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Review Paper

Polymers for Colon Targeted Drug Delivery: A Review

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Abstract

The colon targeted drug delivery has a number of important implications in the field of pharmacotherapy. Oral colon targeted drug delivery systems have recently gained importance for delivering a variety of therapeutic agents for both local and systemic administration. Targeting of drugs to the colon via oral administration protect the drug from degradation or release in the stomach and small intestine. It also ensures abrupt or controlled release of the drug in the proximal colon. Various drug delivery systems have been designed that deliver the drug quantitatively to the colon and then trigger the release of drug. This review covers different types of polymers used in formulation of colon targeted drug delivery systems.

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INTRODUCTION

Drug delivery is the method or process of administering pharmaceutical compound to achieve a therapeutic effect in humans or animals.[1,2] Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy, safety, as well as patient compliance and convenience. Conventional orally administered controlled release products normally lack any special property which would facilitate them for targeting of drug to a specific site in gastrointestinal tract. Targeted delivery of drugs to the colon has attracted much interest recently for local treatment of a variety of colonic diseases as well as systemic absorption of protein and peptides. [3,4]

The colon is an ideal site for both systemic and local delivery of drugs. Treatment of large intestine disorders such as Crohn's disease, irritable bowel syndrome, ulcerative colitis and colon cancer, where a high concentration of active drug is required, can

be improved by colon-targeted drug delivery system. Colon is used for systemic absorption of proteins and peptides also because proteolytic activity of colon mucosa is much less than that observed in small intestine. Drug targeting to specific sites of action offers several advantages over non targeted drugs such as prevention of side effects and reduction of doses. The colon as a site of drug delivery offers various therapeutic advantages because of its near neutral pH and longer transit time.

To reach the colon and release the drug, a dosage form must be formulated taking into account various obstacles introduced by the gastrointestinal tract. Successful delivery of a drug to the colon requires protection of the drug from degradation or release in the stomach and then controlled release of drug in colon. [5,6] The desired properties of colon targeted drug delivery systems can be achieved by using some polymers either alone or in a combination because it is now recognized that polymers can potentially influence the rate of release and absorption of drugs and play an important role in formulating colon targeted drug delivery systems.

COLON SPECIFIC POLYMERS

Polymers are macromolecules having very large chains contain a variety of functional groups, can be blended with low and high molecular weight materials. Polymers are becoming increasingly important in the field of drug delivery. Advances in polymer science have led to the development of several novel drug delivery systems. A proper consideration of surface and bulk properties can aid in the designing of polymers for various drug delivery applications.[7] These newer technological development include drug modification by chemical means, career based drug delivery and drug entrapment in polymeric matrices or within pumps that are placed in desired bodily compartments. These technical developments in drug delivery approaches improve human health. Use of polymeric material in novel drug delivery approaches has attracted the scientists.[8]

Pharmaceutical application of polymers:

- Used to achieve taste masking
- Used as a binder in tablets to viscosity and flow controlling agent in liquids, suspension and emulsions.
- Used as film coating to disguise the unpleasant taste of drug and to enhance drug stability.
- Used to modify drug release characteristics.[9]

MECHANISM OF COLON TARGETING:

A diverse range of mechanisms have been developed to achieve colon targeting of drugs. One of the widely used mechanisms is to coat the formulation using natural or synthetic polymers. In this mechanism, the drug is present in the core of the formulation which is coated with layers of polymer coatings. The first coating (next to core material) is an acid-soluble ploymer and outer coating is an enteric polymer. The core of formulation is comprised of the active material and other desirable excipients. During the transit of formulation (microsphers, tablets, capsules etc) through the GI tract, the formulation remain intact in the stomach due to enteric protection, but the enteric coating will dissolve in the small intestine , where the pH is above 6. The enteric coating starts to dissolve at the pH 5 in the small intestine. Upon entry into the colon, the polysaccharide coating will starts to dissolve. The bacteria will enzymatically degrade the polysaccharide into organic acid. This lowers the pH of the surrounding system and results in the dissolution of the surrounding system and results in dissolution of acid-soluble coating and subsequent drug release.

BIODEGRADABLE POLYMERS:

Biodegradation is a natural process by which organic chemicals in the environment are converted to simpler compounds, mineralized and redistributed through elemental cycles such as carbon, nitrogen

and sulphur cycles. Biodegradable polymers have been widely used in biomedical applications because of their known biocompatibility and biodegradability. Biodegradable polymers are intended for temporary aids, such as sutures, tissue-supporting scaffolds, and drug delivery devices.[10]

Polymers within this group retain their properties for a limited period of time and then gradually degrade into soluble molecules that can be excreted from the body.[11]

Biodegradable polymers are preferred for drug delivery applications, since the need for surgical removal of the depleted device is eliminated. Although the number of biodegradable polymers is large, only a limited number of polymers are suitable for drug delivery applications. Suitable candidates must not only be biodegradable but also fit the high prerequisites of biocompatibility. In addition, a polymer should ideally offer process ability, sterilizability, and storage stability if it is to be useful for biomedical applications.[12] The greatest advantage of degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials do produce degradation by-products that must be tolerated with little or no adverse reactions within the biological environment. These degradation products—both desirable and potentially non desirable—must be tested thoroughly, since there are a number of factors that will affect the biodegradation of the original materials.

- **Factor affecting biodegradation of polymers:-**
- Chemical structure.
- Chemical composition.
- Distribution of repeat units in multimers.
- Presents of ionic groups.
- Presence of unexpected units or chain defects.
- Molecular weight.
- Molecular-weight distribution.
- Morphology (amorphous/semicrystalline, microstructures, residual stresses).
- Presence of low-molecular-weight compounds.
- Processing conditions.
- Annealing.
- Sterilization process.
- Storage history.
- Shape.
- Site of implantation.
- Adsorbed and absorbed compounds (water, lipids, ions, etc.).
- Physicochemical factors (ion exchange, ionic strength, and pH).
- Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress- and solvent-induced cracking, etc.).
- Mechanism of hydrolysis (enzymes versus water).
- Biodegradable polymers mainly investigated for drug delivery applications are of either natural or synthetic origin.

Table 1: List of biodegradable polymers used in drug delivery:

Natural polymers	Synthetic polymers
Pectin Chitosan Guar gum Chondroitin sulfate Dextran Cyclodextrin Inulin Xanthan gum Amylose Locust bean gum Alginates Shellac	Eudragit L 100 Eudragit S 100 Eudragit L 30 D Eudragit RS 30 D Eudragit L 100-55 Polyvinyl acetate phthalate Hydroxypropyl ethylcellulose phthalate 50 Hydroxypropyl ethylcellulose phthalate 55 Cellulose acetate trimelliate Cellulose acetate phthalate

NATURAL POLYMERS IN COLON TARGETING:

Natural polysaccharides are extensively used for the development of solid oral dosage forms for colonic delivery of drugs.[13] Biodegradable polymers are

generally hydrophilic in nature and have limited swelling characteristic in acidic pH. Various bacteria present in the colon secretes many enzymes which can cause hydrolytic cleavage of glycosidic bonds e.g. β-D-galactosidase, amylase, pectinase, β-D-glucosidase, dextranase, α-D-xylosidase. These polymers are inexpensive and are available in a variety of structures. Pectin, starch, guar gum, amylase and karaya gum are a few polysaccharides commonly used in dosage forms. Linear polysaccharides remains intact in stomach and small intestine but the bacteria of human colon degrades them and thus make them potentially useful in colon targeted drug delivery systems.[14]

Pectin:

Pectins are nonstarch linear, heterogeneous polysaccharides that consist of α-1, 4 D-galacturonic acid and 1, 2 D-rhamnose with D-galactose and D-arabinose side chains. 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 oligalactorunates.[15,16]

Pectins are soluble in pure water. Monovalent cations (alkali metal) salt of pectinic and pectic acids are soluble in water; di- and tri-valent cations salts are weakly soluble or insoluble. If used alone it swells, when it comes in contact with aqueous fluids of GI tract and causes the release of entrapped drug through diffusion mechanism. Pectin has been used in the pharmaceutical industry for a wide range of applications.

Spray drying method has been employed to prepare pectin microspheres for oral colon delivery of indomethacin.[17] The prepared microspheres were cross linked with calcium chloride. The release of Indomethacin from the cross linked pectin microspheres was more suppressed than its release from non-cross linked microspheres.

Drug release from pectin microspheres was increased by the addition of pectinase. Release of indomethacin from pectin microsphere was less in acidic pH while it was stimulated at neutral pH (pH 7.4). The results of the study clearly demonstrated that pectin microspheres prepared by spray drying and cross linking methods are potential carriers for colon-specific drug delivery.

Table 2: Colon specific drug delivery using pectin [18]

Dosage form	Type of pectin	Application
Tablets	Calcium pectinate	Compression of calcium pectinate (matrix system)
Tablets	HM-pectin and LM-pectin	Matrix system
Tablets	Amidated LM-pectin and calcium salt of pectin	Direct compression of amidated or calcium of pectin alone or incorporated with ethylcellulose
Gel beads	LM-pectin (amidated)	Calcium pectinate gel beads for protein delivery
Film coated tablets	HM-pectin or LM-pectin	Calcium with HM-pectin or LM-pectin combined with commercially aqueous polymer dispersion
Capsule with plug	LM-pectin	Direct compression of pectin/pectinate-plug

HM-pectin= high methoxy pectin; LM-pectin= low methoxy pectin; HPMC= hydroxypropyl methylcellulose.

Chitosan:

Chitosan is a high molecular weight polycationic polysaccharide derived from chitin by alkaline deacetylation. Chitosan is consisting of the repeated units of (2-amino-2-deoxy-D-gluco-pyranose) which are linked by (1-4) β-bonds.[19,20]

Chitosan is a nontoxic, biodegradable, biocompatible and bioactive polymer. It is used for the colon targeted drug delivery because it has a tendency to dissolve in acidic pH of stomach but get swollen in the intestinal pH.

Chitosan capsules were used for colonic delivery of an antiulcerative colitis drug. 5-Aminosalicylic acid (5-ASA) was used as model drug. A marked increase in the release of drug from chitosan capsule was observed in the presence of the rat cecal content. From the results of this study it was concluded that

chitosan capsules could be an effective carrier for the colon targeted delivery of anti-inflammatory drugs.[21]

A chitosan dispersed system was newly developed for colon-specific drug delivery which was composed of drug reservoir and the outer drug release-regulating layer dispersing chitosan powder in hydrophobic polymer. It was observed that the thickness of the outer layer controls the drug release rate. Since the dispersed chitosan dissolves easily under acidic conditions, an additional outer enteric coating was also provided to prevent the release of drug from chitosan dispersed system in the stomach.[22] Chitosan is used to provide controlled release of many drugs and to improve the bioavailability of degradable substances such as protein, as well as to improve the uptake of hydrophilic substances across the epithelial layers.

Guar gum:

Guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of β 1, 4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side-branches.[23]

Guar gum is used in colon targeted drug delivery systems due to its drug release retarding property and susceptibility to microbial degradation in large intestine. Guar gum has a gelling property which retards the release of drug from the dosage form, making it more likely that degradation will occur in the colon. Guar gum was found to be a colon-specific drug carrier in the form of matrix and compression-coated tablets as well as microspheres.[24,25]

Guar gum-based matrix tablets of rofecoxib were prepared for their intended use in the chemoprevention of colorectal cancer.[26] A colon-specific guar gum–based tablet of 5-FU has also been reported.[27,28]

Krishnaiah *et al.* (2003) in their study performed the pharmacokinetic evaluation of guar gum-based colon-targeted tablets of mebendazole against an immediate release tablet in six healthy human volunteers. Colon-targeted tablets showed delayed t_{max} (9.4±1.7 h) and absorption time, and decreased C_{max} (25.7±2.6 μg/ml) and absorption rate constant when compared to the immediate release tablets. The results of the study indicated that the guar gum-based colon-targeted tablets of mebendazole delivered the drug to the colon resulting in a slow absorption of the drug and making the drug available for local action in the colon.[29]

Chondroitin Sulfate:

Chondroitin sulfate is a soluble mucopolysaccharide that is used as a substrate mainly by *B. thetaiotaomicron* and *B. ovatus* species in large intestine. Chondroitin sulfate is highly water soluble and this property act as a barrier in the formulation of the colon targeted drug delivery.

Rubistein *et al.* (1992) cross-linked Chondroitin sulfate and formulated a matrix form with indomethacin as a drug marker. 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.[30]

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.[31]

Cavalcanti *et al.* (2005) characterized cross linked Chondroitin sulfate for specific drug delivery to colon. Chondroitin sulfate was cross linked with trisodium trimetaphosphate to reduce its hydro solubility.[32]

Dextran:

Dextran is a polysaccharide consisting of α-1, 6 D-glucose and side chain of α-1, 3 D-glucose units. Dextran is a water soluble polymer. It gets degraded by microbial enzyme dextranases which is found in colon.[3,19]

In pharmaceutics, dextran has been used as model of drug delivery due to its unique characteristics like water solubility, biocompatibility, and biodegradability. In recent studies, dextran has been regarded as a potential polysaccharide polymer that can sustain the delivery of proteins, vaccines, and drugs. Injectable and degradable dextran-based systems for drug delivery were generated by a cross-linking reaction with photo-polymerization or free radical polymerization.

McLeod *et al.* (2006) 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 was 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.[33]

In a gene therapy study by Liptay and co-workers, it was reported that recombinant DNA (which contains chloramphenicol acetyltransferase) was successively encapsulated in cationic liposomes and then integrated within dextran. This system was reported to be a suitable delivery system since it could stop transfection efficiency within the colon epithelium wall *in- vivo*.

Cyclodextrin:

Cyclodextrin is a cyclic oligosaccharide consisting of six to eight glucopyranose units joined by α-(1→4) glucosidic linkage.

Cyclodextrins consist an internal lipophilic cavity, which can make complex with hydrocarbon materials. Cyclodextrins 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.[34,35] The *in vivo* drug release behaviour of these drug-cyclodextrin conjugates was investigated in rat. The results reveal that these conjugates were stable in stomach and in small intestine. The study suggested that Cyclodextrin can be used for colon specific delivery of drug.[36]

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 is not hydrolyzed by the endogenous secretions of human digestive tract.[37]

However, bacteria harbouring in the colon and more specifically Bifidobacteria are able to ferment inulin. Vervoort *et al*, developed inulin hydrogels for colonic delivery of drugs and swelling property of these hydrogels was investigated.[38]

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.[39]

Xanthan gum:

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris*.

Xanthan is a free flowing powder soluble in both hot and cold water to give viscous solutions at low concentrations. It is a very effective thickener and stabilizer because it gives highly viscous solutions even at low concentrations as compared to other polysaccharide solutions. Xanthan gum solutions offer very good stability. They are least affected by changes in pH and are stable in both alkaline and acidic conditions.[40]

Xanthan gum and hydroxypropyl methylcellulose were used as hydrophilic matrixing agents for preparing modified release tablets of diltiazem HCl. The amount of hydroxypropylmethylcellulose and xanthan gum exhibited significant effect on drug

release from the tablets prepared by direct compression technique. It was concluded that by using a suitable blend of hydroxypropylmethylcellulose and xanthan gum desired modified drug release could be achieved.

Amylose:

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 but it gets degraded by the bacteroids, bifidobacterium.[41]

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.

Cumming *et al.* used a mixture of amylase and ethocel (1:4) to prepare microspheres of [^{13}C] glucose which was used as a surrogate for drug delivery. The results of the study revealed that combination of amylase 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.[42]

Locust bean gum:

Locust bean gum contains natural polysaccharides which have a molecular weight of 310000. Locust bean gum is also known as 'Carob gum' as it is derived from the endosperm of the seed of the 'Carob' (*Ceratonia Siliqua Linne*, Fam: Leguminosae).

It is irregular shaped molecule with branched β-1, 4-D-galactomannan units. This neutral polymer is only slightly soluble in cold water; it requires heat to achieve full hydration and maximum viscosity.[43]

Studies on the polysaccharides done by Raghavan *et al.* (2002) proved that the combination of locust bean gum and chitosan, as a coating material, is capable of protecting the core tablet containing mesalazine during the condition mimicking mouth to colon transit. The coating was susceptible to the colonic bacterial enzymes which causes the release of drug. It was concluded that the formulation containing locust bean gum and chitosan in the ratio of 4:1 held a better dissolution profile, higher bioavailability and hence a potential carrier for drug targeting to colon.[44]

Alginates:

Alginates are linear polymers that have 1-4'linked β-D-mannuronic acid and α-L-guluronic acid residue arranged as blocks of either type of unit or as a random distribution of each type.

Alginate and their derivates have many unique properties such as biocompatibility, biodegradability, low toxicity, non-immunogenicity, water solubility, relatively low cost, gelling ability, stabilizing properties, and high viscosity in aqueous solutions.[45]

A Eudragit L-30D–coated calcium alginates bead for colonic delivery of 5-aminosalicylic acid has been reported. Different enteric as well as sustained release polymers were applied as coat on calcium alginate beads.

SYNTHETIC POLYMERS IN COLON TARGETING:

The polymers used for colon targeting, however, 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 of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. These processes distribute the drug throughout the large intestine and improve the potential of colon targeted delivery systems. There are various synthetic polymers which are use for colon targeted drug delivery. These can also be called as pH dependent polymers. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose. For colonic drug delivery, drug core is coated with pH sensitive polymers. The drug are includes tablets,

capsules, pellets, granules, micro-particles and nanoparticles.[46] The pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises.

Table 3: List of synthetic/ pH dependent polymers: [47]

Polymer	Threshold pH
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit L 30 D	5.6
Eudragit RS 30 D	6.8
Eudragit L 100-55	5.5
Polyvinyl acetate phthalate	4.5-4.8
Hydroxypropyl ethylcellulose phthalate	5.2
Hydroxypropyl ethylcellulose phthalate 50	5.2
Hydroxypropyl ethylcellulose phthalate 55	5.4
Cellulose acetate trimelliate	4.8
Cellulose acetate phthalate	5.0

Eudragit:

Eudragit products are pH-dependent methacrylic acid polymers containing carboxyl groups. The number of esterified carboxyl groups affects the pH level at which dissolution takes place. Eudragit are of three types: Eudragit L, Eudragit S, and Eudragit RS. Eudragit S is soluble above pH 7 and Eudragit L above pH 6. Eudragit S coatings protect well against drug liberation in the upper parts of the gastrointestinal tract and have been used in preparing colon-specific formulations.

When sites of disintegration of Eudragit S-coated single-unit tablets were investigated using a gamma camera they were found to lie between the ileum and splenic flexure. Site specificity of Eudragit S formulations, both single- and multiple-unit, is usually poor. Eudragit S coatings have been used to target the anti-inflammatory drug 5-aminosalicylic acid (5-ASA) in single-unit formulations on the large intestine. Eudragit L coatings have been used in single-unit tablets to target 5-ASA on the colon in patients with ulcerative colitis or Crohn's disease.[48]

The polypeptide hormone vasopressin and insulin have been administered to rats orally in Eudragit S-coated single-unit capsule. Eudragit S-coated insulin capsules have also been administered orally to hyperglycaemic beagle dogs. In the latter study it was concluded that plasma glucose levels were lowered gradually and reproducibly but that delivery by means of the oral route was not bioequivalent to delivery by means of parenteral route (SC). Eudragit S has been used in combination with another methacrylic acid copolymer, Eudragit L100-55, in colon-targeted systems to regulate drug delivery.[48]

Shellac:

Shellac is the purified product of the natural resin lac which is the hardened secretion of the small, parasitic insect Kerria Lacca, popularly known as the lac insect. It is the only known commercial resin of animal origin. Shellac is a hard, brittle and resinous solid. It is practically odorless in the cold but evolves a characteristic smell on heating and melting.

Shellac is water insoluble. Shellac coatings for food applications are commonly applied from ethanolic solutions. Shellac is unsuitable for a conventional enteric coating it is of interest for colon targeting formulations.[49]

The shellac coating layer remains intact during the passage of the stomach and the small intestine until it reaches the colon with its higher pH. This allows the transport of drugs into the colon for a topical treatment of colonic diseases. Moreover, the peptidase activity in the colon is lower than in the upper GI tract allowing for an oral delivery of peptide drugs such as insulin.[50]

CONCLUSION:

Today the stress is on patient compliance and to achieve this objective there is a spurt in the development of NDDS. Interest in the biodegradable polymers is increasing day by day because these are safe, non-toxic, and economic and are chemically compatible with the other excipients in the formulation. This article has described the various

types of biodegradable and non-biodegradable polysaccharides that have already been used in the initial approaches for colon specific drug delivery. But biodegradable Polysaccharides exhibit favorable properties for fabrication of colonic delivery system. The colon is rich in harboring excellent micrdoflora, which can be used for targeting of drug release to colon. Formulation containing the microbial degradable polymers passes intact from the upper GIT and release the drug in the colon. Thus polysaccharides appear to be promising agents for obtaining colon-specific drug delivery systems.

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