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Review

Modified gums: Approaches and applications in drug delivery

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ABSTRACT

Gums are naturally occurring components in plants, which are essentially cheap and plentiful. They have diverse applications as thickeners, emulsifiers, viscosifiers, sweeteners etc. in confectionary, and as binders and drug release modifiers in pharmaceutical dosage forms. However, most of the gums in their putative form are required in very high concentrations to successfully function as drug release modifiers in dosage forms due to their high swellability/solubility at acidic pH. Hence, gums need to be modified to alter their physicochemical properties. This article is aimed at discussing the modification of gums through derivatisation of functional groups, grafting with polymers, cross-linking with ions etc. The factors influencing these processes in the pursuit of making them suitable for modifying the drug release properties of pharmaceutical dosage forms and for other purposes is discussed with respect to optimization of their performance.

Contents

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1. Introduction

Natural gums are polysaccharides consisting of multiple sugar units linked together to create large molecules. Gums are frequently produced by higher plants as a result of their protection mechanisms following injury. They are heterogeneous in composition. Upon hydrolysis they yield simple sugar units such as arabinose, galactose, glucose, mannose, xylose or uronic acids, etc.

The polysaccharide gums represent one of the most abundant industrial raw materials and have been the subject of intensive research due to their sustainability, biodegradability and biosafety. Many natural gums form three dimensional interconnected molecular networks known as 'gels'. The strength of the gel depends on its structure and concentration, as well as on factors such as ionic strength, pH and temperature. The linear polysaccharides occupy greater volume than branched polymers of comparable molecular weight. Hence, at the same concentration, comparable linear polysaccharides exhibit greater viscosity. Therefore, it is difficult for the heterogeneous gum molecules to move freely without becoming entangled with each other (and any other large molecules also present). Also, the natural gums are often known for their swelling properties. Such properties are due to entrapment of large amounts of water between their chains and branches. Hence, they could be classified depending upon their origin, gelation, etc. (Table 1). The chemical structures of some pharmaceutically useful gums are shown in Fig. 1.

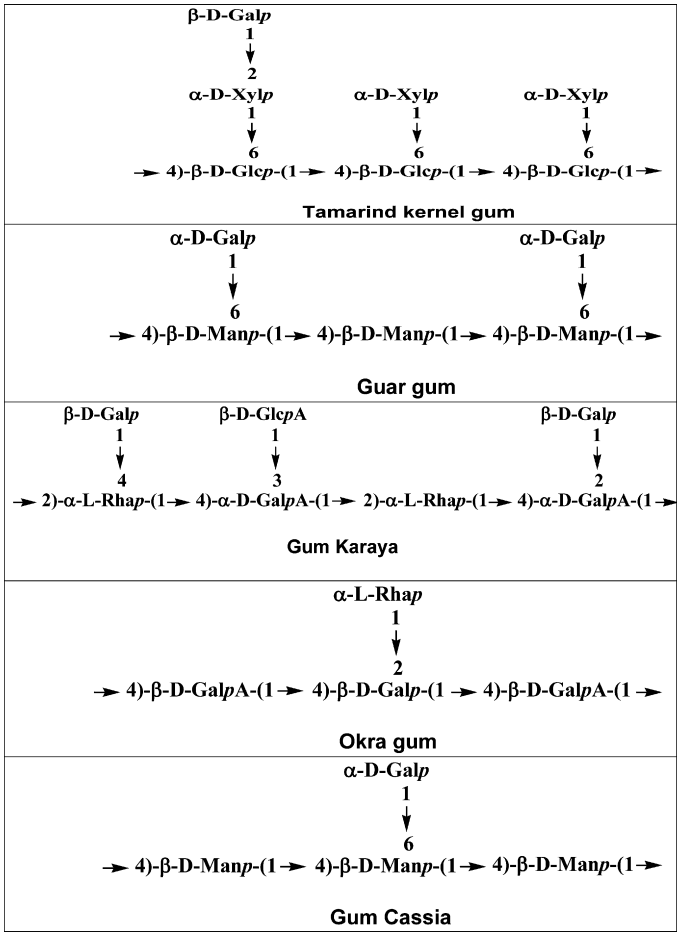

Fig. 1. Chemical structure of some pharmaceutically useful gums.

Natural gums are used in pharmaceuticals for their diverse properties and applications. They have good adhesive and laxative properties and are used in dental preparations. They are used as binders and disintegrants in solid dosage forms. In liquid oral and topical products they are used as suspending, thickening and/or stabilizing agents. Natural gums are preferred over comparable synthetic materials due to their non-toxicity, low cost and availability. Most of the natural gums are safe enough for oral consumption in the form of food additives or drug carriers. Gums are metabolised by the intestinal microflora and ultimately degraded to their individual component sugars (Fig. 2). In addition, enzymes available in the intestine can cleave the gums at specific sites. For example, α-galactosidase can hydrolyse terminal non reducing galactose residues to produce free α-D-galactose.

However, there are certain problems associated with the use of gums. These include uncontrolled rates of hydration, pH dependent solubility, thickening, drop in viscosity on storage, and the possibility of microbial contamination. Chemical modification of gums not only minimizes these drawbacks but also enables their use for specific drug delivery purposes. In light of the above, the present article is aimed at providing a comprehensive review of the various modifications made on gums to make them suitable for modified drug delivery applications.

2. Modifications of gums

2.1. Carboxymethylation/carbomoylethylation of gums

Carboxymethylation of gums increases their hydrophilicity and solution clarity and makes them more soluble in aqueous systems. Modification of tamarind kernel powder, cassia tora gum and guar gum were investigated by Goyal, Kumar, and Sharma (2007), Sharma, Kumar, and Soni (2004, 2003a). The general scheme of carboxymethylation is outlined in Fig. 3. Regardless of the carboxymethyl content, the aqueous gum solutions were characterised by non-Newtonian pseudoplastic behaviour.

Guar gum (GG) was derivatised with monochloroacetic acid to produce carboxymethyl guar gum (CMGG). Carboxymethyl guar gum microbeads were prepared by dropping the solution of CMGG in a solution of divalent or trivalent metal ions. Out of Ca^{2+} and Ba^{2+} ions the Ba^{2+} ions were found to cross-link more efficiently than Ca^{2+}. The Ba^{2+} cross-linked products were able to protect drug release under gastric pH conditions while Ca^{2+} ion cross-linked products released the encapsulated drug when exposed to pH 7.4, i.e. intestinal pH (Thimma & Tammishetti, 2001). Therefore, Ba^{2+} cross-linked CMGG beads were envisaged to possess potential for

Table 1
Classification of polysaccharide gums.

S.No.	Basis	Class	Example
1.	Origin	Seed gums	Guar gum (guar beans), Karaya gum (Sterculia gum)
		Plant exudates	Gum tragacanth (Astragalus shrubs), Chicle gum (From Chicle tree), Konjac glucomannan (From Konjac plant), Gum Arabic (Acacia tree), Gum ghatti (sap of Anogeissus tree), Locust bean gum (carub tree), Mastic gum (mastic tree)
		Microbial exudates (Fermentation)	Gellan gum, Xanthan gum, Tara gum (tara tree) , spruce gum (spruce tree)
		Sea weed	Sodium alginate, Alginic acid
2.	Gelation behaviour	Cold set gels (form gels on cooling the solution)	Gellan gum
		Heat set gels (form gels on heating the solution)	Konjac glucomannan
		Reentrant gels (from which galactose residues are removed)	Xyloglucan
3.	Chemical structure	Galactomannans	Fenugreek gum, guar gum, locust bean gum
		Glucomannans	Konjac glucomannan
		Uronic acid containing gums	Xanthan gum

gastrointestinal drug delivery. Although, the beads produced by cross-linking Ba^{2+} with sodium alginate are not reported to be safe, the literature does not reveal any safety studies pertaining to Ba^{2+} cross-linked CMGG beads. Therefore, toxicity as well as safety investigations are required for Ba^{2+} cross-linked CMGG beads. Out of the various cations that were investigated, only trivalent ions (Al^{3+}, Fe^{3+}) were found to produce beads with smooth morphology and provided greater than 75% drug retention at much lower concentrations as compared to divalent metal ions (Ba^{2+}, Ca^{2+}, Cu^{2+} and Cd^{2+}). The cross-linking efficiency of trivalent ions was found to be higher and this was suggested to be due to their higher valency. The trivalent ions could easily conjugate with at least two cationic sites of sodium carboxymethyl guar gum to effect cross-linking without subjecting the polymer to any folding that may be necessary to accommodate divalent ions. Furthermore, the beads formed by cross-linking CMGG with divalent metal ions were found to be soft and rubbery while with trivalent cations, the beads were soft and brittle which may be due to extensive cross-linking of CMGG

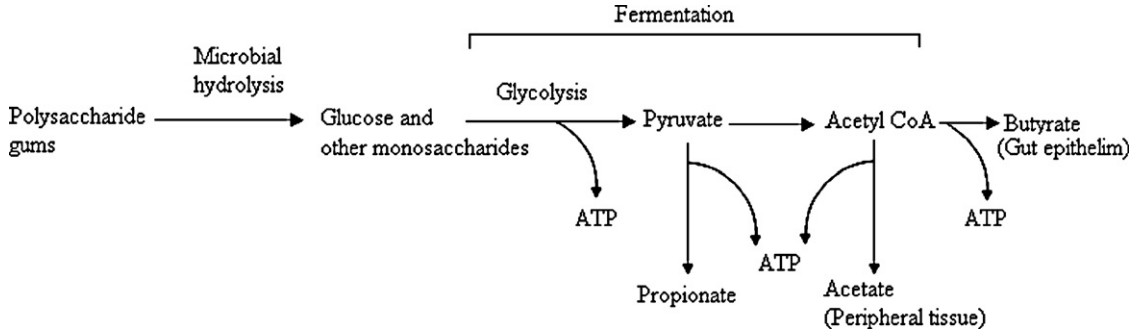

Fig. 2. Biodegradation of polysaccharides in the intestine.

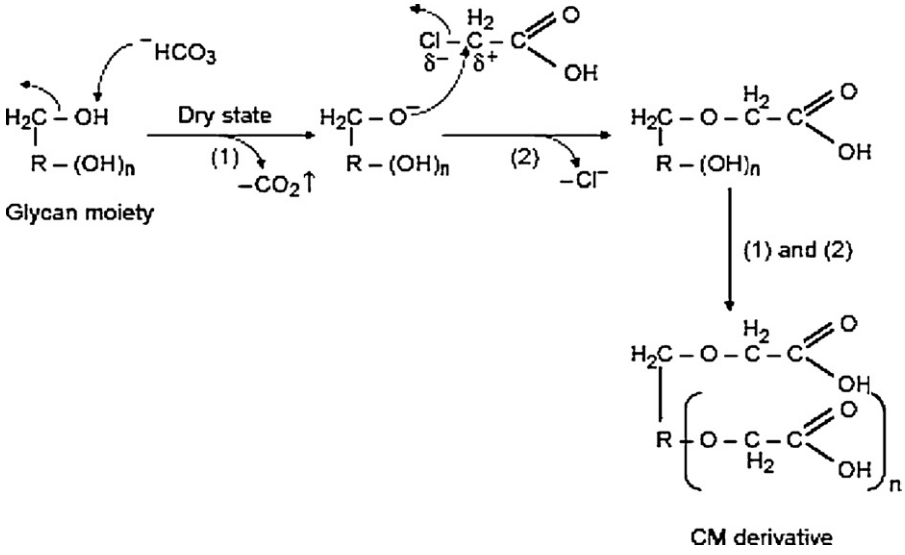

Fig. 3. Carboxymethylation (CM) of gums.

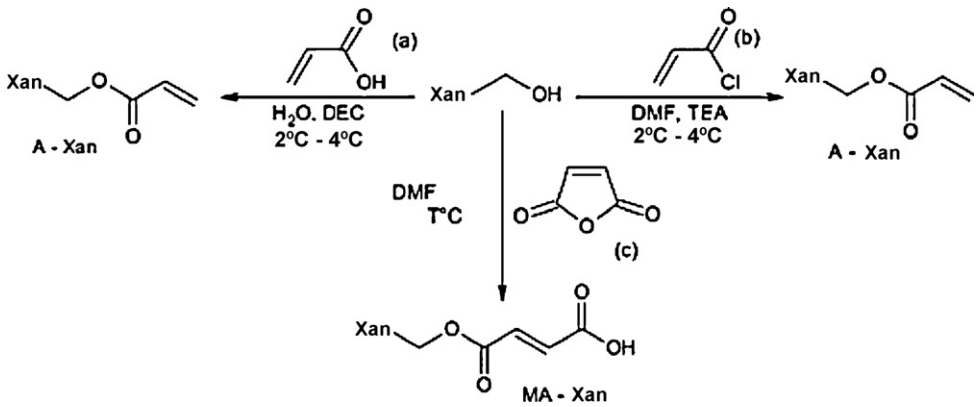

Fig. 4. Strategies for grafting Xanthan gum: (a) acrylic acid; (b) acryloyl chloride; (c) maleic anhydride, A-Xan; Xanthan gum, TEA; Triethanolamine, DMF; Dimethyl formamide, DEC; N′-[3-(dimethylaminopropyl)]-N-ethylcarbodiimide hydrochloride, MA; Maleic anhydride, ACT; Acetone.

by the latter, even at low concentrations (Thimma & Tammishetti, 2001).

Jiangyang, Wang, Liu, and He (2008) reported a method wherein a polyelectrolyte complex was formed between COO^- groups of Konjac glucomannan (KG) and NH_3^+ groups of chitosan. The polyelectrolyte beads were prepared via electrostatic interaction and characterised by IR and DSC analysis. The maximum swelling index of the beads was found at pH 1.2. The polyelectrolyte beads released only 65% of bovine serum albumin (BSA) at pH 5.0 whereas 81% and 73% BSA was released at pH 1.2 and 7.4, respectively in 3 h. Thus, the carboxymethyl konjac glucomannan chitosan beads could be anticipated to be suitable for use as a polymeric carrier for site specific bioactive drug delivery.

2.1.1. Carboxymethylation of cashew gum

Cashew tree gum was carboxymethylated in aqueous alkaline medium using monochloroacetic acid (MCA) as the etherifying agent. In order to provide a better comparison with a carboxymethylated hydrogel, a polysaccharide with a low degree of carboxymethylation (DS) was prepared. The reaction conditions as described by Silva et al. (2004) are briefly described herein. The purified cashew gum (5.00 g) was mixed with water (5 ml) until a homogeneous paste was formed. Sodium hydroxide solution (10 M, 2.7 ml) was added and the mixture was kneaded for 10 min. This was followed by the mixing of monochloroacetic acid (2.62 g) thoroughly with the paste. The mixture was heated at 55 °C, for 3 h. The system was neutralised with hydrochloric acid (1 M) and dialysed against distilled water until all remaining reagents/salts were eliminated (~4–5 days).

Carbamoylethylation of cassia tora gum and guar gum was carried out with acrylamide in the presence of sodium hydroxide under various reaction conditions (Sharma et al., 2003a; Sharma et al., 2004). The optimum conditions for preparing carbamoylethyl cassia tora gum (3.24% N) comprised acrylamide (1.12 mol), sodium hydroxide (1.25 mol) and cassia tora gum (0.197 mol) at 30 °C for 1 h. The optimum reaction conditions for carbamoylethylation of guar gum were: acrylamide (1.0 mol), sodium hydroxide (0.75 mol) and guar gum (0.061 mol) at 30 °C for 2 h (total reaction volume = 500 ml). Rheological properties of carbamoylethyl cassia tora gum solutions showed non-Newtonian pseudoplastic behaviour regardless of the %N. At a constant rate of shear the apparent viscosity of carbamoylethyl cassia tora gum solutions increased with the increase in %N of the product. Similar results were obtained with carbamoylethyl guar gum.

Although, carboxymethylation carbamoylethylation of natural gums can be accomplished relatively easily, the degree of substitution is usually low. This method is expected to be more suitable for gums containing (1,4)-linked units because carboxymethylation/carbomoylethylation occurs primarily at free $-CH_2OH$ groups (i.e. the C6 position of units) due to steric reasons. The steric hindrance by -OH groups present in the gum needs to be considered while attempting such modifications in order to achieve significant degrees of substitution.

2.2. Gums grafted with acrylic acid or its derivatives

Grafting of acrylic acid or its derivatives on gums has been used for modifying the swelling characteristics, film forming properties and drug release properties of the later. The different methods used for grafting other moieties on gums are summarised in Fig. 4.

Poly (acrylic acid) (PAA) and its derivatives are typical pH-responsive polyelectrolytes, which have been widely used for drug delivery to specific regions of the gastrointestinal tract (Ganorkar, Liu, Baudys, & Kim, 1999). However, high water solubility limits their use for delivering drugs to a certain extent, because the drug release takes place before the dosage form reaches the absorption site (Needleman & Smales, 1995). In order to overcome the above drawback, PAA is usually cross-linked with organic cross-linkers to form interpenetrating networks (IPNs) and copolymers. However, the conventional chemically cross-linked hydrogels have many limitations with respect to morphology and properties, e.g., morphological inhomogeneity, mechanical weakness, limited swelling at equilibrium, and slow response to stimuli (Siegel, Falamarzian, Firestone, & Moxley, 1988). It is well understood that PAA has carboxylic acid groups which can be utilised for intermolecular interactions including electrostatic interactions, hydrogen bonding or dipole-ion interactions with other polymers. Many investigators have shown that there are strong interactions between PAA and natural ionic polysaccharides in aqueous solutions. Therefore, this interaction has been advantageously utilised for developing pharmaceutical preparations. For example, chitosan–PAA polyelectrolyte hydrogel for use in controlled drug release formulations has attracted considerable attention, due to its simplicity, feasibility and mild conditions (De la Torre, Enobakhare, Torrado, & Torrado, 2003; Shim & Nho, 2003).

Chemical modification of tamarind kernel powder (TKP) and cassia tora gum through grafting has received considerable attention for imparting new functional groups for different applications. Goyal, Kumar, and Sharma (2008a) developed a method for graft copolymerisation of acrylamide onto TKP. This was carried out in an aqueous medium using a ceric ammonium nitrate-nitric acid initiation system. The maximum grafting efficiency was found to be 93.66%. Also, cassia tora gum was used for graft copolymerisation

of acrylamide using ceric ammonium nitrate–nitric acid as redox initiator (Sharma, Kumar, & Soni, 2002).

Grafting of gums with other polymers or ions requires availability of $-COO^-$ and/or $-CH_2OH$ groups in the gum. The main advantage of these grafted gums is that the resultant molecule can be designed to yield a compound with the desired drug release profile. The grafted molecule could be selected in a way that it does not solubilise while the gum solubilises at a particular pH. In this way, a predetermined drug release profile could be obtained.

2.3. Konjac glucomannan or its derivatives

Konjac glucomannan (KGM) is a non-ionic polysaccharide found in the tubers of *Amorphophallus konjac*, which mainly grows in China and Japan. KGM has long been used as a health food in China and Japan. KGM is regarded as a non-calorie food, the role of which has been displayed in weight loss and cholesterol reduction (Abdulmnem et al., 2008). The Food Chemicals Codex in the United States lists Konjac flour as a food additive (Zhang, Xie, & Gan, 2005). Moreover, low cost, excellent film-forming ability, good biocompatibility, biodegradability, as well as gel-forming properties entitle KGM to be a novel polymeric material. KGM exhibits promising application in various fields like packing and preservation (Luo & Feng, 2004), formulating controlled drug release dosage forms (Wang & He, 2002) and as a wood adhesive (Umemura, Inoue, & Kawai, 2003).

Chemically, it consists of (1,4)-linked β-D-mannose and β-D-glucose in a molar ratio of 1.6:1 (Kato & Matsuda, 1969) with about 1 in 19 units being acetylated (Maekaji, 1978). The KGM backbone possesses 5–10% acetyl-substituted residues, and it is widely accepted that the presence of substituted groups confers solubility to the glucomannan in aqueous solution. If the molecules of KGM lose their acetyl groups with the aid of alkali, the aqueous solution is transformed into a thermally stable gel. This gelation is promoted by heating. The addition of alkali to a KGM dispersion plays an important role in solubilising it in addition to facilitating chain deacetylation (Williams et al., 2000). The molecular weight (length of the main chain backbone) (Zhang et al., 2001) and the acetyl group content in the KGM molecule (Huang, Kobayashi, & Nishinari, 2001; Huang, Takahashi, Kobayashi, Kawase, & Nishinari, 2002) serve as determinants of its gelation characteristics. The physicochemical properties, however, have not been fully elucidated mainly because of the difficulty in obtaining easily soluble and well-fractionated KGM samples.

Increasing demand for materials and products from renewable resources makes it important to develop new functional properties of KGM through physical or chemical modification. Previously, several KGM derivatives were prepared by grafting (Xiao, Gao, Li, & Zhang, 1999), carboxymethylation, palmitoylation, sulfation (Kobayashi, Tsujihata, Hibi, & Tsukamoto, 2002; Zhang, Xie, & Gan, 2005) and their properties and applications assessed. The applications of KGM have been also extended greatly from food and food additives to various fields, such as colon delivery (Luo & Feng, 2004), field-flow fractionation (Benincasa, Cartoni, & Fratte, 2002), ion exchange and adsorption (Luo & Feng, 2004), etc. The reaction scheme for the grafting of KGM with PAA is shown in Fig. 5A.

2.3.1. Cross-linking of konjac glucomannan by organic borate

KGM powder was dispersed in distilled water at room temperature for 1 h, heated to 80 °C and maintained at this temperature for 1 h. Following cooling to room temperature, resultant KGM solution was equilibrated at room temperature for 2 days. After this time, borax solution (200 μL) was added to KGM solution (3.0 g) using a microsyringe, and the solutions were thoroughly mixed by manual stirring using a teflon muddler. The resulting gel was centrifuged at 3000 rpm for 30 min to remove visible bubbles for rheological measurements (Gao, Guo, Wu, & Wang, 2008). All the systems were found to have a pH of 9.0 due to self-buffering by borax (Fig. 5B).

2.4. Cynoethylation of gums

Goyal, Kumar & Sharma (2008b) prepared cyanoethyl tamarind kernel powder (CTKP) using acrylonitrile in the presence of sodium hydroxide under different reaction conditions. The results suggested that optimum CTKP (DS = 0.49) was obtained when 0.008 mol (1.3 equivalent/OH group) of acrylonitrile was reacted at 30 °C for 45 min using 0.026 mol TKP (0.07 mol of OH group) in 100 ml of water. Further, the CTKP was observed to exhibit non-Newtonian pseudoplastic behaviour, relatively high viscosity, cold water solubility, and good solution stability and clarity, as compared to unmodified TKP. In another investigation, cyanoethyl cassia tora gum (DS = 0.44) was produced by mixing 0.608 mol acrylonitrile and 0.625 mol sodium hydroxide at 30 °C for 4 h (Sharma, Kumar, & Soni, 2003b).

3. Cross-linking of gums

3.1. Cross-linking with glutaraldehyde

Natural gums being hydrophilic swell in the presence of dissolution media. Hence, there is a possibility of the entrapped drug leaking out prior to arrival of the drug at its site of absorption. Thus, there is a need to reduce the enormous swelling of the gums by cross-linking.

3.1.1. Cross-linking of alginate guar gum with glutaraldehyde

Alginate guar gum hydrogels were prepared with distinct alginate to guar gum percent weight ratios. Guar gum solution was prepared, the required amount of alginate was added and stirred well to form a uniform mixture. To this mixture glutaraldehyde was added to a final concentration of 0.2% (v/v), blended, and precipitated (in 0.5% (w/v) $CaCl_2$) to form beads. The beads were washed with distilled water to remove any residual glutaraldehyde and calcium chloride, and lyophillised (George & Abraham, 2007). This is depicted in Fig. 6A.

Glutaraldehyde has been used extensively for cross-linking polymers containing hydroxyl groups. It was observed that with an increase in the concentration of glutaraldehyde there was an increase in the cross-link density and as a result there was a decrease in buffer uptake. Drying of the hydrogel to form discs introduced irreversible changes in the hydrogel. Thus, it was observed that when discs were formed by physical entanglements in the polymer network, it resulted in a change in the degree of swelling. However, it was observed that high amounts of glutaraldehyde were required for the cross-linking reaction suggesting that the cross-linking efficiency was low. This could be attributed to (a) low reactivity of guar gum hydroxyl groups as a result of limited water solubility, (b) glutaraldehyde polymerisation during the cross-linking process and (c) possible masking effect of the hexose units of the branched polymer. However, the cross-linked products retained the ability of guar gum to be degraded *in vitro* by a mixture of galactomannase and α-galactosidase (Kabir, Yagen, Penhasi, & Rubinstein, 1998).

In another investigation carried out by Soppirnath, Kulkarni, and Aminabhavi (2000) interpenetrating network microspheres of polyvinyl alcohol and guar gum were prepared. These microspheres were cross-linked with glutaraldehyde. The aldehyde groups of glutaraldehyde reacted with the hydroxyl groups of the polymers to form acetal cross-links. The IR spectra exhibited a corresponding peak at 1251 cm^{-1}. Similarly, DSC studies showed an increase in

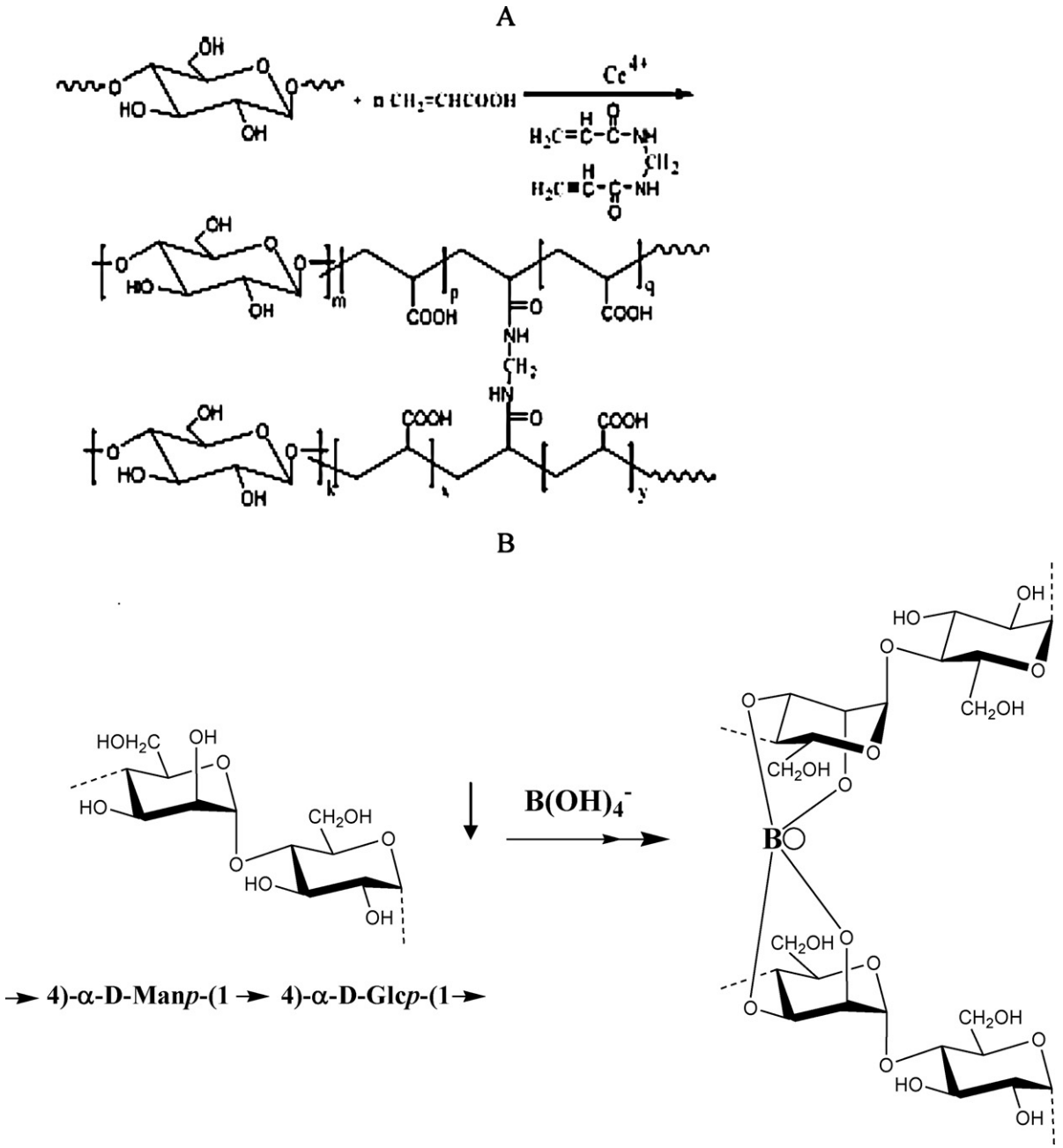

Fig. 5. (A) Grafting of konjac glucomannan (KG) with poly acrylic acid and (B) complexation with Borax ions ($B(OH)_4^-$).

ΔH value. This increase in the ΔH value may be attributed to the high amount of energy required to break the highly cross-linked polymeric network structure. This also suggested the formation of a highly crystalline polymeric matrix due to increase in cross-linking agent density. The crystalline nature of the polymeric matrix dictates its water uptake. An increase in cross-linking leads to formation of a dense macromolecular network. Therefore, a decrease in molecular transport of liquid within such polymeric matrices was observed, resulting in reduced swelling. The *in vitro* release of nifedipine from these microspheres was observed to depend on the extent of cross-linking. This was due to the fact that the solvent uptake by the microspheres decreased with increased cross-linking. Thus, the drug release continued for several hours. The release of the drug from these microspheres increased initially due to the polymer relaxation process as water penetrated and converted the glassy polymer into a rubbery one. However, the latter part of the release profile from the fully swollen polymer was due to a diffusion process.

3.1.2. Cross-linked microspheres of polyacrylamide grafted guar gum (pAAm-g-GG) by water-in-oil (w/o) emulsification method

5.0% (w/v) polymer solution (20 ml) was prepared and acidified with 5 ml dilute sulfuric acid. In order to cross-link the polymer, 2.5, 5 or 7.5 ml of 25% (w/v) glutaraldehyde solution was added to the polymer solution separately. These solutions were then emulsified into 100 ml of light liquid paraffin with 2% (w/v) Tween 80. The hardened microspheres were filtered and washed repeatedly with hexane and water to remove liquid paraffin, unreacted glutaraldehyde and any adhered Tween 80. The hydrogel microspheres were then dried under vacuum at 40 °C overnight and kept in a desicca-

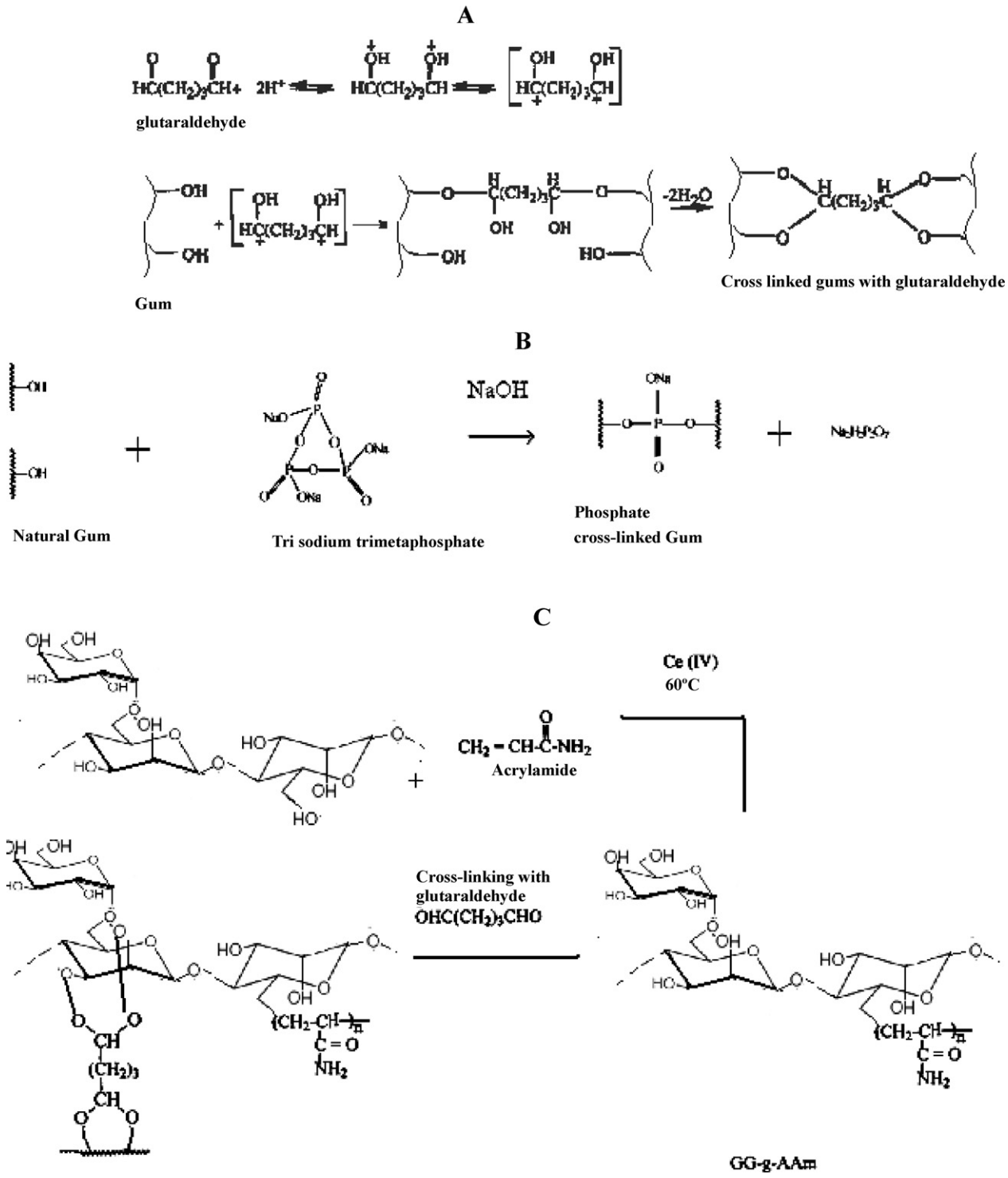

Fig. 6. Cross linking of gums with (A) glutaraldehyde; (B) Tri sodium trimetaphosphate and (C) grafting of guar gum with polyacrylamide (pAAm-*g*-GG) followed by crosslinking with glutaraldehyde.

tor until further use (Soppirnath & Aminabhavi, 2002). The scheme is depicted in Fig. 6C.

3.2. Phosphate cross-linking of natural gums

The high swelling characteristics of natural gums in matrices which leads to burst release does not make them suitable for delivering drugs to distal parts of the gut. Such high swelling can be prevented by phosphate cross-linking (Kabir, Yagen, Penhasi, & Rubinstein, 2000; Kabir, Yagen, Baluom, & Rubinstein, 2000; Dulong et al., 2004). Generally, phosphate cross-linked gums are prepared by dissolving trisodium trimetaphosphate (STMP) in sodium hydroxide solution (1 M, pH 11) at room temperature for 30 min, followed by addition of gum under continuous stirring (Fig. 6B). The dispersion is then stirred slowly to allow maximum swelling of the gum. The mixture is finally poured into a Petri dish and dried. The dried hydrogel obtained is rinsed several times with distilled water to remove unreacted STMP, gum, and other soluble

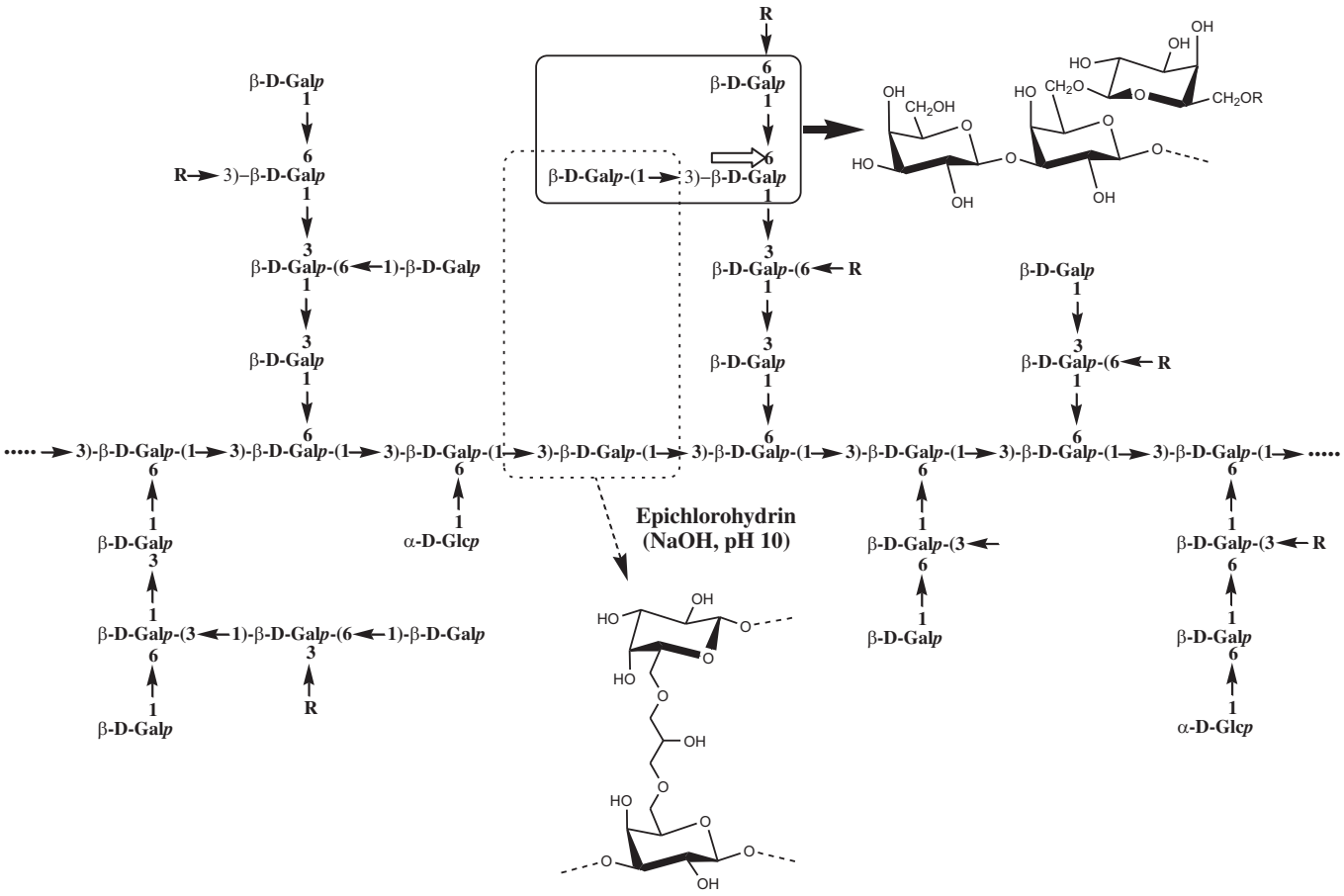

Fig. 7. Scheme of cashew gum cross-linking with epichlorohydrin.

agents and dried to constant weight and stored until further use (Fig. 6B).

3.3. Cross-linking with ions

3.3.1. Preparation of barium ion-cross-linked sodium alginate–CMGG beads

Sodium alginate and carboxymethyl guar gum (CMGG) were dissolved in distilled water at a concentration of 4% (w/v). The polymer solution was then added drop-wise into the gelation medium ($BaCl_2$ solution of definite composition (w/v), 250 mL) at room temperature. The beads, thus formed, were cured in the gelation medium for 20 min and then taken out, washed with distilled water and then allowed to dry to constant weight at 30 °C (Bajpai, Saxena, & Sharma, 2006).

3.4. Miscellaneous methods

3.4.1. Cross-linking of cashew gum with epichlorohydrin

Cashew gum was mixed with sodium hydroxide solution (5 M, 2 ml) and distilled water until a homogeneous paste was formed. Epichlorohydrin (volume in the range of 0.4–0.86 ml) was then added to the mixture and kneaded to afford proper homogenisation. The mixture was heated at 40 °C for 24 h, followed by a second heating time of 15 h at 70 °C (Fig. 7). The cross-linked gel was washed with distilled water, dialysed for 72 h against distilled water and finally, freeze-dried (Silva, Feitosa, Maciel, Paula, & Paula, 2006).

3.4.2. Radiation-induced polymerisation of sterculia gum

Sterculia gum and definite concentration of monomers were dissolved in distilled water (10 ml). The reaction mixture was irradiated with c-rays in a ^{60}Co γ-chamber for 24 h with a total dose of 53.14 kGy. The polymers thus formed were stirred for two hours in a 1:1 mixture of distilled water and ethanol to remove remaining soluble fractions, and were then dried in an oven at 40 °C (Singh & Vashistha, 2008).

Cross-linking of gums requires availability of active functional groups in their basic structure. Hence, gums such as guar gum, cashew gum or sterculia gums that possess free alcoholic and/or carboxylic units seem to be a good choice for modification by cross-linking. However, it is essential to investigate the vulnerability of the cross-linking to different pH in order to use the modified molecule for site specific delivery.

4. Mechanism of cross-linking: modification of gums

Natural gums are generally soluble in water. This is due to the presence of an excessive number of –OH moieties which form hydrogen bonds with water molecules. Hence, these natural gums cannot be used for controlling drug release. Moreover, the –OH moieties are unable to form strong ionic interactions with counter ions. Therefore, these gums need to be modified by derivatisation. A wide variety of functional groups can be attached to natural gums to make them more suitable for controlling the release of drugs from dosage forms. For example, attachment of carboxyl groups, carboxymethyl groups, polyacrylamide groups, phosphate groups etc, have all been extensively investigated for such purposes.

Interestingly, the properties of cross-linked gum derivatives depend mainly on their cross-linking density, namely the ratio of moles of cross-linking agent to the moles of polymer repeating units. Moreover, a critical number of cross-links per chain are required to allow the formation of a network. The types of interactions forming the network depend on the nature of the cross-linker. Therefore, cross-linked gums or their derivatives can be classified as:

(i) Hybrid polymer networks (HPN);
(ii) Semi or full inter-penetrating polymer networks (IPN);
(iii) Ionically cross-linked gums or their derivatives (reversible cross-linking).

4.1. Interaction chemistry

Cross-linked gum or its derivative formed by HPN involves reaction between a structural unit of a gum or its derivative chain and a structural unit of a polymeric chain of another type. In addition, cross-linking of two structural units of the same type and/or belonging to the same polymeric chain cannot be excluded. Semi or full IPNs contain a non-reacting polymer added to the gum or its derivative solution before cross-linking. This leads to the formation of cross-linked gum or its derivative network in which the non-reacting polymer is entrapped. It is also possible to further cross-link this additional polymer in order to have two entangled cross-linked networks, forming a full IPN, where microstructure and properties can be quite different from its corresponding semi-IPN (Song et al., 2001).

In each of the three types of structures, ionic bonds are the main interactions that form the network but other interactions cannot be excluded. Indeed, secondary interactions, such as formation of hydrogen bridges and hydrophobic interactions cannot be totally ruled out.

Ionically cross-linked gum (or its derivative) networks can be divided into two groups depending on the type of cross-linker used (anions or anionic molecules). However, most of their characteristics and properties are identical. A network is formed in the presence of negatively charged entities, which form bridges between the positively charged polymeric chains.

Interactions between the positively charged groups of the cross-linker and the negatively charged groups of the gum derivatives mainly contribute towards ionic interactions inside the network. Their nature depends on the type of cross-linker. Metallic ions induce the formation of co-ordinate covalent bonds between negatively charged groups of gum derivatives. This type of bonding is stronger than the electrostatic interactions formed by anionic cross-linking molecules. Besides the negatively charged groups (e.g. $-COO^{-}$, $-CH_2COO^{-}$, etc.) of gum derivatives, other groups along the gum derivative chains such as hydroxyl groups can also react with ionic cross-linkers. Moreover, additional interactions can occur inside the network. Such interactions include hydrophobic interactions or inter chain hydrogen bonds due to reduced electrostatic repulsion after neutralisation of gum derivatives by cross-linker (Berger et al., 2004; Knapczyk, Majewski, Pawlik, & Wisniewska, 1994; Knapczyk, 1994).

Ionic cross-linking is a simple and mild procedure. In contrast to covalent cross-linking, no auxillary molecules such as catalysts are required (Peppas, 1986). This is of great interest for medical and pharmaceutical applications due to regulatory consideration for safety aspects of catalysts and residual solvents in dosage forms. In fact, ionic cross-linking can be ensured by the classical method of preparing a cross-linked network by adding the cross-linker in either solubilised or dispersed form to the gum or its derivative solution. Gum or its derivative can be cross-linked by simply dipping their pieces into a solution of the cross-linker (Brack, Tirmizi, & Risen, 1997) or by adding the gum derivative solution into a solution of the cross-linker (Knapczyk, Majewski, Pawlik, & Wisniewska, 1994; Monteiro & Airoldi, 1999).

4.2. Factors affecting ionic cross-linking density

As in covalent cross-linking, the cross-linking density is the main parameter influencing important properties of ionically cross-linked derivatives of gums. Important properties of these derivatives being influenced by cross-linking density are mechanical strength, swelling and drug release (Argüelles-Monal, Goycoolea, Peniche, & Higuera-Ciapra, 1998). Therefore, it is important to understand the reaction conditions influencing the cross-linking density in order to modulate the properties of the network.

4.2.1. Size of cross linker

Cross-linking reactions are mainly influenced by the size of the cross-linker. The smaller the molecular size of the cross-linker, the faster is the cross-linking reaction, since its diffusion is easier (Wang, Fang, & Hu, 2001).

4.2.2. Charge density and swelling

Particular attention should be paid to cross-linkers possessing a high charge density, such as tripolyphosphate, that may result in a high cross-linking density. Indeed, in order to allow a pH-dependent swelling with such cross-linkers, cross-linking should be incomplete (Argüelles-Monal, Goycoolea, Peniche, & Higuera-Ciapra, 1998). This can be achieved by a short reaction time and a low cross-linker concentration (Brack, Tirmizi, & Risen, 1997). Another approach for obtaining optimised networks (mechanically stable but with high swelling and drug release) is to combine different cross-linkers such as trisodium trimetapolyphosphate (Brack, Tirmizi, & Risen, 1997).

Ionic interactions between chains of the gums cause swelling, which depend on the cross-linking density set during the formation of the network (Knapczyk, Majewski, Pawlik, & Wisniewska, 1994; Wang, Fang, & Hu, 2001). Therefore, the cross-linking density is modified by external conditions after administration, mainly by the pH of the medium (Yao, Peng, Goosen, Min, & He, 1993). Swelling can occur in both acidic and basic conditions. In the case of the cross-linking of chitosan with gum or its derivatives, pH decreases the charge density of cross-linker and hence the cross-linking density decreases, which leads to swelling. In addition, swelling is favoured by protonation and repulsion of free amino groups present in chitosan. If the decrease in pH is too large, dissociation of ionic linkages and dissolution of the network may occur, which eventually leads to faster release of drug molecules (Brack, Tirmizi, & Risen, 1997). If the pH increases, the protonation of chitosan decreases and induces a decrease in cross-linking density, thus, allowing swelling. If the pH becomes too high, amino groups of chitosan become neutral and ionic cross-linking is inhibited. If the cross-linking density becomes too low, interactions are no longer strong enough to avoid dissolution and the ionic cross-linker itself is released into the medium.

Microgels prepared using polyacrylamide grafted guar gum (pAAm-*g*-GG) showed increased swelling when the pH of the medium was changed from acidic to alkaline (Soppimath, Kulkarni, & Aminabhavi, 2001). For a polymer containing ionic groups, the swelling forces may be greatly enhanced as a result of localisation of charges on the polymer chains. When neutralised with alkali, either partially or totally, the negatively charged carboxylic groups attached to polymer chains set up an electrostatic repulsion, which tends to expand the chain network. However, exceedingly large electrostatic repulsions would prevail when carboxylic ions are present in the presence of hydroxyl ions in the solution. The car-

boxylic groups are ionised at higher pH (i.e. near to 7), while at lower pH, they are protonated. The p*K* value of the carboxylic group of the hydrolysed pAAm-*g*-GG is 4.6. The counter ion concentration inside the gel network increases upon ionisation of the gel. However, due to the higher concentration of the counter ions in the solution inside the gel, an osmotic pressure difference exists between the internal and external solutions of the gel network. This osmotic pressure is balanced by the swelling of the gel. Additionally, the presence of salt ions induces a hydration sheath surrounding the polymer, with a consequent reduction in the degree of ionisation and equilibrium swelling. This movement of ions across the membrane to attain electroneutrality created by the osmotic pressure difference closely resembles the Donnan membrane equilibrium. This effect has also been observed by Durmaz and Okay (2000) while studying the swelling of acrylamide/2-acryamido-2-methylpropane sulfonic acid sodium salt-based hydrogels.

4.3. Ionic cross-linkers

Ionic cross-linking of gums or their derivatives requires multivalent counter ions such as metal ions (Ca^{2+}, Ba^{2+}), anionic molecules (trisodium trimetapolyphosphate,) or polymers (polyvinyl alcohol, polyacrylic acid, polyacrylamide).

5. Pharmaceutical applications of cross-linked or derivatised gums

Cross-linked or derivatised gums are widely being investigated for the design of new delivery systems with tailor-made drug release profiles. An additional advantage of biodegradability confers the property of complete drug release to the dosage form due to the degradation of gums by colonic bacteria and enzymes present in the distal portion of the gastro-intestinal tract. The versatility of gums in designing dosage forms can be judged from the investigations summarised in Table 2. The strategies employed for developing selected dosage forms are discussed below.

5.1. Hydrogels

Spherically cross-linked hydrogels of polyacrylamide-grafted guar gum were prepared by the emulsification method (Soppimath, Kulkarni, & Aminabhavi, 2001). These were selectively derivatised by saponification of the –CONH group to the –COOH group. The derivatised microgels were responsive to the pH and ionic strength of the external medium. The swelling of the microgels increased when the pH of the medium was changed from acidic to alkaline. Transport parameters, solvent front velocity and diffusion coefficients, were calculated from measurement of the dimensional response of the microgels under variable pH conditions. The variation in pH changed the transport mechanism from Case II (in 0.1 M hydrochloric acid) to non-Fickian (in pH 7.4 buffer), and these processes were polymer relaxation-controlled. Ionic strength exerted a profound influence on the swelling of the microgels. Swelling was reversible and pulsatile with the changing environmental conditions. The pH-sensitive microgels were loaded with diltiazem hydrochloride and nifedipine. The release was relatively quicker in pH 7.4 buffer than that observed in 0.1 M HCl and the release followed non-Fickian transport in almost all the cases.

Huang, Yu, and Xiao (2007) synthesised a polyelectrolyte hydrogel combination based on cationic guar gum (CGG) and acrylic acid monomer by photo initiated free radical polymerisation. Fourier transform infrared spectroscopy (FT-IR), scanning electron microscopy (SEM), and differential scanning calorimetry (DSC) confirmed that the formation of the polyelectrolyte hydrogel could be attributed to the strong electrostatic interaction between cationic groups in CGG and anionic groups in polyacrylic acid (PAA). Swelling experiments indicated that CGG–PAA hydrogels were highly sensitive to pH of the environment. Ketoprofen-loaded CGG–PAA matrices demonstrated drug release mainly by non-Fickian diffusion in pH 7.4 buffer solution. However, for tablets, the drug release in pH 7.4 buffer solution was mainly affected by polymer erosion. The pH of the dissolution medium appeared to have a strong effect on the drug transport mechanism. At more basic pH values, Case II transport was observed, indicating that the drug release mechanism was highly influenced by macromolecular chain relaxation (Huang, Lu, & Xiao, 2007).

Gels composed of KG, copolymerised with acrylic acid (AA) and cross-linked by *N*,*N*-methylene-bis-(acrylamide) (MBAAm) were prepared. The influence of various parameters on the equilibrium swelling ratios of the hydrogels was investigated (Chen, Liu, & Zhuo, 2005). The results revealed that swelling ratio was inversely proportional to the content of MBAAm. Also, it was possible to modulate the degree of swelling of the gels by changing the cross-linking density of the polymer. The swelling ratio of the gels responded to variation in environmental pH. The results of degradation tests revealed that the hydrogels retained the enzymatic degradation character of KG and could be degraded by 52.5% in 5 days using Cellulase E0240. *In vitro* release of 5-aminosalicylic acid (5-ASA) in the presence of Cellulase E0240 in pH 7.4 phosphate buffer at 37 °C reached 95.19% after 36 h and was controlled by the swelling and degradation of the hydrogels. The results suggested that although, KG was biodegradable, safe and water soluble, it could not prevent drug release due to its sensitivity to large variations in pH encountered in the gastrointestinal tract. On the other hand, poly(acrylic acid) is pH dependent, but is a non-biodegradable polymer. Therefore, combining KG and poly(acrylic acid) was envisaged for combining the useful properties of these polymers.

Reis, Guilherme, Cavalcanti, Rubira, and Muniz (2006) prepared pH-responsive hydrogel from arabic gum (AG) chemically modified with glycidyl methacrylate (GMA). Water uptake tests of arabic gum–glycidyl methacrylate (AG–MA) hydrogels showed significant pH dependence, which affected the water absorption transport mechanism. In the studied pH range, it was found that the transport of water in AG–MA hydrogel was controlled by Fickian diffusion and polymer relaxation (anomalous transport). At high pH values, the water transport profile became more dependent on polymer relaxation. This effect was attributed to the increase in the ionised groups of glucuronic acid segments, which contributed to electrostatic repulsion among the groups and resulted in expansion of the gel polymer network. AG–MA hydrogels exhibited pH-responsive behaviour, demonstrating them to be appropriate materials for delivering drugs to specific regions in the gut.

Kabir, Yagen, Penhasi, et al. (2000) developed guar gum (GG) cross-linked with increasing amounts of trisodium trimetaphosophate to reduce its swelling properties and for use as a vehicle in oral delivery formulations for targeting drugs to distal portions of the small bowel. Swelling of native GG in artificial gastrointestinal fluids was reduced from 100–120-fold to 10–35-fold depending on the amount of cross-linker used, showing a bell-shape dependency. GG lost its non-ionic nature due to the cross-linking procedure and became negatively charged. This was demonstrated by methylene blue (MB) adsorption studies and swelling studies in sodium chloride solutions with increasing concentrations in which the hydrogel network collapsed. The adsorption of MB was also used to characterise the degree of the GG cross-linking, from which the effective network density was calculated. In addition, effective network density was calculated from elasticity measurements. Both measurements showed that the cross-linking density (but not swelling) of the new products was linearly dependent on the amount of trisodium trimetaphosphate in the reaction. Further, phosphate cross-linked guar gum

Table 2
Pharmaceutical applications of gums in drug delivery.

S. no.	Natural Gum	Model Drug	Dosage form	Remarks	Reference(s)
A. Guar Gum					
1.	97.3%	Dexamethasone	Tablets	• 72-82% of Dexamethasone was delivered to colon.	Kenyon et al. (1997)
2.	340 mg per 420 mg tablet (77.19%)	Indomethacin	Matrix tablets	• In-vitro drug release without rat caecal medium was 29.2% which was increased upto 49.7% and 59.64% with 2% and 4% of rat caecal medium, respectively.	Prasad et al. (1998)
3.	100 mg coating over 80 mg core tablet (125%)	Indomethacin	Tablets	• In-vitro Cumulative percent drug release with rat caecal medium (2%, 21 h study) was ≤20%. • In-vivo Scintigraphy study showed intact tablet in small intestine (2 h), the commencement of disintegration of the coat (4 h), distribution of broken pieces of the tablet in ascending colon, hepatic flexure, transverse colon and splenic flexure (8 h)	Krishnaiah et al. (1998)
4.	20%	Albendazole	Matrix tablets	• In-vitro drug release without rat caecal medium was 20.9% which was increased upto 43.9% with rat caecal medium (4%)	Krishnaiah, Nageswara Rao, Bhaskar Reddy, Karthikeyan, and Satyanarayana (2001a)
5.	20%	Mebendazole	Matrix tablets	• In vitro drug release without rat caecal medium was 44.3% which increased upto 97.5% With Rat caecal medium (4%)	Krishnaiah, Dinesh Kumar, Bhaskar, & Satyanarayana (2001b)
6.	20%	Mebendazole	Matrix Tablets	• In-vitro drug release in SCF (Sorenson's buffer pH7.4) was found to be 57% which was increased upto 97% when SCF with 4% rat caecal medium was used. • Studies also showed that pretreatment of rats with 5-FU at a dose of 0.3 mg/kg or less did not affect drug release	Krishnaiah and Srinivas (2008)
7.	65%	Ornidazole	Matrix tablets	• In vitro drug release without rat caecal medium was 73.42% which increased upto 96.8%With Rat caecal medium (4%)	Krishnaiah, Muzib, Indira Rao, Srinivasa Bhaskar, and Satyanarayana (2003c)
8.	80%	5 FU	Tablets	• In vitro drug release without rat caecal medium was found to be 50.85% • In-vivo studies in healthy human volunteers showed C_{max} (216 ng/ml) at T_{max} (7.6h)	Krishnaiah, Satyanarayana, Dinesh Kumar, Karthikeyan, and Bhaskar (2003a)
9.	260 mg compression coating on 200 mg core tablets (130%)	Tinidazole	Tablets	• In vitro drug release was found to be 67.50% • In-vivo studies healthy human volunteers showed Cmax=2158 ng/mL at 14.9h and AUC was found to be 57740 ng/ml/h	Krishnaiah, Bhaskar, Satyanarayana, and Latha (2003b)
10.	50%	Calcium Sennosides	Matrix tablets	• In-vitro drug release without rat caecal medium was 43%which increased upto 96%With Rat caecal medium (4%)	Momin (2004)
11.	350 mg total coat weight	Mesalazine	Tablets	• Guar gum (Supercol U-NF) grade was found to be suitable for colonic drug delivery, which shows 11.86% drug release after 6 h. • X-ray investigations revealed colonic arrival time of 3-8 h for 6 volunteers and up to 24 h for 2 volunteer	Demiröz, Acartürk, Sevgi, & Oznur (2004)
12.	60%	Rofecoxib	Matrix tablets	• In vitro drug release without rat caecal medium was 47.3% which increased upto 99.5% with Rat caecal medium (4%)	Al-Saidan, Krishnaiah, Satyanarayana, & Rao (2005)
13.	20%	Albendazole β-cyclodextrin	Matrix tablets	• In vitro drug release without rat caecal medium was 63.5% which increased upto 82% with Rat caecal medium (4%)	Shyale, Chowdary, & Krishnaiah, (2005)
14.	50%	Albendazole and Albendazole β-cyclodextrin	Matrix tablets	• In vitro drug release without rat caecal medium was 67.7% • In-vivo studies healthy human volunteers showed Cmax (916.49 ng/mL) at 12 h	Shyale, Chowdary, Krishnaiah, and Bhat (2006)
15.	150 mg coating per 213 mg core tablet (70.42%)	Ondansetron	Matrix tablets	• In-vitro drug release was found to be 19.8% over 8 h. • After galactomannase enzyme addition(19.6 U/L) the drug release was increased up to 84.90% after 10 h	Demiroz and Takka (2006)

Table 2 (*Continued*)

S. no.	Natural Gum	Model Drug	Dosage form	Remarks	Reference(s)
16.	44%	Indomethacin	Pellets (Coatd with Eudragit FS 30D)	• In vitro drug release with GG/ Eudragit FS 30D double coated pellets was found to be 66.56% (After 7 h) which increased up to 100.2%, when drug release was studied in presence of enzymes. • In-vivo study was carried out in Beagle dogs which showed Cmax=1291.51 ng/ml and Tmax=5.41 h with double coated pellets while Eudragit FS 30D coated pellets showed Cmax=3296.87 ng/ml and Tmax=2.46 h	Ji et al. (2007)
17.	75%	Diltiazem	Matrix tablets (coated with double coating of Inulin and shellac)	• In vitro drug release for uncoated GG formulated tablets when unincubated SCF was used was found to be 60% at end of dissolution study (11 h),which was increased up to 80% with incubated medium • With 2% inulin coating 28% was released after 11 h	Ravi, Mishra, and Kumar (2008)
B. Guar gum methacrylate conjugates					
18.	Graft copolymer of GG with acrylamide by crosslinking with glutaraldehyde (5% W/V)	Verapamil (VRP) and Nifedipine(NFD)	Hydrogel Microspheres	• Non-fickion drug release was observed	Soppirnath and Aminabhavi (2002)
19.	Methacrylic acid-g-Guar gum (MAA-g-GG)	Metronidazole	Tablets	• In vitro drug release with Eudragit L 100 coated tablets (with MAA-g-GG:Xanthum gum,3:1) was found to be (86.6%). • The Eudragit L 100 coated tablets (with MAA-g-GG:Xanthum gum,1:3) cause maximum retardation in drug release	Mundargi et al. (2007)
C. Guar gum-alginate conjugates					
20.	Guar gum-Alginate combination cross linked with glutaraldehyde	BSA	Hydrogels	• During one step drug release studies (Separate release studies at pH 1.2 and 7.4 for 10 h) only 20% BSA released after 10 h at pH 1.2. While two step drug release studies (pH 1.2 for 2 h followed by study at pH 7.4 up to 10 h) showed 94% BSA was released after 10	George and Abraham (2007)
D. Crosslinked Guar Gum					
I. Crosslinking with glutaraldehyde					
21.		Indomethacin, Sodium salicylate and Budesonide	Discs	• In-vitro drug release studies showed that Sodium salicylate shows complete drug release within 120 min. while Indomethcin and Budesonide showed negligible drug release for 10 h, which enhanced after galactomannase addition.	Kabir et al. (1998)
22.		Metronidazole	Microsphere	• In vitro drug release without rat caecal medium was 31.23% which was increased with Rat caecal medium (2% and 4%) upto 47.72% and 61.65% respectively which further increased up to 59.35% and 76.72% after enzyme induction.	Chourasia and Jain (2004)
23.		Methotraxate	Microsphere	• In vitro drug release Without rat caecal medium was 38.9% which was icreased with Rat ceacal medium(6%) upto 73.20% which further increased up to 91% after enzyme induction	Chourasia et al. (2006)
24.		Ibuprofen	Hydrogel Discs	• Cumulative percent in vitro drug release(2 h SGF , 3 H SIF) was found to be 2-5%	Das et al. (2006)
II. Crosslinked with tri sodium trimetaphosphate (STMP)					
25.		Hydrocortisone	Hydrogels	• Increase in degree of cross linking caused decrease in extent of degradation during In-vitro drug release in presence of rat ceacal medium.	Kabir et al. (2000a)

E. Xanthan gum					
26.		Caffeine, Indomethacin,Sodium Indomethacin	Matrix tablets	• Within physiologic ionic strength range the swelling of XG matrix tablets shows a reciprocal relation of In-vitro release with salt concentration. • Drug release was influenced by ionic strength and buffer conc. • Drug release depends on swelling behavior.	Talukdar and Kinget (1995)
F. Xanthan gum derivatives					
27.	Combination with Konjac glucomannan,KGM (20%TWG)	Cimetidine	Matrix tablets	• XG shows more In-vitro drug release than konjac glucomannan • β-Mannase accelerates drug release from matrix tablets prepared by Konjac glucomannan but no effect on tablets prepared by XG. • Matrix tablets with a single polysaccharide (either XG or KGM) could not retard drug release from tablets effectively while XG: KGM complex does.	Jiangyang et al. (2008)
28.	XG:GG (10:20)	5-FU	Matrix tablets	• In-vitro drug release was found to be 42.6% which was increased upto 67.2% with 2% and 80.34% with 4% rat caecal medium.	Sinha et al. (2004)
29.	Combination with Konjac glucomannan (both American and Japanese varities)	Diltiazem	Tablets	• In vitro drug releasewith Japanese KGM drug release was complete within 24 h in the presence of β-mannase. There was a smaller effect on release from formulation of American KGM.	Manceñido, Landin, Lacik, and Pacheco (2008)
30.	Xanthum gum:Boswellia gum (3:1) with 300 mg total coat weight and Boswellia gum:HPMC (2:3) with 275 mg total coat weight	5-FU	Compressed coated tablets	• In-vitro drug release was found to be 80.2% which was increased upto 98.22% with 2% rat caecal medium • Studies also showed that XG play a major role in retardation of drug release	Sinha, Singh, Singh, and Binge (2007)
G. Khaya gum and albizia gum					
31.	Khaya gum (300mg) and Albizia gum (400mg)	Paracetamol and Indomethacin	Tablets	• In vitro drug release (After 12 h) of coated with khaya gum(400 mg) was 33.09% for Indomethacin and 36.10% for Paracetamol. • In vitro drug release with rat caecal media (of Indomethacine only) of tablets coated with Khaya gum (400mg) was 98.68% while albizia gum (400mg) coated tablets showed 94.34% drug release • Tablets coated with Khaya:Albizia(1:1) mixture(400mg) showed 97.34% drug release	Odeku and Fell (2005)
H. Crosslinked gellam gum					
32.	A.(I)With Calcium or Deacylated gellam gum crosslinked with calcium	Azathiopurine	Beads (Coated with Eudragit S 100)	• Uncoated tablets showed 32.27% In-vitro drug release at pH 7.4 with galactomannase as compared to coated tablets (28%)	Singh, Trombetta, and Kim (2004); Singh and Kim (2007)
I. Locust bean gum					
33.	Locust bean gum:Chitosan (4:1)	Mesalazine	Compression coated tablets	• 4:1 ratio showed best In-vitro drug release. • In-vivo study (Human):-Cmax=28.25μg/ml,Tmax=16 h,AUC =498.62 μg.h/ml	Raghavan, Muthulingam, Josephine, Jenita, and Ravi (2002)

was evaluated for targeting hydrocortisone to the colon. It was found that phosphate cross-linked guar gum loosely cross-linked with 0.1 equivalents of sodium trimetaphosphate (STMP) was able to prevent the release of 80% of the loaded hydrocortisone for at least 6 h in PBS (pH 6.4). When a mixture of α-galactosidase and β-mannanase was added to the buffer solution, an enhanced hydrocortisone release was observed. *In vivo* degradation studies in the rat cecum showed that despite the chemical modification of GG, its vulnerability to being degraded by enzyme was retained in a cross-linker concentration-dependent manner. Eight days of GG diet prior to the study increased the α-galactosidase activity in the cecum of the rat three-fold, compared to its activity without the diet. However, this increase in enzyme activity was unable to improve degradation of the different phosphate cross-linked GG products. The overall α-galactosidase activity in the rat cecum was found to be extracellular, while the activity of β-mannanase was found to be bacterial cell-wall associated (Kabir, Yagen, Baluom, et al., 2000). The observation that GG cross-linked with STMP could be biodegraded enzymatically and was able to retard the release of a low water-soluble drug suggested that it could potentially be used as a vehicle for colon-specific drug delivery.

Meimei, Jiangyang, Wang, and He (2007) prepared hydrogel systems using KG cross-linked with STMP for targeting to the colon. Interestingly, a bell-shaped dependency for swelling degrees in both solutions (simulated gastric test solution, pH 1.0 hydrochloric acid solution as well as simulated intestinal test solution, pH 7.4 phosphate buffer solutions) was obtained on employing increasing amounts of STMP. *In vitro* release of hydrocortisone was studied in the presence and absence of β-mannanase. KG cross-linked with STMP was able to retard the release of hydrocortisone and could be biodegraded enzymatically. Further, hydrocortisone release was observed to depend on the cross-linking density and controlled by degradation of the hydrogels.

5.2. Microspheres

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). The presence of amide functional groups in these microgels could be used for introducing the required ionic functionalities. The -CONH moieties of polyacrylamide were converted to–COOH moieties resulting in an 'ionic micro gel', which by definition refers to a spherical micron size and covalently cross-linked high molecular mass matrix having the fixed groups bound to its backbone (Eichenbaum, Kiser, Shah, Simon, & Needham, 1999). Such a change in functionality has many advantages over the neutral acrylamide-based polymers (Pradip, Kulkarni, Ghandi, & Modudgi, 1991; Tripathy & Singh, 2000). For instance, the introduction of polyelectrolyte functional groups changes the pAAm-*g*-GG matrix into a polyanionic polysaccharide network and the weakly ionic functional group on the polymeric chain makes them pH-responsive. This approach was advantageous because microgels in micron size exhibited rapid response to the changing environment such as pH and ionic strength.

5.3. Tablets

Toti and Aminabhavi (2004) prepared pAAm-*g*-GG by employing three different ratios of guar gum to acrylamide (1:2, 1:3.5 and 1:5). Amide groups of these grafted copolymers were converted into carboxylic functional groups. Tablets prepared by incorporating diltiazem hydrochloride exhibited release that continued up to 8 and 12 h, respectively, for pAAm-g-GG and hydrolysed pAAm-g-GG copolymers. The release was found to be dissolution-controlled in the case of unhydrolysed copolymer. However hydrolysed copolymers showed swelling controlled release initially (i.e. in 0.1 M HCl), but at a later stage, it became dissolution-controlled in pH 7.4. Hydrolysed pAAm-g-GG matrices were found to be pH sensitive and could be used for intestinal drug delivery.

5.4. Colon specific drug delivery

Kabir et al. (1998) prepared guar gum microspheres by cross-linking with glutaraldehyde to reduce the swelling properties of guar gum. The researchers also reported that there was no effect of cross-linking on guar gum degradation in the presence of colonic enzymes. Chourasia et al. (2006) prepared microspheres of metronidazole by using glutaraldehyde as cross-linking agent for guar gum. It was observed that *in vitro* release in different pH media was affected by changes in guar gum concentration as well as glutaraldehyde concentration. Sinha, Mittal, Bhutani, and Kumaria (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. Das, Wadhwa, and Srivastava (2006) prepared glutaraldehyde cross-linked guar gum hydrogel discs and showed that cross-linking resulted in significant reduction in the swelling of the guar gum. Studies also showed that percentage drug release increased with increasing glutaraldehyde concentration. Kabir, Yagen, Penhasi, et al. (2000) also prepared discs of hydrocortisone by using trisodium trimethophosphate (STMP) cross-linked guar gum and showed that even increased α-galactosidase activity (induced by eight days of guar gum diet) was unable to accelerate the degradation of different guar gum cross-linked products.

Prasad, Krishnaia, and Satyanarayana (1998) and Krishnaiah, Satyanarayana, Rama Prasad, and Narasimha Rao (1998) prepared tablets of indomethacin by direct compression and coated them with guar gum. Studies showed that guar gum matrix tablets containing more than 80% gum were capable of delivering indomethacin to the colon. 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, Xu, and Wu (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, Satyanarayana, Dinesh Kumar, Karthikeyan, and Bhaskar (2003a) 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. Mundargi, Patil, Agnihotri, and Aminabhavi (2007) prepared tablets of metronidazole by using various polysaccharides or by graft copolymerisation using methacrylic acid (MAA) with guar gum, xanthan gum, pectin or carrageenan. *In vitro* release of metronidazole was observed to be enhanced from tablets containing grafts of xanthan gum and MAA-g-GG as well as GG with MAA-g-GG. Ji et al. (2007) observed that pH and enzyme dependent colon targeted tablets of indomethacin could be prepared using film coating of guar gum and Eudragit FS 30D. Studies suggested that the use of guar gum to a weight gain of 44% was enough to provide a lag time of 3.1 h for releasing 10% drug, which provided a basis for dissolution of the guar gum coating in the proposed colon targeted system.

Talukdar and Kinget (1995) prepared xanthan gum matrix tablets by using three drugs having different properties i.e. caffeine as a soluble drug, indomethacin as an insoluble acidic drug and the sodium salt of indomethacin as a soluble acidic drug.

These studies revealed the dependence of drug release on the swelling of the polymer matrix, which in turn was influenced by the ionic strength and buffer concentration. Sinha et al. (2004) prepared rapidly disintegrating core tablets coated with a mixture of xanthum gum and guar gum. It was found that the XG:GG mixture (10:20) coated tablets were able to deliver drug to the colon.

Gellan gum has been investigated as a possible carrier for colonic drug delivery. Singh and Kim (2007) investigated potential interactions among a model drug (azathioprine; AZA), polymers, and a divalent metal ion, which were utilised for developing a novel multiparticulate formulation for colonic drug delivery. The authors prepared beads by ionotropic gelation of deacylated gellan gum (DGG) in the presence of Ca^{2+} ions, followed by coating with Eudragit® S-100. The results of FT-IR studies suggested interactions of DGG with AZA and Eudragit® S-100, and provided evidence for interactions of AZA and DGG with Ca^{2+} ions, which was also supported by results of DSC studies.

6. Conclusions

Gums are abundantly found in nature. They are cheaper than the synthetic polymers available for various purposes. In addition, they are well tolerated by the human body because they are easily degraded to monosaccharides by colonic bacteria. However, the highly swellable nature of their putative form often restricts their use for delivering drugs to distal parts of the gastrointestinal tract.

The present discussion revealed different approaches that have been investigated for modifying the properties of gums. The modified gums were observed to be useful for preparing various dosage forms with modified drug release profiles. Unlike the dosage forms prepared using synthetic polymers, the dosage forms prepared with modified gums do not suffer from the disadvantage of incomplete drug release. This is due to their susceptibility to degradation by colonic microflora.

Certain modifications like carboxymethylation and carbomoylethylation by replacement of few free-OH groups increase the aqueous solubility of gums. Hence, the resultant moiety is not suitable for delaying the drug release. Therefore, these groups need to be cross-linked with the oppositely charged anions. These cross-linked structures are resistant to dissociation in acidic pH but slowly degrade in the intestine, thus providing sustained release of drugs from dosage forms during the transit in the gastrointestinal tract. Similarly, phosphorylation of gums with sodium metaphosphate is reported to be useful in designing dosage forms for colonic drug release.

However, the degree of substitution is the main concern in almost all types of modifications. A low degree of substitution leads to less cross-linking density, which in turn results in premature release of drug in the gastrointestinal tract. Therefore, gums containing galactomannan are ideally suited for modification since they contain carboxylic groups, which are more amenable to cross-linking than hydroxyl groups. The abundance of gums, their economic cost and biodegradability have compelled formulation scientists to design approaches for making them suitable for modifying the drug release of dosage forms. This review should be helpful to researchers in applying appropriate strategies or achieving the desired drug release profiles from biodegradable pharmaceutical systems.

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