

## THE PHARMA INNOVATION

# A Review on Colon Targeting Drug Delivery System: Novel Approaches, Anatomy and Evaluation

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Targeting drugs to the colon is one of the contemporary research areas in pharmaceutical sciences. 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. General approaches for colon targeting drug delivery include use of prodrugs, pH dependent system, time dependent system and clonic microflora activated systems. This article gives an overview on anatomy and physiology of the colon and approaches utilized for colon specific drug delivery. This article also discusses advantages & limitations of the different approaches & evaluation for site specific drug delivery to colon. It is a challenging area for future research and holds lots of promises for novel and efficient approach for targeted drug delivery system.

*Keyword:* Colon Targeting Drug Delivery System, Approaches, Advantages, Evaluation.

**INTRODUCTION:** The challenge of delivering drugs specifically to the colonic region of the g.i.t. is one that has been embraced by scientists over past two decades <sup>[1]</sup>. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not

occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon <sup>[2]</sup>. The colon is a site where both local and systemic delivery can take place. The therapeutic advantages of targeting the drug to the diseased organ include:

- Delivery of the drug in its intact form as close as possible to the target site.
- Reduces conventional dose and frequency
- Reduced incidence of adverse side effects <sup>[3]</sup>

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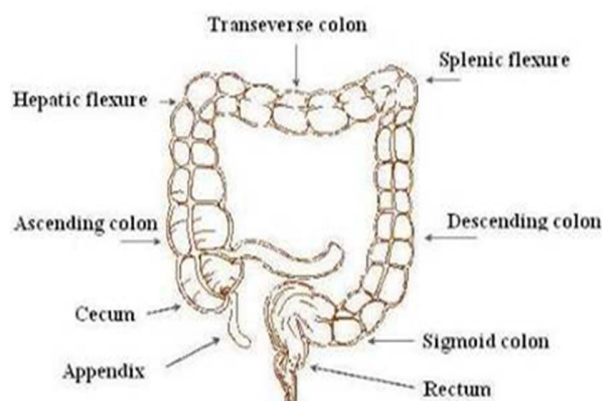
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A local means of drug delivery could allow topical treatment of diseases associated with the colon such as amoebiasis, ulcerative colitis, crohn's disease and colon cancer. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.

Oral drug delivery is the most desired and preferred method of administering therapeutic agents for providing both local as well as systemic in various parts of the gastrointestinal tract<sup>[4]</sup>. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal<sup>[5]</sup>. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. In the recent times, the colon specific delivery systems are also gaining importance for the systemic delivery of protein and peptide drugs. The peptide and protein drugs are destroyed and inactivated in acidic environment of the stomach and/or by pancreatic enzymes, the colon is considered to be more suitable for delivery of peptides and protein in comparison to small intestine<sup>[6]</sup>.

### ANATOMY AND PHYSIOLOGY OF COLON:

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts – colon, rectum and anal canal<sup>[7]</sup>. The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the caecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus.



### FUNCTIONS OF COLON:

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen<sup>[8]</sup>. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. On average, it has been estimated that colon contains only about 220 gm of wet material equivalent to just 35 gm of dry matter. The majority of this dry matter is bacteria. The colon tissue containing the villi, lymph, muscle, nerves, and vessels.

### FACTORS AFFECTING COLON DRUG DELIVERY:

- ✓ Gastrointestinal transit
- ✓ Small intestine transit
- ✓ Colonic transit
- ✓ Stomach and intestinal pH
- ✓ Colonic micro flora and enzymes
- ✓ Disease states<sup>[9]</sup>

### VARIATION IN THE GASTROINTESTINAL TRANSIT

Gastric emptying of dosage form is highly variable and depends primarily on whether the subject is

fed or fasted and on the properties of the dosage form such as size and density. The transit times of dosage forms in tract are shown:

Organ	Transit time (hr)
1.Stomach	<1 (fasting) >3 (fed)
2.Small intestine	3-4
3.Large intestine	20-30

### VARIATION IN THE pH OF THE GIT TRACT:

Location	pH
1.Stomach - fed	1.5-2.0
Unfed	3-5
2.Small intestine	5.0-7.5
Jejunum	5.0-6.5
Ileum	6.0-7.3
3.Large intestine	
Colon	6.4-7.0

### COLONIC MICROFLORA AND ENZYMES:

A large number of anaerobic and aerobic bacteria are present the entire length of the human GI tract. Over 400 distinct bacterial species have been found, 20-30% of which are of the genus bacteroids. The upper region of the GIT has a very small number of bacteria and predominantly consists of gram positive facultative bacteria. The rate of microbial growth is greatest in the proximal areas because of high concentration of energy source.

Concentration of microflora is  $10^{11}$ - $10^{22}$  CFU/ml.

It consists of Bacteroids, Bifidobacterium, Ruminococcus , Eubacterium , Clostridium.

Major metabolic reactions carried by the enzymes released from colonic microflora are hydrolysis and reduction<sup>[10]</sup>

Reducing enzymes	Hydrolytic enzymes
Nitroreductase	Esterases
Azoreductase	Amidases
N-oxide reductase	Glycosidases
Sulphoxide reductase	Glucuronidases
Hydrogenase	Sulfatase

### COLONIC DISEASES :

- ✓ Crohn's Diseases
- ✓ Ulcerative Colitis
- ✓ Diversional Colitis
- ✓ Ischemic Colitis
- ✓ Diverticular Inflammatory Bowel Disease
- ✓ Colon Cancer
- ✓ Lymphoma of the Colon

### DRUG ABSORPTION IN THE COLON:

Drugs are absorbed passively by either paracellular or transcellular route. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, where paracellular absorption involves the transport of drug through the tight junction between cells and is the route most hydrophilic drug takes. The colon may not be the best site for drug absorption since the colonic mucosa lacks well defined villi as found in the small intestine.

The slower rate of transit in colon lets the drug stay in contact mucosa for a longer period than in small intestine which compensates much lower surface area.

The colon contents become more viscous with progressive absorption of water as one travels further through the colon. This causes a reduced

dissolution rate, slow diffusion of drug through the mucosa.

Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum. Recent studies have shown that some drugs (e.g. Theophylline and Metoprolol) continue to be absorbed in the colon<sup>[7]</sup>.

### CRITERIA FOR SELECTION OF DRUGS FOR CDDS :

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyphenolol, Metoprolol,	Amylin, Antisense
Drugs poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Nifedipine	oligonucleotide
Drugs for colon cancer	Antineoplastic drugs	Ibuprofen, Isosorbides,	Cyclosporine, Desmopressin
Drugs that degrade in stomach and small intestine	Peptides and proteins	Theophylline	Epoetin, Glucagon
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Pseudoephedrine	Gonadoreline, Insulin,
Drugs for targeting	Antiartihritic and antiasthmatic drugs	Bromophenaramine, 5-Flourouracil, Doxorubicin	Interferons
		Bleomycin, Nicotine	Protirelin,sermorelin,
		Prednisolone, hydrocortisone,	Saloatonin
		5-Amino-salicylic acid	Somatropin,Urotoilitin

### APPROACHES FOR COLON SPECIFIC DRUG DELIVERY:

#### 1. COVALENT LINKAGE OF DRUG WITH CARRIER.

##### Prodrug approaches<sup>[11]</sup>

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.

##### Azo bond conjugates:

These azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. 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 prodrug. In the latter approach the drug is attached via an azo bond to a carrier<sup>[12]</sup>. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora. Sulphasalazine, used for the treatment of IBD has an azo bond between 5-ASA and sulphapyridine (SP). In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier.

##### Glycoside conjugation:

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Certain 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. They breakdown upon action of

glycosidase, releasing the drug part from the sugar. The presence of glycosidase activity in the small intestine could pose a problem in delivery of these conjugates to the large bowel, because some hydrolysis of the conjugate can be expected in the small intestine. However, the small intestinal transit time, when compared to the large intestinal transit time, is short, and moreover, considering the time required for the hydrolysis of glycosidic bond, these conjugates can be expected to be good colon specific drug carriers. The major glycosidase enzymes produced by the intestinal microflora are  $\beta$ -D-galactosidase,  $\alpha$ -L-arabinofuranosidase,  $\beta$ -D-xylopyranosidase, and  $\beta$ -D-glucosidase. These glycosidase enzymes are located at the brush border and hence are accessible to substrate easily. Example: lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone. Dexamethasone-21- $\beta$ -glucoside, Prednisolone-21- $\beta$ -glucoside.

### Glucuronide conjugates<sup>[13]</sup>

Bacteria of the lower GIT secrete  $\beta$ -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. Example: Opiates, when taken for the relief of pain, cause severe constipation by inhibiting GIT motility and secretions. Narcotic antagonists, when given as antidotes for GIT side effects, immediately relieve constipation but precipitate acute withdrawal. This is because these narcotic antagonists are not selective and they not only affect the GIT activity, but also the central nervous system (CNS). A novel approach would be to target these antagonists to the lower bowel so that they are not absorbed systemically. With this purpose, naloxone and nalmefene glucuronide prodrugs were prepared to target these drugs to the colon. When given orally to morphine dependent rats these prodrugs showed increased GIT motility and secretion in the large bowel results in a diarrhea and The resultant diarrhea flushed out the drug/prodrug from the colon thereby preventing the systemic absorption of the antagonist, which in-turn caused absence of withdrawal

symptoms. Budesonide- $\beta$ -glucuronide prodrug also found to be superior to budesonide itself for the treatment of colitis in the rat.

### Cyclodextrin conjugate:

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 bioavailability. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules. They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine however, Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextrinase activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed. This susceptibility to degradation specifically by colonic micro flora together with their property to form inclusion complexes with various drugs makes them particularly useful in carrying drug moieties to the colon. The  $\alpha$ - and  $\beta$ -cyclodextrins are practically resistant to gastric acid, salivary, and pancreatic amylases. A clinical study has shown clear evidence that  $\beta$ -cyclodextrin is poorly digested in the small intestine but is almost completely degraded by the colonic microflora.

### Dextran conjugate<sup>[14]</sup>

Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolyzed by moulds, bacteria, and mammalian cells. The enzyme responsible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, where as high dextranase activity is shown by anaerobic gram-negative bacteria, especially the Bacteroides, which are present in a concentration as high as 10<sup>11</sup> per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon<sup>[15]</sup>. 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 colon. Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function (-COOH). NASIDS were directly coupled to dextran by using carboxylic groups of drugs. Example is Naproxen-dextran conjugate. Glucocorticoids do not possess -COOH group so these are linked to dextran using spacer molecule. e.g. glucocorticoid-dextran conjugates.

### Amino acid conjugation:

Due to the hydrophilic nature of polar groups like -NH<sub>2</sub> 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. Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme<sup>[16]</sup>.

### Polymeric prodrugs<sup>[17]</sup>

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Subsynthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety.

## APPROACHES TO DELIVER INTACT MOLECULE TO COLON

### pH dependent approach<sup>[18]</sup>

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

### Coating of the drug core with pH sensitive 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. The drug core includes tablets, capsules, pellets, granules, microparticles or nanoparticles. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. 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 or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. The majority of enteric and colon targeted delivery systems are based on the coating of tablets or pellets, which are filled into conventional hard gelatin capsules. The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products. Moreover, there is considerable difference in inter- and intra- individual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the large intestine. Eudragit-L dissolves at a pH level above 5.6 and is used for enteric coating, whereas Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0 (attributable to the presence of higher amounts of esterified groups in relation to carboxylic groups), which results in premature drug release from the system. Problem of premature drug release can be overcome by the use of Eudragit FS.

### Embedding in pH-sensitive matrices:

The drug molecules are embedded in the polymer matrix. Extrusion spherulization technique can be used to prepare uniform-size sturdy pellets for colon targeted drug delivery when it is not possible to obtain mechanically strong granules by other methods. Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increased the pellet size and influenced

pellet roundness. Citric acid promoted the pelletization process resulting in a narrower area distribution. However, EudragitS100 could not cause statistically significant delay in the drug release at lower pH.

Polymer	Threshold pH
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit® L-30D	5.6
Esudragit® FS 30D	6.8
Hydroxypropylmethylcellulose phthalate 50	5.2
Hydroxypropylmethylcellulose phthalate 55	5.4
Cellulose acetate trimellate	4.8

### Time dependent delivery:

It also known as pulsatile release, delayed or sigmoidal release system. 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 which release of drug take place. The lag time in this case is the time requires to transit from the mouth to colon. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms. This system has some disadvantages as follows:

Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea and the ulcerative colitis.

Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon.

### PULSINCAP :

The first formulation introduced based on this principle was Pulsincap® developed by R.R.Scherer International Corporation, Michigan, US. It consists of non disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by 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 length of the plug and its point of insertion into the capsule controlled the lag time. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (eg, saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (eg, pectin).

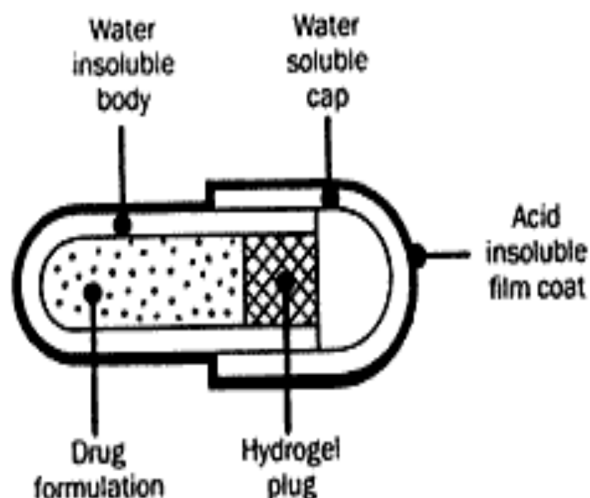


Figure: Design of pulsincap system

**a) Colon-Targeted Delivery Capsule based on pH sensitivity and time-release principles:**

The system contains an organic acid that is filled in a hard gelatin capsule as a pH-adjusting agent together with the drug substance. This capsule is then coated with a three-layered film consisting of an acid-soluble layer, a hydrophilic layer, and an enteric layer (Figure 6). After ingestion of the capsule, these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid, upon which the enclosed drug is quickly released. Therefore, the onset time of drug release is controlled by the thickness of the acid-soluble layer.

**(b) Chronotropic® system <sup>[19]</sup>**

The Chronotropic system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (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 release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the

thickness and the viscosity grades of HPMC. The system is suitable for both tablets and capsules.

**(c) PORT system:**

The Port system (Figure 8) was developed by Therapeutic System Research Laboratory, Ann Arbor, Michigan, USA, and consists of a gelatin capsule coated with a semipermeable membrane. Inside the capsule an insoluble plug (lipidic) consisting of osmotically active agent and the drug formulation. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness <sup>[20]</sup>. The system showed good correlation in lag times of *in-vitro* and *in-vivo* experiments in humans. The system proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children.

**PRESSURE CONTROLLED SYSTEM:**

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of feces. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to



colon-specific oral drug delivery systems. Takaya et al. (1995) have developed pressure controlled colon delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of water insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. The preferred thickness of the capsule wall is about 35-60  $\mu\text{m}$ . The system also appeared to depend on capsule size and density. In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

### OSMOTIC CONTROLLED DRUG DELIVERY:

The OROS-CT system (Figure 9) can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule. Each push-pull unit is bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. In principle semipermeable membrane is permeable to the inward entry of water and aqueous gi fluids and is impermeable to the outward exit of the drug. An orifice is drilled into the semipermeable membrane to the drug layer. The outside surface of the semipermeable membrane is then coated by eudragit®S100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at  $\text{pH} \leq 7$ . As a result water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 h in the colon.

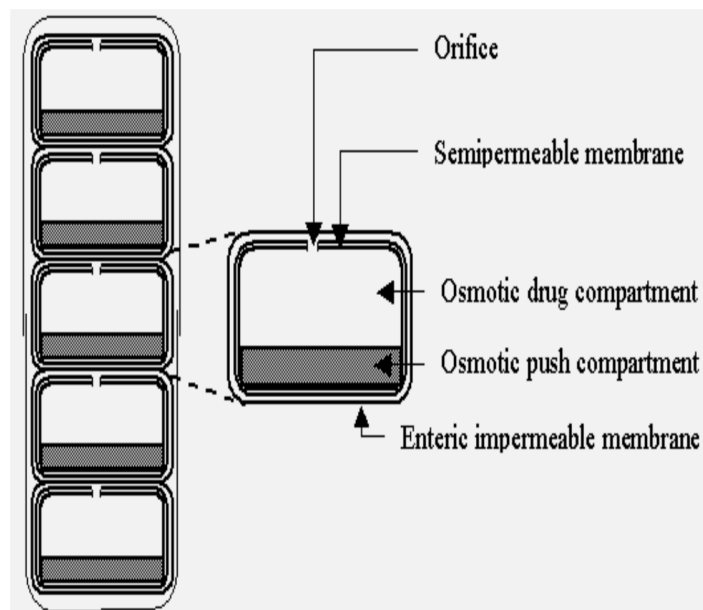


Figure: Cross section of the OROS-CT colon targeted delivery system.

### ADVANTAGES:

- ✓ Predictable, reproducible and short gastric residence time.
- ✓ Less inter- and intra-subject variability.
- ✓ Improve bioavailability.
- ✓ Reduced adverse effects and improved tolerability.
- ✓ Limited risk of local irritation.
- ✓ No risk of dose dumping.
- ✓ Flexibility in design.
- ✓ Ease of combining pellets with different compositions or release patterns.
- ✓ Improve stability.
- ✓ Improve patient comfort and compliance.
- ✓ Achieve a unique release pattern.
- ✓ Extend patent protection, globalize product, and overcome competition.

### SHORTCOMINGS :

- ✓ Low drug loading.
- ✓ Proportionally higher need for excipients.
- ✓ Lack of manufacturing reproducibility and efficacy.
- ✓ Large number of process variables.
- ✓ Multiple formulation steps.
- ✓ Higher cost of production.
- ✓ Need of advanced technology.
- ✓ Trained/skilled personal needed for manufacturing

### EVALUATION:

***In Vitro* Evaluation:** No standardized evaluation technique is available for evaluation of CDDS because an ideal *in vitro* model should possess the *in vivo* conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and other components of food. Generally these conditions are influenced by the diet and physical stress and these factors make it difficult to design a slandered *in vitro* model. *In vitro* model used for CDDS are:

***In vitro* dissolution test:** Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic *in vivo* conditions such as those relating to pH, bacterial environment and mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize 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 media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileal segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. *In vitro* test for intactness of coatings and carriers in simulated conditions of stomach and

intestine Drug release study in 0.1 N HCl for 2 hours (mean gastric emptying time) Drug release study in phosphate buffer for 3 hours (mean small intestine transit time)

***In vitro* enzymatic test:** For this there are 2 tests:

1. Incubate carrier drug system in fermenter containing suitable medium for bacteria (*Streptococcus faecium* or *B.ovatus*) amount of drug released at different time intervals determined.

2. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

***In Vivo* Evaluation** A number of animals such as dogs, guinea pigs, rats and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Eg. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS a novel model has been proposed. In this model the human fetal bowel is transplanted into a subcutaneous tunnel on the back of thymic nude mice, which vascularizes within 4 weeks, matures and becomes capable of developing of mucosal immune system from the host.

### CLINICAL EVALUATION :

Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

**High frequency capsule:** Smooth plastic capsule containing small latex balloon, drug and radiotracer taken orally. Triggering system is high

frequency generator. Release of drug & radiotracer triggered by an impulse, the release is monitored in different parts of GIT by radiological localization. It checks the absorption properties of drug in colon.

**Gamma scintigraphy:** By means of gamma scintigraphic imaging, information can be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine, and disintegration. Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained. Gammascintigraphic studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphic studies (pharmacoscintigraphy).

#### LIMITATION AND CHALLENGES

i) One challenge in the development of colon-specific drug delivery system is to establish an appropriate dissolution method in designing in-vitro system. Due to the rationale after a colon delivery system is quite diverse. As, a site for delivery offers a near neutral pH, reduced digestive enzymes activity, a long transit time, and increased responsiveness to absorption enhancers, hence targeting is complicated, with reliability and delivery efficiency.

(ii) Limiting factors for poorly soluble drug as the fluid contents in colon is much lower and it is more viscous than in upper part of GI tract, For successful delivery through this site, drugs require to be in solution form before it arrives to colon and/or it should dissolve in luminal fluid of colon.

(iii) The resident microflora could also affect colonic performances via metabolic degradation of drug.

(iv) Lower surface area and relative 'tightness' of the tight junction in the colon can also restrict drug transport across the mucosa and into the systemic circulation.

#### FUTURE PROSPECTS :

Recent reports indicate interest in colon as a site where poorly absorbed drug molecules may have improved bioavailability. The distal colon is considered to have less hostile environment as well as enzyme activity compared to stomach and small intestine. The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for oral peptide delivery in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines.

However, drug release is not the end point of oral delivery. The bioavailability of protein drugs delivered at the colon site needs to be addressed. The use of drug absorption enhancers into the drug delivery systems is likely to enhance therapeutic efficacy. Studies on drug absorption by the intestinal system have focused on drug transporters that mediate drug influx and efflux and agents which can enhance drug absorption. The colon segment is designed by nature mainly to expel metabolism products rather than to absorb nutrients. Therefore, more research that is focused on the specificity of drug uptake at the colon site is necessary. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

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