COLON TARGETED DRUG DELIVERY SYSTEM: PHARMACEUTICAL APPROACHES WITH CURRENT TRENDS

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ABSTRACT
Colon drug delivery system is gaining importance in most of the days because colon is a site where in both local and systemic delivery of drugs can take place. This article gives an overview on anatomy and physiology of the colon and approaches utilized for colon targeted drug delivery. This article also discusses advantages & limitations of the different approaches & evaluation for site specific drug delivery to colon.

KEY WORDS: Colon, pH, microflora, inflammatory bowel disease, approaches.

INTRODUCTION:

The oral aspect is considered to be most convenient for administration of drugs to Patients. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as drugs needs to be protected from the hostile environment of upper GIT. Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowel diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in stomach as well as small intestine, and neither the bioactive agent should be degraded either of the dissolution sites, but only released absorbed once the system reaches the colon.
DISEASES ASSOCIATED WITH COLON: \[36\]

- **Inflammatory bowel diseases:**
  
  Crohn’s disease and ulcerative colitis are two inflammatory bowel diseases that cause chronic inflammation in the gastrointestinal (GI) tract.

  - **Crohn’s disease**
    
    Crohn’s disease can affect any part of the GI tract, from the mouth to the anus. It most commonly affects the end of the small intestine (the ileum) where it joins the beginning of the colon. Crohn’s disease may appear in “patches,” affecting some areas of the GI tract while leaving other sections completely untouched. In Crohn’s disease, the inflammation may extend through the entire thickness of the bowel wall of the affected area.

  - **Ulcerative colitis**
    
    Ulcerative colitis is limited to the large intestine (colon) and the rectum. The inflammation occurs only in the innermost layer of the lining of the intestine. It usually begins in the rectum and lower colon, but may also spread continuously to involve the entire colon.

- **Colorectal cancer**

  Colorectal cancer is cancer that starts in the colon or the rectum. These cancers can also be referred to separately as colon cancer or rectal cancer, depending on where they start. Colon cancer and rectal cancer have many features in common. They are discussed together in this document except for the section about treatment, where they are discussed separately.

**COLON TARGETED DRUG DELIVERY SYSTEMS ARE MAINLY USED FOR** \[2\]

(1) Drugs used for local effects in colon inflammatory bowel disease like ulcerative colitis and Crohn’s disease. E.g. 5-amino salicylic acid, Sulphasalazine, hydrocortisone acetate, 5-fluorouracil.

(2) Macro molecule structures peptide and proteins for systemic effects, because colonic environments are less hostile to these drugs. e.g.: calcitonin, interleukin, interferon, insulin, growth hormone, erythropotien, analgesic peptides oral vaccines, contraceptives, peptides etc.

(3) Drugs which are poorly absorbed orally, as colon has longer residence time and is highly responsive to agents that enhance the absorption of poorly absorbable drugs.

(4) For the avoidance of hepatic first pass metabolism of drugs.

(5) Where the delay in systemic absorption is therapeutically desirable, especially in disease susceptible to diurnal variation.
Some orally administered drugs which exhibit poor uptake in upper gastrointestinal to show enzymatic action. e.g.: Metoprolol, Nifedipine, Isosorbide, Theophylline, Diclofenac, and Ibuprofen

ANATOMY AND PHYSIOLOGY OF COLON [9]

In GIT, large intestine starts from the ileocecal junction to the anus having a length of about 1.5 m (adults) and is divided into three parts, viz. colon, rectum and anal canal. The colon consists of caecum, ascending colon, transverse colon, descending colon and sigmoid colon. Colon is made up of four layers, serosa, muscularis externa, submucosa and mucosa. The epithelium consists of a single layer of cells, which lines the crypts and covers the surface of the mucosa. Three major cell types found in the epithelium are the columnar absorptive cells, goblet (mucous) cells and entero endocrine cells. Adjacent columnar absorptive cells are attached to one another near apical margins by a junctional complex. Mucus production in the colon is a function of goblet cells and the proportion of goblet cells increases in the elderly.

The colon and the rectum have an anatomic blood supply. The arterial blood supply to the proximal colon is from the superior mesenteric artery and the inferior mesenteric artery supplies the distal colon. The venous drainage is via the superior (proximal colon) and inferior (distal colon) veins. The arterioles and capillary branches pass to the epithelial surface between the crypts and form an extensive network of capillary plexi. The mucus lining of GIT forms a barrier against bacterial invasion of the gut wall.

![Anatomy of Colon](image)

Fig 1: Anatomy of Colon.

COLONIC MICRO FLORA [2]

The sluggish movement of material through the colon allows a large microbial population to succeed there. Over 400 species of bacteria found, for the most part anaerobes and a small number of fungi. The bacterial count (colony forming unit/mL, CFU/mL) is $10^{11}-10^{12}$
CFU/mL in colon. Most of them are anaerobes. E.g.: Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus and Clostridium; others are facultative anaerobes e.g.: E.Coli. Among all of them 20-30% are Bacteroides.

**pH IN THE COLON**[2]

Radio telemetry has been used to measure the gastrointestinal pH in healthy human subjects. The average pH of the caecum and colon lumen is 6.8 – 7.0. The highest pH levels (7.5 – 8.0) were found in the terminal ileum. On entry into the colon, the pH dropped to 6.4 –7.0. The pH in the mid-colon was measured at 6.6 – 7.4 and in the left colon, 7.0 – 7.7. The fall in pH on entry into the colon is due to the presence of short chain fatty acids arising from the bacterial fermentation of polysaccharides. Colonic pH has been shown to be reduced in disease.

**FUNCTIONS OF THE COLON**[2]

The major function is the consolidation of the intestinal contents into faeces by the absorption of water and electrolytes. The absorptive capacity is very high. In healthy human colon, sodium and chloride ions are usually absorbed and potassium and bicarbonate ions are usually secreted. Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements caused by circular muscle and causing the appearance of the sac-like haustra, predominate and resulting in mixing of the luminal contents. Significant propulsive activity, associated with defecation and affected by longitudinal muscle, is less common and occurs an average of three or four times daily.

**BARRIERS TO COLONIC DRUG ABSORPTION**[9]

Drug absorption through the colon can be limited by number of barriers. In the lumen itself, specific and non-specific drug binding can occur through the interaction of drug with dietary components and products released from bacteria residing in the colon. The mucus barrier at the epithelial surface can present a formidable physical barrier to uptake as a result of specific and non-specific drug binding. Mucus-drug incompatibility can be compounded if the delivered drug stimulates the mucus secreting goblet cells because the transit through mucus is diffusion limited, the greater the thickness of this barrier, longer the time required for an individual molecule to reach the epithelial surface. The unstirred water layer (the space between mucus layer and epithelial cells) presents another barrier to colonic absorption, particularly for lipophilic drugs. A pH gradient may also exist across the unstirred water layer. This lower pH at the colonocyte surface may dramatically alter drug solubility and...
since drug transport within the unstirred layer is driven by chemical potential, altered drug solubility can affect absorption. Probably the most significant barrier to epithelial transport of drugs in the colon occurs at the level of the epithelium. Here, the lipid bilayers of the individual colonocytes and the occluding junctional complex (OJC) between these cells provide a physical barrier to drug absorption.

FACTORS AFFECTING COLONIC DRUG DELIVERY\(^9\)

There are many factors that influence the drug delivery to colon. They include

1. **Transit through GIT**
   
   In order to reach colon in an intact form, the drug delivery systems should surpass the barriers in the stomach and small intestine. Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hours to reach the ileocecal junction. During this period the dosage form is exposed to enzymes present in small intestine. Compared to the other region of GIT, movement of material through the colon is slow. The colonic transit time of a capsule in adult is 20-35 hrs. Improved residence time with subsequent longer transit time and the contact of dosage form with microflora in colon govern the release and absorption of drug from dosage form.

2. **Gastric emptying**

   Once the dosage form enters the stomach, the primary concern is how long it will remain there before being discharged into the duodenum. Emptying generally completes in 5-10 min up to 2 hours depending on phase of the stomach at the time of drug administration. It is preferable for a colonic delivery system to spend little time in the stomach. Such system may release the drug at a distant locus from the colon.

3. **Stomach and intestinal pH**

   The pH of GIT must be considered when enteric coatings (bioerodible polymers) are used to deliver drugs to colon. Since, in such systems, GIT pH gradient is used to trigger drug release.

4. **Colonic microflora**

   Microflora of the colon has a number of implications in health and the treatment of diseases such as IBD. The concentration of gut microflora rises considerably in the terminal ileum to
reach extraordinarily high levels in the colon. The gut bacteria are capable of catalysing a wide range of metabolic events. Many colon-specific drug delivery systems rely on enzymes unique to gut microflora to release active agents in the colon. However, only two or three enzyme systems namely azoreductases and glycosidases (including glucuronidase) have been explored in this area. A large number of polysaccharides are actively hydrolysed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. The second class of enzymes used to trigger the release of drugs in the colon is glycosidases (including glucuronidases). The main bacterial groups responsible for β- glycosidases activity are lactobacilli, bacteroides and bifidobacteria.

5. Gastrointestinal Disease State

Gastrointestinal diseases such as IBD (inflammatory bowel disease), crohn's disease, constipation, diarrhoea and gastroenteritis may affect the release and absorption of drug from colon-specific drug delivery system.

Table 1: GIT diseases that affect the colonic absorption.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Effects on colonic absorption of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer, Inflammatory Bowel Diseases (Crohn's Disease and Ulcerative Colitis)</td>
<td>Diarrhoea, fever, anaemia, obstruction of lymphatic drainage and hyperplasia of lymphoid tissue, which are associated with these condition may affect the drug release and absorption.</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Hypermotility and frequent passage of hypertonic liquid faeces significantly affect drug absorption and release.</td>
</tr>
<tr>
<td>Antibiotic associated</td>
<td>Overgrowth of Clostridium difficile and resulting toxin production, which alters mucosal surface area, may reduce drug absorption.</td>
</tr>
<tr>
<td>Constipation</td>
<td>Decreased peristaltic movement of bowel decreases diffusion and availability of drug at absorption sites. Severe constipation reduces bowel movement once or twice a week and interferes with the movement of formulations.</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Diarrhoea due to increased mucosal secretion may affect the performance of formulations.</td>
</tr>
<tr>
<td>GIT infections</td>
<td>Diarrhoea due to colonic protozoal and bacterial infections causes extremely low transit time and increased mucus production, interferes with localization of drug and absorption.</td>
</tr>
</tbody>
</table>

**COLONIC ABSORPTION**[^9]

As absorption capacity of colon is very high which is attributed to the colon transit time, which can be as long as 20-35 hours, hence it is ideally suited for absorption.

The absorption is influenced by the transport of water, electrolytes and ammonia across the mucus and it is more in the proximal colon than the distal colon. Drug molecules pass from the apical to basolateral surface of epithelial cells by-

- Passing through colonocytes (trans cellular transport), or
- Passing between adjacent colonocytes (para cellular transport)

Small amphipathic drugs may pass this barrier through transcellular transport. Paracellular transport may be the most promising means of general drug absorption in colon. Additionally, carrier mediated uptake of the drug in the colon is not extensive and usually related to the metabolic events of the resident bacteria. Receptor mediated endocytosis and pinocytosis could, however lead to transcellular transport of drug.

**ADVANTAGES OF COLON TARGETING DRUG DELIVERY SYSTEM**[^10,11,12,13,14,15,16,17]

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

LIMITATIONS OF COLON TARGETING DRUG DELIVERY SYSTEM: [10,11,12,13,14,15,16,17]
- Multiple manufacturing steps.
- The resident microflora could also affect colonic performance via metabolic degradation of the drug.
- Incomplete release of drug.
- Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- Drug should be in solution form before absorption and therefore rate limiting step for poor soluble drugs.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.
- An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve.
- Limitations of prodrug approach is that it is not very versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage.

DIFFERENT APPROACHES USED FOR COLON TARGETING: [28]
- Prodrug approach
- Probiotic approach
- Hydrogel approach
- pH-Dependent system
- Time dependent
- Microbially triggered system
- CODES technologies
- Osmotic controlled drug delivery system
- PULSINCAP System
- Port system
- Polysaccharide based system
- Pressure controlled drug delivery
- Multiparticulate approach
- Bioadhesive system
- Nanoparticulate system
- Chronotopic system
- COLAL-PRED system
- Pulsatile colon delivery

**Prodrug approach:**[18]

(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.

**a) Azo bond conjugate**[20, 21]

Sulfasalazine is mainly used for the treatment of inflammatory bowel diseases. It is 5- Amino Salicylic Acid (5-ASA) prodrug. 85% of oral dose of sulfasalazine reaches to the colon unabsorbed, where it is reduced by the anaerobic environment into 5- ASA and sulphapyridine.

**b) Glucuronide conjugate**[22]

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

**c) Cyclodextrin conjugates**[23, 24, 25]

The hydrophilic and ionisable cyclodextrins can serve as potent drug carriers in the immediate release and delayed release-formulations, while hydrophobiccyclodextrins can retard the release rate of water. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. Conjugates of a drug with cyclodextrins can be a versatile means of constructing a new class of colon targeting prodrugs soluble drugs.
d) Amino-acid conjugates\cite{26,27}
Due to the hydrophilic nature of polar groups like NH2 and COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids.

Probiotic approach\cite{28}
The Probiotic approach is one of the latest approaches for colon targeting. In this approach, three components are desirable namely probiotic strain, microbially digestable carrier and triggering temperature. Probiotic strains include inactive microflora like *Bifidobacterium* and *Lactobacillus* species. At body temperature, these strains triggered to be active and start digesting the carrier and ultimately release the drug at desired place. This approach gained success in colon drug delivery system because these conditions are only available in colon.

Hydrogel approach\cite{29}
Amydated pectin hydrogel beads prepared for colon specific delivery of indomethacin and sulfamethoxazole. Glutaraldehyde cross-linked dextran capsules were prepared for colon targeting. Along with magnesium chloride and PEG 400 in water the capsule caps and bodies were prepared on nylon molding pins. Then the dextran capsules were filled with model drug (Hydrocortisone) and drug release was studied. The drug release pattern was suitable for colon specific delivery. The hydrogels formed by cross-linked polyvinyl alcohol were suitable for colon specific drug delivery systems.

pH- dependent system\cite{28}
During fasting, the pH range of the stomach is in between 1-2 but on eating its increases. The pH of proximal small intestine is about 6.5 and in the cecum are about 6.4. However, pH values as low as 5.7 has been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and in the descending colon 7.0. These different polymers having different threshold pH and according to that release the drug at same pH. Mostly the Eudragit L and S are used for the preparation of colon drug delivery, these dissolved at the pH of 6 and 7 respectively. The decrease in the pH from the end of the small intestine to the colon have many problems like increases lag times at the ileocecal junction or fast elimination through the ascending colon, which can affects poor site specificity of the single unit formulation. Several factors affects the formulation, such as combinations of different
polymers, pH of the media, coating level of the tablets and presence of plasticizers, influence the dissolution rate of Eudragit®.

Table 2: Different pH dependant polymers with their threshold pH.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Polymer</th>
<th>Threshold pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Eudragit S-100</td>
<td>7</td>
</tr>
<tr>
<td>2.</td>
<td>Eudragit L-100</td>
<td>6</td>
</tr>
<tr>
<td>3.</td>
<td>Eudragit FS 30D</td>
<td>&gt;7</td>
</tr>
<tr>
<td>4.</td>
<td>Eudragit RS 100</td>
<td>&lt;6</td>
</tr>
<tr>
<td>5.</td>
<td>Eudragit L 30D</td>
<td>5.6</td>
</tr>
<tr>
<td>6.</td>
<td>Eudragit L 100-55</td>
<td>5.5</td>
</tr>
<tr>
<td>7.</td>
<td>Hydroxy propyl methyl cellulose phthalate</td>
<td>&gt;5.5</td>
</tr>
<tr>
<td>8.</td>
<td>Shellac</td>
<td>7</td>
</tr>
<tr>
<td>9.</td>
<td>Hydroxy propyl ethyl cellulose Phthalate</td>
<td>5.2</td>
</tr>
<tr>
<td>10.</td>
<td>Hydroxypropylmethylcelluloseacetate succinate (HPMCAS)</td>
<td>&gt;5.5</td>
</tr>
<tr>
<td></td>
<td>LF Grade</td>
<td>&gt;6</td>
</tr>
<tr>
<td></td>
<td>MF Grade</td>
<td>&gt;6.8</td>
</tr>
<tr>
<td>11.</td>
<td>Polyvinyl acetate phthalate</td>
<td>4.5-4.8</td>
</tr>
<tr>
<td>12.</td>
<td>Cellulose acetate terimellate</td>
<td>4.8</td>
</tr>
</tbody>
</table>

The coating specifies the release of bio actives, depending on the type of coating material and size of dosage form like granules and tablets.

Table 3: pH dependant polymers for various drugs.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Polymer used</th>
<th>Drug used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Eudragit L100 and S100</td>
<td>Mesalazine,</td>
</tr>
<tr>
<td>2.</td>
<td>Eudragit L100 and S100</td>
<td>Flurbiprofen</td>
</tr>
<tr>
<td>3.</td>
<td>Eudragit L100 and S100</td>
<td>Diclofenac sodium and 5-ASA</td>
</tr>
<tr>
<td>4.</td>
<td>Eudragit S, Eudragit FS, And Eudragit P4135F</td>
<td>Prednisolone</td>
</tr>
</tbody>
</table>
Time dependent approach\[^{[28]}\]

In this approach, the basic principle is the release of the drug after a predetermined lag time from dosage form at the site of action at right time and in right amount. Both large single-unit formulations and small multiple-unit formulations take three to four hours to pass through the small intestine, that can be unaffected by particle size, density or composition of the meals, because the time taken to leave the formulation to the stomach was not predicted. Ideally, formulation was to be designed that are not affected by the individual difference in gastric emptying time, pH of the stomach, small intestine or presence of anaerobic bacteria in the colon at the site of delivery. This formulation is comprised of three parts first a centre core containing a drug and swelling excipients, secondly an inner semipermeable polymer membrane containing a plasticizer which allow water influx but prevents the outward diffusion of drug and lastly an outer enteric-coating which dissolves above pH 5.5. Time dependent polymers are mostly cellulose based and showed their potential in different studies incorporating drugs in them.

Table 4: Different polymers used for various drugs.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Polymer used</th>
<th>Drug used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydroxy propyl methylcellulose</td>
<td>Pseudoephidrine HCL</td>
</tr>
<tr>
<td>2</td>
<td>Hydroxyethyl cellulose, Ethyl Cellulose</td>
<td>Theophylline</td>
</tr>
<tr>
<td>3</td>
<td>Microcrystallinecellulose Lactose/behinic Acid</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>4</td>
<td>Hydroxy propyl methylcellulose acetate succinate</td>
<td>Diltiazem HCL</td>
</tr>
</tbody>
</table>
**Microbially triggered system**[28]

The basic principle involved in this method is degradation of polymers coated on the drug delivery system by microflora present in colon and there by release of drug load in colonic region because the bio environment inside the human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms. In this method, drugs and/or dosage forms are coated with the biodegradable polymers i.e., the polymers degrade due to influence of colonic microorganisms. When the dosage form passes through the GIT, it remains intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating. This approach is different from probiotic approach because in probiotic approach, we are providing microflora from external source which assist the interior flora.

**Table 5: Microbial Triggered based polymer for various drugs.**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Polymers used</th>
<th>Drug used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Chitosan</td>
<td>Diclofenac sodium</td>
</tr>
<tr>
<td>2.</td>
<td>Chitosan</td>
<td>Budesonide</td>
</tr>
<tr>
<td>3.</td>
<td>Pectin</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>4.</td>
<td>Guar gum</td>
<td>5-Flourouracil</td>
</tr>
<tr>
<td>5.</td>
<td>Guar gum</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>6.</td>
<td>Chondroitin Sulphate</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>7.</td>
<td>Amylose</td>
<td>5-Acetyl salicylic acid</td>
</tr>
<tr>
<td>8.</td>
<td>Sesbania gum</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>9.</td>
<td>Guar gum</td>
<td>5-Acetyl salicylic acid</td>
</tr>
</tbody>
</table>

**CODES Technologies**[28, 30, 31, 32]

CODESTM is an unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon. It has been developed for the site specific release in the colon by utilization of a unique triggered mechanism involving lactulose. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the
technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release.

![Diagram of CODES System]

**Fig 2: Schematic design of CODES system.**

**Osmotic controlled drug delivery system**[^33,^34]

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable.[^50] The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence
no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hours 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 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon.Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

Fig 3: Cross-Section of the OROS-CT system.

PULSINCAP system [1, 28]
This technique was introduced by R.R.Scherer International Corporation, Michigan, US, to target a water insoluble capsule. 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, glycerylmonoooleate), and enzymatically controlled erodible polymer (eg, pectin).

Port System: [28, 35]
This technique was introduced by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA. The port system consists of a capsule coated with a semipermeable membrane. The capsule consists of an insoluble plug with an osmotically active agent and the drug formulation. When the capsule comes in contact with the dissolution fluid, water enters through semipermeable membrane leading to the pressure development inside the capsule and after a lag time, the insoluble plug gets expelled. The dosage form is designed in such a manner that after ingestion, the first drug release pulse occurs within 1-2 hours, followed by period during which no release occurs. Second dose is released in 3-5 hours after ingestion. This is again followed by a second no release interval. Release of third dose occurs within 7-9 hours of ingestion. This system avoids second time of dosing.

Polysaccharide based system [17, 18]
Dosage forms enjoy the shielding effect of polysaccharide in upper part of GIT and drug is released in the colon by swelling and biodegradable action of polysaccharides.
Polysaccharides naturally occurring in plant (e.g., pectin, guar gum, inulin), animal (e.g., chitosan, chondroitin sulfate), algal (e.g., alginates), or microbial (e.g., dextran) origins were studied for colon targeting. These are broken down by the colonic microflora to simple saccharides by saccharolytic species like bacteroides and bifidobacteria. Hydrolysis of the
glycosidic linkages on arrival in the colon triggers the release of the entrapped bioactive. Although specifically degraded in the colon, many of these polymers are hydrophilic in nature, and swell under exposure to upper GI conditions, which leads to premature drug release. To overcome this problem, the natural polysaccharides are chemically modified and mixed with hydrophobic water insoluble polymers, whereas in the case of formulations they are usually coated with pH sensitive polymers. A pectin/chitosan-based colonic delivery system has been developed. The use of calcium pectinate as a carrier was based on the assumption that, like pectin, it can be decomposed by specific pectinolytic enzymes in the colon but retains its integrity in the physiological environment of the small bowel.

Pressure controlled drug delivery[1]

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.

Multiparticulate approaches[29]

Multi particulates (pellets, non-peariles etc.) are used as drug carriers in pH sensitive, time dependentandmicrobially control systems for colon targeting. Multi particulate systems have several advantages in comparison to the conventional single unit for controlled release technology, such as more predictable gastric emptying and fewer localized adverse effect than those of single unit tablets or capsules.

Bioadhesive system[1]

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. 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. Bioadhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery systems.

**Nanoparticulate system**\(^{[35]}\)

Nanoparticle size colloidal carriers composed of natural or synthetic polymers have been investigated for colon targeting. Different types of drugs given with nanoparticles such as carriers shows enhanced solubility, permeability and bioavailability. Proteins and peptides can also be given through nanoparticulate delivery. Bioadhesion can also be achieved through nanoparticulate delivery system. Due to large specific surface of nanoparticles, it shows high interactive potential with biological surfaces. The interaction is of non-specific nature hence, bioadhesion can be induced by binding nanoparticles with biological surfaces. The nanoparticle surface has to show free functional groups, such as carboxylic or amine residues for covalent attachment.

**Chronotropic system**\(^{[28]}\)

In this technology, a drug release after a particular lag time, surrounding with a soluble barrier layer, which consists of a core containing drug reservoir coated by a hydrophilic polymer like HPMC. The coating of additional enteric coating film outside that layer to overcome the gastric emptying variability and lag time of the drug was controlled by coating thickness and viscosity grade of the polymer.

Enteric coat

![Fig 5: Schematic design of Chronotropic system.](image-url)
COLAL-PRED system\(^{[28]}\)

COLAL-PRED is a proprietary gastrointestinal product developed by Alizyme for the treatment of ulcerative colitis (US). It is an effective anti-inflammatory treatment for ulcerative colitis without the typical side effects of steroids. A product with the profile of COLAL-PRED would represent a significant advance in the management of ulcerative colitis. COLAL-PRED has a coating that is broken down only in the colon by bacteria. This leads to topical delivery of steroids to the colon without significant systemic exposure with minimizing steroid related side effects.

**Pulsatile colon delivery**\(^{[28]}\)

Pulsatile drug delivery systems (PDDS) can be divided in site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the gastrointestinal tract, e.g., on pH, presence of enzymes, and the pressure in the gastrointestinal tract. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling layers.

**EVALUATION OF COLON TARGETED DRUG DELIVERY SYSTEM:** \(^{[1, 28, 35]}\)

The drug release in colon from different colon drug delivery system is evaluated by different in vitro and in vivo methods.

**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 completely mimic in vivo conditions such as 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 behaviour of formulations at different pH levels. Dissolution tests of a colon targeted formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. The media chosen are, 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
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. Carrier drug system is incubated in fermenter containing suitable medium for bacteria (*Streptococcus faccium* or *B.ovatus*). The amount of drug released at different time intervals is 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 rats and guinea 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. Eg. Guinea pigs are commonly used for experimental IBD model.

**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 used to evaluate colon drug delivery systems.

- **High frequency capsule**: Smooth plastic capsule contains a small latex balloon, drug and radiotracer is taken orally. High frequency generator acts as a triggering system. Release of drug & radiotracer is triggered by an impulse and the release is monitored in different parts of GIT by radiological localization. It evaluates the absorption of drug in colon.

- **Gamma scintigraphy**: By gammascintigraphic imaging study, information relating to time of arrival of a colon-specific drug delivery system in the colon, time of transit through the stomach and small intestine, and disintegration can 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.
CONCLUSION
The colonic region of GIT has become an important site for drug delivery and absorption. Colon drug delivery system offers therapeutic benefits to patients in terms of both local and systemic drug delivery. Considering the sophistication of colon-specific drug delivery systems, and the uncertainty of current dissolution methods in establishing possible in-vitro/in-vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

REFERENCES