thickening, drop in viscosity on storage, microbial contamination, and the like (8).

This review provides a comprehensive review of the area of natural and modified gums used as carriers in the sustained release of drugs.

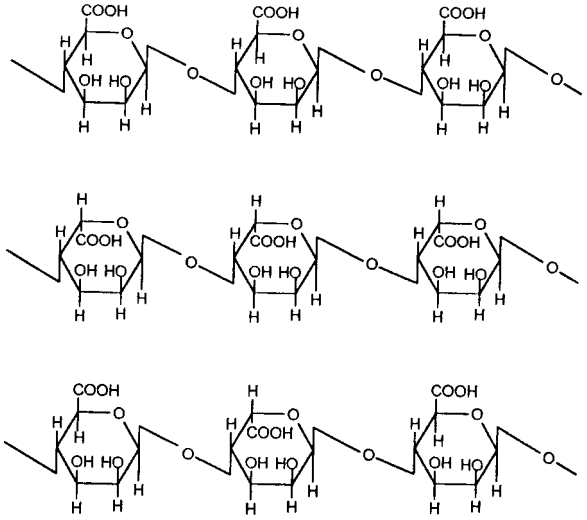


Figure 1. Structure of the polymer segments contained in alginic acid.

AGAR BEADS

Agar has been used as culture media in microbiology, and agarose, which is a purified form of agar, has been employed extensively in separation and purification in biochemistry. Possible use of agar for sustained release of sulfamethizole has been investigated (9). The choice of agar other than agarose was largely economic. Sulfamethizole was incorporated into agar beads. The release profile from the beads showed that the agar beads exhibited sustained release of drug. A possible advantage of agar beads over conventional sustained-release formulations is complete release of the drug from the beads.

SODIUM ALGINATE

Sodium alginate is a natural hydrophilic polysaccharide derived from seaweed. It is the sodium salt of alginic acid, a high molecular weight linear random copolymer consisting of blocks of $1 \rightarrow 4$, linked D-mannuronic acid and L-guluronic acid residues, in addition to reagents in which the two uronic acid residues alternate (Fig. 1) (10). Alginate is easily gelled in the presence of a divalent cation as calcium ion. The gelation or cross-linking is due to the stacking of the guluronic acid blocks of alginate chains (11). Calcium alginate beads can be prepared by dropwise addition of the solution of sodium alginate into the solution of calcium chloride. Recently, many have prepared calcium alginate beads for the controlled release of drugs (12–24).

The alginate beads have the following advantages:

1. Alginate is known to be nontoxic when taken orally and also to have a protective effect on the mucous membrane of the upper gastrointestinal tract.
2. Since dried alginate beads reswell, they can act as controlled-release systems.
3. Since their property of reswelling is susceptible to environmental pH, acid-sensitive drugs incorporated into the beads would be protected from gastric juice.

However, porosity gives alginate beads not only a fast release pattern of incorporated drugs, but also very low efficiency of incorporation of low molecular weight drugs, except for sparingly soluble drugs (12). Therefore, it appeared that alginate beads could be used for a controlled-release system of macromolecular drugs or low molecular weight drugs bound to macromolecules through covalent or noncovalent bonds. The release of blue dextran (MW $\cong$ 2,000,000) from alginate beads at pH 6.8 showed a nearly zero-order release rate, which was more rapid than that at pH 1.2 (13). The influence of erosion of calcium-induced alginate gel matrix on the release of brilliant blue has also been reported (14). Gel beads reinforced by chitosan, which forms a complex with alginate, eroded slowly in phosphate buffer (pH 6.8), and this behavior led to suppression of the initial

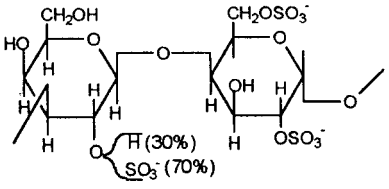
release rate of the drug (15). Further, control of drug release from calcium-induced alginate gel beads by application of a complex formed between chondroitin sulfate and chitosan was investigated (16). The complex suppressed the disintegration of the gelled beads, and the release pattern of diclofenac incorporated within them was changed. Although the prolongation of the preparation time gradually decreased the apparent release rate, the pattern of release was not affected markedly. In a comparative study, hard spherical beads of aluminum alginate and aluminum carboxymethyl cellulose were prepared to sustain the release of diclofenac sodium. Beads prepared from sodium alginate showed a nonsignificantly ($p > .05$) faster rate of drug release than that prepared from sodium carboxymethyl cellulose. The two formulations of beads resulted in the sustained-release action of diclofenac sodium for 24 hr. The relative bioavailabilities of the two formulations were 59.01% and 47.96%, respectively, relative to that of the commercial Voltaren Retard tablets of Ciba Geigy (17).

Sodium alginate rapidly forms viscous solutions and gels on contact with aqueous media. The property has been exploited by the pharmaceutical industry in its wide application as a carrier in hydrophilic matrix controlled-release oral dosage forms. Matrices incorporating either a single alginate salt or combinations of salts have been employed to sustain release of many drugs in vitro and in vivo (25–28). Melia and coworkers (29) studied the effect of pH and drug solubility on the release kinetics of sodium alginate matrices. Release of a highly soluble model drug, chlorpheniramine maleate, was significantly faster in simulated gastric fluid than in simulated intestinal fluid, whereas the opposite effect was observed for hydrochlorothiazide, a drug of poor solubility. Cryogenic electron microscopy revealed the hydrated surface layer formed by alginate matrices in simulated gastric fluid to be particulate and porous in nature, in contrast to the highly hydrated continuous gel layer formed in simulated intestinal fluid.

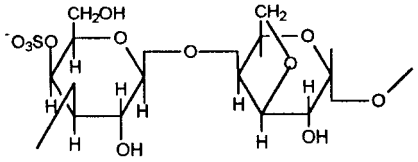
Novel modified lactose particles containing a gel-forming polymer were prepared for controlling the drug release rate from the resultant matrix tablets. The method used was spray-drying of an aqueous solution of α-lactose monohydrate and sodium alginate. The drug release from the matrix tablets prepared with the spray-dried particles and acetaminophen at pH 1.2 was more prolonged than that of physically mixed tablets of lactose, sodium alginate, and the drug because of improved gel-forming properties of sodium alginate formulated in spray-dried particles (30).

CARRAGEENANS

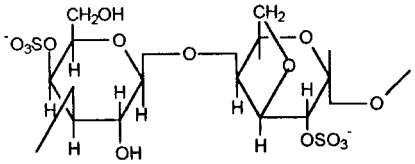
Carrageenans are marine hydrocolloids obtained by extraction from some members of the class Rhodophyceae. The most important members of this class are *Chondrus crispus* and *Gigartina stellata.* There are three different types of carrageenans: κ-, ι-, and λ-carrageenan (Fig. 2). All consist chiefly of the sulfated esters of D-galactose and 3,6-anhydro-D-galactose copolymers, linked α-1,3 and β-1,4 in the polymer. The λ-carrageenan does not contain 3,6-anhydro galactose and is highly sulfated. It does not gel and is used as a thickening agent.



λ-Carrageenan



κ- Carrageenan



ι- Carrageenan

Figure 2. Different types of carrageenans.

The κ- and ι-carrageenan are very similar, except ι-carrageenan is sulfated at carbon-2. Both polymers swell and form gels. The κ-carrageenans form strong, rigid, and brittle gels. A very small amount of potassium ion is essential for this. The ι-carrageenan forms elastic gels that show thixotrophy, mainly in the presence of calcium ions (31).

Carrageenans were mainly used as gelling and thickening agents. Only a few studies have dealt with carrageenans for controlled-release tablets (18,32,33). These studies dealt only with drug delivery from tablets on a hydraulic press or from tablets that contain the carrageenans in a mixture with other excipients.

In a study of four natural hydrophilic gums formulated as minimatrices in hard gelatin capsules, it was concluded that carrageenan used in the study did not produce sufficient sustained release (34). In recent studies, the compaction and consolidation behavior of carrageenan were determined to prove their usefulness in tableting excipients for controlled-release tablets. The results indicated that the carrageenans were suitable tableting excipients for controlled-release tablets. The compacts were formed easily, and the material behaved viscoelastically during compression. The resulting compacts were of high robustness, and they showed good compactibility, indicated by a high tensile strength. The release behavior of model drugs diclofenac sodium and theophylline indicated that drug release was increased when water sorption and the extent of swelling decreased and viscosity increased (35–37).

CELLULOSE ETHERS

Cellulose is a linear polymer of β-anhydro glucose units. Each anhydro unit contains three hydroxyl groups. Cellulose ethers are cellulose derivatives prepared by etherification of these available hydroxyl groups (e.g., hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methylcellulose, ethylcellulose, and cellulose acetate phthalate). Cellulose ethers are hydrophilic polymers that are quite popular in the design of controlled delivery dosage forms. They are biologically compatible and nontoxic. Apart from these advantages, their property of easy compression and the abilities to hydrate rapidly at body temperature and to accommodate a large percentage of the drug with negligible influence of the processing variables on the release rates are the main reasons for their popularity. The use of cellulose ethers in drug delivery for controlled-release dosage forms has been reviewed by many (38–40).

CHITOSAN

Chitosan is a hydrophilic cationic polyelectrolyte obtained by alkaline *N*-deacetylation of chitin (Fig. 3). Chitin is the most abundant natural polymer next to cellulose and is obtained from crab and shrimp shells.

Chitosan has been found useful as a vehicle for sustained-release preparations of indomethacin, papavarine hydrochloride, and water-soluble drugs such as propranolol hydrochloride (41–43). It was observed that, when dissolution was performed in acid medium, these dosage forms show an excellent sustained-release property. In another study, chitosan granules were prepared to achieve sustained release of indomethacin (44). A unique characteristic of the chitosan granules was that they gradually swelled and floated in acid medium at pH 1.2. This floating property of the granules on the acid medium can be applied to the formulation of sustained-release preparations of various drugs. The effect of the cross-linking procedure on the drug release patterns from chitosan granules was also examined. The release of the drug from granules could be controlled by varying the cross-linking procedure. In vivo performance of indomethacin-chitosan granules was shown to be superior to conventional commercial capsules in terms of decrease in the peak of plasma concentration and maintenance of indomethacin concentration in plasma (45,46).

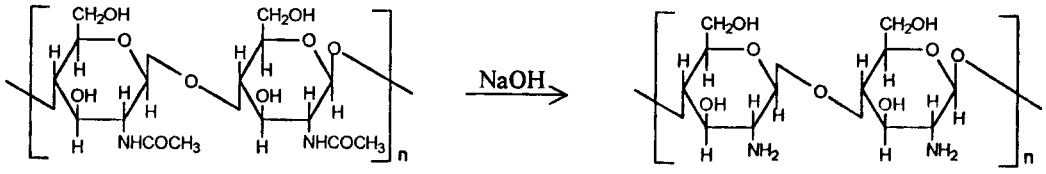


Figure 3. Conversion of chitin to chitosan.

The sustained-release characteristics of chitosan have been investigated in the presence of citric acid or carbomer 934P in tablets containing theophylline as the model drug (47). When chitosan was used alone in a concentration greater than 50% of tablet weight, an insoluble nonerosion type of matrix was formed. Tablets prepared with chitosan concentrations less than 33% were fast releasing, and around 10% of chitosan acted as a disintegrant. Citric acid and carbomer 934P were used as coadjuvants in this study as acidifying agents, which gelled the chitosan and thus imparted sustained-release properties. Only 10% chitosan was needed to prepare theophylline sustained-release tablets in these mixtures (47). Kawashima et al. (48) prepared a prolonged release tablet of aspirin by massing with acetic acid solution or gel of chitosan. Adusumilli and Bolton synthesized chitosan citrate complexes, which were found to be very effective in sustaining the release of theophylline and were directly compressible (49).

A combination of chitosan with sodium alginate for sustaining the release of theophylline has also been studied (50). It was found that the release is independent of the pH of the medium. Various groups of researchers also prepared chitosan beads that exhibited sustained drug release (51–54). Gabr and Meshali (55) investigated and characterized the possible interaction between the natural cationic (chitosan) and anionic (pectin and acacia) polysaccharides. The solid complexes so formed were separated and dried to be used as tablet matrices. The release of water-soluble chlorpromazine hydrochloride from tablets containing various concentrations of each of the polymers alone, the complexes, or physical mixtures of chitosan and of pectin and acacia in the same ratio as their respective complexes was evaluated. The physical mixture displayed the most efficient sustained release.

A chitosan/polyethylene vinyl acetate comatrix has been developed for the controlled release of aspirin-heparin to prevent cardiovascular thrombosis. The amount of drug release initially was much higher, followed by a constant slow-release profile for a prolonged period. The released aspirin-heparin from the comatrix system showed antiplatelet and anticoagulant functions. The results propose the possibility of delivering drug concentrations with synergistic effects for therapeutic applications (56).

DRIED MOLASSES

Dried molasses are natural product derivatives that are widely available and extensively used in the food industries as a flavor, sweetener, source of dietary fiber, and natural color. Uko-Nne and Memdes (57) conducted a feasibility study to evaluate the potential use of dried molasses as direct tableting carriers. The dissolution studies of a vitamin C formulation showed that about 90% of the drug was released over 3 hr. It was also observed that dried molasses matrix formed a pseudo gel-like mucilagenous layer around an inner dry core tablet when it came in contact with liquid. Further, the dried molasses matrix was modified by incorporation of hydroxypropyl methylcellulose at four concentration levels (12.5%, 15.0%, 20%, and 28.57%) to obtain a gel layer of suitable characteristics. It was concluded that, depending on the concentration of hydroxypropyl methylcellulose and the dissolution fluid used, the duration of release ranged from 3 to 36 hr (58,59).

GELLAN GUM

Gellan gum (Fig. 4) is an anionic polysaccharide secreted by *Pseudomonas clodea*. It is capable of gelation in the presence of mono- and divalent ions. Gelrite®, a deacetylated gellan gum, has the unique property that, when dispersed in low concentrations (<1%) in water, it forms a slightly viscous solution that can subsequently increase markedly in apparent viscosity when introduced into the presence of a physiological level of cations (60).

Alhaique et al. (61) investigated the behavior of dried beads obtained from a gellan calcium gel. Metribuzin, employed for weed control in agriculture, and well-known drugs such as theophylline and benzamide were selected as model molecules for the in vitro release experiments. The results indicated that gellan is suitable for the formulation of sustained-release beads. The swelling of the matrix seems to be the most likely factor responsi-

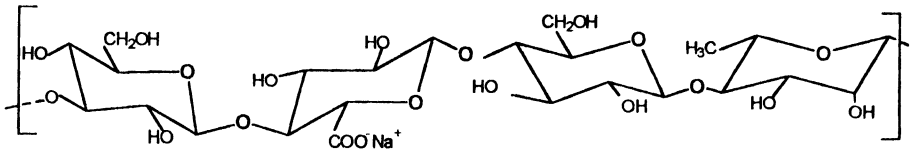


Figure 4. Gellan gum.

ble for the overall rate of delivery. In a comparative study, salbutamol sulfate beads were prepared using anionic and cationic polysaccharides, Gelrite, and chitosan. Alginate beads were also prepared for comparison. The drug release was dependent on the ionic properties of the polymers and the pH of the release media. In acidic media (pH 1.2), chitosan beads showed rapid drug release, whereas sustained drug release was obtained from Gelrite beads. In contrast, the drug release in phosphate buffer (pH 7.4) was rapid from Gelrite, and chitosan showed sustained drug release. The results of drug release from Gelrite were comparable to that from alginate beads (54).

GUAR GUM

Guar gum is a gum obtained from the ground endosperms of *Cyamposis tetragonolobus* (Leguminosae family). It consists chiefly of high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages. The structure of guar gum is a linear chain of β-D-mannopyranosyl units linked (1 → 4) with single-member α-D-galactopyranosyl units occurring as side branches (Fig. 5) (62).

Guar gum is an interesting polymer for the preparation of hydrophilic matrix tablets because of its high water swellability, nontoxicity, and low cost. Various groups of workers have used guar gum as a controlled-release carrier (25,63–67). Nakano and Ogata (25) examined five natural gums as matrices for sustained release of theophylline. The release rate from guar gum tablets decreased with time. Baveja et al. (65) examined 12 natural gums and mucilages as sustaining materials in tablet dosage forms. Tablets prepared using guar gum as the sustaining material dissolved in 2 hr due to the high erosion rate of the matrix. Bhalla and Gulati (66) evaluated sustained-release theophylline tablets with Eudragits and guar gum.

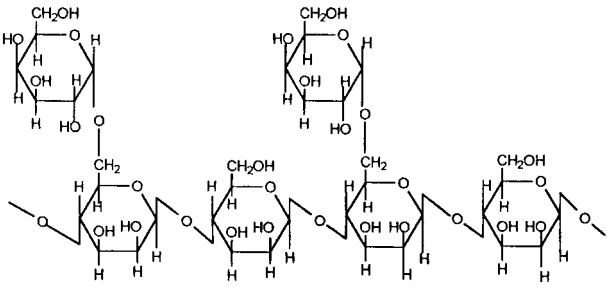


Figure 5. Guar gum.

Formulations based on 5% guar gum gave an appropriate release pattern over a period of 12 hr.

Alataf and coworkers (67,68) examined the use of guar gum to sustain the release of diltiazem. Results showed that varying the lot of guar gum as well as using guar gum from different suppliers had little effect on diltiazem dissolution. The stabilities of guar-based formulations under stressed conditions were also established. All four formulations gave similar plasma concentrations over time in pharmacokinetic studies of healthy volunteers. It was concluded that matrix tablets based on guar gum represent a simple and economic alternative to existing diltiazem sustained-release dosage forms. Khar et al. (69) evaluated guar gum in the preparation of sustained-release matrix tablets. It was found to be effective in prolonged drug release. After hydration of the gum, the drug release was essential through a diffusion process. Gebert and Friend (70) purified guar galactomannan and assessed certain pharmaceutical attributes. The viscosity of an aqueous 1% purified galactomannan solution is typically 40–50% higher than its unpurified precursor. The hydration rate of 1% aqueous solution increases by 100% after purification. These data demonstrated the need for less guar gum to sustain the release of water-soluble drug.

In spite of the wide pharmaceutical applications of guar gum, its use is limited by its uncontrolled rate of hydration, decreased viscosity on storage, and microbial contamination. Paranjothy and Thampi (71,72) synthesized derivatives of guar, such as guar acetate, guar phthalate, guar acetate phthalate, guar succinate, guar benzoate, polygalactomannan (borate reaction), oxidized guar gum, hydroxypropyl guar, and sodium carboxymethyl guar. The solubility studies showed that sodium carboxymethyl guar gave a transparent gel. A 2% sodium carboxymethyl guar solution in water poured over a mercury pool produced a very good flexible, clear, transparent film. Later, a transdermal patch of verapamil hydrochloride was prepared using sodium carboxymethyl guar as a polymer matrix (73). In vitro release studies through mouse skin showed that sodium carboxymethyl guar was a suitable polymer.

In an attempt to improve the interaction coefficient of guar gum, Misra and Baweja (74) carried out controlled hydrolysis of guar gum using hydrochloric acid. The swelling characteristics and dissolution profile from guar gum/hydrolyzed guar gum matrices were studied and compared with those from hydroxypropyl methylcellulose. The results suggested that controlled hydrolysis produces guar gum with an improved interaction coefficient and dissolution profile. Furthermore, guar gum and meth-

ylated guar gum were used to prepare hydrophilic matrix controlled-release tablets using chlorpheniramine maleate as a model drug (75). Drug release profiles from guar gum matrix tablets show a high percentage of drug release (31.06% ± 2.56%) in the first half hour, and then the rate of drug release decreased with time. In the case of methylated guar gum, significant reduction in the amount of drug released in the first half hour (18.77% ± 0.68%) was observed. The rate of hydration increased; hence, the onset of the obstructive gel layer formation was faster compared to guar gum. The results also showed that the rate of drug release increased with degree of methylation, which can also be explained in terms of reduced viscosity of the methylated guar gum.

GUM ACACIA

Gum acacia or gum arabic is the dried gummy exudate obtained from the stem and branches of *Acacia senegal* (Linne) Willdenow and other related species of acacia (Leguminosae family). The gum has been recognized as an acidic polysaccharide containing D-galactose, L-arabinose, L-rhamnose, and D-glucuronic acid (76). Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges and as a tablet binder (77). Its use as sustained-release carrier has been investigated by Baveja et al. (65). Matrix tablets made using gum arabic and drug in a ratio of 4:1 completely dissolved within 2 hr.

Ray et al. (78) prepared gum arabic pellets from which sustained release of ferrous sulfate was achieved for 7 hr. Release was further sustained for 12 and 600 hr by coating the pellets with polyvinyl acetate and ethylene vinyl acetate, respectively. An increase in the amount of gum arabic in the pellets decreased the rate of release due to the gelling property of gum arabic. The gel layer acted as a barrier and retarded the rate of diffusion of ferrous sulfate through the pellet. In coated pellets, an increase in thickness of membrane help to sustain the release of ferrous sulfate for a longer duration. Further, a blend of synthetic polyvinyl alcohol and the natural macromolecule gum arabic was characterized (79). Characterization of these blends by nuclear magnetic resonance (NMR), differential scanning calorimetry (DSC), and viscoelastic studies revealed a blend composition with synergistic properties. This blend composition was used to release various antimicrobial drugs. The duration and release of the drug depended on the amount of drug loaded in the matrix and the solubility of the drug in the matrix and release medium. The advantage of this system is that the release kinetics of the drug from the system can be tailored by adjusting plasticizer, homopolymer, and crosslinker compositions depending on the drug to be released.

KARAYA GUM

Karaya gum (from the sterculia tree) is a partially acetylated polymer of galactose, rhamnose, and glucuronic acid. Munday et al. (34) showed that minimatrix prepared using karaya gum was able to retard drug release. After 24 hr, the cumulative amount of drug release was 71%.

KONJAC GEL

In an attempt to examine the applicability of hydrogels for sustained-release preparations, Nakano and coworkers (80) examined the release of dibucaine, a local anesthetic, from konjac gels gelatinized with borax. The results indicated that release of the drug dispersed in konjac gel was sustained. The release experiments in vivo, following rectal administration of the gels, showed good correlation with in vitro data (81). Since borax, the gelatinizing agent employed, is not suited for oral administration, konjac gels were prepared in another study using the gelation procedure for food, and theophylline was then absorbed into the gel (82). Sustained release of the drug from the dried konjac gels was obtained. No marked difference was observed in the release patterns in the range of pH values expected in the gastrointestinal tract, and the drug contained in the gels was released completely.

LOCUST BEAN GUM

Locust bean gum is a linear chain of β-D-mannopyranosyl units with nonuniformly spaced side branches. Nakano and Ogata (25) examined five natural gums as matrices for sustained release of theophylline. From a locust bean gum tablet, about one-half of the drug was released very rapidly, but the rest was released slowly. Since locust bean gum is reported to enhance the gel strength of carrageenan, a mixture of the two gums was also examined. The drug was released more slowly from a tablet prepared from a 2:1 mixture of carrageenan and locust bean gum than from a carrageenan tablet. Munday et al. (34) evaluated locust bean gum as minimatrix formulations enclosed in a hard gelatin capsule in an attempt to design an oral sustained-release multiple unit dosage

form for diclofenac sodium. The release profile in buffered dissolution medium (pH 7.0) showed that sustained release of diclofenac sodium up to 77% of drug content was achieved from a minimatrix containing locust bean gum.

MODIFIED STARCHES

Starch, in its native and modified forms, is used extensively throughout the pharmaceutical industry as a disintegrating agent, as a binder, or as a diluent in the tableting process. Starches can be gelatinized to make them cold-water swellable. When formulated as a tablet, these starches can form a hydrophilic gel matrix that prolongs the release of an active ingredient. Different processes are proposed for pregelatinization, drum drying, extrusion, and a controlled pregelatinization–spray-drying technique. The nontoxicity and low production costs of thermally modified starches make them of great interest for the formulation of controlled-release tablets.

For many years, a number of chemical modifications have been developed to improve the properties of starches. Because of the abundance of hydroxyl groups in the polymer, cross-linking occurs when starch is treated with a bifunctional or multifunctional reagent such as acid anhydride, aldehyde, ethylenic compound, and the like. Cross-linking reinforces hydrogen bonds holding the granules together. This produces considerable changes in the gelatinization properties of starch granules and leads to a restriction in swelling properties.

Modified starches have been investigated as possible matrix-forming excipients by various groups (83–87). Mohile (88) reported the formulation of an acetyl salicylic acid sustained-release tablet based on modified starches (pregelatinized starch). Acetyl salicylic acid was mixed with pregelatinized starch, and the blend was compressed into tablets. These tablets, when exposed to aqueous fluids, rapidly released a fraction of drug. However, due to hydration and gelation of the starch at the tablet-liquid interface, remaining acetyl salicylic acid exhibited prolonged dissolution profiles.

Aerde and Remon (89) investigated a variety of starches as possible hydrophilic matrices for controlled drug release using theophylline as the model drug. The modifications were both physical and chemical, such as pregelatization by drum drying or by extrusion, partial hydrolysis, and cross-linking. The tablets made of native cornstarch, cornstarch partially depolymerized by acid hydrolysis, and purely cross-linked cornstarch disintegrated completely within 10 min; consequently, they cannot be used as matrices for sustained release. The tablets made of pregelatinized starches presented prolonged drug release. Pregelatinization by extrusion seems to induce slower release in comparison to starches pregelatinized by the drum drying process. Pregelatinization coupled with an increasing cross-linking degree reduced the delay of drug release.

A fundamental study on the production and characterization of thermally modified starches was reported (90). The study pointed out that both the chemical composition of starch and modification technique have considerable influence on the physical properties of the modified starches. As regards the application as hydrogel matrices in controlled-release tablets, promising results were seen for those extruded and drum dried containing medium to high amounts of amylopectin. In vitro and in vivo studies also show the same results (91,92). In an another study, Visavarungroj and coworkers (93) evaluated different types of cross-linked starches and pregelatinized cross-linked starches for their use as hydrophilic matrices. The results indicated that cross-linked starches, either pregelatinized or not, are not suitable for sustained-release agents.

Lenaerts and coworkers introduced amylose cross-linked by epichlorhydrin as a matrix for controlled release of drugs (94,95). Different reticulation degrees were obtained by varying the degree of epichlorhydrin to amylose. A linear release of theophylline from the cross-linked amylose tablets was observed in all cases. Linear increase in the cross-linking degree of the cross-linked amylose used for tablet preparation generated nonlinear diminution of the release time. For the tablets obtained from cross-linked amylose-7.5 containing theophylline up to 20% w/w, a release that was close to linear was found over a period of 15 hr. For a moderate increase in cross-linking degree (cross-linked amylose-12 and cross-linked amylose-20), the release time was drastically decreased to 1–2 hr. When the degree of cross-linking was less, fewer 3-D transverse glyceric bridges were present. As a consequence, it is assumed that a significant number of hydrogen bonds can be created between neighboring polymeric chains. The slow theophylline release was attributed to slow water penetration due to the presence of numerous intragranular hydrogen bonds. At a higher cross-linking degree, the fewer hydrogen bonds formed do not allow good cohesion of the tablet. On swelling, individual polymeric granules separate, and drug is released rapidly. Advantages of this material include the ease in tablet manufacturing, the possibility of achieving

controlled release at high drug concentration, and the relative independence of release kinetics from drug loading within certain limits.

A new starch product for controlled drug release was introduced (96). It consists of a linear glucose polymer with a mean degree of polymerization of 30 and was prepared by enzymatic degradation of gelatinized potato starch, followed by precipitation (retrogradation), filtration, and washing with ethanol (97). The last process created powders with specific surface area greater than 1.5 m^2/g. Tablets compressed from a physical mixture of this material with theophylline released the drug with a decreasing rate due to porous diffusion when the tablet porosity was more than 7%, but nearly constant drug release was observed for lower porosity. Release rates from retrograded pregelatinized starch tablets can be enhanced or decreased to the desired profile by such different parameters as geometries of the tablet, compression forces, and the incorporation of additional excipients (98).

Matrix pellets have been prepared by combining microcrystalline waxes, pregelatinized starches, and hydrolyzed starches (99). Ibuprofen, sodium salicylate, benzoic acid, sodium benzoate, and chloroquine phosphate were used as model drugs. The drug release rate was decreased on increasing the wax concentration, having the melting range between 68°C and 72°C. Pellets containing drum-dried cornstarch failed to form matrix pellets. The slowest drug release was obtained from the formulation containing waxy maltodextrin, releasing 95% of the incorporated ibuprofen after 48 hr. Drug release was controlled by pores and matrix diffusion. The release of sodium salicylate and sodium benzoate from the wax-starch matrix pellets was characterized by an initial burst release, followed by a block of the drug release. The bioavailability studies of ibuprofen from the pellets based on microcrystalline wax and starch derivatives demonstrate that pellets based on a combination of microcrystalline wax and starch derivatives can be used to formulate sustained-release, as well as immediate-release, formulations (100).

PECTINS

Pectins are important ionic polysaccharides found in plant cell walls. They consist mainly of linearly connected α-(1 $\rightarrow$ 4)-D-galacturonic acid residues, which have carbonyl groups. It has been shown that pectins form water-soluble complexes with certain nonsteroidal anti-inflammatory drugs (NSAIDs) (101). The dissolution rate of benzydamine hydrochloride/pectin coprecipitate and a physical mixture of benzydamine hydrochloride and pectin was very slow in comparison with intact benzydamine hydrochloride and a physical mixture of benzydamine hydrochloride and galacturonic acid. This suggested the usefulness of pectin as an additive for sustained-release preparations, and this might afford a mean for reducing adverse reactions of NSAIDs in the stomach after oral administration.

Recently, pectin beads prepared by the ionotropic gelation method have been investigated as a sustained-release drug delivery system. However, the use of pectin beads has some drawbacks due to their rapid in vitro release (102,103). In another study, calcium pectinate gel beads of indomethacin, a poorly soluble drug, were prepared (104). The indomethacin was dispersed in a solution of pectin, and then the dispersion was dropped in calcium chloride solution. The droplets instantaneously formed gelled spheres by ionotropic gelation. The effects of several factors (such as pectin type, the presence of hardening agent, and the drug loading) on the percentage of drug entrapped, size distribution, and drug release from calcium pectinate gel beads were investigated. Strong spherical beads with narrow size distributions, high yield, and good entrapment efficiencies could be prepared. The mechanism of drug release from calcium pectinate gel beads followed the diffusion-controlled model for an inert porous matrix. Therefore, calcium pectinate gel could be a useful carrier for controlled-release drug delivery of poorly soluble drugs.

A new binary polymer matrix tablet has been developed for oral administration (105). Highly methoxylated pectin and hydroxypropyl methylcellulose at different ratios were used as major formulation components, and prednisolone was used as the drug model. The result indicated that, by increasing the ratio of pectin to hydroxypropyl methylcellulose, release rates were increased, but zero-order kinetics prevailed throughout the dissolution period.

SCLEROGLUCAN

Scleroglucan is a natural exocellular polysaccharide secreted by a fungus from the genus *Sclerotium rolfsii*. It is β (1 $\rightarrow$ 6)-D-glucan with a single pendant glucose group attached through a β (1 $\rightarrow$ 3) linkage (Fig. 6). It exhibits a gel-like structure in aqueous solution at low temperatures.

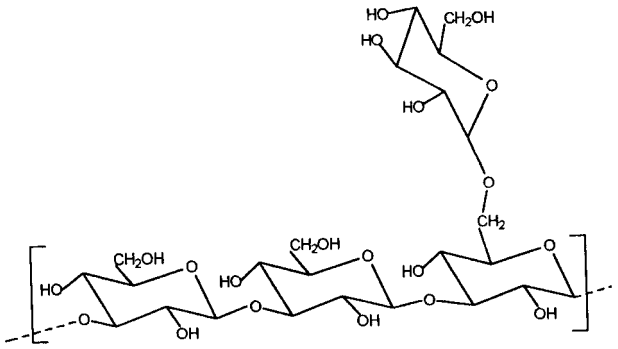


Figure 6. Scleroglucan.

In recent years, particular attention has been focused on the possible utilization of scleroglucan because the physicochemical properties of this polysaccharide suggest its solubility as a sustained-release monolithic swellable matrix. The viscosity of scleroglucan solution and its stability over a range of temperature, pH, and salt concentrations have been studied (106). It was concluded that the high viscosity of scleroglucan solution at a low concentration (1–3% w/w) together with its stability make this polymer a subject of exploration for pharmaceutical preparations. In an another study, physicochemical and mechanical characteristics of scleroglucan were investigated. The physicochemical properties of Actigum CS 11 (scleroglucan) suggested its suitability as a gelling polymer carrier matrix for slow-release matrices (107).

Subsequently, pharmaceutical compatibility of this polymer with two common diluents, Lactose Fast Flo® and Emcompress® was checked (108). In an another study, directly compressed hydrophilic matrices of theophylline were prepared with scleroglucan as the gelling agent (109). It was concluded that, when a porous scleroglucan matrix is brought in contact with dissolution medium, the formation of the gel layer more or less quickly blocks the surface pores and prevents the ingress of the dissolution medium, assuming control of drug transport.

Alhaique et al. (110–113) studied the release behavior from tablets prepared with scleroglucan and concluded that the drug delivery is related directly to the penetration rate of the solvent into the polymer matrix and not to the outward diffusion of the drug through the gel layer that is formed around the tablet. Further, the behavior of cross-linked scleroglucan indicated that the polymers could be used as monolithic swellable systems for the sustained release of the drugs or as films capable of regulating the diffusion of bioactive substance (114). Recently, a co-cross-linked polysaccharide hydrogel of scleroglucan and gellan gum was prepared (115). For the characterization of the co-cross-linked polysaccharide, diffusion experiments through the swelled hydrogel were carried out in different environmental conditions, and the release from the tablets prepared with co-cross-linked polysaccharide and theophylline was evaluated. The addition of calcium chloride in the formulation of the dosage forms allowed a further marked reduction in delivery rate to be obtained. This effect is related to the free ionized carboxylic groups still present in the gellan moiety of co-cross-linked polysaccharide.

XANTHAN GUM

Xanthan gum is a high molecular weight extracellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β-D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain. The terminal D-mannose residue may carry a pyruvate function, the distribution of which is dependent on the bacterial strain and the fermentation conditions. The non-terminal D-mannose unit in the side chain contains an acetyl function. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain (Fig. 7) (116).

Xanthan gum offers potential utility as a drug carrier because of its inertness and biocompatibility. Xanthan

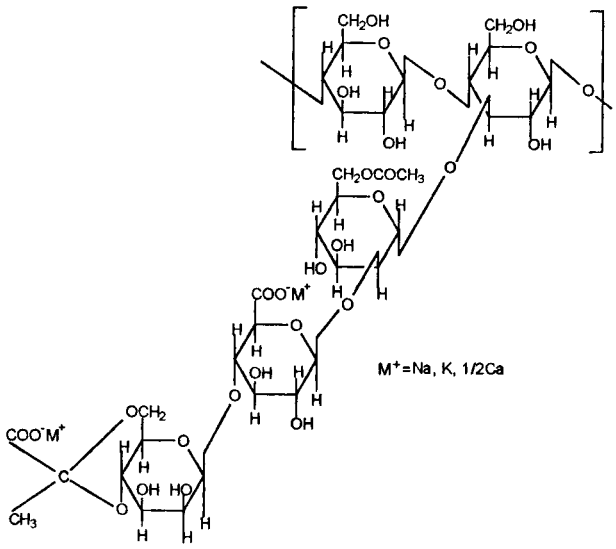


Figure 7. Xanthan gum.

gum is compatible with virtually all salts, and solution pH and temperature have very little effect on the viscosity of its gel. It has been reported by many group of workers that xanthan gum can be used as an effective excipient for sustained-release formulations. Combinations of xanthan gum, hydroxypropyl methylcellulose, hydroxypropyl cellulose, and ethylcellulose in coated tablets also have been evaluated for sustained release (117). The tablets contained 30–72 wt% of a mixture of polymers. Dhopeshwarkar and Zatz (118) evaluated xanthan gum as a matrix former for the preparation of sustained-release tablets (118). It was very effective in prolonging the release of soluble (chlorpheniramine maleate) and sparingly soluble (theophylline) drugs. The rate of release was slowed by decreasing the particle size of the gum or by increasing gum concentration. The release of soluble drugs was mainly via diffusion, whereas sparingly soluble or insoluble drugs were released principally via erosion. Drug release from the xanthan gum matrix was slightly faster in acidic media due to more rapid initial surface erosion. After hydration of the gum, drug release was essentially pH independent.

Xanthan gum not only retards in vitro drug release and provides time-independent release kinetics, but also works effectively in vivo and establishes constant drug plasma levels (119–124). Talukdar et al. (125) undertook a comparative investigation to assess the performance of xanthan gum and hydroxypropyl methylcellulose as hydrophilic matrix-forming agents in respect to compaction characteristics and in vitro drug release behavior. Xanthan gum matrices have some important pharmaceutical and economic advantages (e.g., absence of initial burst release, higher drug-retarding ability, more reproducibility in drug release, and the possibility of zero-order release kinetics) over hydroxypropyl methylcellulose matrices. Considering the influence of ionic strength of the medium on drug release behavior, xanthan gum has the disadvantage that the drug release is influenced by the total salt concentration within the range of the gastrointestinal tract, whereas the drug release from hydroxypropyl methylcellulose matrices is independent of ionic strength. Compaction characteristics between the two polymers are quite similar, but the flowability of xanthan gum is better than that of hydroxypropyl methylcellulose.

To find the reason for an observed difference in the retarding ability of drug release from xanthan gum and hydroxypropyl methylcellulose, rheological characteristics and drug diffusion in hydrated matrices were studied (126,127). In the concentration range 4–7%, xanthan gum solution exhibits ''gel-like'' behavior, while hydroxypropyl methylcellulose behaves as a typical polymer solution. Also, under identical experimental conditions, the drug diffusivity in hydroxypropyl methylcellulose gel is higher than in xanthan gum gel.

Xanthan gum has been cross-linked with epichlorhydrin to obtain a hydrogel for use in drug retardation (128). The obtained gel shows swelling degrees up to 100. Theophylline was inserted by diffusion into this gel. Controlled release of theophylline was estimated by elution in a closed recirculation system. The zero-order kinetic was obtained in the diffusion process of theophylline into the eluent within a 14-hr time interval.

CONCLUSION

Natural gums are promising biodegradable polymeric materials. These can be chemically modified to have tailor-made materials for drug delivery systems. In addition, they are nontoxic, freely available, and less expensive compared to their synthetic counterparts. Therefore, in the years to come, there is going to be continued interest in the natural gums and their modifications with the aim to have better materials for drug delivery systems.

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