DIFFERENT APPROACHES FOR COLON DRUG DELIVERY SYSTEMS: A REVIEW

ABSTRACT

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. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process. Colon specific drug delivery system has attracted considerable attention for the past few years in order to develop drug delivery systems that are able to release drugs specifically in the colon in a predictable and reproducible manner. The colon is a site where both local and systemic delivery of drugs can take place. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in the upper portion of the gastric intestinal tract (GIT) and then to be ensured abrupt or controlled release in the proximal colon. This review is aimed at understanding recent approaches for dosage forms which is targeting to colon through pH sensitive system, microbially triggered system i.e., prodrugs and polysaccharide based system, timed release system, osmotically controlled drug system, pressure dependent release system, etc.

Key Words: Colon drug delivery system, colonic delivery system, primary approaches, new approaches, evaluation of colon targeted drug delivery systems, Advantages.
INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn’s disease, amebiasis, 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 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. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative 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 duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability and finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.²,⁹

The oral aspect is considered to be most convenient for administration of drugs to Patients. Normally dissolves in stomach field as intestinal fluid and absorb from these regions of GIT. 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.²,²¹

Oral route is the most convenient and preferred route but other routes for CDDS may be used. 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.⁶ 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 of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching

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the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity.\(^2\)

The major functions of the colon are:\(^2,^{26}\)

1) The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and to store the feces until excretion. The absorptive capacity is very high; each day about 2000 mL of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed.

2) Creation of a suitable environment for the growth of colonic microorganisms, such as Bacteroides, Eubacterium, and Enterobacteriaceae.

3) Expulsion of the contents of the colon at a suitable time.

4) Absorption of water and Na\(^+\) from the lumen, concentrating the fecal content, and secretion of K\(^+\) and HCO\(_3\)\(^-\).

**Rational for the Development of Oral Colon Targeted Drug Delivery:**\(^{14}\)

1. Treatment of local pathologies.
2. Chronotherapy (asthma, hypertension, cardiac).
3. Arrhythmias, arthritis or inflammation.
4. Greater responsiveness to the absorption enhancers.
5. Less enzymatic activity.
7. Oral delivery of vaccines as it is rich in lymphoid tissue.
8. 

**Advantages:**\(^{14,22}\)

1. Predictable, reproducible and short gastric residence time.
2. Less inter- and intra-subject variability.
3. Improve bioavailability.
4. Reduced adverse effects and improved tolerability.
5. Limited risk of local irritation.
6. No risk of dose dumping.
7. Flexibility in design.
8. Ease of combining pellets with different compositions or
10. Improve stability.
11. Improve patient comfort and compliance.
12. Achieve a unique release pattern.

<table>
<thead>
<tr>
<th>Target sites</th>
<th>Disease conditions</th>
<th>Drug and active agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical action</td>
<td>Inflammatory Bowel Diseases,</td>
<td>Hydrocortisone, Budesonide, Prednisolone, Sulfasalazine,</td>
</tr>
<tr>
<td></td>
<td>Irritable bowel disease and Crohn’s disease.</td>
<td>Olsalazine, Mesalazine, Balsalazide</td>
</tr>
<tr>
<td></td>
<td>Chronic pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Local action</td>
<td>Pancreatocomy and cystic fibrosis, Colorectal cancer.</td>
<td>Digestive enzyme supplements 5-Flourouracil</td>
</tr>
<tr>
<td>Systemic action</td>
<td>To prevent gastric irritation</td>
<td>NSAIDS Steroids Insulin Typhoid</td>
</tr>
<tr>
<td></td>
<td>To prevent first pass metabolism of Orally ingested drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral delivery of peptides</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral delivery of vaccines</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Colon Targeting Diseases, Drugs and Target Sites.27
NEED OF COLON TARGETED DRUG DELIVERY?

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn’s Disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. 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. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

Anatomy and physiology of the colon:

The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5 m long. The colon is upper five feet of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 2-3 inches in diameter. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal. The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.

Fig 1: Anatomy of the colon.
In terms of size and complexity, the human colon falls between that of carnivores which has no identifiable junction between ileum and colon, and herbivores which have a voluminous cecum. The human cecum is small and there is a rudimentary appendix. The human colon can be divided into three functional areas, The cecum and proximal colon, which act as a fermentation chamber, The transverse colon, the motor patterns of which may hold material in the proximal colon or propel it distally but that may also be an important site for the absorption of water and the rectum, Proximal colon acts as a reservoir for fecal material and allows defecation to be delayed until socially convenient.

<table>
<thead>
<tr>
<th>Region of GI Tract</th>
<th>Length (cm)</th>
<th>Internal Diameter (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire GI Tract</td>
<td>500-700</td>
<td></td>
</tr>
<tr>
<td>Small Intestine</td>
<td></td>
<td>3-4</td>
</tr>
<tr>
<td>Duodenum</td>
<td>20-30</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>150-200</td>
<td></td>
</tr>
<tr>
<td>Ileum 200-350</td>
<td>200-350</td>
<td></td>
</tr>
<tr>
<td>Large Intestine</td>
<td>90-150</td>
<td>6</td>
</tr>
<tr>
<td>Cecum</td>
<td>6-7</td>
<td></td>
</tr>
<tr>
<td>Ascending colon</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Transverse colon</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Descending colon</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Anal canal</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Summary of anatomical and physiological regions of GI tract.21
The physiology of the proximal and distal colon differs in several respects that relate to their function and may affect drug absorption at each site. The physical properties of the luminal contents of the colon also change from liquid in the cecum to semisolid in the distal colon. In addition to the site of the colon, there may also be differences in the environment of a drug or molecule depending on whether it is in the bulk phase or next to the mucosa, and whether it is free in the aqueous phase or bound to, or trapped in, solid material such as dietary fiber residues.

<table>
<thead>
<tr>
<th>Point of Differentiation</th>
<th>Proximal</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Fermentation Chamber</td>
<td>Absorption Storage</td>
</tr>
<tr>
<td>Innervation</td>
<td>Vagal/pelvic Splanchnic/lumbar Muscle more distensible</td>
<td>Pelvic, lumbar, greater Sensitivity to neural Stimulation</td>
</tr>
<tr>
<td>Blood supply</td>
<td>Superior mesenteric Artery and vein, Greater blood flow</td>
<td>Inferior mesenteric Artery and vein</td>
</tr>
<tr>
<td>Absorption</td>
<td>92% of chloride-dependent transport is electro neutral greater overall capacity</td>
<td>Chloride-dependent Transport mainly, Amiloride sensitive</td>
</tr>
<tr>
<td>Luminal contents</td>
<td>Liquid, lower pH (4.6-7.8), higher SCFA, very active bacterial metabolism</td>
<td>Semisolid, neutral pH, lower SCFA, lower bacterial activity.</td>
</tr>
</tbody>
</table>

Table 3: Pharmaceutical approaches for formulation of colon specific drug delivery systems:
A variety of approaches have been used and system have been developed in past for the purpose of achieving colonic delivery. These approaches are either drug specific (prodrugs) or formulation – specific (coated or matrix preparations). The must commonly used mechanisms are,

1. pH – dependent delivery.
2. Time – dependent delivery.
3. Pressure – dependent delivery.
4. Bacteria - dependent delivery.

1. pH- and time- dependent systems:\textsuperscript{5,23,37} pH-sensitive enteric coatings have been used routinely to deliver drugs to the small intestine. These polymer coatings are insensitive to the acidic conditions of the stomach yet dissolve at the higher pH environment of the small intestine. This pH differential principle has also been attempted for colonic delivery purposes, although the polymers used for colonic targeting tend to have a threshold pH for dissolution that is higher than for those used in conventional enteric coating applications. Most commonly, copolymers of methacrylic acid and methyl methacrylate that dissolve at pH 6 (Eudragit® L) and pH 7 (Eudragit® S) have been investigated. This approach is based on the assumption that gastrointestinal pH increases progressively from the small intestine to colon. In fact, the pH in the distal small intestine is usually around 7.5, while the pH in the proximal colon is closer to 6. These delivery systems therefore have a tendency to release their drug load prior to reaching the colon. To overcome the problem of premature drug release, a copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate (Eudragit® FS), which dissolves at a slower rate and at a higher threshold pH (7–7.5), has been developed recently. A series of in vitro dissolution studies with einter and intrasubject variability in gastrointestinal pH and possibly certain other intrinsic variables such as electrolyte concentration and transit time will therefore impact on the in vivo behaviour of pH-responsive systems, ranging from early drug release in the small intestine to no release at all, with the formulation passing through the gut intact. The latter situation will also arise when the pH of the colon, and possibly the small intestine, is considerably lower than normal, as is the case in patients with ulcerative colitis. In spite oftheir limitations, pH-sensitive delivery systems are commercially available for mesalazine (5-aminosalicylic acid) (Asacol® and Salofalk®) and budesonide (Budenofalk® and Entocort®) for the treatment of ulcerative colitis and Crohn’s disease.
2. Time-Dependent Systems: ⁵,⁸,⁵³

Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that the patient receives the drug when needed or at a pre-selected site of the GIT. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms. Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time-based. In these systems, the site of drug release is decided by the transit time of a formulation in the GIT, which makes it challenging to develop a formulation in order to achieve a precise drug release in the colon. The formulations are designed such that the site of delivery is not affected by the individual differences in the gastric emptying time, pH of the stomach and small intestine or presence of anaerobic bacteria in the colon. An orally administered dosage form takes about 3 hrs to travel through the length of the small intestine to the beginning of the colon. Compared to gastric emptying rate, the small intestinal transit time is relatively consistent. A system in the form of a tablet formulation, which could release the drug consistently in the colon via a time-dependent explosion mechanism. The formulation is comprised of three parts: (i) a central core containing the drug and swelling excipients (ii) an inner semi-permeable polymer membrane containing a plasticizer which allows water influx but prevents the outward diffusion of drug and (iii) an outer enteric-coating which dissolves at or above pH 5.5. The outer enteric coat keeps the tablet intact until it reaches the small intestine. Upon arrival in the small intestine, the enteric coat dissolves allowing for GI fluid to diffuse through the semipermeable membrane into the core. The core swells during the transit of the tablet through the small intestine. Finally, after a consistent period of 4-6 h transit in the small intestine, the swollen core bursts the semi-permeable membrane releasing the drug in the colon.

![Time-controlled capsule for colonic delivery](image)

Fig 2: Time-controlled capsule for colonic delivery. ³,⁵
3. Pressure – dependent delivery: Gastrointestinal pressure has also been utilised to trigger drug release in the distal gut. This pressure, which is generated via muscular contractions of the gut wall for grinding and propulsion of intestinal contents, varies in intensity and duration throughout the gastrointestinal tract, with the colon considered to have a higher lumenal pressure due to the processes that occur during stool formation. Systems have therefore been developed to resist the pressures of the upper gastrointestinal tract but rupture in response to the raised pressure of the colon. Capsule shells fabricated from the water-insoluble polymer ethylcellulose have been used for this purpose. The system can be modified to withstand and rupture at different pressures by changing the size of the capsule and thickness of the capsule shell wall. Proof of concept studies have been conducted in dogs and, to a limited extent, in humans. Although the results appear promising, it has not been proven definitively that rupture occurs in the colon. One must also question the influence of co-administered food on performance, as fed state contractions may be sufficiently powerful to disintegrate the capsule in the stomach.

4. Bacteria – dependent delivery: The resident gastrointestinal bacteria provide a further means of effecting drug release in the colon. These bacteria predominantly colonise the distal regions of the gastrointestinal tract where the bacterial count in the colon is 10^{11} per gramme, as compared with 10^{4} per gramme in the upper small intestine. Moreover, 400 different species are present. Colonic bacteria are predominantly anaerobic in nature and produce enzymes that are capable of metabolising endogenous and exogenous substrates, such as carbohydrates and proteins that escape digestion in the upper gastrointestinal tract. Therefore, materials that are recalcitrant to the conditions of the stomach and small intestine, the susceptible to degradation by bacterial enzymes within the colon, can be utilized as carriers for drug delivery to the colon. This principle has been exploited commercially to deliver 5-aminosalicylic acid to the colon by way of a prodrug carrier. The prodrug sulphasalazine consists of two separate moieties, sulphapyridine and 5-aminosalicylic acid, linked by an azo-bond. The prodrug passes through the upper gut intact, but once in the colon, the azo-bond is cleaved by the host bacteria, liberating the carrier molecule sulphapyridine and the pharmacologically active agent 5-aminosalicylic acid. This concept has led to the development of novel azo-bond-based polymers (azo-polymers) for the purpose of obtaining universal carrier systems. However, issues with regard to the safety and toxicity of these synthetic polymers have yet to be addressed. To overcome such concerns, natural materials, essentially those that are polysaccharide-based, offer a viable alternative to the problem. Such potential materials include amylose, chitosan, chondroitin sulphate, dextran, guar gum, inulin and pectin.
They are hydrophilic in nature, which renders them either soluble or prone to swelling in an aqueous environment and hence unsuitable as drug carriers. To fully realise the potential of these polysaccharides for colonic delivery, some form of structure modification and/or formulation strategy is required. In the case of pectin, e.g., a highly methoxylated and poorly water-soluble derivative has been utilized in the form of a relatively thick compression coating on tablets. On testing in human volunteers, the coated tablets remained intact in the stomach and small intestine, but disintegrated on reaching the colon. Pectin, in the form of calcium pectinate, has also been used in the form of a matrix for colonic delivery. Although the relatively open structure of such systems renders them liable to drug release prior to colonic arrival. Colon specificity has also been achieved using a delivery system based on the polysaccharide amylose (COLAL™). Amylose is one of the two major components of starch, the other being amylpectin. In comparison with other polysaccharides, amylase and amylpectin are degraded by a broader range of colonic bacteria. While, amylpectin is metabolised by pancreatic enzymes in the small intestine, amylose, in its glassy amorphous state, is resistant, but, at the same time, susceptible to digestion by amylaseproducing bacteria residing within the colon. This material, in combination with the water-insoluble polymer ethylcellulose, which is necessary to control the swelling of amylose, has been exploited as a film coating. After application to solid dosage forms, these film coatings have been shown to withstand simulated gastric and small intestinal conditions and allow drug release specifically within a colonic environment. A number of gamma scintigraphic studies have provided confirmatory evidence for the targeting performance of the COLAL™ delivery system in humans. Moreover, the system has come through a Phase II study successfully in which the anti-inflammatory agent prednisolone metasulphobenzoate was delivered to the colon of patients with active ulcerative colitis, thereby providing proof of concept data in diseased subjects.

B. Primary Approaches for CDDS:

a. pH Sensitive Polymer Coated Drug Delivery to the Colon:

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although, a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor. The decline in pH from the end
of the small intestine to the colon can also result in problems, lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.

b. Time Controlled Release System Release Drug Delivery to Colon:
Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonic availability. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h.

The disadvantages of this system are:
i. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
ii. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
iii. Accelerated transit through different regions of the colon has been observed in patients with 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. The time-release function should work more efficiently in the small intestine as compared to the stomach. In the small intestine drug carrier will be delivered to the target side and drug release will begin at a predetermined time point after gastric emptying. On the other hand in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time.

c. Microbially Triggered Drug Delivery to Colon:
The microflora of the colon is in the range of 1011 - 1012 CFU/mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus, etc. This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc. For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches. These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by
micro-organism, or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer.

(i) Prodrug Approach for Drug Delivery to Colon

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 up on oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.

(ii) Azo-Polymeric Prodrugs

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. 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 S.

Fig 3: Hydrolysis of Sulphasalazine.21
C. New Approaches for CDDS:

a. Pressure Controlled Drug-Delivery Systems:8,36

Higher pressures are encountered in the colon than in the small intestine. In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure controlled ethylcellulose 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 humans.

b. Novel Colon Targeted Delivery System (CODESTM):8

CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems.47,48 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, (Fig. 2). The system consists of a traditional tablet core containing lactulose, which is over coated with an 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

Fig 4: Schematics of the conceptual design of CODES.8
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 effect the dissolution of the acid soluble coating and subsequent drug release.

![Diagram](https://example.com/diagram.png)

**Fig 5:** Schematics of Conceptual Design Of CODESTM.5,8

c. Osmotic controlled drug delivery:5,27,36

The OROS-CT system 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®S 100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at pH≤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.

EVALUATION:\[5,8,21\]

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 standardized 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, eg. 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

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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.

**In vitro enzymatic test:**

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 glucuronidase 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 tullel 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.

**Platform Technologies for CTDDS:**

1. PULSINCAP.
2. OROS-CT.
3. CODESTM.
4. PORT® SYSTEM.
5. TIME CLOCK® SYSTEM.
CONCLUSION

The colonic region of the gastrointestinal tract has become an increasingly important site for drug delivery and absorption. Targeted drug delivery would offer considerable therapeutic benefits to patients, in terms of both local and systemic treatment. Systems that rely on gastrointestinal pH, transit times or pressure for release are unlikely to function as reliable and effective colon-specific delivery vehicles. Colon specificity is more likely to be achieved with systems that utilise natural materials that are degraded by bacterial enzymes of colonic origin. Moreover, the cost and ease of manufacture of the delivery system are further considerations that will impact on its likely commercialisation and hence, availability to patients. A bacteria-sensitive natural film coating that can be applied to a range of solid oral dosage forms using conventional processing technology would therefore appear to be the delivery system of choice.

Future developments:

Currently, there are several MR solid formulation technologies available for colonic delivery. These technologies rely on GI pH, transit times, enterobacteria and luminal pressure for site-specific delivery. Each of these technologies represents a unique system in terms of design but has certain shortcomings, which are often related to degree of site-specificity, toxicity, cost and ease of scale up manufacturing. It appears that microbially-controlled systems based on natural polymers have the greatest potential for colonic delivery, particularly in terms of site specificity and safety. In this, formulations that employ a film coating system based on the combination of a polysaccharide and a suitable film forming polymer represents a significant technological advancement. Further developments in this area require means to improve the coprocessing of the polymeric blend of a polysaccharide(s) and a film forming material. While, maintaining the propensity of the composition to microbial degradation in the colon.

Earlier research indicates interest in colon 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 drugs with low bioavailability because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for oral delivery of drug in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for delivery of drugs like peptides, proteins, oligonucleotides and vaccines. Therefore, more research has been focused on the specificity of drug uptake at the colon site. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

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