A REVIEW: NOVEL APPROACHES OF COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

The colonic drug delivery has gained importance for drug delivery for local disease treatment associated with colon and included systemic delivery of protein and therapeutic peptide-anti-asthmatic drugs, antihypertensive drugs. Colon is site for local and systemic delivery of drugs. For the treatment of inflammatory bowel disease such as crohn’s disease, colon cancer, amebiosis, ulcerative colitis by topical and systemic delivery colon targeted drug delivery system (CDDS) is an promising tool. CDDS cause lower the systemic side effects. On the disease site lowers the requirement of higher dose of drugs thus cause in reducing the drug cost and frequency of dosage. If the drug to be delivered directly to colon than the treatment should be more effective.

This review also focuses on the novel approaches as pressure controlled colonic delivery, CODESTM, osmotic controlled drug delivery.

KEYWORDS: peptideanti-asthmatic, amobebiasis, crohn’s disease, colon cancer.

INTRODUCTION:

Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as (ulcerative colitis, crohan’s disease) amebiosis, colonic cancer, and for local treatment of local colonic pathologies, and the systemic delivery of protein and peptide drugs.[1] The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to colon (i.e. drug release and absorption should not occur in the stomach and the small intestine and bioactive agent should not be degraded)[2] and to allow drug release only in the colon.
The colon is believed to be a suitable site for absorption of peptides and protein drugs for following reasons.

(i) Less diversity and intensity of digestive enzymes.

(ii) Comparatively proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum and eventually releases drugs in the ileum or colon which leads to greater systemic bioavailability.

(iii) The colon has along residence time (upto 5 days)\(^3\) and is highly responsive to absorption enhancers.\(^4\)

Drug preparation for intrarectal administration is supplied as solutions, foam and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery topically active drug to the large intestine.\(^5\)

**Advantages of colon targeted drug delivery\(^6,7\)**

1- Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, crohn’s disease etc.)

2- By producing the ‘friendlier’ environment for peptides and proteins as compared to upper gastrointestinal tract.

3- Minimizing extensive first pass metabolism of steroids.

4- Preventing the gastric irritation produced by oral administration of NSAIDS.

5- Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.

6- Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn’s disease, etc.

7- Decreases the side effects in the treatment of colon diseases.

8- Prevents gastric irritation resulting due to the administration of NSAIDs.

9- Minimizes first pass metabolism.

10- Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.

**Disadvantages of colon targeted drug delivery\(^6,8\)**

1- Difficult to access colon.

2- Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
3- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa into the systemic circulation.

4- Non availability of an appropriate dissolution testing method to evaluate the dosage form in vitro.

5- Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, mucus or fecal matter.

6- Multiple manufacturing steps. The resident microflora could also affect colonic performance via metabolic degradation of the drug.

**Table 1: Colonic diseases, its sites and active drug components[^9]**

<table>
<thead>
<tr>
<th>Targeted drug</th>
<th>Diseases</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Chronic pancreatitis, Cystic fibrosis, Colorectal cancer, Pancreatectomy</td>
<td>Digestive enzyme, 5-fluorouracil</td>
</tr>
<tr>
<td>Systemic</td>
<td>To prevent first pass metabolism of orally administered drugs oral delivery of peptide, to prevent gastric irritation, oral delivery of vaccine</td>
<td>Typhoid, NSAIDS, Steroids Insulin</td>
</tr>
<tr>
<td>Topical</td>
<td>Inflammatory bowel diseases (Crohn's disease, Ulcerative colitis), Irritable bowel diseases, Amoebiasis</td>
<td>Hydrocortisone, Prednisolone, Sulfasalazine, Mercaptopurine, Tinidazole, mebendazole</td>
</tr>
</tbody>
</table>

**Anatomy of colon**

There are following parts from mouth to anus consist GIT. It is consists of 2 parts namely, stomach and intestine. Large intestine and small intestine includes in intestine. The length of GIT is about 5 meters long. GIT is further divided into different parts namely upper and lower gastrointestinal tract. Upper GIT consists of oesophagus, stomach, and duodenum. And lower GIT consists small intestine and large intestine.[^10]

![Fig 1- Anatomy of colon][11]
The length of small intestine measures an average of about 6.9-7.1 meters, and it includes duodenum, jejunum, and ileum. Absorption of nutrients and minerals from food is the main function of small intestine. It has 3-5 hr retention time. The length of large intestine about 1.5 meters long. It includes caecum, colon and rectum. It acts as a house for over 700 species of bacteria. Large intestine has 3-10 hrs retention time.

The colon is made up of 4 parts- ascending colon, transverse colon, descending colon and sigmoid colon. Colon extracts water and salts from solid wastes before they are eliminated from the body. The parts of colon are located either in the abdominal cavity or behind it in retro peritoneum. The ascending and descending colon and rectum are retroperitoneal, while transverse colon is intra peritoneal. The colon pH varies from 5.5 to 7.[6,7]

### Table 2- Measures of different parts of GIT.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine</td>
<td>3m</td>
</tr>
<tr>
<td>Duodenum</td>
<td>25cm</td>
</tr>
<tr>
<td>Jejunum</td>
<td>1m</td>
</tr>
<tr>
<td>Ileum</td>
<td>2m</td>
</tr>
<tr>
<td>Large intestine</td>
<td>1.5m</td>
</tr>
<tr>
<td>Cecum</td>
<td>6cm</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
</tr>
<tr>
<td>Ascending colon</td>
<td>20-25cm</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>10-15cm</td>
</tr>
<tr>
<td>Descending colon</td>
<td>40-45cm</td>
</tr>
<tr>
<td>Sigmoid portion</td>
<td>35-40cm</td>
</tr>
<tr>
<td>Rectum</td>
<td>20cm</td>
</tr>
<tr>
<td>Anal colon</td>
<td>3cm</td>
</tr>
</tbody>
</table>

**Factors affecting colon targeting drug delivery system**[12]

1- Physiological factors.
2- Pharmaceutical factors.

1- **Physiological factors**-
   a. Gastric emptying
   b. pH of colon
   c. Colonic microflora and enzymes.

2- **Pharmaceutical factors**
   a. Drug candidate
   b. Drug carrier
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 times.

Table 3-Transit time of different part of GIT\(^\text{[13]}\)

<table>
<thead>
<tr>
<th>Parts of GIT</th>
<th>Transit time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted state</td>
<td>10min – 2hr</td>
</tr>
<tr>
<td>Fed state</td>
<td>&gt;2hr</td>
</tr>
<tr>
<td>Small intestine transit</td>
<td>3-4hr</td>
</tr>
<tr>
<td>Colon transit</td>
<td>20-35hr</td>
</tr>
</tbody>
</table>

b. pH of colon

GIT pH varies between the different individuals. The diseased state, food intake etc. effects 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 site.

Table 4: pH in different of colon.

<table>
<thead>
<tr>
<th>Parts of GIT</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach Fasted state</td>
<td>1.5-2</td>
</tr>
<tr>
<td>Fasted state</td>
<td>2-6</td>
</tr>
<tr>
<td>Small intestine</td>
<td>6.6-7.5</td>
</tr>
<tr>
<td>Colon Ascending colon</td>
<td>6.4</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>6.6</td>
</tr>
<tr>
<td>Descending colon</td>
<td>7.0</td>
</tr>
</tbody>
</table>

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 GIT.
Table 5: Different microflora, enzymes released and action-

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Enzyme</th>
<th>Metabolic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli, Bacteroids</td>
<td>Nitroreductase</td>
<td>Reduces aromatic &amp; heterocyclic nitro compounds</td>
</tr>
<tr>
<td>Clostridia, Lactobacilli</td>
<td>Hydrogenase</td>
<td>Reduces carbonyl groups &amp; aliphatic double bonds</td>
</tr>
<tr>
<td>Clostridia, Eubacteria</td>
<td>Glucosidase</td>
<td>Cleavage of β-glycosidase of alcohols &amp; phenols</td>
</tr>
<tr>
<td>Eubacteria, Clostridia, Streptococci</td>
<td>Sulfatase</td>
<td>Cleavage of O- sulphates &amp; Sulfamates</td>
</tr>
</tbody>
</table>

1- Pharmaceutical factors

a. **Drug candidate**- 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.

Table 6- Criteria for selection of drug for CDDS[^14]

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Pharmacological class</th>
<th>Non peptide drug</th>
<th>Peptide drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs used for local action in colon against GIT diseases</td>
<td>Anti-inflammatory drugs</td>
<td>Metoprolol, Nifedipine</td>
<td>Amylin, Oligonucleotide</td>
</tr>
<tr>
<td>Drugs used for colon cancer</td>
<td>Antineoplastic drugs</td>
<td>Pseudoephedrine</td>
<td>Epoetin, Glucagon</td>
</tr>
<tr>
<td>Drugs poorly absorbed</td>
<td>Antihypertensive &amp; Antianginal drugs</td>
<td>Ibuprofen, Theophylline</td>
<td>Cyclosporine, Desmopressin</td>
</tr>
<tr>
<td>Drugs that undergo extensive first pass metabolism</td>
<td>Nitroglycerin &amp; Corticosteroids</td>
<td>Bleomycin, Nicotine</td>
<td>Sermorelin, Saloatonin</td>
</tr>
</tbody>
</table>

Criteria for selection of drug for colon drug delivery system [CDDS]

1- **Drug candidate**

2- **Drug Carrier**

A. **Formation of prodrugs**

(Example: Azo-Prodrug, Glucuronide conjugate, etc.) 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.[^15]
Approaches for colonic drug delivery

1) Covalent linkage of drug with carrier

1.1) Prodrug approaches
Pharmacologically inactive derivative of a parent molecule is prodrug that requires enzymatic transformation in the biological environment to release the active drug at the target site. The approach of covalent linkage involves between the drug and the carrier in such a manner the upon oral administration and moiety remains intact in the small intestine and stomach, and after reached in the colon, enzymatic cleavage regenerate the drug.\(^\text{[16]}\)

![Prodrug approach](image)

**Fig 2- Prodrug approach**

1.2) Azo bond conjugate
The azocompounds are extensively metabolized in the intestine by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. These azo compounds are used for colon- targeting has been in the form of hydrogels as a coating material for coating the drug cores and as a prodrug. The drug is attached via an azo bond to the carrier in the latter approach. The azo bond is stable in the upper part of GIT and is cleaved in the colon by the azoreductases produced by the microflora. The treatment of IBD, drug has an azo bond between the 5-ASA and sulphapyridine, that is sulphasalazine.\(^\text{[17]}\)

In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier SP which shown in (Figure 2).
1.3) 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 β-D-galactosidase, α-L-arabinofuranosidase, β-D-xylopyranosidase, and β–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.

1.4) Glucuronide conjugates

Bacteria of the lower GIT secrete b-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 diarrhoea and the resultant diarrhoea flushed out the drug from the colon thereby preventing the systemic absorption of the antagonist, which in-turn caused absence of withdrawal symptoms. Budesonide-b-glucuronide prodrug also found to be superior to budesonide itself for the treatment of colitis in the rat.\(^{[18]}\)

### 1.5) 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 cyclodextranase 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.\(^{[19]}\)

### 1.6) Dextran conjugates

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 1011 per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon. 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.[20]

1.7) Amino acid conjugation
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. 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.[21]

1.8) Polymeric prodrugs
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. [22]

B. Hydrogels
Hydrogels can be used for site specific delivery of peptide and protein drugs through colon. The Hydrogels are composing of acidic commoners and enzymatically degradable azo aromatic crosslinks. In the acidic pH, gels shows 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.[23]

C. Coating with pH dependent polymers
The pH in the terminal ileum and colon in higher than in any other region of the gastrointestinal tract and thus dosage forms which disintegrate at high pH ranges can be target 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 from moves through the ileocecal junction from the terminal ileum into the cecum. Delayed release tablets containing mesalazine and coated with eudragit S-100 were studied. 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. The formulation was successful in achieving site specific delivery of mesalazine, failure of the coating to dissolve has been reported. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose. For colonic drug delivery, drug core is coated with pH sensitive polymers. The drug are includes tablets, capsules, pellets, granules, micro-particles and nanoparticles. Tablet containing mesalazine were investigated which was coated with two polymers eudragit L100 and eudragit S100 in combination 1:0, 4:1, 3:2, 1:1, 1:5, and 0:1. Chitosan microspheres contain Ondansetron were prepared by emulsion cross linking method. Analysis regression values suggest that the possible drug release was Peppas model[24]

Table 7: Threshold pH of different polymers suitable for pH dependent drug delivery[24]

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Threshold pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit S-100</td>
<td>7.0</td>
</tr>
<tr>
<td>Eudragit L-30D</td>
<td>5.6</td>
</tr>
<tr>
<td>Eudragit FS-30d</td>
<td>6.8</td>
</tr>
<tr>
<td>Eudragit L-100-55</td>
<td>5.5</td>
</tr>
<tr>
<td>Polyvinyl acetate phthalate</td>
<td>5.0</td>
</tr>
<tr>
<td>Hydroxy Propyl Methyl Cellulose Phthalate</td>
<td>4.5-4.8</td>
</tr>
<tr>
<td>Hydroxy Propyl Methyl Cellulose Phthalate 50</td>
<td>5.2</td>
</tr>
<tr>
<td>HPMC 55</td>
<td>5.4</td>
</tr>
<tr>
<td>Cellulose Acetate Trimelliate</td>
<td>4.8</td>
</tr>
<tr>
<td>Cellulose Acetate Phthalate</td>
<td>5.0</td>
</tr>
<tr>
<td>Eudragit L-100</td>
<td>6.0</td>
</tr>
</tbody>
</table>

4. Timed released systems[25]

(Example: Pulsatile release, Pulsincap, Delayed release, Sigmoidal release system) 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. 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 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. In the upper GIT, the drug delivery system is not directly subjected to the luminal pressure, since sufficient fluid is present in the stomach and small intestine. Due to raised luminal pressure in the colon, the system ruptures and releases the drug. A novel time and pH dependent system was investigated. The system consists of the core tablet of Mesalamine which is compression coated with hydroxypropyl methylcellulose (HPMC K4M). This is then coated with eudragit L100. The result revealed that as the amount of HPMC increases, the lag time and t50 value also increases. Osmotic pressure controlled systems: The unit reaches intact to the colon where drug release takes place due to osmotic pressure generated by the entry of the solvent. It is also known as OROS.

5. 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.

6. 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.

Platform technologies for colon targeted drug delivery systems[26]

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 placed within body plugged with hydrogel plug. When it is administered, after predetermined time the enteric coat dissolves and the hydrogel plug starts to swell.

![Fig 3 - Drug release by Pulsincap system](image)

**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 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.

![Fig 4 – Codes system](image)
**Port system:** It consists 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.

![Drug Release Mechanism From PORT System](image)

**Fig 5 – Drug release mechanism from PORT System**

**Oros system**
There are two oros systems for colon drug delivery.
1. Osmet pump
2. Oros ct

**A. Osmet pump**
It consists of an enteric coated semi-permeable shell which encloses an osmotic layer along with a central impermeable and collapsible reservoir filled with drug. The interior of this compartment is connected with the external environment through a delivery orifice at one end. After dissolution of the gastric-resistant film, water is allowed to penetrate through the semi-permeable membrane, thus raising the pressure inside the device. Which cause inner reservoir to shrinks and drug formulation to pump out.
B. Oros ct
Immediately after ingestion, the hard gelatin capsule shell dissolves. The push and pull unit is
prevented from absorbing water in the acidic medium of stomach by enteric coating. The
osmotic pumping action results when the coating dissolves in the drug is delivered out of the
orifice at a rate controlled by the rate of water transport across the membrane. 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.

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.

Target technology
Target technology is based on the application of pH sensitive coating injection-molded starch capsules. That is designed for site-specific delivery of drugs to the colonic region. The CDDS has been developed for the treatment of local pathologies of lower GIT disease. The clinical data which is generated that has showed its suitability in colon targeted drug delivery.

Evaluation test of Colon Drug Delivery System
In vitro evaluation
There are no standardized evaluation technique is available for evaluation of CDDS as an ideal in-vitro model should possess in-vivo condition of GIT such as volume, pH, stirring, bacteria, enzyme activity, enzymes and components of food. The above conditions are influenced by diet and physical stress. The in-vitro evaluation of CDDS includes the in-vitro dissolution study & in-vitro enzymatic test.

1- In-vitro dissolution test
The testing of dissolution is done using the conventional basket method. The dissolution testing is done in the different types of buffers to characterize the behavior of formulations at the different pH levels. There are the different media that are used for 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 test of colon targeted drug delivery system are applied for 2hr in 0.1N HCL, 3hr in pH 6.8 phosphate buffer and finally at pH 7.4 phosphate buffer. Buffers above the pH are prepared to evaluate the colon targeted drug delivery systems. [27]

2- In-vitro enzymatic test
There are two test available for the in-vitro enzymatic test. the carrier drug system is incubated in fermenter by containing a suitable medium for bacteria. At the different time
interval the amount of drug released is determined. And the released study of drug is performed in buffer medium containing enzymes pectinase, dextranase pig or rat or guinea or rabbit cecal contents. The rate of degradation of polymer carrier is directly proportional to the amount of drug released in a particular time.\cite{28}

**In-vivo evaluation**

This evaluation of the CDDS is done in dogs, guinea pigs, rats and pigs as they resemble the anatomic and physiological conditions, microflora of human GIT. The various enzyme distribution in GIT of rat and rabbit is comparable to that in human.\cite{29}

**CONCLUSION**

There are some benefits of local and systemic effects offers by colon targeted drug delivery system. CDDS offers near neutral pH, long transit time, reduced enzymatic activity and increased responsiveness to absorption enhancers, these are the advantages of CDDS. In the comparison of primary approaches, novel approaches are more specific. The need of today’s business and patient community is to identify the appropriate approach that can result in the delivery of drugs in a safe, effective and less expensive manner with minimum fluctuation in terms of release of drugs at target site. By combining various other strategies in future, CDDS will find the central place in novel drug delivery.

**REFERENCE**


22. www.drug delivery technology.com


