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Review

Polysaccharides in colon-specific drug delivery

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Abstract

Natural polysaccharides are now extensively used for the development of solid dosage forms for delivery of drug to the colon. The rationale for the development of a polysaccharide based delivery system for colon is the presence of large amounts of polysaccharidases in the human colon as the colon is inhabited by a large number and variety of bacteria which secrete many enzymes e.g. β-D-glucosidase, β-D-galactosidase, amylase, pectinase, xylanase, β-D-xylosidase, dextranase, etc. Various major approaches utilizing polysaccharides for colon-specific delivery are fermentable coating of the drug core, embedding of the drug in biodegradable matrix, formulation of drug-saccharide conjugate (prodrugs). A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose and locust bean gum. Recent efforts and approaches exploiting these polysaccharides in colon-specific drug delivery are discussed.

Keywords: Colon-specific drug delivery; Colon targeting; Polysaccharides; Oligosaccharide

1. Introduction

Many protein and peptide drugs like insulin, cannot be administered through the oral route because of their degradation by the digestive enzymes of the stomach and the small intestine. Delivery of drugs to the systemic circulation through colonic absorption represents a novel mode of introducing peptides and protein drug molecules and drugs that absorb poorly from the upper gastrointestinal tract (GIT) as the colon lacks various digestive enzyme present in the upper GIT. Also, for treatments of local diseases of the colon like ulcerative colitis, Crohn's disease and colon cancer, drug targeting not only reduces the dose to be administered, but also reduces the incidence of possible adverse effects associated with these chemotherapeutic agents.

The various approaches used for targeting the drugs to the colon include, formation of a prodrug, multicoating time-dependent delivery systems, coating with pH-sensitive polymers,

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pressure dependent systems, and the use of biodegradable polymers.

A prodrug is a pharmacologically inactive derivative of a parent molecule that requires spontaneous or enzymatic transformation within the body to release the active drug moiety. For targeting drugs to the colon, drug is to be protected from the hostile environments of the stomach and small intestine (SI). This protection in the upper GIT is affected by conjugation with carrier moieties, forming prodrugs. These prodrugs undergo enzymatic cleavage in the colon and regenerate the drug. An example of such a prodrug, which is extensively used in Crohn's disease and ulcerative colitis is sulphasalazine (Riley and Turnberg, 1990). It consists of 5-aminosalicylic acid (5-ASA) linked via an azo bond to sulphapyridine (SP). This prodrug when given orally is minimally absorbed in the stomach and the small-intestine and largely reaches the colon, where the bacterial azoreductase cleaves the azo bond thereby releasing 5-ASA, the drug moiety from SP, which acts only as a carrier (Azad Khan et al., 1977). Glycosidic prodrugs (Friend and Chang, 1984, 1985; Friend and Tozer, 1992; Friend, 1995), dextran prodrugs (Harboe et al., 1989a) and cyclodextrin conjugated prodrugs (Hirayama et al., 1996) of various drugs have been developed for colon-specific drug delivery. Though these prodrugs provide site specific drug delivery, these are new chemical entities and detailed toxicological studies need to be performed before their use.

Time dependent formulations are designed to resist the release of the drug in the stomach with an additional non-disintegration or lag phase included in the formulation (which equals to the small intestinal transit time) and the release of the drug takes place in the colon. An example of such a system is Pulsincap® (MacNeil and Stevens, 1990). This capsule consists of a non-disintegrating body having an enteric coated cap. The enteric coated cap dissolves in the small intestine and a hydrogel plug swells to create a lag phase. This plug ejects on swelling and releases the drug from the capsule. The large scale manufacturing of these systems, however, needs a lot of technological advancement and skills. Another limitation of the time dependent release systems are the variation in the gastric emptying time and small intestinal transit time (Davis et al., 1984). But, due to the use of enteric coating over most of these systems, the large variation in gastric emptying is overcome by most of these systems. However, there is still likely to be a considerable variability in the in vivo performance of the timed release systems by virtue of the variations in small intestinal transit time.

The pH of the GIT is acidic in the stomach and increases in the small and large intestine. This pH variation in different segments of GI has been exploited for colon-specific delivery. Coating the drug core with pH-sensitive polymers e.g. Eudragit® (methyacrylic acid-methylmethacrylate copolymers) has been successfully used for colon drug delivery in Asacol®, Salofalc®. These polymers are insoluble in acidic media, but dissolves at a pH of 6 or more, thereby providing protection to the drug core in the stomach and to some extent in the SI releasing the drug in the colon. However, the pH of GIT is subject to both inter and intra individual variations, depending upon the diet, disease, age, sex and the fed/fasted state (Wilson and Washington, 1989; Rubinstein, 1990). But due to the simplicity of the formulation of this device many marketed preparations utilize this approach. On prolonged use, these polymers may accumulate in the body so the use of biodegradable polymers is essential.

Osmotic systems independent of gastric residence time and metabolism by bacterial flora have also been developed for colon delivery of drugs. These systems are essentially timed release systems. OROS-CT systems developed by Theeuwes et al. (1990) consist of a single or 5–6 units. These enteric coated push–pull units contain an osmotic push compartment and a drug compartment, both surrounded by a semipermeable membrane with an orifice. As the unit enters the SI, the enteric coating dissolves and the osmotic push compartment containing an osmopolymer and an osmotic agent swells. Swelling of the osmotic push compartment forces the drug gel out of the orifice. These systems can be programmed to delay the drug release for varying durations (Theeuwes et al., 1993).

Another strategy relies on the strong peristaltic waves in the colon that lead to a temporarily increased luminal pressure (pressure-controlled drug delivery). Pressure-sensitive drug formulations release the drug as soon as a certain pressure limit is exceeded. The pressure and the destructive force induced by peristaltic waves is certainly high in the distal part of the large intestine (Muraoka et al., 1998). However, little is known about the reproducibility of this pressure and the duration of this high-pressure phase (Leopold, 1999).

The upper part of GIT, i.e. the stomach and the duodenum has a microflora of less than 10^3–10^4 CFU/ml. These are mainly gram-positive facultative bacteria (Gorbach, 1971; Simon and Gorbach, 1986). The microflora of colon on the other side is in the range of 10^{11}–10^{12} CFU/ml (Moore and Holdeman, 1975) consisting mainly of anaerobic bacteria, e.g. *Bacteroides*, *Bifidobacteria*, *Eubacteria*, *Clostridia*, *Enterococci*, *Enterobacteria*, etc. This vast microflora fulfils its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g, di- and tri-saccharides, polysaccharide etc. (Rubinstein, 1990; Cumming and Englyst, 1987). For this fermentation, the microflora produces a vast number of enzymes like β-glucuronidase, β-xylosidase, α-arabinosidase, β-galactosidase, nitroreductase, azoreductase, deaminase and urea dehydroxylase (Scheline, 1973). Because of the presence of these biodegradable enzymes only in the colon, the use of bacterial degradable polymers for colon-specific drug delivery seems to be a more site specific approach as compared to other approaches. These polymers shield the drug from the environments of the stomach and the small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism (Potts et al., 1973) or degradation by enzyme (Huang et al., 1979; Swift, 1992) or breakdown of the polymer backbone (Ratner et al., 1988; Hergenrother et al., 1992) leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer (Park et al., 1993).

Biodegradable polymers have been used (a) as a linkage to form a prodrugs with the drug moiety, (b) as a coating material to coat the drug core or (c) as an embedding media to embed the drug moiety in their matrices or hydrogels. Examples of such systems include azo polymers which are film forming and are used to coat the drug core. A synthetic polymer used to coat the drug capsule of insulin and vasopressin is a copolymer of styrene and hydroxyethyl methacrylate, cross-linked with 4-4′-divinylazobenzene and *N*,*N*′-bis (β-styrene sulphonyl)– 4,4′-diaminoazobenzene. (Saffran et al., 1986, 1991). The azoreductase present in the colon degrades the coating and then releases the drug from the capsule. The use of such synthetic polymers, requires a more detailed toxicological studies.

The ability of natural polymers i.e. the polysaccharides, from algal origin (e.g. alginates), plant origin (e.g. pectin, guar gum) microbial origin (e.g. dextran, xanthan gum) and animal origin (chitosan, chondroitin) to act as substrates for the bacterial inhabitants of the colon together with their properties, such as swelling, film forming and their biocompatability, biodegradability invites their use as colon-carriers.

The purpose of this review is to attempt to discuss the use of such natural polysaccharides as colon-specific drug delivery system.

2. Polysaccharides

Polysaccharides are polymers of monosaccharides (sugars). They are found in abundance, have wide availability, are inexpensive and available in a variety of structures with a variety of properties (Hovgaard and Brondsted, 1996). They can be easily modified chemically and biochemically and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition biodegradable, which suggests their use in targeted drug delivery systems.

Problem encountered with the use of polysaccharides is their high water solubility. An ideal approach is to modify the solubility while still retaining their biodegradability. Large number of polysaccharides have already been tried for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate,

cyclodextrins, dextrans, guar gum, inulin, pectin, locust bean gum and amylose.

2.1. Chitosan

Chitosan is a high molecular weight, polycationic polysaccharide derived from naturally occuring chitin by alkaline deacetylation (Felt et al., 1998). Chemically, it is a poly(*N*-glucosamine) (Fig. 1).

Chitosan has favourable biological properties such as nontoxicity (Knapczyk et al., 1984), biocompatability (Hirano et al., 1990) and biodegradability (Struszczyk et al., 1991). Chitosan however is soluble in dilute acid and precipitates at a pH above 7. Because of the solubility of chitosan at low pH ranges, its successful use in colon-specific delivery requires an enteric layer over the chitosan which would protect it against the acidity of the stomach. As the formulation reaches the intestine, the pH increases and the enteric layer dissolves releasing the chitosan coated core. These cores are acted upon by microflora of the colon, degrading the chitosan and releasing the drug.

Chitosan capsules enteric coated with a layer of hydroxypropylmethylcellulose (HPMC) phthalate have been evaluated for colon delivery of drugs (Tozaki et al., 1997). In vitro studies showed that the capsules loaded with a soluble dye, 5-(6)-carboxyfluorescein (CF) showed little release in simulated gastric juice for 2 h (transit time in stomach) and in artificial intestinal juice (next 4 h), but the presence of rat cecal contents (33%) in the dissolution fluid increased the release rate of the drug, CF from the capsules from 20 to 100% in the next 4 h. This suggests that the flora present in the rat cecal content may have produced enzymes for the degradation of chitosan or alternatively, the bacterial fermentation in the cecal contents may have decreased the pH of its contents and chitosan may have easily dissolved under acidic condition. In vivo studies carried out in wistar rats using insulin as the drug, showed improvement in absorption of insulin using these capsules. Also, the effect of absorption enhancers in increasing the absorption of insulin from these capsules was assessed. Results were compared with the oral administration of insulin in a solution form and in a gelatin capsule form. The hypoglycemic effect and the plasma levels of insulin was assessed from time to time. The latter two formulations showed no hypoglycemic effect or peak insulin concentration. However, sharp peaks of plasma insulin concentrations and marked hypoglycemic effect was seen 6–12 h after the administration of oral chitosan capsules loaded with insulin and sodium glycocholate. Hypoglycaemic effect started 6 h after administration of capsule, thus showing that the absorption started in the large intestine. It was also seen that insulin absorption in the large intestine increased in the presence of absorption enhancers like sodium glycocholate. Comparing the effect of various absorption enhancers and protease inhibitors on the absorption of insulin showed that maximum increase in the absorption was caused by sodium glycocholate followed by aprotinin, soyabean trypsin inhibitor (STI), sodium oleate, bacitracin and *n*-dodecyl-β-D-maltopyranoside.

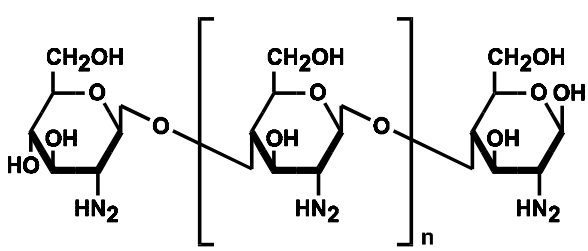

Fig. 1. Structure of chitosan.

Similarly, acceleration in the healing effect of R68070 (a new thromboxane synthase inhibitor) on 2,4,6-trinitrobenzene sulfonic acid-induced ulcerative colitis in rat using chitosan capsule as a carrier was compared to a carboxymethylcellulose (CMC) suspension of R68070 (Tozaki et al., 1999). The colitis in male wistar rats was not affected much with the administration of lower doses of both the above formulations. However, when the doses were increased a marked reduction in colitis was seen with R68070 when given in chitosan capsules rather than in CMC suspension leading to the same conclusion that these capsules have a good potential for being used as carriers in colon-specific drug delivery systems. Suzuki et al.

(1998) prepared hard capsules of chitosan with enteric coating for the drug delivery specifically to the colon. The results shown by these capsules were also promising.

Chitosan microspheres of sodium diclofenac were prepared by spray drying technique (Lorenzo-Lamosa et al., 1998). These microspheres were enteric coated with Eudragit L-100 or Eudragit S-100. Eudragit coating gave a pH-dependent release profile and the change in molecular weight of chitosan or use of different salt like chitosan glutamate could control the release rate of sodium diclofenac from the core. No release was seen in acidic pH for 3 h, but at higher pH Eudragit dissolved and swelling of chitosan started leading to continuous drug diffusion which completed in the next 4 h. Infra red studies revealed an ionic interaction between the amine group of chitosan with the carboxyl group of Eudragit, which provided another release controlling mechanism.

Semisynthetic derivatives of chitosan i.e. chitosan succinate and chitosan phthallate were prepared by reacting chitosan seperately with succinic and phthalic anhydrides (Aiedeh and Taha, 1999). Sodium diclofenac was dispersed in their matrices. In vitro studies showed that these matrices resisted dissolution under acidic conditions and showed improved dissolution under basic conditions, suggesting their suitability for colon-specific drug delivery systems. However, in vivo studies would be required to establish the suitability of these derivatives for colon-specific drug delivery.

Cores of acetaminophen, were coated with chitosan as inner coating layer and gastric acid resistant material phytin as an outer coat (Tominaga et al., 1998). Phytin protected the core from gastric pH and dissolved in the small intestine. Chitosan protected the core in the small intestine and released the core upon biodegradation in the colon.

2.2. Pectins

Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. They are predominantly linear polymers of mainly α-(1-4)-linked D-galacturonic acid residues interrupted by 1,2- linked L-rhamnose residues. Pectin has a few hundred to about one thousand building blocks per molecule, corresponding to an average molecular weight of about 50 000 to about 180 000 (Fig. 2).

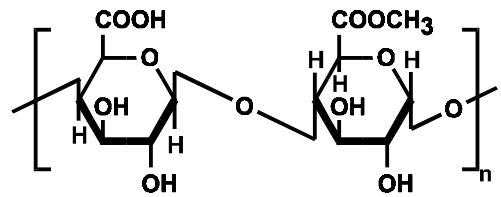

Fig. 2. Structure of pectin.

These polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon (Werch and Ivy, 1941; Salyers et al., 1977).

Being soluble in water, pectin is not able to shield its drug load effectively during its passage through the stomach and small intestine. It was found that a coat of a considerable thickness was required to protect the drug core in simulated in vivo conditions (Ashford et al., 1993). So, the focus shifted to the development of such derivatives of pectin which were less water soluble but were degradable by the colonic microflora (Rubinstein et al., 1993). Calcium salts of pectin reduced their solubility by forming an 'egg-box' configuration (Morris et al., 1982). Amount of calcium in the formulation should be carefully controlled to ensure optimum drug delivery (Ashford et al., 1994). Matrix tablets of indomethacin were prepared with calcium pectinate and also with pectin. Release of indomethacin from these matrices were studied in presence of (a) pectinolytic enzymes, (b) *Bacteroides ovatus* and (c) rat cecal contents (Rubinstein et al., 1993). The release of indomethacin from pectin-indomethacin tablets in 6 h was 0% in the absence of enzymes. The increase in percentage of pectinolytic enzymes in the dissolution medium increased the release of indomethacin. At 120 FDU/ml enzyme concentration, drug release was 100% within 2 h. When these tablets were studied in the presence of *B. ovatus* drug release was 12–21%. For calcium

pectinate-indomethacin tablets release was only $16.2 \pm 2.2\%$ after 72 h in absence of enzymes. In presence of pectinolytic enzymes the total amount of drug was released within 6 h. In the presence of rat cecal contents, release was about $60.8 \pm 15.7\%$ as compared to $4.9 \pm 1.1\%$ of the control medium without cecal contents. This study showed calcium salt of pectin as a promising colon drug targeting matrix since significant difference between indomethacin levels were observed in the presence of rat cecal content and control, at each time.

Further studies comparing the utility of compression coating technique to deliver two different types of drugs to the colon, firstly, a water insoluble drug, indomethacin and secondly, a water soluble drug, insulin as compared to plain matrix tablet technique (Rubinstein and Radai, 1995). Calcium pectinate-indomethacin tablets of both types, i.e. compression coated and matrix tablets showed no release of indomethacin at a pH of 1.5 for 2 h. When these tablets were shaken at a pH of 7.4 a drug leak was seen in plain matrix tablets but not in compression coated tablets. In the presence of pectinolytic enzymes, a sudden release of indomethacin was seen in both, the types of tablets but the rate and the percentage of release were lower (only $57.6 \pm 2.5\%$) in compression coated tablets as compared to plain matrix tablets ($74.2 \pm 4\%$) after 12 h. However, in vivo studies of insulin tablets in pancreatectomized dogs showed that neither the plain matrix tablet nor the compression coated tablet were able to avoid the initial drug leak from the tablet. Compression coated tablet showed a much better performance because delayed absorption (5–8 h delay) was seen after an initial leak. The initial leak was explained on the basis of the difficulty encountered in compression coating technique in centering the core tablet within the compression coat and thereby not giving a uniform coat thickness. Any portion where the thickness was less will lead to leak of the drug. Compression coating technique was found to be useful for coating of water insoluble drugs like indomethacin. But for water soluble drug the need of an additional barrier was suggested.

Two types of enteric coated calcium pectinate matrix tablets were formulated by Adkin et al. (1997), one using pectin as a binder (CaP/P) and the other using guar gum as a binder (CaP/GG). Scintigraphic evaluation of gastrointestinal transit and disintegration in ten healthy human volunteers showed that the intact tablets arrived in the colon where the complete disintegration occurred for both the formulations. However, CaP/GG tablet showed slower disintegration as compared to CaP/P tablet. The time and location of complete tablet disintegration was more reproducible with CaP/P tablet as compared to CaP/GG tablet. Studies using rats showed colonic degradation of the polysaccharide, as significant difference was observed between degradation in antibiotic treated and non-treated rats in the two formulations.

Methoxylated pectin system where the acid group had been 70% methoxylated, applied as a compression coat was found to be protective to the core tablet during conditions mimicking mouth to colon transit (Ashford et al., 1993). In the colon coating was susceptible to enzymatic attack. These findings were confirmed in vivo using gamma-scintigraphy. Low methoxylated pectin was more susceptible to degradation and it was assumed that the presence of calcium increased the susceptibility to enzymatic attack.

Another derivative of pectin, amidated pectin was considered for colonic delivery because of its biodegradability, higher tolerance to pH variations and fluctuations in calcium levels. They were susceptible to enzymatic breakdown (Wakerly, 1995). Pectin 920 and 4200 having different degrees of substitution were evaluated (Wakerly et al., 1997). However, the release of paracetamol from both these substituted polysaccharides in vitro was quite high and it was found that they were not able to resist the drug release before arrival into the colon. Inclusion of calcium as cross-linking agent increased the viscosity of amidated pectin gels to a maximum. Pectin 920 formed strong gels, which showed drug release retarding properties. This pectin might be of value in colonic delivery either alone or in combination, possibly in the form of a coating.

Many of the colon-specific drug delivery systems developed are single unit systems. A drawback of single unit system is that they may exhibit a delay at the ileocecal junction, leading to drug loss prior to entry into the colon. This can be avoided with the use of multiparticulate systems. Multiple unit systems like pellets have been shown to spread out on their entry to the colon (Hardy et al., 1985). This increases the surface area causing rapid bacterial breakdown and is followed by a rapid drug release and thereby improved absorption. So, multiparticulate system consisting of hydrogel beads based on amidated pectin as matrices were developed. These were found to resist release of indomethacin in upper GIT but could not resist the release of relatively water soluble sulphamethoxazole. Coating of these beads with chitosan significantly reduced the drug release of indomethacin and sulphamethoxazole in the upper GIT by forming polyelectrolyte complex around the beads (Munjeri et al., 1997). These multiparticulate systems released the drug in simulated colonic conditions within 135 min.

In another attempt to overcome the drawback of high solubility of pectin, mixed films of pectin with ethyl cellulose were investigated (Wakerly et al., 1996) as a coating material for colon-specific drug delivery. These films combined the colon-specific degradation properties of pectin with protective properties of water insoluble polymer ethyl cellulose. The results showed that release rate of paracetamol could be decreased by either increasing the content of ethycellulose in the film or by increasing the coat thickness and vice versa. These films were degradable in presence of enzymes showing colon-specific degradation.

Working on similar grounds, the leaching of pectin from the mixed films prepared with Aquacoat® ECD 30, Surelease clear®, Eudragit® RS30D or Eudragit® NE 30D (Semde et al., 1998a) was studied in presence and absence of pectinolytic enzymes. Pectin was quickly released from all the films except the mixed films of pectin – Eudragit® RS. However, these films showed significantly increased leaching of pectin in the presence of pectinolytic enzymes. Further studies using aqueous dispersions of Eudragit® RL, NE, RS, Aquacoat and surelease mixed with pectin/calcium pectinate (Semde et al., 2000a,b) showed the decrease in release rate of theophylline in presence of pectinolytic enzymes as compared to release rate in absence of enzymes. This was explained on the basis that hydrophilic polymers like pectin and calcium pectinate incorporated in water soluble coating, hydrated, forming pectin channels through which the hydrophilic drug could diffuse. Enzymatic degradation of pectin from these films suppressed the hydration of these films, which then restructure. Restructuring plugs the possible pores and slows down the drug release. This showed that such systems were unsuccessful for targeting drugs to the colon.

Further, these workers prepared an ionic complex of high methoxylated, polyanionic pectin (HM) with polycationic Eudragit® RL and incorporated it in a swellable polymer Eudragit® NE30D. This mixture was evaluated as a coating material for targeting drugs to the colon (Semde et al., 2000b). The release of theophylline from the coated tablet was studied in presence and absence of enzyme. This was found to be dependent upon pectin HM content. When pectin HM content was higher than 20% w/w of Eudragit® RL (i.e. the optimum amount required for formulation of complex) the presence of enzyme decreased the drug release and vice versa. A non-significant modification of drug release rate was seen at a 20% w/w pectin HM content related to Eudragit® RL. This was because any excess of hydrophilic pectin favours release of theophylline. Degradation of pectin decreased the hydration and permeability of coating to theophylline.

Various mechanisms have been proposed for the release of drug from such mixed films. All these films can be considered as matrix polymeric systems from which pectin macromolecules can diffuse out. Diffusion of small molecular size substances like water soluble plasticizers from polymeric films is known (Bodmeier and Paeratakul, 1992). Another explanation is the formation of aqueous channels in the mixed films, by the leaching of water soluble plasticizers from cellulose acetate films, through which encapsulated drug can diffuse during dissolution (Guo, 1994). Other workers (Sato and Kim, 1984) postulated that the diffusion mechanism of macromolecules through

the polymer film is mainly a partition phenomenon rather than a pore type phenomenon.

An inter-polymer complex of pectin with chitosan was prepared by Meshali and Gabr (1993). In vitro studies of the potential of this mixture for colon-specific delivery was further investigated by Fernandez-Hervas and Fell (1998). They used indomethacin and paracetamol as model drugs to represent poorly soluble and soluble drugs. In vitro studies using pectin and chitosan as a compression coat showed that this coat could offer greater protection at a lower coat weight in the upper GIT than pectin alone (in which a substantially thick coat is required for protection). Results were better with water insoluble drug as compared to water soluble drug.

Epichlorohydrin cross-linked pectin for colonic drug delivery has been suggested (Semde et al., 1998b). As the degree of cross-linking increased drug release decreased. Release rate increases in the presence of enzymes suggesting the suitability of this cross-linkage for targeting drugs to the colon.

Combination of pectin, chitosan and HPMC films have also been studied for their potential as colon-specific drug delivery systems (MacLeod et al., 1999a,b). These films having pectin, chitosan and HPMC in the ratio 3:1:1 were found to be insoluble and showed different degrees of swellings on varying the concentration of pectin and chitosan. These films were degradable by the pectinolytic enzymes. Core tablets were coated with these mixed films and a radioactive marker technetium-99 was introduced into the tablet by drilling a hole in the centre. This hole was sealed with pectin and chitosan followed by enteric coating of the prepared tablet. In vitro studies of these tablets carried out in 0.1 M HCl (for 2 h) and in Sorensen's buffer (for 3 h) showed minimal release of the radioactive marker. However, in the presence of pectinolytic enzymes the release was almost 100% in the next 2.5 h. In vivo studies were done in human volunteers. The radioactivity imaging studies showed that release of radioactivity was much lower in the stomach and SI, because the radioactivity was concentrated in a small area till the small intestine and once the tablet reached the colon the radioactivity spreaded through the ascending colon and transverse colon indicating the degradation of the coating, releasing the technetium.

Different studies conducted on cross-linked and variously derivatized pectin show their potential for acting as colon drug carriers. Mixed films also presently seem to be an encouraging area for further research in colon targeting.

2.3. Guar gum

Guar gum derived from the seeds of *Cyamopsis tetragonolobus* is a naturally occuring galactomannan polysaccharide. It is made up of a linear chain of β-D-mannopyranose joined by β-(1-4) linkage with α-D-galactopyranosyl units attached by 1,6-links in the ratio of 1:2 (Fig. 3).

Guar gum contains about 80% galactomannan, 12% water, 5% protein, 2% acid insoluble ash, 0.7% ash and 0.7% fat. Guar gum hydrates and swells in cold water forming viscous colloidal dispersions or sols (Johnson and Gee, 1981; Cheetham and Mashimba, 1991; Brosio et al., 1994). This gelling retards the drug release from the tablets (Elsabbagh et al., 1978; Bhalla and Shah, 1991; Jain et al., 1992). Guar gum is being used to deliver drug to the colon due to its drug release retarding property and susceptibility to microbial degradation in the large intestine (Bayliss and Houston, 1986; Tomolin et al., 1989; Macfarlane et al., 1990).

Guar gum based matrix tablets of dexamethasone and other antinflammatory agents have

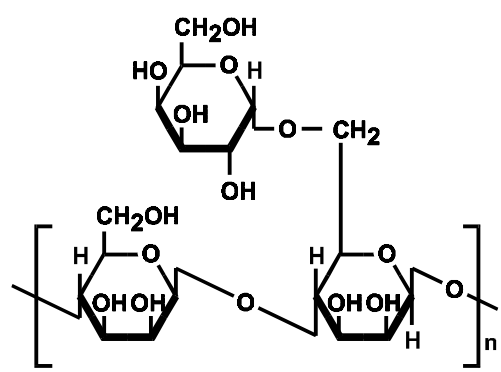

Fig. 3. Structure of guar gum.

shown very encouraging results as colon-carriers. Matrix tablets of dexamethasone and budesonide were prepared using 60.5% w/w of guar gum in the tablet (Wong et al., 1997). The study showed negligible drug release in simulated gastric and intestinal fluid whereas in simulated colonic fluid significant increase in drug release was observed. The study demonstrated that the galactomannanase ($>0.1\%$) accelerated dissolution of dexamethasone and budesonide from guar gum matrix tablet. The extent of drug dissolution depended on concentration of galactomannanase.

Delivery of dexamethasone to the colon using guar gum was tried in healthy human volunteers (Kenyon et al., 1997). One formulation was designed for rapid release while the other three were designed for delayed release of the drug. Formulations were labeled with radioactive 153 Sm. Scintigraphs in human volunteers were taken from time to time after oral administration of dosage form. Serum concentration profiles and scintigraphs showed that the rapid release-tablet disintegrated in the stomach. One of the delayed delivery dosage forms began to disintegrate in the small intestine. While the other two tablets showed disintegration times of 5.8 ± 2.3 and 3.6 ± 1.6 h, respectively. All three formulations disintegrated completely in the colon releasing 72–82% of drug, thereby showing suitability to deliver drug to colon.

Further investigations were also conducted to evaluate the suitability of guar gum as a carrier in colonic drug delivery. In one study, matrix tablet of indomethacin with guar gum were prepared (Rama Prasad et al., 1998). These tablets were found to retain their integrity in 0.1 M HCl for 2 h and in Sorensen's phosphate buffer (pH 7.4) for 3 h. releasing only 21% of the drug in these 5 h. However, in presence of 2% rat cecal contents the drug release increased and further increased with 4% concentration of cecal contents. The drug release improved to about 91% in 4% cecal content medium after enzyme induction of rats. This study suggests the specificity of these matrices for enzyme trigger in the colon to release the drug. In the absence of enzyme system the guar gum swells to form a viscous layer that slows down the seeping of the dissolution fluid into the core. The initial 21% release can be attributed to the dissolution of indomethacin present on the surface of the tablet.

In another in vivo study, matrix tablets containing around 77% guar gum were loaded with technetium-99m-DTPA as tracer and scintigraphs were taken at regular intervals in six healthy human male volunteers (Krishnaiah et al., 1998). These tablets were found to remain intact releasing only small amount of tracer in the stomach and the small intestine. However, bulk of the tracer was released in the ascending colon thereby suggesting the enzyme trigger degradation by colonic bacteria.

Guar gum has also been evaluated as a compression coating to protect the drug core of 5-ASA in upper GIT (Krishnaiah et al., 1999). The tablets coated with 300, 200 and 150 mg of guar gum showed cumulative mean drug release percentages of 5.98 ± 0.70, 8.67 ± 0.35 and 12.09 ± 0.29 respectively after 26 h while tablets coated with 125 mg guar gum disintegrated within 5 min in simulated gastric fluid. Cores with guar gum coat as high as 300 and 200 mg could not successfully release the drug in presence of rat cecal contents even in 26 h as drug release was 23.85 ± 3.13 and $63.43 \pm 6.30\%$, respectively. However, the formulation with 150 mg of guar gum as a coating showed $95.51 \pm 1.50\%$ of 5-ASA release in presence of rat cecal contents after 26 h. Percent drug release from tablet increased considerably from 11th hour and the tablets were completely disintegrated in 26 h. The results of drug release studies on compression coated tablets suggested that the thickness of guar gum coating in the range of 0.61–0.91 mm was sufficient to deliver the drugs selectively to the colon.

Rubinstein and Gliko-Kabir (1995) reported a biodegradable property of guar gum cross-linked with borax. The in vitro rate of degradation of cross-linked guar by galactomannase from *Aspergillus niger* was found to be same as for guar gum. The time required for degradation of these cross-linked guar showed that release of drug would be in proximal colon. However, more detailed study in in vivo conditions are required to confirm these promising results.

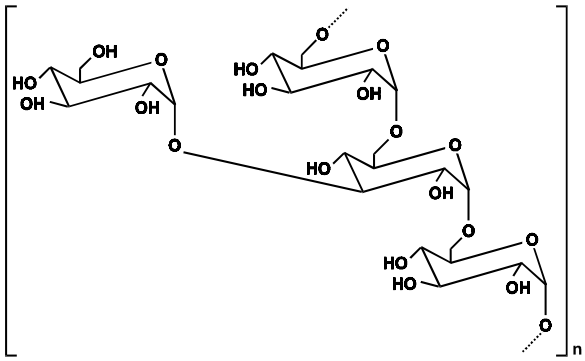

Fig. 4. Structure of dextran.

Phosphated cross-linked low swelling guar-gum hydrogels were prepared and analysed in vitro and in vivo for their potential as colon drug carriers (Gliko-Kabir et al., 2000). These hydrogels were loaded with hydrocortisone and were able to resist the release of 80% of the drug for 6 h in phosphate buffer pH 6.4. Addition of α-galactosidase and β-mannanase (enzymes which act upon guar gum) in the buffer solution increased the drug release. In vivo studies in rat showed that modified guar gum was degraded by enzymes in concentration dependent manner showing the suitability of the phosphated cross-linked guar gum for colon drug delivery.

2.4. Dextrans

Dextrans are a class of polysaccharides with a linear polymer backbone with mainly 1,6-α-D-glucopyranosidic linkages. They are obtained from bacterial cultures of *Leuconostoc mesenteroides* NRRL B-512. These glycosidic linkages are hydrolysed by moulds (Hultin and Nordstom, 1949), bacteria (Ingelman, 1948; Sery and Hehre, 1956; Bailey and Clarke, 1959; Jonson and Porath, 1966) and also by the mammalian cells (Rosenfeld and Lukomskaya, 1957). Dextranases are the enzymes which hydrolyse these glycosidic linkages. Dextranases activity of the colon are shown by anaerobic gram-negative intestinal bacteria especially the *Bacteroides* (Hehre and Sery, 1952). Dextran has also been found to be degraded in human feaces due to bacterial action (Aberg, 1953) (Fig. 4).

Various drug-dextran prodrugs in which the drug molecule is linked to the polar dextran macromolecule remain intact and unabsorbed from the stomach and the small intestine but when the prodrug enters into the colonic microflora containing as much as 10^{11} *Bacteroides* per gram (Drasar and Hill, 1974) it is acted upon by dextranases which cleave the dextran chain randomly and at the terminal linkages releasing the drug, free into the colon.

Increasing interest is being focused on dextran prodrugs. First attempt was carried out by Harboe et al. (1989a) who conjugated naproxen to dextran by ester linkage. Dextran ester prodrugs of ketoprofen and naproxen using dextran with molecular weight (M.W.) 10 000–500 000 were shown to release the drug specifically in the colon region of pig (Larsen et al., 1989, 1991; Harboe et al., 1989a,b). The release of naproxen was upto 17 times higher in the cecum and colon homogenates of pig than in control medium or homogenates of SI. A series of prodrugs, naproxen-dextran, ketoprofen-dextran and ibuprofen-dextran have been tested in vitro and in vivo in pigs. They postulated this prodrug system as a potential system for site specific delivery showing high bioavailability of the drug but still no absorption of the prodrug into the circulation. Also, this system could provide protection to the drug in the upper GIT and selective regeneration in the cecum/colon. This approach delivers drug specifically to the colon and can be used for colon targeting.

In another study, dextran with molecular weight 72 600 were used to deliver to the colon (McLeod et al., 1993, 1994a). Methyl prednisolone and dexamethasone prodrugs with dextrans were prepared. Since the glucocorticoids did not have a functional group for attachment of dextrans, these were attached to dextrans using a spacer molecule (McLeod et al., 1994a,b). It was found that dextran conjugates showed little hydrolysis in upper GIT contents, but were degraded rapidly in the cecal and colonic contents. These polymeric prodrugs were much more effective than the parent drug itself when tested in colitis-induced rats (McLeod et al., 1994c).

Jung et al. (1998) prepared dextran prodrugs of 5-ASA. This prodrug was stable and no 5-ASA

was released in contents of SI of rats. Even the presence of diluted cecal contents in the dissolution medium increased the release of 5-ASA from the prodrug.

Apart from prodrug approach biodegradable dextran hydrogels using diisocyanate as a cross-linking agent (Brondsted et al., 1995a) have been found to be fully degradable by dextranases in vitro and in vivo in the rat cecum (Brondsted et al., 1995b). These have also been found to be completely degradable in the human colonic fermentation model (Simonsen et al., 1995) though, the fermentation of the gels started only after around 24 h. This would however, cause a delay in drug release which would take place in the distal colon where conditions for absorption are very reduced.

pH-sensitive dextran hydrogels (Chiu et al., 1999) were prepared by activation of dextran with 4-nitrophenyl chloroformate followed by conjugation of activated dextran with 4-aminobutyric acid and cross-linking with 1,10-diaminodecane. Bovine serum albumin (BSA) was loaded in these dextran hydrogel discs by immersing the discs in BSA solutions. After equilibrating in the BSA solution for 5 days, the discs were washed and dried. The release rate of bovine serum albumin from these hydrogels discs was primarily determined by the swelling extent which in turn depended upon the content of carboxylic acid and the degree of cross-linking. The release rate was enhanced by the addition of dextranase in the dissolution media.

In another approach, Glutaraldehyde cross-linked dextran capsules were used for colon-specific drug delivery (Brondsted et al., 1998). These capsules were loaded with hydrocortisone and drug release studies were conducted in vitro. Ten percent of drug was released in initial 3 h and only about 35% in 24 h at pH 5.4. Addition of dextranase enzyme after 24 h resulted in a rapid degradation of the capsule leading to fast and complete release of hydrocortisone. However, these results reflect only an experimental condition and not the in vivo situation.

Colon degradable dextran fatty acid esters which were film forming and insoluble in gastric and small intestinal fluids were synthesized for colon drug delivery (Bauer and Kesselhut, 1995). Out of these esters lauroyl dextran esters with molecular weight of approximately 250 000 and degree of substitution ranging from 0.11 to 0.3 were found to be suitable for colon drug delivery as film coatings. Initial studies carried out in vitro with lauroyl dextrans esters having degree of substitution between 0.12 and 0.40 and using theophylline as the drug (Hirsch et al., 1997) showed that release rate was inversely proportional to the amount of ester applied on the coating. Addition of dextranase degraded the coating releasing the drug. However, further studies showed that dispersion of lauroyldextrans were not suitable as degradable coating material (Hirsch et al., 1999), as they did not display ideal zero order dissolution before and quick disintegration after enzyme addition.

2.5. Inulin

Inulin is a naturally occurring polysaccharide (Van Loo et al., 1995) found in many plants, such as onion, garlic, chicory, artichoke. Chemically, it consists of β 2-1 linked D-fructose molecules, having a glucosyl unit at the reducing end (Roberfroid, 1993) (Fig. 5). Inulin is not hydrolysed by the secretions of the human digestive tract (Dysseler and Hoffem, 1995). Bacteria present in the colon especially *bifidobacteria*, which constitute up to 25% of the normal gut flora in man (McKellar and Modler, 1989) are known to ferment inulin (Wang and Gibson, 1993; Gibson and Roberfroid, 1995).

To overcome the poor film forming property and to control the swelling of inulins, they have been evaluated for colon-targeting in combination with synthetic film forming polymers. The mixed films thus prepared resisted degradation in the upper GIT and fermented in the colon by *Bifidobacteria* and *Bacteroides*. Vervoort and Kinget (1996) incorporated highly polymerised inulin in Eudragit RS films which were degraded in human fecal medium. Also, the permeability of these membranes increased significantly after incubation in the fecal medium.

A series of studies were carried out on chicory inulin (Vervoort et al., 1997). Methacrylated in-

ulin was synthesised and aqueous solutions of Methacrylated inulin upon free radical polymerisation, were converted to cross-linked hydrogels (Vervoort et al., 1997). Rheological studies and characterization of there hydrogels showed that higher substituted inulins had better network and higher mechanical strength (Vervoort et al., 1999). These hydrogels were then studied for their swelling properties (Vervoort et al., 1998a) and degradation in vitro (Vervoort et al., 1998b). Degradation studies carried out in the presence of inulinase showed that increasing enzyme concentration and incubation time degraded inulin faster. However, increasing the substitution on inulin molecules resulted in stronger hydrogels with less enzyme diffusion thereby less degradation.

2.6. Chondroitin sulphate

Chondroitin sulphate is a mucopolysaccharide found in animal connective tissues especially in cartilage. Chemically, it consists of D-glucuronic acid linked to *N*-acetyl-D-galactosamide (Wastenson, 1971; Toledo and Dietrich, 1977) which is sulphated at C-6 (Fig. 6).

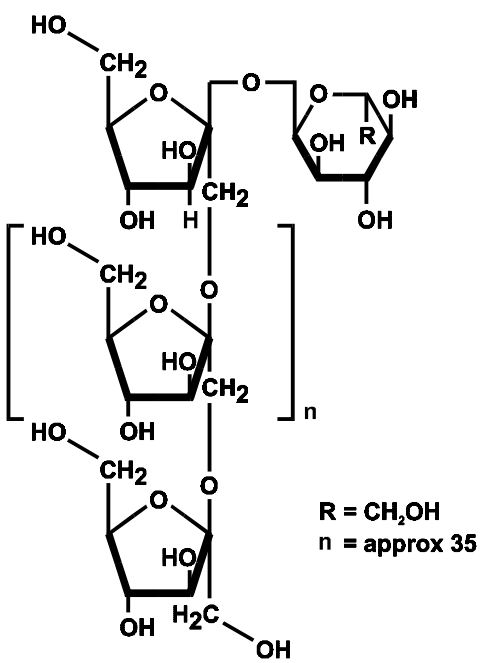

Fig. 5. Structure of inulin.

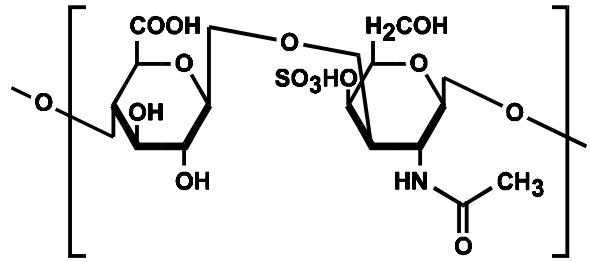

Fig. 6. Structure of chondroitin sulphate.

Chondroitin sulphate is degraded by the anaerobic bacteria of the large intestine mainly by *Bacteroides thetaiotaomicron* and *B. ovatus* (Salyers, 1979; Salyers and Brien, 1980). Such a degradation profile suggests the use of chondroitin sulphate as a drug carrier to deliver drugs especially to the large intestine where *bacteroides* are found in abundance. However, the high water solubility of chondroitin sulphate is disadvantageous. There was 100% release of indomethacin within 1 h of dissolution test using chondroitin sulphate alone as a carrier (Rubinstein et al., 1992a). To overcome this difficulty, cross-linked chondroitin was developed as a drug carrier for colon-specific delivery (Rubinstein et al., 1992a,b; Sintov et al., 1995). Chondroitin sulphate was cross-linked with 1,12-diaminododecane via dicyclohexylcarbodiimide activation. Cross-linked chondroitin sulphate was used to form a matrix tablet (Rubinstein et al., 1992a,b) with indomethacin. Release of indomethacin from this tablet was studied in the presence of rat cecal contents as compared to release in phosphate buffer saline. A significant difference in drug release was observed after 14 h in the two dissolution media. Also, different degree of cross-linked chondroitin sulphate were used to study their effect on drug release from the matrices. The cumulative percent release of indomethacin from cross-linked chondroitin matrix tablet showed that release was increased in the presence of rat cecal contents. Studies on rat cecal contents with various cross-linked chondroitin sulphate showed greater cumulative drug release when cross-linking was less and as cross-linking increased the

cumulative release decreased i.e. a linear relationship was found between the degree of cross-linking of polymer and the amount of drug released in rat cecal content. This suggests that the drug release in the colon can be controlled by adjusting the relative amount of different cross-linked chondroitin sulphate in the matrices.

2.7. Amylose

Amylose is a polysaccharide from plant extracts and a component of starch. It consists of D-glucopyranose residues linked by α-(1→4) bonds. It is a poly(1,4′-α-D–glucopyranose) (Fig. 7). This naturally occurring polysaccharides possesses the ability to form films. These films are water swellable and are potentially resistant to pancreatice α-amylase (Leloup et al., 1991) but are degraded by colonic bacterial enzymes (Englyst and MacFarlane, 1986; Ring et al., 1988).

Amylose-Ethocel® coating system resistant to gastric acid and small intestinal enzymes, but degradable by colonic bacteria were prepared and evaluated in vitro for their potential as colon drug carrier. Varying concentrations of Amylose and Ethocel® in the form of aqueous dispersions were used to coat 5-ASA pellets. A coating formulation comprising Amylose and Ethocel® in the ratio of 1:4 w/w showed optimum drug release retarding properties in gastric and intestinal fluids (Milojevic et al., 1995, 1996a). This coating with amylose: ethycellulose in ratio of 1:4 could suppress the in vitro release of 5-ASA from coated pellets in simulated gastric and small intestinal media over a period of 12 h and was fermented in simulated colonic environment (containing mixed fecal bacteria of human origin) releasing the drug in 4 h (Milojevic et al., 1996a).

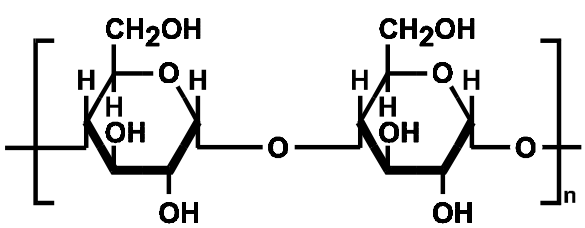

Fig. 7. Structure of amylose.

Further, the same group found that this amylose–ethycellulolse coating (1:4) was also suitable to deliver a highly water soluble drug glucose to the colon (Cummings et al., 1996; Milojevic et al., 1996b). Cores were made using glucose and Avicel® PH 101 (microcrystalline cellulose). To retard glucose solubilization, additional binders were added to the cores and secondly, amylose fraction in coating mixture was increased. As the thickness of the coat was increased, the glucose release decreased. Pellets core containing 20% glycerol monostearate, 50% glucose and 30% Avicel PH 101 coated with the Amylose–Ethocel® mixture (1:4) with 6.8% amylose concentration could resist glucose release in upper GIT conditions. In vitro fermentation studies in 5% mixed human fecal slurry showed an early release of glucose from these coated pellets. In vivo studies carried out in healthy human volunteers using gamma scintigraphy and breath samples for CO_2 showed that a delay of 2.7 h occurred between arrivals of pellets to the cecum and their significant breakdown. The release of glucose occurred over a period of time indicating that the site specific delivery in addition had a sustained release profile (Cummings et al., 1996).

Organic solvent based amylose–ethylcellulose films have also been evaluated as potential coatings for colonic drug delivery. Varying the concentration of amylose and ethylcellulose in the films could vary the drug release rate from these films (Siew et al. 2000a). These films were found to be susceptible to digestion by bacterial enzymes in a simulated colonic environment. The extent of digestion was directly proportional to the amylose content in the film. Amylose–ethylcellulose films were also evaluated for delivery of 5-ASA pellets to the colon by this group (Siew et al., 2000b). The rate of release was inversely proportional to the thickness of the coat and also influenced by the amount of amylose present in the film. It was found that a film coating containing amylose and ethylcellulose in a ratio of 1:1 and 15% total weight gain after coating, could resist release of 5-ASA in upper GIT and gave a rapid drug release in simulated colonic condition. These films are believed to offer promises in the processing of drug molecules that are thermolabile and/or sensitive to water for colonic delivery.

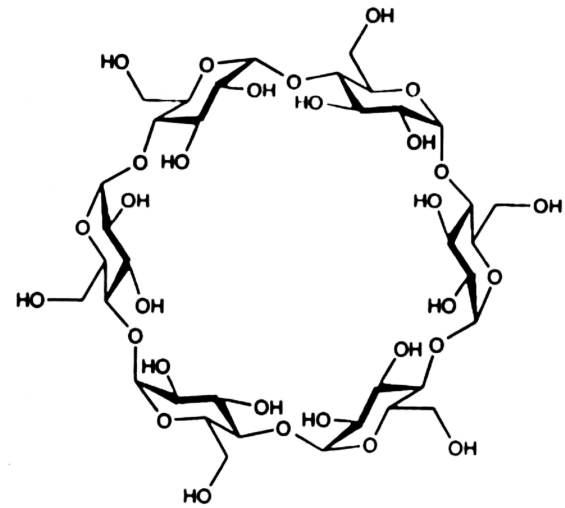

Fig. 8. Structure of cyclodextrins.

2.8. Cyclodextrins

Cyclodextrins are cyclic oligosaccharides. They consist of 6–8 glucose units linked through α-1,4′-glucosidic bonds (Fig. 8).

Cyclodextrins are neither hydrolysed nor absorbed from the stomach and small intestine. However, in the colon the vast microflora present breaks these into small saccharides and thus are absorbed in the large intestine (Andersen et al., 1983; Antenucci and Palmer, 1984; Gerloczy et al., 1985; Flourie et al., 1993). This property of being able to be degraded by colonic bacteria especially *Bacteroides* led to its use as a colon targeting carrier.

Ester conjugates of biphenylyl acetic acid with β-cyclodextrin released the drug preferentially when incubated with rats cecal contents and almost no release was observed on incubation with contents of stomach and small intestine (Hirayama et al., 1996). Studies were carried out for the prodrugs of α, β and γ cyclodextrins with biphenylyl acetic acid (BPAA) (Uekama et al., 1997; Minami et al., 1998) for colon-specific delivery. Both ester and amide type prodrugs were prepared and in vivo release studies conducted in rat. Studies on ester prodrug showed that a large portion of the prodrug was recovered intact from stomach and only negligible amount of free BPAA was present. In the cecum and colon BPAA was produced and absorbed into the blood, suggesting that ring-opening hydrolysis takes place in the cecum and colon and the resulting small saccharide ester conjugates are rapidly hydrolysed to BPAA. These results were in accordance with the in vitro studies. The amide prodrug, however, in the in vivo studies was observed to be intact in the entire GIT but was hydrolyzed to BPAA-maltose conjugate in the cecum or colon. After 6 h of dosing, whole of the prodrug moved to the colon and intact prodrug and maltose conjugate were present in colon. Neither the prodrugs, nor BPAA-maltose, nor BPAA were present in the blood and urine suggesting that hydrophilic carbohydrate conjugates are less absorbed from rat GIT. These observations indicated that the cyclodextrins prodrug passes intact from the rat stomach and small intestine but are subjected to ring opening process in the cecum and colon.

2.9. Alginates

Alginates are a linear polymer which have 1-4′ linked-β-D-mannuronic acid and α-L-guluronic acid residues arranged as blocks of either type of unit or as a random distribution of each type

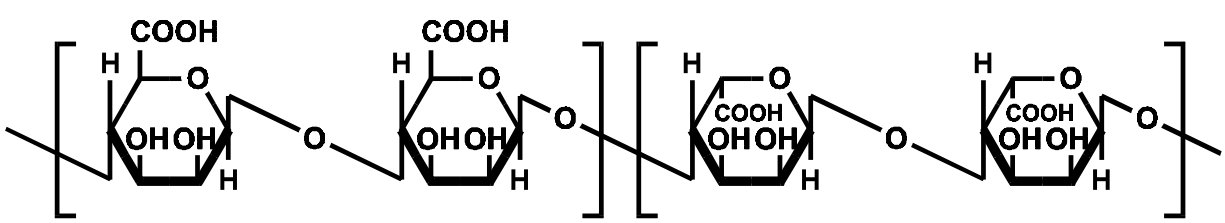

Fig. 9. Structure of alginates.

(Fig. 9). Alginates do not gel since they have poly(L-gluronic acids) which are rigid, Ca^{++} ions induce gelation.

Calcium alginate beads (Shun and Ayres, 1992) were made as cores and 5-ASA was spray coated on them. These beads were coated with different percentages of enteric coating polymer and/or sustained release polymer. Aquacoat is a pH independent polymer which is insoluble in both acidic and intestinal fluid and Eudragit L-30D dissolves above pH 5.6. A system was formulated by coating 5-ASA calcium alginate beads with aquacoat (4% w/w) followed by 6% w/w coat of Eudragit L-30D. The Eudragit layer protected the coat in acidic medium but dissolved in the basic media. There, the rate of drug release was controlled by aquacoat. When drug loaded calcium aliginate beads swell sufficiently (osmotic gradient) to exceed the strength of the outer sustained released coat, the film bursts to release the drug. Such a system delivers drug to the distal intestine with minimal initial leak and gives sustained release in the colon. Also alginate beads coated with dextran acetate were prepared. These beads showed minimal drug release in the absence of dextranase but significant drug release was seen in presence of dextranases in vitro (Kiyoung et al., 1999).

2.10. Locust bean gum

Locust bean galactomannan were found to be soluble in water. Cross-linked galactomannan however led to water-insoluble film forming product showing degradation in colonic microflora (Bauer and Kesselhut, 1995). However, dissolution study performed on theophylline tablets coated with cross-linked galactomannan showed the mechanical instability of these coatings in the dissolution media (Hirsch et al., 1999), thereby suggesting the nonsuitability of such films as colon carriers.

3. Conclusion

There is an increasing interest in targeted delivery of drug to the colon via the oral route. Targeting drugs to the colon has major advantages in the direct treatment of the local disease and also for allowing the possibility of using colon for systemic therapy since the residence time is more than 24 h. Currently, several strategies are being used for targeting the drug specifically to the colon viz. systems that are, pH dependent, time-controlled, pressure-controlled, prodrugs and those based on biodegradable polymers (enzyme controlled). Every approach has pros and cons over each other and are more or less affected by the changes in diet, environmental conditions and diseased state. Failure of pH-dependent system may be expected due to inter and intra subject variation of GI pH, pH variation due to pathological conditions and diet composition. Enteric coated time dependent systems with reproducible lag-time are more suitable for colon-specific drug delivery. The suitability of pressure controlled delivery system is dependent on reproducibility of pressure of peristaltic waves, its duration and diseased state.

The drug release from the system activated by colonic microflora appears to be more suitable with regard to selectivity. Some polysaccharides which are degraded by human colonic microflora, have been investigated for their potential as colonic drug delivery carriers. Exploiting the use of these naturally occurring dietary polysaccharides for colonic drug carrier means that issues of safety, toxicity and availability are simplified. An important pre-requisite for a colon-specific drug carrier made of natural and modified polysaccharide hydrogel, is its ability to hydrate and resultant swelling which creates a diffusion barrier at the surface of the solid dosage form during its passage through the GI tract. These hydrated layers of polymers allow the penetration of colonic enzymes/bacteria which leads to the degradation of the polysaccharide barrier, hence releasing the drug at the target site.

Polysaccharides with a large number of derivatizable groups, a wide range of molecular weight, varying chemical composition and above all being stable, safe and biodegradable, offer properties preferable over all the other approaches. A number of studies have been conducted on plain and derivatized pectin, guar gum, dextran and chitosan. Relatively lesser amount of studies have

been conducted on chondroitin, insulin, alginates, amylose etc. However, a substantial amount of research remains to be conducted to develop a polysaccharide based colon-specific drug delivery dosage form which is easier and simpler to formulate and is highly site-specific.

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