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# RECENT ADVANCES IN COLON TARGETED DRUG DELIVERY SYSTEMS

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## Abstract

The colon route can be employed for both local and systemic delivery of drugs. 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. This article, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems. These achieved limited success and had limitations as compared with newer CDDS. Newer platform technologies are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process.

**Keywords:** - Colon targeted drug delivery systems, Drug targeting, Colon cancer.

## Introduction

Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. 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 but also for its potential for the delivery of proteins and therapeutic peptides. To achieve successful colonic delivery, a drug needs to be protected from absorption and /or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. Colon targeting is naturally of value for the topical treatment of diseases of colon such as Chron's diseases, ulcerative colitis, colorectal cancer and amebiasis.

## Colon targeting for systemic delivery of drugs

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Peptides, proteins, oligonucleotides and vaccines pose potential candidature for colon targeted drug delivery. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorption from these regions of the GIT depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.

1. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.
2. This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine.
3. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
4. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of perorally applied, undigested, unchanged and fully active peptide drugs.

5. As the large intestine is relatively free of peptidases such special delivery systems will have a fair chance to get their drug sufficiently absorbed after peroral application.
6. Colon targeting has advantage for Chronotherapy (asthma, hypertension, cardiac arrhythmias, arthritis or inflammation).

## ANATOMY AND PHYSIOLOGY OF COLON

The colon forms the lower part of the gastrointestinal tract and extends from ileocaecal junction to the anus divided in to three parts colon, rectum and anal–canal. The colon is made up of caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon, and the sigmoid colon. It is about 1.5 m long. The transverse colon is the lowest and the most mobile part with average diameter of about 6.5 cm. However, it varies in diameter from approx. 9.0 cm. in caecum to 2 cm in sigmoid colon. Unlike the small intestine, the colon does not have any villi but due the presence of plicae semilunares, which are cresentic folds, the intestinal surface of the colon is increased to 1300 $cm^2$. The wall of colon is made of four layers, serosa, muscularis externa, sub mucosa and mucosa. The serosa is the exterior coat of the large intestine and consists of arioler tissue, i.e., covered by a single layer of squamous mesothelial cells. Muscularis externa is the major coat of the large intestine and is composed of an inner circular layer of fiber that surrounds the bowel and of the outer longitudinal layer. The submucosa is the layer of connective tissue that lies immediately beneath the mucosa. The mucosa is divided in to epithelium, lamina propria and muscularis mucosae. The muscularis mucosae consist of a layer of smooth muscle and separate the mucosa from the lamina propria.The activity in the colon can be divided in to segmenting and propulsive movements. Segmenting movements by circular muscles causes the appearance of the sac-like haustra. The significant propulsive activity associated with defecation and affected by longitudinal muscles is less common and occurs on an average of 3-4 times daily. Retrograde movements are common in the proximal portion of the colon and increase the retention of the material in the ascending colon and caecum. In the middle section of the colon, segmenting movement's results in a slow progression of feaces towards the rectum, where as propulsive activity predominates in distal portion of colon.

A large number of anaerobic and aerobic bacteria are present throughout the entire length of human GIT. The concentration of bacteria in the human colon is $10^{11}$-$10^{12}$ CFU/ml (colony forming units/ml). The bacterial flora of colon is predominantly anaerobic and composed of more than 400 strains. The most important anaerobic bacteria are Bacteriodes, Bifidobacterium, Eubacterium, Eptococcus, Peptostreptococcus, Ruminococcus, Clostridium and Propionibacterium. The important facultative bacteria in large intestine are E.coli and lactobacillus. The principle source of nutrition for colonic microorganisms are carbohydrates, arriving in intestinal chime, including starch, non starch polysaccharides such as cellulose, hemi cellulose, guar gum, pectin, ispagola, sugar and oligosaccharides such as lactose, sorbitol and xylitol. It is evident that colonic bacterial population will have a significant impact, both negative and positive, on colonic drug delivery. The ability of selective metabolism of certain carbohydrates and anaerobic environment has been exploited in the development of delivery systems. On the other hand, significant proteolytic activity has implications for delivery of peptides and protein drugs. pH of colon in various regions is given in Tab. 1.

**Table-1: pH of colon in various regions**

| Location | Average pH |
|---|---|
| Ascending colon | 6.4 |
| Transverse colon | 6.0-7.4 |
| Descending colon | 6.0-7.4 |

### Gastrointestinal transit

The gastric emptying of dosage form is highly variable and depends primarily on whether the subject is fed or fasted and the property of dosages form (such as size and density). The mean transit time from mouth to anus is 53.3hrs. The total mean colonic transit time is 25.0 hrs. and is shorter in males than females. Transit time of dosage form in GIT is given in Tab. 2.

**Table-2: Transit time of dosage form in GIT**

| Organ | Transit time of dosage form in GIT (hrs) |
|---|---|
| Stomach | <1 (fasting), > 3 (fed) |
| Small intestine | 3-4 |
| Large intestine | 20-30 |

## VARIOUS APPROACHES FOR COLON TARGETING

To achieve successful colon targeted drug delivery, a drug needs to be protected from degradation, release and absorption in the upper portion of the GI tract and then ensure abrupt or controlled release in the proximal colon.

### (a) Prodrug approach

It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. This approach chiefly involves the formation of prodrug, which is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biological environment to release the active drug. Following type of linkage is possible:

- Azo bond conjugates
- Glycoside conjugates
- Glucuronide conjugates
- Cyclodextrin conjugates
- Dextran conjugates
- Amino-acid conjugates
- Polymeric prodrugs

### (b) Coating with polymers

The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon.

- Coating with pH-sensitive polymers
- Coating with biodegradable polymers
- Compression coating

### (c) Matrix systems

- Embedding in biodegradable matrices
- Embedding in pH- sensitive matrices

### (d) Timed release systems

This approach is based on the principle of delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug takes place. The lag time in this case is the time required for transit of dosage form from the mouth to colon. It is similar in appearance to hard gelatin capsule; the main body is made water insoluble (exposing the body to formaldehyde vapor which may be produced by the addition of trioxymethylene tablets or potassium permanganate to formalin or any other method).

### (e) Multiparticulate Formulations

Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. Multiparticulate approaches tried for colonic delivery includes:

- Microbially controlled systems
- Microparticulate systems
- Pressure dependent release systems
- pH- and time- dependent systems
- Bioadhesive systems
- Osmotic controlled drug delivery

## PLATFORM TECHNOLOGIES FOR COLON TARGETED DRUG DELIVERY SYSTEMS:

Nowadays design of dosage form is becoming complex because there is a vast use of technology in the dosage forms for controlling various aspects. Few examples are mentioned in case of colon targeted drug delivery:

### PULSINCAP:

Pulsincap was the first formulation developed based on time-release principle. It was similar in appearance to hard gelatin capsule. It consists of water insoluble body water soluble

enteric coated cap. The contents are plased with in body plugged wih hydrogel plug. When it is administered, after predetermined time the enteric coat dissolves and the hydrogel plug starts to swell.

**CODES:**

CODES is a unique colon targeted drug delivery system that was designed to avoid the inherent problems associated with pH or time dependent systems. It consists of core tablets coated with three layers of polymer coatings. The first coating is an acid soluble polymer (Eudragit) and outer layer is enteric with a HPMC barrier layer in between to prevent any possible interaction between the oppositively charged polymers. The core tablet is comprised of the active ingredients and one or more polysaccharides. The polysaccharides are degraded by enterobacteria to generate organic acid. During its transit through GIT, CODES remain intact in the stomach due to enteric protection, but the enteric barrier coating dissolves in the small intestine, where pH is is above 6. Because Eudragit-E starts to dissolves at pH 5; the inner Eudragit-E coating is only slightly permeable and swellable in small intestine. Upon entry into the colon, the bacteria enzymetically degrade the polysaccharide into organic acid.

**PORT SYSTEM:**

It consist of a gelatin capsule coated with a semi-permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation. When in contact with aqueous medium, water diffuses across the semi-permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time.

**OROS-CT:**

Alza Corporation developed OROS-CT an osmotically controlled dosage form. It can be used to target the drug locally to the colon for the management of diseases, which are not responding to the systemically absorbed drug. It can be made up of single unit or may incorporate as many as 5-6 push pull units, each with in 4 mm in diameter, encapsulated within hard gelatin capsule. When it reaches to small intestine the enteric coating get dissolved and water enters through the semi-permeable membrane, causing osmogen to swell and the drug compartment gets converted in to flow able gel.

**TIME CLOCK SYSTEM:**

It consist of a solid dosages form with lipidic barriers containing carnauba-wax and bee-wax along with surfactants, such as polyoxyethylene sorbitan monooleate, In order to prevent the pre mature release of drug in the small intestine the system was further coated with enteric polymers. The release of the drug is independent of the pH and the digestive state of the gut. The release mainly depends upon the thickness of the coat applied. As soon as the coat erodes or emulsifies in the aqueous environment after predetermined lag time, the core gets exposed to the colonic environment resulting in complete release of drug.

**CRONOTROPIC SYSTEM:**

It consists of a drug containing core coated by hydrophilic swell able HPMC, which is responsible for a lag phase in the onset of release. In, addition, through the application of an outer gastric resistant enteric film, the variability in gastric emptying time can be overcome, and a colon specific drug release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and viscosity grades of HPMC.

**TARGIT TECHNOLOGY:**

It is based on the application of pH sensitive coating onto injection–molded starch capsules. It is designed for site-specific delivery of drugs to the colonic region. This system has been developed for the treatment of local pathologies of lower GI disease. The clinical data generated has showed its suitability in colon targeted drug delivery.

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