

Role of Natural Polymers in the Development of Multiparticulate Systems for Colon Drug Targeting

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ABSTRACT

Colon-specific drug delivery has gained increased importance for the delivery of drugs for the treatment of local diseases associated with the colon. To deliver the compounds in a non-degraded form to the lower part of the gastrointestinal tract, they must first of all pass through the stomach, the upper part of the intestine and must use the characteristics of the colon to specifically release the drugs in this part of the digestive tract. The use of biodegradable polymers holds great promise to achieve targeted drug release to the colon. The family of natural polymers has great appeal to drug delivery as it comprises polymers with a large number of derivatizable groups, a wide range of molecular weights, varying chemical compositions, low toxicity, and biodegradability yet high stability. Polysaccharidases are bacterial enzymes that are available in sufficient quantity to degrade these natural polysaccharides. This article also discusses few delivery systems designed to target a drug to the colon.

Introduction

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome, etc., but also for the potential systemic delivery of proteins and therapeutic peptides. The large intestine, though difficult to reach by peroral delivery is still deemed to be the ideal site for the delivery of agents to cure the local diseases of the colon.^[1,2] The most critical challenge in such a drug delivery approach is to preserve the formulation during its passage through the stomach and about first 6 m of the small intestine.^[3] In order to develop a reliable colonic drug delivery system, the transit time of dosage forms through the gastrointestinal (GI) tract needs to be understood very well. The transit of peroral formulations administered through the GI tract is highly variable and depends on various factors such as the diseased state of the lumen (diarrhea, diabetes, peptic ulcer, etc.), concomitant administration of other drugs (domperidone, cisapride, metoclopramide, etc.), body posture (vertical or supine), and food type (fat and protein content) that can influence the gastric emptying rate.^[4-7] A successful colon drug delivery also requires careful consideration for the number of factors including the properties of drug, type of delivery systems, and its interaction with healthy or diseased gut.

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Criteria for selection of drugs for colon-specific drug delivery systems

- Drugs used for local effects in colon against GIT diseases such as oxprenolol and metoprolol.
- Drugs poorly absorbed from upper GI tract like Ibuprofen, isosorbides, etc.
- Drugs used for colon cancer i.e. methotrexate.
- Drugs that degrade in stomach and small intestine such as gonadoreline, insulin, etc.
- Drugs that undergo extensive first pass metabolism such as nitroglycerin and corticosteroids.

General considerations for design of colon delivery formulations

Colonic delivery formulation are in general may be designed to provide either for 'burst release' or for sustained/prolonged release once reaching the colon.^[8] The proper selection of a formulation approach depends upon several important following factors.^[9]

- a) Pathology and pattern of diseases especially the affected parts of the lower GI tract or physiology and physiological compositions of the healthy colon if the formulation is not intended for localized treatment.
- b) Physicochemical and biopharmaceutical properties of the drug such as solubility, stability, and permeability at the intended site of delivery, and

- c) The desired release profile of the active ingredient. The most common physiological factor considered in the design of delayed release colonic formulations is pH gradient of the GI tract. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH = 6.6 + 0.5) to the terminal ileum (pH = 7.5 + 0.4), therefore, a decrease in the cecum (pH = 6.4 + 0.4), and then a slow rise from the right to the left colon with a final value of 7.0 + 0.7.^[10] Some reports suggested that alterations in GI pH profiles may occur in patients with inflammatory bowel disease, which should be considered in the development of delayed release formulations.^[11]

Single-unit system for colon targeting

Single-unit colon-targeted delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastic changes in patients with inflammatory bowel disease (IBD) than seen in healthy volunteers. In one study involving six patients with ulcerative colitis, the colonic pH of three patients varied from 5.0 to 7.0, whereas in the case of other three patients, very low pH of 2.3, 2.9 and 3.4 were observed.^[12] Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single-unit systems because of their potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation, and predictable gastric emptying.^[13]

Multiparticulate system for colon targeting

Approaches for colonic delivery include formulations in the form of pellets, granules, microparticles, and nanoparticles. The use of multiparticulate drug delivery systems in preference to single-unit dosage forms for colon targeting purposes dates back to 1985 when Hardy and co-workers showed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively prolonged period of time.^[14] Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability. Moreover, multiparticulate systems tend to be more uniformly dispersed along the GI tract and also ensuring more uniform drug absorption.^[15-17]

Nanoparticulate systems

Nanoparticle-size colloidal carriers, composed of natural or synthetic polymers, have also been investigated for colon targeting. Orally administered nanoparticles that serve as carriers for various types of drugs have been shown to enhance their solubility, permeability, and bioavailability. Nanoparticles have also been investigated for the delivery of protein- and peptide-type drugs along with other bioadhesion purposes. These systems have a large specific surface, which is indicative of high interactive potential with biological surfaces.^[18]

Microsphere

Microspheres that are biodegradable can be efficiently taken up

by macrophages. Therefore, the direct uptake of anti-inflammatory agent-loaded microspheres by macrophages would have a superior immunosuppressive effect and be more useful for treatment of patients with IBD. Hiroshi and co-workers studied incorporation of dexamethasone into poly(DL-lactic acid) microspheres^[19] and administered to mice induced with experimental colitis. It was found that serum dexamethasone levels were not increased after oral administration of dexamethasone microspheres, but at the same time the microspheres facilitated mucosal repair of experimental colitis. This strategy could be ideal for the treatment of IBD where local action in colon is needed without systemic drug burden. A new pH-sensitive polymer Eudragit P-4135 F was used to prepare microparticles of an immunosuppressant drug tacrolimus, for colonic delivery. They also used Eudragit P-4135 F in the microencapsulation of 5-fluorouracil for the treatment of colorectal cancer.^[20]

The multiparticulate system of chitosan microspheres is coated with Eudragit L100 or S100 for the colonic delivery of metronidazole for the treatment of amoebiasis.^[21]

Pellets

Pellets of 5-ASA were prepared by extrusion spherulization and coated with mixed dispersion of amylose and ethyl cellulose in varying ratios using the fluidized bed-coating technique. Amylose was also mixed with Eudragit RS/RL 30D aqueous dispersions and the coating was applied to the pellets.^[18]

A recent patent assigned to Roehm GmbH and Co. KH described a multiparticulate formulation containing two forms of pellets, which comprise a drug in the core and have different polymer coatings.^[22] One type of pellet is coated with an enteric polymer that rapidly dissolves at pH 5.5, while other form of pellet is coated with an acrylic copolymer (Eudragit FS) that allows less than 20% drug release at pH 6.8 in 6 h but releases more than 50% of the drug at pH 7.2 at the end of 6 h. The combination of pellets therefore enables a uniform and prolonged release of the drug throughout the intestinal region (small and large intestines).

Beads

Hydrogel beads were formed by chitosan and tri-poly-phosphate (TPP) for the delivery of protein in the colon.^[23] TPP was used as a counter ion to positively charged chitosan to form gel beads. The beads were loaded with bovine serum albumin (BSA), a protein that is liable to degradation in the upper parts of GI tract. The cross-linking of chitosan with TPP resulted in reduced solubility of chitosan thereby resulting in lesser protein release during upper GI transit. At the same time, the cross-linking and reduced solubility did not affect the degradability by microbial flora in the colon as shown by the *in vitro* studies where the rat caecal contents were able to attack and degrade the cross-linked chitosan.

Importance of polymer in designing of multiparticulate system

Coating with pH-sensitive polymers

Human GIT pH increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum.

Tablets, capsules, or pellets coated with pH-sensitive polymers provide delayed release and protect the active drug from hostile gastric fluid. For colon targeting, polymers used should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine, and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. These processes release the drug throughout the large intestine and thus provide the potential of the colon-targeted delivery system.

Methacrylic acid co-polymers, Eudragit L100 and Eudragit S100, are commonly used pH-dependent coating polymers for peroral delivery that dissolve at pH 6.0 and 7.0, respectively. Combination of these two polymers in varying ratios makes it possible to manipulate drug release within 6.0-7.0 pH range. It has been reported earlier that the use of Eudragit S alone is not suitable for colonic delivery.^[24] Studies in human volunteers have shown that since the pH drops from 7.0 at terminal ileum to 6.0 of ascending colon, such systems sometimes fail to release the drug.^[25] In order to overcome this problem, a proper combination of polymers Eudragit S100 and Eudragit L100 ensures that the release of drug from formulation will occur even when the pH value of the GI tract does not reach more than 6.8.

The various enteric polymers utilized for formulation development with their pH soluble characteristics^[9] are shown in Table 1.

Coating with biodegradable polymers

Drugs coated with the biodegradable-type polymers are showing degradability due to the influence of colonic microorganisms that can be exploited in designing drugs for colon targeting. These bacterial degradable polymers especially azo polymers have been explored in order to release an orally administered drug in the colon. Actually, upon passage of the dosage form through the

GIT, it remains intact in the stomach and small intestine where very little microbially degradable activity is present that is quiet insufficient for the cleavage of polymer coating. Release of the drugs from azo polymer-coated formulation is supposed to take place after reduction and thus degradation of the azo bonds by the azo reductase enzymes released by the azo bacteria present in the colonic microflora.

Embedding in matrices

The drug molecules are embedded in the polymer matrix. The polymers used for this technique should exhibit degradability in the colon for the liberation of entrapped drug.

Embedding in pH-sensitive matrices

Extrusion-spheronization and pelletization have been used for the preparation of pH-sensitive matrix pellets for colon-targeted drug delivery.^[26] The authors studied the effects of three independent variables (amounts of Eudragit® S, citric acid, and spheronizing time) on pellet size, shape (roundness and aspect ratio), and drug release was studied with central composite design. Nykanen *et al.* used ibuprofen as a model drug and Eudragit® S and Aqoat AS-HF as enteric polymers for developing site-specific systems for release of a drug in the lower part of the small intestine or in the colon. The target of this study was to investigate whether on using organic acids as excipients could influence the drug-release rate from enteric matrix granules. It was concluded that although inclusion of an organic acid in a formulation retarded *in vitro* release of the model drug, no corresponding effect was evident in case of *in vivo* studies.^[27]

Embedding in biodegradable matrices and hydrogels

Polysaccharides, the polymer of monosaccharides, retain their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine, but once they reach in the colon, they are acted upon by the bacterial polysaccharidases and results in degradation of the matrices. A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, and locust bean gum have been investigated for their use in colon-targeted drug delivery systems. The most important fact in the development of polysaccharide derivatives for colon-targeted drug delivery is the selection of a suitable biodegradable polysaccharide. As these polysaccharides are usually soluble in water, they must be made water insoluble by cross-linking or hydrophobic derivatization. The important factor is an optimal proportional of the hydrophobic and hydrophilic parts, respectively, and the number of free hydroxy groups in the polymeric molecule.

Bioadhesive systems

Bioadhesion is a process by which a dosage form remains in contact with a particular organ for an augmented period of time. Their longer residence time of a drug would have high local concentration or improved absorption characteristics in the case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes, and polyethylene oxide-polypropylene oxide copolymers have been investigated as materials for bioadhesive systems.^[28,29]

Table 1: Represents various enteric polymers utilized in the development of modified-release formulations for colonic delivery

Enteric polymers	Optimum pH for dissolution
Polyvinyl acetate phthalate (Coateric ^{®b})	5.0
Cellulose acetate trimellitate	5.5
Hydroxypropyl methylcellulose phthalate	
HP-50	>5.0
HP-55 and HP-55S	>5.5
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)	>5.5- >6.8
Methacrylic acid copolymer, Type C (Eudragit® L100-55 ^a)	
Methacrylic acid copolymer dispersion (Eudragit® L30D-55 ^b)	5.5
Methacrylic acid copolymer, Type A (Eudragit® L-100 ^a and Eudragit® L12,5)	6.0
Cellulose acetate phthalate (Aquateric ^{®b})	6.0
Methacrylic acid copolymer, Type B (Eudragit® OS-100 ^a and Eudragit® S12,5)	7.0
Eudragit® FS30D ^b	7.0
Shellac (MarCoat 125 ^c and 125N ^c)	7.0

^aSuitable for aqueous dispersion; ^bAvailable as aqueous dispersion;

^cAvailable as aqueous solution

Natural polysaccharides for colon-specific drug delivery

Polysaccharides are promising agents for obtaining colon-specific drug delivery systems. This article describes the different polysaccharides that have already been used in the initial approaches for colon-specific drug delivery. These natural polymers are strongly appealing to use in a truly colon-specific commercially available drug delivery system. The reasons for this are that they are non-toxic, easy to work with, and will be FDA approved. Also very important is that they are selectively degraded in the colon.^[30]

Polysaccharides from plant source

Starch

It is a polymer which occurs widely in plants. In general, the linear polymer, amylose, makes up about 20% weight of the granule, and the branched polymer, amylopectin, make the rest of the weight. Amylose is crystalline and can have a number average molecular weight as high as 500 000, but it is soluble in boiling water. Amylopectin is insoluble in boiling water, but in their use in foods, both fractions are readily hydrolyzed at the acetal link by enzymes. The α -1, 4-link in both components of starch is attacked by amylases and the α -1, 6-link in amylopectin is attacked by glucosidases.

Amylose

It is a poly(1-4- α -D-glucopyranose) that consists of D-glucopyranose residues linked by α - (1-4) bonds. Those substances, present naturally in the diet, have the advantages of being safe, nontoxic, and easily available. These are resistant to pancreatic α -amylase, but are degraded by colonic bacterial enzyme.^[31] Mixed films of amylose and ethyl cellulose as coatings have shown a great potential as colon delivery carriers.^[32] Delayed release compositions comprising glassy amylose and an active compound were designed to permit the release when the composition reaches the large intestine. The release of the active compound reported to be delayed in an aqueous environment of pH 1-9 at 37°C.^[33] The release was triggered when exposed to an enzyme capable of clearing the amylase. This delivery system can be made into a powder or monolithic form. This composition is useful in the diagnosis and therapy of diseases of the colon. The above composition may also be applied for delivery of anti-arthritis drugs and also for pesticidal delivery.

Cellulose

It has very long molecular chain consisting of one repeating unit (cellobiose), which is a differentiating factor from other polysaccharides produced by plants. Naturally, it occurs in a crystalline state. From the cell walls, cellulose is isolated from microfibrils by chemical extraction. In all forms, cellulose is a very highly crystalline, high-molecular-weight polymer, which is infusible and insoluble. In anaerobic environments, such as in colon, bacteria secrete both endo- and exo-enzymes, some of which form complexes that act jointly in degrading cellulose to form carbohydrate nutrients, which is utilized by the microorganisms for survival.

Pectin

It is non-starch linear polysaccharides that consist of α -1, 4D-galacturonic acid and 1, 2d-rhamnose with d-galactose and

d-arabinose side chains having average molecular weights between 50 000 and 150 000. It is refractory to host gastric and small intestinal enzymes but is almost completely degraded by the colonic bacterial enzymes to produce a series of soluble oligogalacturonates.^[34,35] Pectin is highly soluble in water, which puts hurdles in the development of colon-targeted drug delivery systems. If used alone it swells when it comes in contact with aqueous fluids of the GI tract and causes the release of the entrapped drug through the diffusion mechanism.

Inulin

It is a naturally occurring polysaccharide found in many plants such as garlic, onion, artichoke, and chicory. Chemically, it belongs to the glucofructans and consists of a mixture of oligomers and polymers containing 2-60 (or more) β -2-1 linked D-fructose molecules. Most of these fructose chains have a glucose unit as the initial moiety. It is not hydrolyzed by the endogenous secretions of the human digestive tract.^[36] Bacteria harboring in the colon and more specifically bifidobacteria are able to ferment inulin.^[37,38] The inulin has been incorporated into Eudragit RS films for preparation of mixed films that resisted degradation in the upper GI tract but digested in the human fecal medium by the action of bifidobacteria and bacteroides.^[39] Various inulin hydrogels have been developed that serve as potential carriers for the introduction of drugs into the colon.^[40]

Locust bean gum

It is also called carob gum, as is derived from carob (*Ceratonia siliqua*) seeds. Locust bean gum has an irregularly shaped molecule with branched β -1, 4-D-galactomannan. Cross-linked galactomannan however led to water-insoluble film forming product-showing degradation in colonic microflora.^[41] The colon-specific drug delivery systems based on polysaccharides, locust bean gum, and chitosan in the ratio of 2:3, 3:2, and 4:1 were evaluated using *in vitro* and *in vivo* methods.^[42]

Guar gum

Guar gum is being extensively studied by many researchers for colon targeting.^[43-47] It is obtained from the ground endosperms of *Cyamopsis tetragonolobus*, consists of chiefly high-molecular-weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and shows degradation in the large intestine due to the presence of microbial enzymes.^[48-51] The structure of guar gum is the alinear chain of β -D-mannopyranosyl units linked (1 \rightarrow 4) with a single member α -D-galactopyranosyl units occurring as side branches.^[52] This gelling property retards release of the drug from the dosage form, and it is susceptible to degradation in the colonic environment.

Polysaccharides from animal source

Chondroitin sulfate

It is a soluble mucopolysaccharide used as digestive a substrate mainly by the bacteroid inhabitants of the large intestine such as *Bacteroides thetaiotaomicron* and *B. ovatus*.^[53-55] Periplasmic enzymes are probably responsible for chondroitin breakdown apparently an outer membrane receptor binds chondroitin sulfate and brings it in contact with enzymes like chondroitin-sulfate-lyase.^[56]

Hyaluronic acid

It is a naturally occurring biopolymer, which serves important

biological functions in bacteria and higher animals including humans. Naturally occurring hyaluronic acid may be found in the tissue of higher animals, particularly as intercellular space filler. It is found in greatest concentrations in the vitreous humor of the eye and in the synovial fluid of articular joints.^[57] Hyaluronic acid comprises linear, unbranching, polyanionic disaccharide units consisting of glucuronic acid (GlcUA) an *N*-acetyl glucosamine (GlcNAc) joined alternately by β -1-3 and β -1-4 glycosidic bonds. Hyaluronic acid solutions are characteristically viscoelastic and pseudoplastic. The viscoelastic property of hyaluronic acid solutions that is important in its use as a biomaterial is controlled by the concentration and molecular weight of the hyaluronic acid chains. As a microcapsule, it can be used for targeted drug delivery.^[58]

Chitosan

It is a functional linear polymer derived from chitin, the most abundant natural polysaccharide next to cellulose, which is not digested in the upper part of the GI tract by human digestive enzymes.^[59,60] Chitosan is a copolymer consisting of 2-amino-2-deoxy- D-glucose units linked with β - (1>4) bonds. It should be susceptible to glycosidic hydrolysis by microbial enzymes in the colon because it possesses glycosidic linkages similar to those of other enzymatically depolymerized polysaccharides.

Polysaccharides from bacterial sources

Dextran

It is a polysaccharide consisting of linear chains of α -D glucose molecules, 95% of the chains consists of 1:6- α -linked linear glucose units while the side chains consist of 1:3- α -linked moieties. They are obtained from microorganisms of the family *Lactobacillus* (*Leuconostoc mesenteroides*). Dextran is colloidal, hydrophilic, and water-soluble substances which are inert for the biological system and also not affecting cell viability. Dextranase is the enzyme that hydrolyzes glycosidic linkages of the dextran. Anaerobic Gram-negative intestinal bacteria show dextranase activity of the colon especially by the bacteroides of colon.

Various dextran ester prodrugs have been prepared and evaluated for their efficacy to deliver the drug to the target organ.^[61,62] Glucocorticoid-dextran ester prodrugs have been prepared and proved efficacious in delivering drugs to colon.^[63,64]

Cyclodextrins

They are cyclic oligosaccharides consisting of six to eight glucose units joined through α -1, 4 glycosidic bonds. Cyclodextrin remains intact during their passage throughout the stomach and small intestine of the GI tract. However, in colon, they undergo fermentation in the presence of vast colonic microfloras into small monosaccharide and thus absorbed from these regions.^[65,66] β -cyclodextrins are degraded to a very small extent in the small intestine but are completely digested in the large intestine. Most bacterial strains found abundantly in human beings are capable of degrading cyclodextrins polysaccharide.

Curdlan

It is a neutral, essentially linear (1, 3)- β -glucan that may have a few intra- or inter-chain (1, 6) linkages. Curdlan's unusual rheological properties among natural and synthetic polymers underlie its use as a thickening and gelling agent in foods.^[67] Apart from being

tasteless, colorless, and odorless, the main advantages are that in contrast to cold-set gels and heat-set gels, the heating process alone produces different forms of curdlan gel with different textural qualities, physical stabilities, and water-holding capacities.

Polysaccharides from algae

Alginate

It is natural hydrophilic polysaccharide derived from seaweed, consisting of 1-4, linked d-mannuronic acid and l-glucuronic acid residues. Alginates are easily gelled in the presence of a divalent cation such as calcium ion. The gelation or cross-linking is due to the stacking of the glucuronic acid blocks of alginate chains. Calcium alginates beads can be prepared by drop-wise addition of the solution of sodium alginate into the solution of calcium chloride. The alginate beads have the advantage of being non-toxic, and dried alginate beads re-swell in the presence of dissolution media and can act as controlled release systems. Calcium alginate beads were prepared as cores and 5-ASA was spray-coated on them.^[68] Different enteric as well as sustained release polymers were applied as coat on calcium alginate beads. A system was prepared by coating calcium alginate beads with Aquacoat[®] that is a pH-independent polymer followed by 2% w/w coating of Eudragit L-30D.

Polysaccharides from fungal

Scleroglucan (Scgl)

It is a branched homopolysaccharide consisting of a main chain of (1-3)-linked β -D glucopyranosyl units bearing, every third unit, a single β -D-glucopyranosyl unit linked (1-6). This polysaccharide is resistant to hydrolysis and its solutions show an interesting rheological behavior: Viscosity remains practically constant, even at high ionic strength, upto pH 12 and to 90°C.^[69]

Conclusion

The colonic region of the gastrointestinal tract has become an increasingly important site for drug delivery and absorption. Targeted drug delivery offers considerable therapeutic benefits to patients, in terms of both local and systemic treatment. Systems that rely on gastrointestinal pH, transit times, or pressure for release are unlikely to function as reliable and effective colon-specific delivery vehicles. The purpose of designing multiparticulate dosage form is to develop a reliable formulation that comprises all the advantages having in single unit formulations but yet devoid of the danger of alteration in a drug release profile and formulation behaviour due to unit to unit variation, change in gastro-luminal pH and enzyme population. A generally accepted view is that multiparticulate systems perform better *in vivo* than single-unit systems, as they spread out throughout the length of the GI tract causing less irritation, slower transit through the colon, and provide more reproducible drug release. In order to achieve this goal, a wide number of natural polymers are being used by many of workers over past decades and they concluded that polysaccharides appear to be promising agents for obtaining a colon-specific drug. The reasons for this are that they are non-toxic, easy to work with, and will be FDA approved. Also very important is that they are selectively degraded in the colon. So, the challenges in future will be to find a polysaccharide from which one might be able to obtain a non-permeable film or coating and at the same time a high degradability.

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