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REVIEW ARTICLE

COLON SPECIFIC DRUG DELIVERY SYSTEMS: CURRENT TRENDS AND APPROACHES

Obot Solomon Sunday

Department of Biochemistry, University of Calabar, Cross River State, Nigeria.

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*Address for Correspondence:

Obot Solomon Sunday, Department of Biochemistry, University of Calabar, Cross River State, Nigeria.
 E-mail: solmarion17@gmail.com

Abstract

The colon is a site where both local and systemic delivery of drugs can take place. The colon targeted drug delivery system is used for the treatment of various diseases related to colon like Crohn's disease, ulcerative colitis, etc and systemic delivery of therapeutic peptides and proteins. It can be possible to target disease site thus lowers the requirement of higher doses of drug and reducing the dosage frequency and cost of the drugs. It also lowers the systemic side effects. For successful colon targeted drug delivery, a drug needs to be protected from degradation, release and absorption in the upper portion of the gastric intestinal tract and then to be ensured abrupt or controlled release in the proximal colon. This article gives detail description on anatomy and physiology of the colon and approaches utilized for colon specific drug delivery like prodrugs, pH and time dependent, prodrug, osmotic pressure controlled drug delivery.

Keywords: Colon, Crohn's disease, osmotic pressure controlled drug delivery, prodrugs.

INTRODUCTION

Since the past decades research is going on in developing the methods to deliver therapeutic amount of drug to the specific organ so that the desired concentration can be achieved swiftly and then maintained¹. Colon targeted drug delivery is used to deliver the substances that are polar and degraded by the digestive enzymes in the gastrointestinal tract. Proteins and peptides such as insulin, calcitonin and vasopressin, cytokine inhibitors and antibiotics may be delivered systematically via colonic absorption. Anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents can also be delivered systemically². It is also used for the treatment of various diseases like ulcerative colitis, Crohn's disease, intestinal cancer, diarrhea, for the treatment of diseases sensitive to circadian rhythms like asthma, angina, for the delivery of steroids, etc³. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon. Formulations for colonic delivery are also suitable for delivery of drugs which are susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides⁴.

Advantages: Colon-specific drug delivery system offers the following therapeutic advantages-

1. Reduction of the adverse effects during the treatment of colonic diseases i.e. ulcerative colitis, colorectal cancer, Crohn's disease etc.
2. Avoidance of first pass metabolism of steroids.
3. Prevention of the gastric irritation produced after oral administration of NSAIDS⁵.
4. Delayed release of drugs in treatment of diseases i.e. angina, asthma and rheumatoid arthritis.
5. Decreased frequency of drug administration, increased patient compliance⁶.
6. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes⁷.
7. Increase bioavailability of poorly absorbable drugs⁸.

Limitations

1. Multiple manufacturing steps.
2. Incomplete release of drug.
3. Bioavailability of drug may be low due to potentially binding of drug with dietary residues, intestinal secretions, mucus or fecal matter⁹.
4. The resident microflora may affect colonic performance through metabolic degradation of the drug.

5. Non availability of a suitable dissolution testing method to evaluate the dosage form *in-vitro*.
6. It is necessary that drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs¹⁰.

Anatomy of colon

The GIT consists of parts from mouth to anus. It mainly consists of stomach, small intestine and large intestine. The GIT measures about 5 meters long. The different parts of GIT are divided into upper and lower gastrointestinal tract. The upper GIT includes oesophagus, stomach, and duodenum. The lower GIT includes small intestine and large intestine¹¹.

The large intestine extending from the ileocecal junction to the anus is divided into three main parts. These are the colon, the rectum and anal canal. Colon is about 5 feet (150 cm) long, and is divided into five major segments. The entire peritoneal folds called as mesentery, supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon¹². The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid.

Criteria for selection of drug for colonic drug delivery drug candidate^{13,14,15}

1. It should poorly absorb from stomach and small intestine e.g. peptides.
2. It should be compatible with carrier molecule and easily biotransform in large intestine.
3. It should be stable at alkaline pH of GIT.
4. It should have both local and systemic effects.
5. Drug use in treatment of various intestinal disorders such as ulcerative colitis, amoebiasis and colon cancer, inflammatory bowel disease, diarrhea are ideal candidates for local colon delivery e.g. sulfasalazine, olsalazine, mesalazine, steroids like fludrocortisone, budesonide, prednisolone and dexamethasone.

Factors affecting colon targeted drug delivery

1. Physiological factors
2. Pharmaceutical factors

1. 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 times¹⁶.

b. pH of colon

The pH of GIT varies between different individuals. The food intake, diseased state, etc. influences the pH of the GIT. 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 site¹⁷.

c. Colonic microflora and enzymes

The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. Growth of this microflora 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 GIT¹⁸.

2. Pharmaceutical factors

a. Drug candidates:

Due to high retention time of colon, colon causes an increase in the absorption of poorly

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 molecule¹⁹.

Approaches for the development of colon targeted drug delivery

Chemical or Prodrug Approach

A prodrug is a medication or compound that, after administration, is metabolized (i.e., converted within the body) into a pharmacologically active drug.

In this method, the prodrugs are designed to undergo minimum absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the carrier²⁰.

1. Azo bond conjugate

In this approach the drug is attached via an azo bond to a carrier. Azo compounds are metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora. The use of these azo compounds for colon-targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrug²¹.

2. Cyclodextrin conjugate

Cyclodextrin is non toxic and bulky molecule; it has limited absorption from the GIT hence it is used as the carrier for some drug which are unstable in stomach and intestinal environment. Cyclodextrins are cyclic oligosaccharides consisted of six to eight glucose units through -1, 4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability²².

Interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, form inclusion complexes with various drug molecules. After oral administration, cyclodextrin form of biphenyl acetic acid were selectively reach in to the colon and release drug without absorb from upper GIT²³.

3. Glycoside conjugation

Some drugs can be conjugated to different sugar moieties to form glycosides. The drug part forms the aglycone and is linked to the sugar part, which forms the glycone part of the glycoside. Because they are bulky and hydrophilic, these glycosides do not penetrate the biological membranes upon ingestion. Enzyme glycosidases produce by various human microflora are β -D-galactosidase, α -L-arabinofuranosidase and β -D-glucosidase. Steroid glycosides and the unique glycosidase activity of the colonic

microflora form the basis of a new colon targeted drug delivery system. Glycosides are hydrophilic and poorly absorb from GIT because of this properties it use as the carrier for delivering drug to colon. Drug targeted by this approach are lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone²⁴.

4. Glucuronide conjugates

Glucuronide conjugation is the major metabolic pathway of drug. Bacteria present in lower GIT secrete β -glucuronidase and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption. This concept is used to deliver drug to colon, where drug is couple with glucuronid conjugation after oral delivery²⁵.

5. Dextran conjugate

Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function. Dextran is the carbohydrate and colonic flora use it as the energy source. Dextran are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. Dextranase enzymes are responsible for the hydrolysis of these linkages. In the colon, dextran's glycosidic bonds are hydrolyzed by dextranases to give shorter prodrug oligomers, which are further split by the colonic esterases to release the drug free in the lumen of the colon²⁶.

6. Amino acid conjugation

Polar groups like -NH₂ and -COOH are hydrophilic in nature and are present in the proteins and their basic units (i.e. the amino acids). They reduce the membrane permeability of amino acids and proteins. Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. Thus the amino acid conjugate are more enzymatic specificity for hydrolysis by colonic enzymes²⁷.

7. Polymeric prodrugs: In newer approaches, polymers are used as drug carriers to deliver it, to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose²⁸.

Pharmaceutical approach

1. Coating of the drug core with pH sensitive polymers:

Drug molecule can be coated with the suitable polymers, which degrade only in the colon. In this way the intact drug molecule can be delivered to the colon without absorbing at the upper part of the intestine. The drug core includes tablets, capsules, pellets, granules, microparticles or nanoparticles. The use of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid²⁹.

The limitation of this approach is that the intestinal pH is not stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products.

2. Time dependent delivery

It also known as pulsatile release, delayed or sigmoidal release system. In this approach, drug release from the system after a predetermined lag time according to transit time from mouth to colon. It is based on the

concept of preventing the release of drug 3–5hr after entering into small intestine i.e. delaying the release of the drug until it enters into the colon³⁰. These systems consist of a non disintegrating half capsule body sealed at the open end with a hydrogel plug, covered by a water-soluble cap. The entire 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. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms³¹.

3. Bioadhesive systems

Bioadhesion is a process by which a dosage form remains in contact with particular organ for a specific period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. Polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers are used as materials for bioadhesive systems³².

4. Multiparticulate systems

The various multiparticulate approaches include pellets, microparticles, granules and nanoparticles are used as drug carriers in pH-sensitive, time dependent and microbially control systems for colon targeting. Multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time and hence increased bioavailability. 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 variability³³. Limitations associated with single unit colon targeted drug delivery system can be avoided like unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon.

5. Osmotic controlled drug delivery

This system consists of osmotic units either singly or as many as 5-6 push pull units that are encapsulated in a hard gelatin capsule. The push pull units are bilayered with outer enteric impermeable membrane and inner semi permeable membrane. In principle semipermeable membrane is permeable to the inward entry of water and aqueous gastrointestinal fluids and is impermeable to the outward exit of the drug³⁴. Whenever water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon.

Evaluation of CDDS

1. In-vitro evaluation: Different *in vitro* methods are used to evaluate the colonic drug delivery systems. In *in-vitro* studies the ability of the coats/carriers to remain intact in the physiological environment of the stomach and small intestine is assessed by drug release studies in 0.1N HCl for two hours (mean gastric emptying time) and in pH 7.4 phosphate buffer for three hours (mean small intestine transit time) using USP dissolution apparatus. The amount of drug released at different time intervals during the incubation is estimated to find out the degradation of the carrier under study³⁵. The dissolution testing is

done using the conventional basket method. The dissolution testing is done in different buffers to check the behavior of formulations at different pH levels. Dissolution tests of a colon-specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. 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. Formulations are tested for 2 hr 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 systems³⁶.

2. Enzymatic test

There are 2 tests-

- i. The carrier drug system is incubated in fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals is determined.
- ii. 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 carrier³⁷.

3. 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 human³⁸.

CONCLUSIONS

Colon targeted drug delivery system offers benefits of local and systemic effects. The main advantage of CDDS is that reduced incidence of systemic side effects, lower dose of drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site. Colon offers near neutral pH, a long transit time, reduced enzymatic activity and increased responsiveness to absorption enhancers. The novel approaches are more specific compared to the primary approaches. The biodegradable polymers are used for the colon specific delivery of the drug. These systems provide friendlier environment for protein and peptide drugs that reducing the adverse effects in the treatment of colonic diseases, site specific release to treat colonic cancer, amoebiasis, and helminthiasis etc, minimizing the extensive first pass metabolism of steroids and produces delay in absorption of drugs to treat rheumatoid arthritis, angina and nocturnal asthma etc. For the *in vitro* evaluation of the system the current dissolution techniques are not suitable. Research is going on to develop suitable dissolution methods to evaluate the colon targeted drug delivery systems.

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AUTHOR'S CONTRIBUTION

Sunday OS: Writing original draft, review, methodology, data curation, literature survey, editing.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None to declare.

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