Characteristics of Natural Polysaccharides for Colon Drug Targeting

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ABSTRACT

Targeting drugs directly to the colon is advantageous in the topical treatment of colonic diseases such as ulcerative colitis and Crohn’s disease and has shown potential in gaining the oral delivery of peptides and other labile drugs. A colonic drug delivery system is required to protect a drug during its transit through the upper gastro-intestinal (G.I.T.) tract and allow its release in the colon. Several methods of colonic targeting have been proposed. These include taking advantage of the apparent consistency of small intestinal transit times, the utilization of pH changes within the G.I. tract and the exploitation of bacterial enzymes localized in the colonic region of the G.I. tract. Among the different approaches to achieve targeted drug release to the colon, the use of polymers especially biodegradable by colonic bacteria holds great promise. Polysaccharides are bacterial enzymes that are available in sufficient quantity to be exploited in colon targeting of drugs. Based on this approach, various polysaccharides have been investigated for colon-specific drug release. These polysaccharides include pectin, guar gum, amylose, inulin, dextran, chitosan, and chondroitin sulfate. This family of natural polymers has an appeal to drug delivery as it is comprised of polymers with a large number of derivatizable groups, a wide range of molecular weights, varying chemical compositions, and, for the most part, low toxicity and biodegradability yet high stability. The most favorable property of these materials is their approval as pharmaceutical excipients. Polysaccharides are bacterial enzymes that are available in sufficient quantity to degrade these natural polysaccharides.

KEYWORDS: Colonic drug delivery system; Biodegradable; Natural polysaccharides.

Introduction

Various strategies, currently available to target the release of drugs to colon, include formation of prodrug, coating of pH sensitive polymers, use of colon-specific biodegradable polymers, timed released system, osmotic systems, and pressure-controlled drug delivery systems. Among the different approaches to achieve targeted drug release to the colon, the use of polymers especially biodegradable by colonic bacteria holds great promise (Bagyalakshmi et al., 2011).

Biopolymers are promising materials in the delivery of drugs due to their compatibility, degradation behavior, and nontoxic nature on administration. On suitable chemical modification, these polymers can provide better materials for drug delivery systems. Biopolymers like natural polysaccharides obtained from various sources are being extensively used for the development of solid dosage forms for delivery of drug to the colon. The rationale for the development of a biomaterial based drug delivery system for colon is the presence of large amounts of polysaccharides 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. A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as the polysaccharides, from algal origin (e.g. alginates), plant origin (e.g. pectin, guar gum, locust bean gum, khaya gum, konjac glucomannan) microbial origin (e.g. dextran, xanthan gum) and animal origin (Chitosan, chondroitin, hyaluronic acid). The ability of these natural polysaccharides to act as substrates for the bacterial inhabitants of the colon together with their properties, such as swelling and film forming has appeal to area of colon specific drug delivery as it is comprised of polymer with large number of derivatizable groups, with wide range of molecular weight, varying chemical composition, biocompatibility, low toxicity and biodegradability and a high stability (Parul et al., 2012).

The use of naturally occurring polysaccharides attracts a lot of attention for drug targeting to the colon, since these polymers are found in abundance, are inexpensive and are available in a variety of structures with different properties. They can be easily chemically and biochemically modified and are highly stable, safe, non-toxic, hydrophilic and gel forming, and, in addition, biodegradable (Xiaoxia, 2009; Sinha and Kumria, 2001).
They include naturally occurring polysaccharides obtained from superior plants (guar gum, inulin, pectin), animals (chitosan, chondroitin sulphate), algae (alginites) or microbes (dextran), and can be broken down by the colonic microflora to simple saccharides (Vandamme et al., 2000).

Colonic bacterial enzymes are capable of degrading a variety of polysaccharides present in the diet that are not affected either in the stomach or in the small intestine. These non-toxic and biodegradable polysaccharides have the potential of delivering drugs specifically to the colon. Rubinstein et al. have demonstrated the usefulness of pectin, calcium pectinate and chondroitin sulphate as potential colon-specific drug delivery carriers. Studies were also carried out on pectin formulations by Ashford et al. using pectinolytic enzymes and in vivo gamma scintigraphic studies. A suspension of natural polygalactomannans in polymethacrylate solution was used to form a degradation coating. This was found to delay the drug release in the small intestine by forming a swellable layer around the drug core and is degraded by colonic bacterial enzymes thereby releasing the drug in the colon (Rama et al., 1998).

Figure 1 illustrates an overview and summary profile of polysaccharides for colon drug delivery. Various approaches have been used for targeting the drugs to the colon including, formation of a prodrug, multi-coating time-dependent delivery systems, coating with pH-sensitive polymers, pressure-dependent systems, and systems formulated making use of biodegradable polymers. Every system has advantage as well as shortcoming. However, biodegradable systems formulated making uses of naturally occurring polysaccharides are increasingly being developed. Natural polysaccharides remain undigested in the stomach and the small intestine and are degraded by the vast anaerobic microflora of the colon, for example, *bacteroides*, *bifidobacteria*, *eubacteria*, to smaller monosaccharides, which are then used as energy source by the bacteria. In an earlier study these were used in the form of binders in tablet formulation (Sinha et al., 2004).
Characteristics of different types of Natural Polysaccharides and their method of preparation for Colon Specific Drug Delivery System

**Alginate:** Alginate is a linear, naturally occurring polysaccharide extracted from brown sea algae. It contains D-mannuronic (M) and L-guluronic (G) acids which are arranged in homopolymeric MM or GG blocks separated by blocks with an alternating sequence, MG blocks. While alginic acid is insoluble in water, alginic acid salts with monovalent cations and magnesium do dissolve in water. In the presence of various divalent (generally Ca\(^{2+}\) but also Ba\(^{2+}\) and Zn\(^{2+}\)) or trivalent ions (Al\(^{3+}\)), an elastic gel is formed due to ionic interaction between the ions and the carboxyl groups of mainly guluronic blocks (González et al., 2002). Therefore, the alginate monomer composition (proportion of poly G-blocks and their length in alginate) has an important influence on gelling properties and consequently on drug release properties of different dosage forms (Ostberg et al., 1994). The ability of alginate to form a gel in the presence of multivalent ions has been used to prepare multiparticulate systems incorporating numerous drugs, proteins, cells, or enzymes (Tonnesen et al., 2002). The beads are most commonly produced by the so-called ionotropic gelation method, where the dispersion of alginate and material to be encapsulated is added dropwise into a multivalent ion solution. The contact of droplets with multivalent ions results in the instantaneous formation of gel spheres containing uniformly dispersed material to be encapsulated throughout the cross-linked alginate matrix.

Alginate is one among numerous polysaccharides (pectin, chitosan, inulin, dextran, guar gum, etc.) that are selectively degraded in the colon by colonic microbial enzymes; therefore, it can be used for preparation of colon specific drug delivery systems. However, it is well known that by incorporation of drugs into calcium alginate beads it is difficult to provide delayed release of hydrophilic, low molecular weight drugs (Ostberg et al., 1994). To avoid premature drug release, a polysaccharide degradable specifically in colon and time and/or pH-controlled mechanism should be combined in the formulation. This could be achieved by coating of calcium alginate beads with suitable polymer and in this step the bead characteristics, especially shape of the beads and morphology, are of critical importance. Therefore, the influence of drug incorporated as well as process parameters on bead properties has to be understood in detail. It has been reported that several formulation parameters (type and concentration of alginate, combination of alginate with different polymers, and drug polymer weight ratio) and processing parameters (hardening time, calcium concentration, drying conditions, and type of multivalent ions) affect drug content and drug release as well as bead size and morphology (Smrdel et al., 2006).

**Preparation of Alginate Beads**

The beads were prepared by ionotropic gelation technique (Daris et al., 1997) 100mL of Sodium Alginate (SA) solutions at different concentration were prepared by stirring sodium alginate powder in deionized water for 30 minutes then, an accurately weighed quantity of drug was added to afford homogeneous dispersions. The SA-drug dispersion was then added drop wise into a 100mL of cross linking solution (different concentration and type) using a 10mL of hypodermic syringe fitted with a 20 gauge needle and stirred at 500 rpm. The formed alginate beads were cured at different time interval. On expiration of this period the solution of cross-linking agent was decanted and the alginate beads were washed repetitively for three times with 50mL de ionized water. The alginate beads were thereafter dried at 60°C for 2 hours in a hot air oven.

**Pectin:** Pectins are polysaccharides components of plant cell walls and consist of linear polymers of d-galacturonic acid residues with varying degrees of methyl ester substituents (Sinha et al., 2001). The degree of esterification (DE) and degree of amidation (DA), which are both expressed as a percentage of carboxyl groups (esterified or amidated), are important means to classify pectins. Pectins are broken down by various microbial sources including human colonic bacteria and may therefore be utilized as colonic delivery systems if their solubility is reduced. Therefore, major efforts have been focused on looking for pectin derivatives, which are more water resistant, while still enzymatically degradable (Liu et al., 2003).

**Preparation of Pectinate Gel Beads**

Pectin aqueous solution at a concentration of 4% (w/v) was prepared overnight. Then, an appropriate amount of the model drug ketoprofen (2% w/v) was dispersed into the solution until a uniform dispersion was obtained.
This bubble-free dispersion was added drop-wise, at an average rate of 2 mL/min, using a nozzle of 0.8 mm inner diameter, into a gently agitation solution of the crosslinking agent (CaCl₂ or Zn (CH₃COO)₂) with two concentrations (5 or 10%) and two different pH (1.6 or 6 adjusted by using an adequate amount of HCl  N). The falling distance was 3 cm. The gelled beads, instantaneously formed, were allowed to cure in the cross-linking solution for 20 min, and were then separated by filtration, washed with deionized water and dried at 37°C for 48 h in a drying room (Chambin et al., 2006).

**Chitosan**: Chitin, a naturally abundant mucopolysaccharide, and the supporting material of crustaceans, insects, etc., is well known to consist of 2-acetamido-2-deoxy-b-D-glucose through a β (1→4) linkage. Chitin can be degraded by chitinase. Chitin is a white, hard, inelastic, nitrogenous polysaccharide and the major source of surface pollution in coastal areas. Chitosan is the N-deacetylated derivative of chitin, although this N-deacetylation is almost never complete (Majeti et al., 2000).

Chitosan, with excellent biodegradable and biocompatible characteristics, is a naturally occurring polysaccharide. Due to its unique polymeric cationic character and its gel and film forming properties, chitosan has been extensively examined in the pharmaceutical industry for its potential in the development of drug delivery systems (Shu et al., 2000).

Chitosan is a biodegradable, hydrophilic, biocompatible and natural linear biopolyaminosaccharide with good potential for pharmaceutical applications due to its high charge density, non-toxicity and mucoadhesive. In addition, chitosan was studied as a carrier for microsphere drug delivery. Reacting chitosan with controlled amounts of multivalent anion results in crosslinking between chitosan molecules. This crosslinking has been used extensively for the preparation of chitosan microspheres. They are the most widely studied drug delivery systems for the controlled release of drugs such as antibiotics, antihypertensive agents, anticancer agents, proteins, peptide drugs and vaccines (Aysu et al., 2010).

Chitosan is completely digested by the colonic bacteria and is toxicologically harmless material of low cost and turned out to be a useful excipient in various pharmaceutical formulations (Dodane et al., 1998). Chitosan has been used for colon-specific drug delivery as the forms of microspheres (Lorenzo et al., 1998) and capsules (Tozaki et al., 1997) because of its biodegradable properties by colonic bacteria. Under the presence of rat cecal contents in the dissolution medium, chitosan is degraded. It is also suggested that the enzymes, which are produced for the degradation of chitosan decrease the pH of the cecal contents and chitosan is dissolved. Since chitosan owns a number of amine groups, it dissolves in weak acidic conditions, but is insoluble in higher pH conditions due to the deprotonation of the amines (Ravindra et al., 1998). Chitosan is hardly dissolved in organic solvents, in which the water-insoluble polymers are dissolved (Norihito et al., 2002).

**Preparation of Chitosan Beads**

The beads were prepared by two methods (conventional method and novel method), and described as follows.

(a) **Mixture solution preparation**: A model drug (FITC-dextran or brilliant blue) was dissolved or dispersed in double-distilled water and added to an aqueous solution of chitosan, containing gelatin dissolved in acetic acid, at 37°C under agitation. The component concentration in the solution was (w/v): chitosan 4%, gelatin 4%, and model drug 1%.

(b) **Preparation of beads by crosslinking methods**: All the formulations were prepared by using ionotropic gelation method. Diclofenac sodium used in the formulation were initially passed through sieve #40 separately before mixing. A
2% v/v acetic acid solution was prepared by dissolving 2 mL of glacial acetic acid in distilled water that was then made up to a volume of 100 mL. A 2% w/v chitosan solution was prepared by accurately weighing an approximate amount of 2 gm of chitosan and dissolving it in 100 mL of the pre-prepared 2% v/v acetic acid in a 1000 mL size glass beaker. This mixture was stirred using digital high-speed lab stirrer (Remi Motors LTD) at 30 °C and 50 rpm for 30 minutes and stirring was continued for overnight so that chitosan get completely swelled in glacial acetic acid media. After complete dissolution of the chitosan, the solution was labelled (A). Approximately 2 g of the drug (diclofenac sodium), that was accurately weighed, was dispersed into 100 mL of solution A using a high-speed lab stirrer (Remi Motors LTD). This mixer was run at 800 rpm for 10 minutes, and then at 1000 rpm for 15 minutes at 25 °C. This diclofenac sodium suspension was labeled (B) and it was used in the subsequent cross-linking experiments.

Cross-Linking to form Gels

Accurately measured quantities of the different cross-linking agents were dissolved in distilled water to complete the following concentrations:
(a) Sodium-tri-polyphosphate (STPP, 3, 6, 10% w/v)
(b) Oleic acid (OA, 3, 6, 10% v/v)
(c) Polysorbate 80 (T80, 3, 6, 10% v/v)

Finally, mL sodium-tri-polyphosphate (STPP, 3, 6, 10% w/v) (C) were finally chosen for cross-linking experiments. The resultant homogeneous bubble free suspension (B) was dropped using a disposable syringe (No.18) as shown in figure no-2 into 100mL of sodium tri-polyphosphate (STPP) solution for 20 minutes. The beads were collected after filtration and washed with deionised water. Beads were dried at room temperature (Ketan et al., 2012).

(c) Preparation of chitosan beads: Initially, 200 mg chitosan was dissolved in 10 mL of a 1% acetic acid solution under stirring for 20 min at room temperature. Then, theophylline was dispersed in this solution and finally theophylline-chitosan mixture was added dropwise the into triplyolphosphate aqueous solution at room temperature, using a syringe. The formed beads were allowed to stand in the triplyolphosphate solution for 15 min to be cured. The beads were separated with paper filter, then washed twice with water and dried by freeze- drying (Reza et al., 2004).

(d) Preparation of Sulfate, citrate and (sodium triplyolphosphate) TPP cross-linked chitosan beads: Sulfate, citrate and (sodium triplyolphosphate) TPP cross-linked chitosan beads were prepared according to our recently reported method (Shu and Zhu, 2000) and described as follows. Model drug (riboflavin) were dispersed in double-distilled water and added to an acetic acid (4% w/v) solution of chitosan containing gelatin at 37 °C under agitation. The component concentration in the solution (w/v): chitosan 4%, gelatin 4% and model drug 1%. Some 2 mL of the above mixture solution (37 °C) was dropped through a syringe needle (0.45 mm in diameter) into 250 mL cold sesame-seed oil (4 °C) to induce the coagulation of gelatin. After 30 min, the oil was discarded and 100 mL cold cross-linking solution was added under gentle agitation at 4 °C. The cross-linking solution contained sodium sulfate, sodium citrate or TPP with a concentration of 0.25–5.0% (w/v) (pH 7.0). After a certain time, the beads were separated and washed with cold double-distilled water (4 °C), then used in the following experiments or dried under vacuum at room temperature. During the bead preparation process, the aqueous phase was collected and the drug content in aqueous phase was determined by UV visible spectrophotometer at 444 nm. Usually 95% model drug was loaded in the beads (Shu and Zhu, 2002).

(e) Preparation of chitosan–alginate beads: Various types of beads were prepared and named after their multivalent components: chitosan, alginate and polyphosphate. Chitosan–alginate beads were produced by the gelation method (Anal et al., 2003). A homogenous mixture of 2% (w/v) sodium alginate and 20% (w/v) ampicillin in distilled water was used as dope. The pH was adjusted to 5.5±0.1. Homogenous aqueous solutions of chitosan (CTS) and calcium chloride (CaCl2) is made in various fluids. Chitosan (1%, w/v) was dissolved in 1% (v/v) acetic acid at room temperature. The coagulation fluids were prepared by diluting the chitosan stock solution to the desired chitosan concentration with CaCl2 solutions of sufficient concentration. The composition of the coagulation fluids is listed in Table 1. The solutions were mixed for 2 h before use. The pH of the coagulation fluids was adjusted to 4.5±0.1. Dope (20 mL) was dropped through a 27 gauge blunt ended needle into 200 mL of coagulation fluid under mechanical stirring at 200 rpm. The flow rate of the dope was maintained at 10 mL/h using compressed nitrogen. The smooth, spherical and homogenous beads obtained were kept for an hour in the coagulation fluid under stirring. Thereafter beads were collected, washed with distilled water and air-dried. Three batches of beads were prepared for further study (Anil et al., 2005).

Guar gum

Guar gum is a natural hetero-polysaccharide obtained from the endosperm of the guar plant, Cyamopsis tetragonolobus, which has been extensively used in
various industrial applications. It is a high molecular weight hydrocolloidal hetero-polysaccharide composed of galactan and mannan units. It possesses several attractive and industrially useful properties. Guar gum has been modified by derivatization, grafting and network formation to improve its property profile for a wide spectrum of end-uses (Thakur et al., 2004).

Among the hydrophilic polysaccharides, guar gum (GG) is generally considered as a potential candidate for colon-specific drug delivery application due to its drug release retarding property and susceptibility to microbial degradation in the large intestine. GG is also a prospective hydrophilic matrix carrier for oral controlled delivery of drugs with varying solubility and therefore many reports have been published on the use of GG for oral delivery of drugs (Prabaharan, 2011).

Guar gum is commonly used in the food industry as a thickening agent. In pharmaceutics it has been suggested as a vehicle for oral controlled release purposes (Kulick, 2004; Khare, 1995) and for colon targeting (Alcock, 1996; Kinage, 2009). Since a major restriction in the design of Guar gum matrices for drug delivery is its high swelling characteristics (a property which requires high compression forces at production to avoid premature burst release), a chemical modification of Guar gum to reduce its enormous swelling properties is a practical alternative solution, especially for orally administered colon specific drug delivery systems. Guar gum could be modified by reacting it either with borax or glutaraldehyde and that its enzyme degradation properties would still be maintained (Kajale et al., 2004).

**Preparation of Alginate-guar gum microbeads:** Specified quantity of drug was dispersed in the alginate solution (3% w/v). Then calcium carbonate was added to the above solution in the ratio of 0.5:1 (CaCO$_3$: alginate wt%). The resulting solution was dropped through a 26 gauge needle in to the 100 mL cross linking solution (calcium chloride (1%w/v) + acetic acid (10%v/v). For Preparing alginate/HPMC and alginate/Guar gum beads, HPMC (0.5%w/v) and Guar gum (0.5%w/v) were added respectively to drug /alginate/ CaCO$_3$ solution and dropped in to cross linking solution (Raja et al., 2011).

**Formulation of floating alginate-guar gum microbeads:** To the aqueous solution of sodium alginate (30%w/v) the drug theophylline (5%w/v) and guar gum (1% w/v) were added with continuous stirring. Then the gas forming agent such as calcium carbonate were added to the above solution in different concentration (0.25, 0.5, 0.75, 1%w/v). Then the prepared batches were extruded with help of 26G syringe needle to a beaker containing mixture of calcium chloride (1%w/v) and acetic acid (10%w/v) on continuous stirring with the help of a magnetic stirrer. The stirring was continued for further 10min and then beads were collected washed with distilled water and dried at room temperature 36 ± 2°C (Sangeetha et al., 2010).

**Preparation of alginate-guar gum hydrogels:** The hydrogel beads used for the study were prepared by extrusion of the mixture through a syringe having a diameter of 0.1 mm. Alginate-guar gum hydrogels with distinct alginate to guar gum percentage weight ratios were prepared (4:0, 3.75:0.25, 3.5:0.5, 3.25:0.75, 3:1, 2.75:1.25). The guar gum solution of the required concentration is prepared first and then the required amount of alginate is added and stirred well to form a uniform mixture. To this mixture, glutaraldehyde was added to a final concentration of 0.25, 0.3, 0.4 and 0.5% (w/v), followed by BSA to a final concentration of 0.2% (w/v), and blended well. The final solution is kept undisturbed for some time to remove the trapped air bubbles. Beads are made in 0.5M CaCl$_2$ solution, cured for 1 h in the same solution and then removed by filtration and washed with deionized water to remove excess glutaraldehyde and CaCl$_2$. The beads were then either lyophilized or air-dried at room temperature and then stored in the refrigerator (George and Abraham, 2010).

**Chondroitin sulfate:** Chondroitin sulfate is a soluble mucopolysaccharide that is used as a substrate by *Bacteroides* species in the large intestine mainly by *B. thetaiotaomicron* and *B. ovatus*. Chondroitin sulfate consist of β-1,3-D-glucuronic acid linked to N-acetyl-D-galactosamine. Natural chondroitin sulfate is cross linked and readily water soluble, but it may not be able to sustain the release of most drugs from the matrix. Chondroitin sulfate is degraded by the anaerobic bacteria of the large intestine mainly by *Bacteroids thetaiotaomicron* and *B. ovatus* (Chourasia et al., 2003).

Chondroitin sulfate is highly water soluble and this property act as a barrier in the formulation of the colon targeted drug delivery (Rubinstein et al., 2010). Cross linked chondroitin sulfate with 1,12-diaminododecanec (9364.8 mg) was used as a carrier for indomethacin specifically for the large bowel. Cross linking took place between the carboxyl group in chondroitin and the amino group in diaminododecanec and formed a dimer of chondroitin sulfate. The degree of cross linking was determined by measuring the amount of methylene blue which was adsorbed as a result of cation exchange. The cross-linked polymer was mixed with indomethacin and compressed into tablets. An enhanced release was observed on incubation with rat cecal contents.

Rubinstein et al cross-linked chondroitin sulfate and formulated a matrix form with indomethacin as a drug marker. Cross linking was characterized qualitatively as well as quantitatively and the drug release kinetics was analyzed using phosphate buffer saline solution. The amount of drug released was increased linearly with the increase in the degree of cross linking. Results of the study revealed that drug targeting to the colon may be achieved by varying the amount of cross-linked chondroitin sulfate in formulations.

Amrutkar et al (2009) have prepared matrix tablet for colon specific delivery of indomethacin using chondroitin sulfate and chitosan as carrier and binder. Chondroitin sulfate was used to form polyelectrolyte complexes (PEC) with chitosan, and its potential as a colon-targeted drug carrier was investigated. The study confirmed that selective delivery of drug to the colon can be achieved using cross-linked chitosan and chondroitin sulfate.
polysaccharides. Cavalcanti et al., characterized cross-linked chondroitin sulfate for specific drug delivery to colon (Cavalcanti et al., 2005). Chondroitin sulfate was cross-linked with trisodium trimetaphosphate to reduce its hydrosolubility.

**Dextran:** Dextran is a polysaccharide consisting of α-1,6 D-glucose and side chain of α-1,3 D-glucose units. These highly water-soluble polymers are available commercially as different molecular weights with a relatively narrow molecular weight distribution. Dextran contains a large number of hydroxyl groups, which can be easily conjugated to drugs and proteins. Dextran gets degraded by the microbial enzyme dextranases, which is found in the colon. Pharmacodynamically, conjugation with dextran has resulted in prolongation of the effect, alteration of toxicity profile, and a reduction in the immunogenicity of drug.

Dextran was oxidized using sodium periodate and coupled the aldehyde product with the α-amino group of 5-amino salicylic acid (5-ASA) (Ahmad et al., 2006). It was reported that less oxidized dextran yields the minimum 5-amino salicylic acid conjugation, which were susceptible to dextranase hydrolysis while highly oxidized dextran yields the maximum 5-ASA conjugation, which were resistant to dextranase hydrolysis. Therefore, it was concluded that dextran can potentially be used to treat bowel inflammatory diseases.

The prepared dextran hydrogels were characterized by equilibrium degree of swelling and mechanical strength (Hoygaard et al., 1995). Degradation study of the hydrogels was done in vitro using dextranase, in vivo in rats and in a human fermentation model. The study indicated that the equilibrium degree of swelling, mechanical strength and degradability of the hydrogels can be controlled by changing the chemical composition. Dextran hydrogels degraded in vivo in the cecum of rats but not in the stomach suggesting that dextran hydrogels can be used as drug carriers for colon-specific drug delivery.

McLeod et al (2005) synthesized glucocorticoid-dextran conjugates in which dexamethasone and methylprednisolone were attached to dextran using dicarboxylic acid linkers (succinate and glutarate). Dextran conjugates resisted hydrolysis in upper GI tract contents but were rapidly degraded in cecal and colonic contents where the bacterial count is high. The results of this study indicate that dextran conjugates may be useful in selectively delivering glucocorticoids to large intestine for the treatment of colitis.

**Inulin:** Inulin is a naturally occurring glucofructan and consists of β 2-1 linked D-fructose molecule having a glycosul unit at the reducing end. It can resist the hydrolysis and digestion in the upper gastrointestinal tract. Inulin can be fermented by colonic microflora. Vervoort et al. developed inulin hydrogels for colonic delivery of drugs and swelling property of these hydrogels was investigated. The influence of various parameters such as the degree of substitution, feed concentration of methacrylated inulin, varying concentrations of the initiators of the polymerisation reaction, the effect of pH, ionic strength on the swelling property of hydrogels were studied. In another study Vervoort and Rombaut investigated the in vitro enzymatic digestibility of the inulin hydrogels using an inulinase preparation derived from Aspergillus niger. It was concluded that the inulinase enzyme can diffuse into the hydrogels resulting in the degradation of the hydrogels.

**Amylose:** Amylose is the polysaccharide which is obtained from the plant extracts and a component of starch. Amylose is unbranched linear polymer of glucopyranose units (α-1,4-D-glucose) linked through α-D-(1-4) linkage. Amylose is resistant to pancreatic amylases in its glassy amorphous form, but it gets degraded by the bacteroids, bifidobacterium.

Amylose can form film by gelation, which can be used for tablet coating purpose. But coating made up of amylose solely becomes porous and release the drug under simulated gastrointestinal conditions. To avoid this problem, water insoluble polymers are added to the amylose film as these water insoluble polymers control the amylose swelling. Addition of ethylcellulose to amylose gives a suitable polymer mixture for colon targeting. In vitro dissolution of various coated pellets was performed under simulated gastric and simulated intestinal conditions and it was concluded that amylose:ethylcellulose coat (1:4) resist these conditions over a period of 12 h (Milojeyic et al., 1996).

Pellets were prepared by extrusion and spheronisation using glucose as model drug. In vitro evaluation of these glucose containing pellets coated with an amylose-Ethocel® mixture (ratio 1:4 w/w) was performed. Gastric and small intestine resistance of the formulation was proved in vitro by dissolution release profile. In vitro fermentation study demonstrated the susceptibility towards bacterial enzymatic attack. Lenaerts team has prepared the cross-linked amylose by epichlorohydrin treatment and used it as a matrix for controlled release of drugs (Lenaerts et al., 1991).

Cumming et al. used a mixture of amylose and ethocel (1:4) to prepare microspheres of [13C] glucose which was used as a surrogate for drug delivery. The results of the study revealed that combination of amylose and ethylcellulose can be used for coating of pellets which results in controlled release of contents for targeted delivery of drug to the large bowel during a period of 12–24 h.

**Conclusion and Prospects**

Drug targeting to the diseased colon are advantageous in reduced systemic side effects, lower dose of drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site. Successful colonic delivery could be achieved by protecting the drug from absorption and/or the environment of the upper GIT and then be abruptly released into the proximal colon, which is considered the optimum site for colon targeted delivery of drugs.
Dosages form based on the use of polysaccharides would appear to be promising. Firstly, the polysaccharides described above and their degradation products are non-toxic and are already used as pharmaceutical excipients. Secondly, the colonic flora does appear to present many modifications and remains qualitatively similar from one individual to another. Chemical modifications made to polysaccharides make it possible to reduce release of the drugs in the gut. However, the kinetics of degradations and of solute release from hydrogel depends on numerous parameters and on the nature of the drugs. For these reasons, the formulation of a hydrogel designed to permit specific drug delivery to colon, is depend on the physicochemical characteristics of the drugs incorporated into the dosage forms.

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon-specific drug delivery systems, and the uncertainty of current dissolution methods in establishing possible *in-vitro/in-vivo* correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

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