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Colon Targeted Drug Delivery: Different Approaches

Jose S, Dhanya K, Cinu TA, Litty J, Chacko AJ

Department of Pharmaceutical Sciences, Mahatma Gandhi University, Cheruvandoor Campus, Ettumanoor, Kerala-686 631, India

Address for correspondence: *Mr. Jose S; E-mail: sajanjose@hotmail.com*

ABSTRACT

Oral colon-targeted drug delivery systems have recently gained importance for delivering a variety of therapeutic agents for both local and systemic administration- local treatment of a variety of colonic diseases as well as systemic absorption of proteins and peptides. Targeting of drugs to specific sites of action provides several advantages over non-targeting of drugs. The colon, as a site for drug delivery, is also beneficial for the treatment of diseases sensitive to circadian rhythms and delivery of poorly absorbable drugs. The successful targeted delivery of drugs to the colon via the gastrointestinal tract requires the protection of a drug from degradation and release in the stomach and small intestine and then ensures abrupt or controlled release in the proximal colon. This review will cover both past and present approaches for achieving colon specific drug delivery.

Key words: Colon targeted delivery, inflammatory bowel diseases, pH dependent approach, pressure dependent approach, time dependent approach

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INTRODUCTION

Targeted delivery of drugs to the colon has attracted much interest recently for local treatment of a variety of colonic diseases such as irritable bowel syndrome (IBS), colorectal cancer, and inflammatory bowel diseases (IBD), which includes both ulcerative colitis and Crohn's disease. Apart from this local treatment, the colon is used for the systemic absorption of proteins and peptides and also for those drugs where a delay in drug absorption is required from a therapeutic point of view e.g., in case of nocturnal asthma, arthritis, and cardiac arrhythmias that are effected by circadian biorhythms. Targeting of drugs to specific sites of action provides several advantages over non targeting of drugs such as the prevention of side effects of drugs on healthy tissues and a reduction of doses.

The colon as a site of drug delivery offers numerous therapeutic advantages on account of a near neutral pH and much longer transit time. Drugs that are destroyed by the digestive enzymes and metabolized by pancreatic enzymes are minimally affected in the colon.[1] Furthermore, the colon was found to be a promising site for systemic absorption of peptides and proteins because of the less hydrolytic hostile environment in comparison with the stomach and small intestine as well as the existence of specific transporters. Additionally, the colon is a highly responsive site for the absorption of poorly absorbable drugs.[2]

The successful targeted delivery of drugs to the colon via the gastrointestinal tract (GIT) requires the protection of a drug from degradation and release in the stomach and small intestine and then ensures abrupt or controlled release in the proximal colon. This might be achieved by the use of suitably designed drug delivery systems (DDS) that can

protect the drug during its transfer to the colon. Targeting relies on exploiting a unique feature of the intended site and protecting the active agent until it reaches that site.[3]

Several approaches have been developed for targeted colonic drug delivery. Most of them utilize the physiological properties of the GIT and colon such as pH of GIT, transit time of the small intestine, luminal pressure of the colon, and the presence of microbial flora localized in the colon.

Prodrug approach

A prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release active drug at the target site. This approach involves covalent linkage between the drug and its carrier so that upon oral administration the moiety remains intact in the upper part of the gastrointestinal tract and after reached in the colon, enzymatic cleavage will regenerate the drug. This approach has improved delivery properties over the parent drug molecule.

The metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes. An example for such a prodrug is sulfasalazine, chemically known as salicylazosulphapyridine (SASP), which was actually introduced for the treatment of rheumatoid arthritis. Later, it was found that sulfasalazine was also useful in patients with IBD; the active moiety effective in IBD was 5-amino-salicylic acid (5-ASA) and sulphapyridine (SP) acted only as carrier. The azo bond between these two moieties undergoes reduction in the colon [Figure 1].

Due to a number of side effects associated with SP, studies were conducted to find a suitable carrier that could facilitate

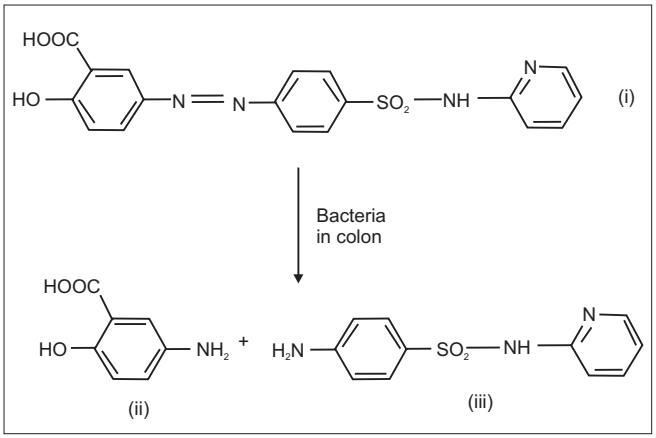

Figure 1: Hydrolysis of sulfasalazine (i) into 5-aminosalicylic acid (ii) and sulfapyridine (iii)

delivery of 5-ASA to the large intestine with minimal side effects. This led to the formation of ipsalazine and balsalazine where p-amino benzoyl glycine and 4-amino benzoyl-β-alanine, respectively act as carriers[4] and finally olsalazine, where two molecules of 5-ASA were joined together and one acted as carrier for other.[5]

Amino acids consisting of polar groups like -NH2 and -COOH have been used as carriers for colon-targeted drug delivery. These prodrugs were designed to be bulky and hydrophilic to remain unabsorbed in the upper GIT. However, the intestinal microflora of the colon hydrolyzed the drug-amino acid conjugate and the drug was released free into the lumen of the colon. An example of such amino acid conjugates includes amide linkage formed between 5-ASA and glycine.[6] Another type of conjugates is that the glucuronide conjugates where glucuronic aid is conjugated to the drug moiety. These conjugates were stable in the upper GIT and glucuronidase in the colon hydrolyze this linkage releasing the free drug in the colon. An example for drugs, which are involved in such glucuronide linkage includes Nalaxone/Nalmefene,[7] Budenoside,[8] and Dexamethasone.[9] Sugar moieties like glucose, galactose, and cellobiose have also been conjugated to drug moieties to form glycosides. These linkages were found to be selectively hydrolyzed by glucosidase, galactosidase, and cellobiosidase enzymes of bacteria in the cecum and colon.[10] Dextran ester prodrugs were prepared by covalently attaching methylprednisolone and dexamethasone to dextran by the use of a succinate linker.[11]

pH Dependent approach

This approach utilizes the existence of the pH gradient in the GIT that increases progressively from the stomach (pH 1.5-3.5) and small intestine (pH 5.5-6.8) to the colon (6.4-7.0). The most commonly used pH-dependent polymers are derivatives of acrylic acid and cellulose. By combining the knowledge of polymers and their solubility at different pH environments, delivery systems have been designed to deliver drugs at the target site.

Coating of the drug core with pH sensitive polymers has been successfully used for colonic drug delivery. The drug core includes tablets, capsules, pellets, granules, microparticles, or nanoparticles. When coated pellets, granules, microparticles, or nanoparticles are filled into a gelatin capsule or compressed together with conventional excipients in the form of tablets, the formulation is regarded as a multi-particulate dosage form.

Various pH-dependent coating polymers include cellulose

acetate phthalate(CAP) (Aquateric®), poly vinyl acetate phthalate(PVAP) (Coateric®), hydroxylpropyl methyl cellulose phthalate(HPMCP), and methacrylic acid copolymers, commonly known as Eudragit® (Registered Trademark of Rohm Pharmaceuticals, Darmstadt, Germany; Table 1).

Mesalazine tablets coated with Eudragit® L-100 are commercially available as Claversal®, Salofalk®, Mesasalâ, and Rowasa®. These tablets can effectively deliver mesalazine to the terminal ileum and proximal colon in patients with inflammatory bowel disease. Delayed-release tablets containing mesalazine and coated with Eudragit® S-100 are marketed in a number of countries (Asacol®). These tablets dissolve at a pH level of 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon. Although this formulation is generally successful in achieving site-specific delivery of mesalazine, failure of the coating to dissolve has been reported, with patients observing intact tablets in their feces.[12]

Multiparticulate formulations for colonic delivery are less likely to be affected by food and demonstrate more consistent absorption compared with single unit systems. In addition, these systems have greater potential of providing a uniform distribution of the drug particles to the inflamed parts of the GI tract, which is advantageous for the topical therapy of inflammatory bowel disease.[13] 5-Fluorouracil microsphere for colonic delivery using pH sensitive polymer Eudragit® P-4135F is used alone and in combination with Eudragit® RS100.[14] These polymer mixtures can prolong the drug release only for a relatively short period of time. However, this new formulation is a good candidate for application in oral treatment for colon cancer.

An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. It is possible that enteric coating alone may lead to premature drug release in the small intestine due to a variation in GI motility in individual patients and in different disease states. Occasionally, failure of the coating to dissolve may also occur particularly when the pH of the colon, and possibly the small intestine drops below normal in patients with ulcerative colitis.[15] These issues have prompted the development of other types of delivery systems.

Table 1: List of various methacrylic acid copolymers

Type of polymethacrylates	Solubility/permeability	Application
Eudragit S 100	Soluble from pH 7	Enteric coating
Eudragit L 100	Soluble from pH 6	Enteric coating
Eudragit L 100-55	Soluble from pH 5.5	Enteric coating
Eudragit FS 30D	Soluble from pH 7	Enteric coating
Eudragit RD 100 disintegrating film	High permeability	Rapid
Eudragit RL 12.5	High permeability	Sustained release
Eudragit RS 100	Low permeability	Sustained release
Eudragit NE 30 D tablet matrix	Swellable, permeable	Sustained release,
Kollicoat 30 D	Soluble from pH 5.5	Enteric coating

Time dependent approach

The time-dependent approach is also known as pulsatile release, delayed, or sigmoidal release system. In this approach, drug release from the system occurs after a pre-determined lag time, which corresponds to time for the transit from mouth to colon. The lag time depends upon the size of the dosage form and gastric motility associated with the pathological condition of the individual. In general, the time-dependent formulation for colonic delivery contains a pH-dependent coating component because the transit of a formulation in the GI tract is largely influenced by the gastric emptying time. This coating is also used to prevent rapid swelling and disintegration in the upper GI tract since other controlled-release components based on the mechanism of swelling, osmosis, or a combination of the two are often included in the time-dependent release formulations.

One of the earliest approaches is the Pulsincap® device.[16] This device consists of a non disintegrating half capsule body sealed at the open end with a hydrogel plug, which is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine, the enteric coating dissolves and the hydrogel plug starts to swell. The amount of hydrogel is adjusted so that it pops out only after the stipulated period of time to release the contents. Another formulation approach was in the form of a bead or granule with a four-layered spherical structure, which consists of a core, a drug, swelling agent (e.g., sodium starch glycolate or carboxy methyl cellulose sodium), and an outer membrane of water-insoluble polymer (e.g., ethyl cellulose, Eudragit® RL). The penetration of GI fluids through the outer membrane causes the expansion of the swelling agent. The resulting stress due to swelling force leads to the destruction of the membrane and subsequent rapid drug release. Another new approach was enteric-coated timed-release press-coated tablets (ETP tablets). These tablets were developed by coating enteric polymer on timed-released press-coated tablets composed of an outer shell of hydroxyl propyl cellulose and core tablets containing diltiazem hydrochloride as a model drug.[17]

In another approach, organic acids were filled into the body of a hard gelatin capsule as a pH-adjusting agent together with the drug substance. The joint of the capsule was sealed using an ethanolic solution of ethylcellulose. The capsule was first coated with an acid soluble cationic polymer (Eudragit® E 100), then with a hydrophilic polymer hydroxypropyl methylcellulose and finally enterically coated with hydroxy propyl methyl cellulose acetate succinate. After ingestion of the capsule, the outermost enteric layer of the coating prevents drug release in the stomach. The enteric layer and the hydrophilic layers dissolve quickly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid, the acid soluble layer dissolves and the enclosed drug is quickly released.[18] A delivery system called the Time Clock® has been developed, which is composed of a solid dosage form coated with a hydrophobic surfactant layer to which a water-soluble polymer is added to improve adhesion to the core. The coating slowly erodes away and the core is then available for dispersion. In a study with human volunteers, it was shown that the lag time was independent of gastric residence time and hydrophobic film redispersing did not appear to be influenced by the presence of intestinal digestive enzymes or by the mechanical action of the stomach.[19]

Another formulation approach to achieve time-dependent delivery to the colon is an osmotically controlled system, commonly referred as a push-pull OROS-CT system, and comprises as many 5 push-pull units encapsulated within a hard gelatin capsule.[20] Each push-pull unit is a bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable layer. In principle, the semipermeable membrane is permeable to the inward entry of water or aqueous GI fluids and is impermeable to the outward exit of the drug. An orifice is laser drilled into the semipermeable membrane to the drug layer. The outside surface of the semipermeable membrane is then coated by Eudragit® S-100 to delay the drug release from the device during its transit through the stomach. Upon arrival in the small intestine, the coating dissolves at a pH ≥7. As a result, water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into the colon. The drug release kinetics is precisely controlled by the rate of influx of water through the semipermeable membrane [Figure 2].

This approach relies on the strong peristaltic waves in the colon that lead to temporarily increased luminal pressure. These delivery systems release the drug as soon as a certain pressure limit is exceeded.

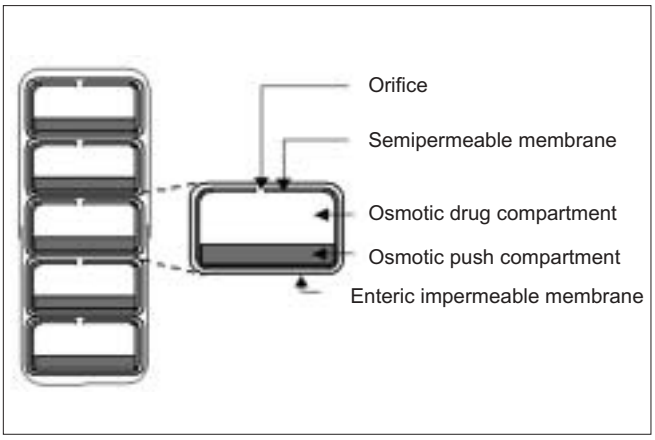

Figure 2: Cross section of the OROS-CT colon targeted drug delivery system pressure response dependent approach

A pressure-controlled colon delivery capsule (PCDC) made of ethyl cellulose has been developed to target the drugs to the colon.[21] The PCDC is composed of drug, dispersed in a suppository base, and coated with hydrophobic polymer and ethyl cellulose. Once swallowed, the temperature of the body causes the suppository base to melt and increase in volume and the system resembles a liquid-filled ethyl cellulose balloon. The balloon is able to withstand the luminal pressure of the small intestine resulting from peristalsis, but will rupture when subject to the pressure of more intense contractions of the colon and contents of thicker viscosity. Such systems have been assessed for their ability to deliver model drugs in beagle dogs and humans.

Microbial degradation dependent approach

The use of GI microflora as a mechanism of drug release in the colonic region has been of great interest to researchers in recent times. The majority of bacteria are present in the distal gut although they are distributed throughout the GI tract. The colonic bacteria are predominately anaerobic in nature and secrete enzymes that are capable of metabolizing both endogenous and exogenous substrates such as carbohydrates and proteins that escape digestion in the upper GI tract. The most common mechanisms of microbial activation in the colon are azo bond reduction and glycosidic-bond hydrolysis.

Sulphasalazine, a prodrug consisting of the active ingredient 5-amino salicylic acid was the first bacteria-sensitive delivery system designed to deliver the drug to the colon. The concept of bioactivation of prodrugs via azo reduction in the colon has led to the development of several novel azo polymers. Drugs that are coated with the azo polymers remain intact in the stomach and small intestine where very little microbially degradable activity

is present that is quiet insufficient for cleavage of polymer coating and release of the drugs is supposed to take place after reduction; thus, degradation of the azo bonds by the azo reductase enzymes released by the azo bacters present in the colonic microflora. Copolymers of 2-hydroxyethyl methacrylate and methyl methacrylate in the presence of bis (methacryloylamino) azobenzene were prepared. In vitro and in vivo tests prove that it is possible to use the polymers to deliver drugs to the large intestine.[22]

Another development was crosslinked hydrogels, which contain azo bonds and exhibit pH-dependent swelling. Novel hydrogels based on N, N-dimethylacrylamide, N-t-butylacrylamide, and acrylic acid cross-linked with azoaromatic compounds were synthesized. Drug release occurs in the colon by a combination of pH-dependent swelling and microbial degradation of the hydrogels by enzymatic cleavage of the azo bonds by azo reductases. Disulfide bond containing polymers can also be utilized as carriers for colon-specific delivery. These polymers are also sensitive to redox potential of the colon, like azo polymers. Even though azo-polymers are relatively stable in the upper GI tract, there are several problems associated with its microbial reduction, which includes formation of toxic intermediates such as aromatic amines and hydrazo compounds and also slower drug release.[23] To overcome these limitations and toxicity concerns of these synthetic polymers, natural polymers, especially glycosidic bond containing materials, offer a viable alternative for colonic drug delivery. The glycosidic bond-containing polymers include disaccharides, oligosaccharides, and polysaccharides.

Polysaccharides naturally occurring in plant (e.g., pectin, guar gum, inulin), animal (e.g., chitosan, chondroitin sulfate), algal (e.g., alginates), or microbial (e.g., dextran) origins were studied for colon targeting. These are broken down by the colonic microflora to simple saccharides by saccharolytic species like *bacteroides* and *bifidobacteria*. Hydrolysis of the glycosidic linkages on arrival in the colon triggers the release of the entrapped bioactive. Although specifically degraded in the colon, many of these polymers are hydrophilic in nature, and swell under exposure to upper GI conditions, which leads to premature drug release. To overcome this problem, the natural polysaccharides are chemically modified and mixed with hydrophobic water insoluble polymers, whereas in the case of formulations they are usually coated with pH sensitive polymers.

A pectin/chitosan-based colonic delivery system has been developed.[24] In this system, a direct compression coat of pectin USP or pectin in a 1:10 mixture with chitosan is made around the core tablet. Even though both formulations were able to protect the drug core from premature release, a substantially thick coat was present in a pectin-alone formulation to protect the drug. Another approach was the development of derivatives of pectin, which were less water-soluble but had the capability to be degraded by the colonic microflora. Calcium pectinate, the insoluble salt of pectin, was used for colon-targeted drug delivery of indomethacin.[25] The use of calcium pectinate as a carrier was based on the assumption that, like pectin, it can be decomposed by specific pectinolytic enzymes in the colon but retains its integrity in the physiological environment of the small bowel. Other derivatives such as methoxylated and amidated pectins are also developed. The formulation of Guar gum based matrix tablets of metronidazole/tinidazole were developed and the influence of the concomitant administration of these drugs on the usefulness of guar gum as a carrier for colon-specific drug delivery using guar gum matrix tablets of albendazole was studied as a model formulation.[26] In order to overcome the high water solubility of chondroitin sulfate, cross-linked chondroitin sulfate was developed and used to form matrix tablets of indomethacin.[27] Another approach was the formulation of Chitosan capsules containing 5-ASA to accelerate healing of 2, 4, and 6- trinitro benzene sulfonic acid sodium salt (TNBS) induced colitis in rats.[28]

Enteric coating is another formulation approach used to prevent the rapid swelling and/or disintegration of polysaccharide-based formulations in the upper GI tract. Formulation is prepared by coating a solid compressed core first with Chitosan, which is degraded by enzymes in the colon and then top-coated with an enteric polymer such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS) or hydroxypropyl methyl cellulose hexahydrophthalate in order to prevent drug release in the upper part of the GIT.[29] Recently, a unique colon-specific drug delivery system (CODES™) has been developed and evaluated. Drug release from this system is triggered by colonic microflora coupled with pH-sensitive polymer coatings. The colon specificity of drug release has been confirmed in healthy human volunteers using γ-scintigraphy imaging. In brief, a typical CODES™ configuration consists of a core tablet coated with 3 layers of polymer. The first coating (next to the core tablet) is an acid-soluble polymer, and the outer coating is enteric with a hydroxypropyl methylcellulose barrier layer interposed to prevent any possible interactions between the oppositely charged polymers. The core tablet comprises the active ingredient, one or more polysaccharides (e.g., lactulose), and other desirable excipients. During its transit through the gastrointestinal tract, the CODES™ remains intact

in the stomach because of the enteric protection, but the enteric and barrier coatings dissolve in the small intestine, where the pH is above 6. Upon entry into the colon, the polysaccharide inside the core tablet dissolves and diffuses through the coating. The bacteria enzymatically degrades the polysaccharide into organic acids. This lowers the pH level surrounding the system enough to affect the dissolution of the acid-soluble coating and subsequent drug release.[30]

Biodegradable matrix films, consisting of a sustained release coating material and a poorly water-soluble but degradable additive, are used if the additive by itself does not exhibit good film-forming properties. As degradable additives, a variety of oligo- and polysaccharides have been investigated, such as β-cyclodextrin, galactomannans, glassy amylose, pectin, and inulin. The best example for such formulation is the utilization of the combination of amorphous amylose and water-insoluble film forming polymer for development of colon-specific controlled release formulations.[31] In these compositions, use of a water-insoluble polymer such as ethyl cellulose or an acrylic polymer is necessary to control the swelling of amylose. The film coating system based on a combination of amorphous amylose and ethyl cellulose has recently been commercialized as COLAL™ (Alizyme plc, Cambridge, UK).

A new multiparticulate approach has been developed in which drug-loaded cellulose acetate butyrate (CAB) microspheres are coated by an enteric polymer (Eudragit S). Both CAB cores and pH-sensitive microcapsules were prepared by the emulsion-solvent evaporation technique in an oily phase. Ondansetron (OS) and budesonide (BDS), two interesting drugs with a potentially new application for the local treatment of intestinal disorders, were efficiently microencapsulated in CAB microspheres.[32]

CONCLUSION

The importance of a successful colon targeted drug delivery system is that the drug release from the system should be sensitive to physiological conditions particular to the colon. Various approaches are being investigated to achieve drug delivery at the desired site in the colon. So far, five approaches have been discussed, all of which have their own advantages and limitations and extensive research is being conducted to further improve these approaches.

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