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Review on colon targeted drug delivery for inflammatory bowel disease

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Abstract

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. Targeted drug delivery system is the system in which the dosage form is modified to deliver the drug at the target region or at the disease region. This targeting of drug to the disease site lowers the requirement of higher doses of drug thus reducing the dosage frequency and cost of the drugs. 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, inflammatory bowel disease etc but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents.

Keywords: Colon drug delivery, Crohn's disease, inflammatory bowel disease

Introduction

Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs (degraded by digestive enzymes of stomach and small intestine) but also for the delivery of low molecular weight compounds used to treat diseases associated with the colon or large intestine such as ulcerative colitis, diarrhoea, and colon cancer. Delivery of drugs via colon offers many therapeutic advantages. Drugs, which are destroyed by the stomach acid and metabolized by pancreatic enzymes, are protected.

The delivery of drugs to the colon via gastrointestinal (GI) tract requires the protection of a drug from being released in stomach and small intestine. It can be achieved by the use of drug delivery system (DDS) that can protect the drug during its passage to colon^[1]. Targeting depends on exploiting a unique feature of specific site and protecting the drug until it reaches to the site. Sustained release of drugs into colon can be useful in the treatment of certain diseases. The colonic delivery is also useful for the systemic absorption of drugs like nifedipine, isosorbide, and theophylline^[2].

The colon is the most suitable site for absorption of peptides and protein drugs for the following reasons

- less degradation by digestive enzymes,
- Proteolytic activity of colon mucosa is less than that observed in small intestine, thus CDDS protect peptide and protein drugs from hydrolysis, and enzymatic degradation in the duodenum and jejunum, and releases the drug into the ileum or colon which produces greater systemic bioavailability.

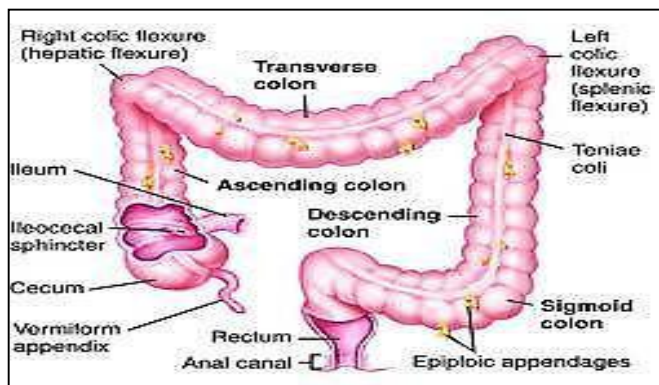
The colon has a long residence time which is up to 5 days and hence it is highly responsible for enhancement of absorption. The human colon has about 400 different species of bacteria as resident flora. The reactions carried out by this gut flora are azoreduction and enzymatic cleavage i.e. glycosides.

Anatomy and Physiology of Colon

The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5 m long. The colon is upper five feet of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa the pathway is called the lumen and is approximately 2-3 inches in diameter. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoid colon, rectum

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and the anal canal. The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.



Advantages of Colon Targeting Drug Delivery System

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs (NSAIDs).
- Bypass initial first pass metabolism.
- Extended day time or night time activity.
- Improve patient compliance.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route [3].

Need of Colon Targeted Drug Delivery

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
2. Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
3. The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticosteroids and sulphasalazine (targeted).
4. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
5. Formulations for colonic delivery are also suitable for delivery of drugs which are polar or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular,

therapeutic proteins and peptides.

Factors Affecting Colon Targeted Drug Delivery

1. Physiological factors
2. Pharmaceutical factors

Physiological factors

a. Gastric emptying

Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times.

b. pH of colon

The pH of GIT varies between different individuals. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site.

c. Colonic micro flora and enzymes

The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. Growth of this micro flora is controlled by the GIT contents and peristaltic movements. The enzymes released by different microorganisms *E. coli*, *Clostridia*, *Lactobacilli*, *Eubacteria*, *Streptococci* are responsible for the various metabolic reactions that take place in the GIT.

Pharmaceutical factors

a. Drug candidates

Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.

b. Drug carriers

The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. The various physicochemical factors of drug that effect the carrier selection includes chemical nature, stability, partition coefficient, functional groups of drug molecule etc.

Polymers Used In Colon Targeting

Polymer contains a large number of structural unit joined by same type linkage, form into a chain like structure. These are nowadays used in formulating various pharmaceutical products. Naturally found polymer, which include gummy exudates, proteins, enzymes, muscle fibre, polysaccharides. In olden days natural polymers are widely used in pharmacy but a variety of synthetic polymer are used nowadays for pharmaceutical and cosmetic development, using these Polymer many therapeutic system of body namely controlled drug delivery systems, are achieved [4, 5, 6].

Natural polymer

Guar gum, Pectin, Cyclodextrin, Dextran, Amylase, Chitosan, Chondroitin sulphate, Locust bean gum.

Synthetic polymer

Shellac, Ethyl cellulose, Cellulose acetate phthalate, Hydroxy propyl methyl cellulose, Eudragit, Polyvinyl acetate phthalate.

Colonic Absorption

The surface area of the colon is much less compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 hours). Different factors affecting colonic absorption were reported:

- Passes through colonocytes (Transcellular transport).
- Passes between adjacent colonocytes (Paracellular transport).

Transcellular absorption involves the passage of drugs through cells and thus the route for most lipophilic drugs takes, whereas paracellular absorption involves the transport of drug through the tight junctions between the cells and is the route of most hydrophilic drugs. Drugs shown to be well absorbed include glibenclamide, diclofenac, theophylline, ibuprofen, metoprolol and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide, buflomedil, atenolol.

Requirements of Colon Targeted Drug Delivery

Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. A number of diseases of the colon eg. colorectal cancer, helminthes, ulcerative colitis or Crohn's disease might also be capable of being treated more effectively if drugs were targeted to the colon.

Limitations of Colon Targeting Drug Delivery System

- Multiple manufacturing steps.
- The resident microflora could also affect colonic performance via metabolic degradation of the drug.
- Incomplete release of drug bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- 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. Normal in patients with ulcerative colitis.
- Limitations of prodrug approach is that it is not very versatile approach as it's formulation depends upon the functional group available on the drug moiety for chemical linkage
- Non availability of an appropriate dissolution testing method to evaluate the dosage form *in-vitro*

Methods Used For Drug Targeting to the Colon

Formation of prodrugs

Prodrug is defined as an inert drug that becomes active only after it is transformed or metabolized by the body. Covalent linkage is formed between drug and carrier which upon oral administration reaches colon without being absorbed from upper part of GIT. In the colon drug release is triggered by high activity of certain enzymes in comparison to stomach and small intestine.

a) Azo bond conjugate

Sulfasalazine is mainly used for the treatment of inflammatory bowel diseases. It is 5- Amino Salicylic Acid (5-ASA) prodrug. 85% of oral dose of sulfasalazine reaches to the colon unabsorbed where it is reduced by the anaerobic environment into 5- ASA and sulphapyridine. Various studies are conducted on sulphapyridine which lead to the formation of other prodrug like Olsalazine, Balsalazine, 4-amino benzoyl- β -alanine. Intestinal microflora produces glycosidase, one of prominent group of enzyme.

b) Glucuronide conjugate

Glucuronide and sulphate conjugation is the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower gastrointestinal tract secrete glucuronidase that glucuronidate a variety of drugs in the intestine. Since the glucuronidation process results in the release of active drug and enables its reabsorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery.

c) Cyclodextrin conjugates

The hydrophilic and ionisable Cyclodextrins can serve as potent drug carriers in the immediate release and delayed release-formulations, while hydrophobic Cyclodextrins can retard the release rate of water. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. Conjugates of a drug with Cyclodextrins can be a versatile means of constructing a new class of colon targeting prodrugs soluble drugs.

d) Dextran conjugates:

Dextran ester prodrugs of metronidazole have been prepared and characterized. Dextran ester prodrugs of dexamethasone and methyl prednisolone was synthesized and proved the efficacy of the prodrugs for delivering drugs to the colon. Methyl prednisolone and dexamethasone were covalently attached to the dextran by the use of a succinate linker.

e) Amino-acid conjugates:

Due to the hydrophilic nature of polar groups like NH₂ and COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to Salicylic acid.

Hydrogels

Hydrogels can be used for site specific delivery of peptide and protein drugs through colon. The hydrogels are composed of acidic commoners and enzymatically degradable azo aromatic crosslinks. In the acidic pH, gels show less swelling that protect the drug against degradation in stomach. As the pH of environment increases i.e. become basic, swelling increases. This result is easy access of enzymes like azoreductase, which ultimately release of drug ^[7, 8, 9].

Coating with pH dependent polymers

The pH in the terminal ileum and colon is higher than in any other region of the gastrointestinal tract and thus dosage forms which disintegrate at high pH ranges can be targeted into the region. A level of pH is higher in the terminal ileum

region then in the cecum. Dosage forms are often delayed at the ileocecal junction, careful selection of enteric coat composition and thickness is needed to ensure that disintegration does not occur until the dosage form moves through the ileocecal junction from the terminal ileum into the cecum. These tablets dissolved at a pH level of 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon.

Timed released systems

It is based on the concept of preventing the release of drug 3–5 hr after entering into small intestine. In this approach, drug release from the system after a predetermined lag time according to transit time from mouth to colon. The lag time depends upon the gastric motility and size of the dosage form. One of the earliest approaches is the Pulsincap device. 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. 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, 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 ^[10].

Designing formulations using polysaccharides

Dosage forms enjoy the shielding effect of polysaccharide in upper part of GIT and drug is released in the colon by swelling and biodegradable action of polysaccharidases. 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. A pectin/chitosan-based colonic delivery system has been developed. 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.

Redox sensitive polymer coating

Analogues to azo bond cleavage by intestinal enzymes, novel polymers that hydrolyzes nonenzymatically by enzymatically

generated flavins are being developed for colon targeting. A common colonic bacterium, bacteroidesfragilis was used as test organism and the reduction of azo dyes amaranth, Orange II, tartrazine and a model azo compound, 4, 4'-dihydroxyazobenzene were studied. It was found that the azo compounds were reduced at different rates and the rate of reduction could be correlated with the redox potential of the azo compounds.

Bioadhesive systems

Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in 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.

Approaches for Colon Targeted Drug Delivery

Colonic Microflora Dependent drug delivery

In the small intestine the microflora is mainly aerobic, but in the large intestine it is anaerobic. Both aerobic and anaerobic microorganisms inhabit the human gastrointestinal tract. Carbohydrates arriving from the small intestine form the main source of nourishment for bacteria in the colon. In the proximal colon the pH is lower than at the end of the small bowel because of the presence of short chain fatty acid and other fermentation products. The presence of colonic microflora has formed a basis for development of colon-specific drug delivery systems. However, the colonic microflora varies substantially between and within individuals, reflecting diet, age and disease. Such variations need to be taken into account in developing colon-specific formulations depending on the presence of colonic microflora. On reaching the colon, they undergo degradation by enzyme or breakdown of the polymer structure leading to release of the drug in the colon.

Prodrug Approach

Prodrug have been used in targeting drugs to the colon. Prodrug are designed to undergo minimal absorption and hydrolysis in the tracts of upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the drug carrier. Subsynthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety. These have been shown to be susceptible to cleavage by the azoreductase enzyme in the large bowel. In the low pH range of the stomach the gels have a low equilibrium degree of swelling and the drug is protected against digestion by enzymes, but at high pH levels they swell ^[11].

Polysaccharide approach

An extensive range of drug delivery systems based on polysaccharides has been investigated. The advantage of these materials is that most are easily available, are found in abundance, have wide availability, are inexpensive and are available in a variety of structures with varied properties. In preparing dosage forms from polysaccharides it is necessary to ensure that no drug is released until it reaches the colon. Amylose has been used in coatings of colon-specific formulation. Pectin is a polysaccharides, found in the cell wall

of plants. It is totally degraded by colonic bacteria but is not digested in the upper gastrointestinal tract. The film coating properties of pectin have been improved through use of ethylcellulose. Chitosan is a high molecular weight polysaccharides that is degraded by colonic microflora. This formulation depends for drug delivery on both variations in gastrointestinal pH and the presence of colonic microflora [12].

Gastrointestinal transit time dependent drug delivery

Transit time through the small intestine is independent of type of formulation. It has been found that both large single-unit formulations and small multiple unit- formulations take 3-4 hours to pass through the small intestine. Because the time taken by formulations to leave the stomach varies greatly, the time of the arrival of a formulation in the colon cannot be accurately predicted. However, the effects of variations in gastric residence time can be minimized by using systems that are protected in the stomach and the drug release can be targeted on the colon by means of formulations that release the drug after a certain time of gastric emptying. Transit time through the colon that are faster than than normal have been observed in patients with irritable bowel syndrome, diarrhoea and ulcerative colitis [13].

pH dependent drug delivery

In the stomach pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. The pH declines significantly from the ileum to the colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises [14].

Evaluation test of Colon Drug Delivery System

A. *In vitro* evaluation

No standardized evaluation technique is available for evaluation of CDDS as an ideal *in-vitro* model should possess *in-vivo* conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and components of food. These conditions are influenced by diet and physical stress. The *in-vitro* evaluation of colon targeted drug delivery systems includes the *in-vitro* dissolution study and *in-vitro* enzymatic test.

In-vitro dissolution test

The dissolution testing is done using the conventional basket method. The dissolution testing is done in different buffers to characterize the behaviour of formulations at different pH levels. The different media that are used for the dissolution testing of colon targeted drug delivery are pH 1.2 to simulate gastric fluid, pH 6.8 to simulate small intestine, pH 7.4 to simulate large intestine. The colon targeted drug delivery systems are tested for 2hr in 0.1N HCl, 3hr in pH 6.8 phosphate buffer and finally at pH 7.4 phosphate buffer. Buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems [15].

In-vitro enzymatic test

There are 2 tests for the *in-vitro* enzymatic test:

- The carrier drug system is incubated in fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals is determined.
- Drug release study is performed in buffer medium

containing enzymes pectinase, dextranase or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is directly proportional to rate of degradation of polymer carrier [16].

B. *In-vivo* evaluation

The *in-vivo* evaluation of the CDDS is done in dogs, guinea pigs, rats and pigs as they resemble the anatomic and physiological conditions, micro flora of human GIT. The distribution of various enzymes in GIT of rat and rabbit is comparable to that in human [17].

Conclusion

Colon targeted drug delivery systems offers benefits of local and systemic effects. The main advantages of colon targeted drug delivery systems is that the colon offers near neutral pH, a long transit time, reduced enzymatic activity and increased responsiveness to absorption enhancers. Various approaches are being researched in attempts to understand and achieve the desired goal of targeting the delivery of specific organ, the colon. The novel approaches are more specific compared to the primary approaches. The biodegradable polymers are used for the colon specific delivery for the drug. The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Colon specificity is likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. For the *in-vitro* evaluation of the system the current dissolution techniques are not suitable for drug release studies. Research is going on to develop suitable dissolution methods to evaluate the colon targeted drug delivery systems.

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