Primary and novel approaches for colon targeted drug delivery – A review

Gaurav Tiwari1*, Ruchi Tiwari1, Pranay Wal1, Ankita Wal1, Awani K. Rai1

Abstract

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery could, for example, allow topical treatment of inflammatory bowel disease. Treatment could be made more effective if it were possible for drugs to be targeted directly on the colon. Systemic side effects could also be reduced. Colon specific systems might also allow oral administration of peptide and protein drugs, which are normally inactivated in the upper parts of the gastrointestinal tract. Primary approaches for CDDS (Colon Specific Drug Delivery), which includes prodrugs, pH and time dependent systems and microbially triggered drug delivery system achieved limited success and having limitations. Newly developed CDDS, which includes pressure controlled colonic delivery capsules (PCDCS), CODESTM and osmotic controlled drug delivery are unique in terms of achieving in vivo site specificity and feasibility of manufacturing process. This review also focuses on evaluations of CDDS in general.

Keywords: Colon drug delivery systems; Primary approaches; Newly developed approaches; evaluation of colon targeted drug delivery systems

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].

Oral route is most convenient and preferred route [5] but other routes for CDDS may also be used. Rectal administration offers the shortest route to targeting...
drugs on the colon. However, reaching the proximal part of the colon via rectal administration is difficult. Rectal administration can also be uncomfortable for the patient 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 locally active drug to the large intestine [7]. 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 topical application. The concentration of drug reaching the colon will depend on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to remain mainly in the rectum and sigmoid colon enema solutions have a great spreading capacity. Because of the high water absorption capacity of colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to $10^{10}$ bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules like insulin by oral administration. (Chein) Colonic diseases, drugs and target sides are given in table 1.

**Advantages of CDDS**

Chronic Colitis e.g. ulcerative colitis and crohan’s disease is currently treated with glucocorticoids and another anti-inflammatory agent. Administration of glucocorticoids e.g. Dexamethasone and methyl prednisolone by the oral and i.v. routes produces systemic side effects including adenosuppression, immunosuppression, Cushinoid symptoms and bone resorption. Thus the selective delivery of drug to colon could lower the required dose and hence reduce the systemic side effects [8]. The system has the advantage of more effective therapy a reduced dose and reduced undesirable side effects often associated with high doses [9].

### Table 1. Colon targeting Diseases, Drugs and Sites

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

### Criteria for selection of drug for CDDS

**Drug Candidate**

Drugs which show poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea and colon cancer are ideal candidates for local colon delivery [10]. Criteria for selection drugs for CDDS are summarized in table 2.

**Drug Carrier**

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug and the type of
Table 2. Criteria for selection of drugs for CDDS

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Pharmacological class</th>
<th>Non-peptide drugs</th>
<th>Peptide drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs used for local effects in colon against GIT diseases</td>
<td>Anti-inflammatory drugs</td>
<td>Oxyrenolol, Metoprolol, Nifedipine</td>
<td>Amylin, Antisense oligonucleotide</td>
</tr>
<tr>
<td>Drugs poorly absorbed from upper GIT</td>
<td>Antihypertensive and Antianginal drugs</td>
<td>Ibuprofen, Isosorbides, Theophylline, Doxurubicin</td>
<td>Cyclosporine, Desmopressin</td>
</tr>
<tr>
<td>Drugs for colon cancer</td>
<td>Antineoplastic drugs</td>
<td>Pseudoephedrine</td>
<td>Epoetin, Glucagon</td>
</tr>
<tr>
<td>Drugs that degrade in stomach and small intestine</td>
<td>Peptides and Proteins</td>
<td>Bromophenaramine, Flourouracil, Doxurubicin</td>
<td>Gonadoreline, Insulin, Interferons</td>
</tr>
<tr>
<td>Drugs that undergo extensive first pass metabolism</td>
<td>Nitroglycerin and Corticosteroids</td>
<td>Bleomycin, Nicotine</td>
<td>Protirelin, Sermorelin, Saloatonin</td>
</tr>
<tr>
<td>Drugs for targeting</td>
<td>Antiarthritic and Antiasthamatic drugs</td>
<td>Prednisolone, Hydrocortisone, 5-Amino-salicylic acid</td>
<td>Somatropin, Urotoilitin</td>
</tr>
</tbody>
</table>

absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule [11]. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems [12].

**Approaches used for site specific drug delivery to Colon (CDDS)**

Approaches used for site-specific drug delivery are:

[A] Primary approaches for CDDS [10]

a. pH sensitive polymer coated drug delivery to colon
b. Delayed (Time controlled release system) release drug delivery to colon
c. Microbially triggered drug delivery to colon

(i) Prodrug approach for drug delivery to colon
(ii) Azo-polymeric approach for drug delivery to colon
(iii) Polysaccharide based approach for drug delivery to colon

[B] Newly developed approaches for CDDS [8]

a. Pressure controlled drug delivery system (PCDCS)
b. CODESTM (A Novel colon targeted delivery system)
c. Osmotic controlled drug delivery to colon (OROS-CT)

[A] Primary Approaches for CDDS

a) pH sensitive polymer coated drug delivery to colon

In the stomach pH ranges between 1 and 2 during fasting but increases after eating [13]. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine [11]. From the ileum to the colon pH declines significantly. It is about 6.4 in the ceacum. However, pH values as low as 5.7 have been measured
in the ascending colon in healthy volunteers [9] The pH in the transverse colon is 6.6, in the descending colon 7.0. 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 even in the lower small intestine, and the site-specificity of formulations can be poor [12]. 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 can also result in poor site-specificity of enteric-coated single-unit formulations [11].

b) Delayed (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. However due to potentially large variation of gastric emptying time of dosage forms in humans [13], in this approach colon arrival time of dosage forms can not accurately predicted, resulting in poor colonical availability. The dosage forms may also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5 hours (range 5 to 6 hours), [14]. 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 [10]. (iii) Accelerated transit through different regions of the colon has been observed in patients with the IBD, [15], the carcinoid syndrome and diarrhea and the ulcerative colitis [16]. Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. That is since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hour [14]. The time-release function (or timer function) should work more efficiently in the small intestine as compared 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 [10].

Enteric-coated time-release press coated (ETP) tablets

ETP tablets are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer, time release function) and an enteric coating layer (acid resistance function), [17]. Tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins slowly erode the press coated polymer (HPC) layer and when the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time there is no drug release period (lag phase) after gastric emptying. The duration of lag phase controlled either by the weight or composition of the polymer (HPC) layer [18] Figure 1.

c) Microbially triggered drug delivery to colon

The microflora of colon is in the range of $10^{11} - 10^{12}$ CFU/mL [15], 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 [17]. For this fermentation the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase,
deaminase, and urea dehydroxylase [13]. 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 [12]. 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-organisms or degradation by enzyme or break down of the polymer backbone 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 [18].

Table 3. Prodrugs evaluated for colon specific drug delivery

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Drug investigated</th>
<th>Linkage hydrolysed</th>
<th>In vitro / in vivo model used</th>
<th>Performance of the Prodrug / conjugates</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azo conjugates</td>
<td>5-ASA</td>
<td>Azo linkage</td>
<td>Human</td>
<td>Site specific with a lot of side effects associated with SP</td>
<td>Khan et al., 1977</td>
</tr>
<tr>
<td>Suphapyridine (SP)</td>
<td>5-ASA</td>
<td>Azo linkage</td>
<td>Human</td>
<td>Delivers 2 molecules of 5-ASA as compared to sulphasalazine</td>
<td>Chan et al., 1983</td>
</tr>
<tr>
<td>Amino acid conjugates</td>
<td>Salicylic acid</td>
<td>Amide linkage</td>
<td>Rabbit</td>
<td>Absorbed from upper GIT, though metabolized by microflora of large intestine</td>
<td>Shibasaki et al., 1985</td>
</tr>
<tr>
<td>glycine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrosine/methionine</td>
<td>Salicylic acid</td>
<td>Amide linkage</td>
<td>Rabbit</td>
<td>Absorbed from upper GIT, though metabolized by microflora of large intestine</td>
<td>Nakamura et al., 1992a</td>
</tr>
<tr>
<td>L – Alanin/D-Alanine</td>
<td>Salicylic acid</td>
<td>Amid linkage</td>
<td>In vitro</td>
<td>Salicylic acid-l-alanine was hydrolysed to salicylic acid by intestinal microorganism but salicylic acid-D-alanine showed negligible hydrolysis thereby showing enantiospecific hydrolysis</td>
<td>Nakamura et al., 1992b</td>
</tr>
<tr>
<td>Glycine</td>
<td>5-ASA</td>
<td>Amid linkage</td>
<td>In vitro</td>
<td>Prodrug was stable in upper GIT and was hydrolysed by cecal content to release 5-ASA</td>
<td>Jung et al., 1998</td>
</tr>
<tr>
<td>Saccharide carriers</td>
<td>Dexamethasone</td>
<td>Glycosidic linkage</td>
<td>Rat</td>
<td>Dexamethasone prodrug was site specific and 60% of oral dose reached the cecum. Only 15% of prednisolone prodrug reached the cecum.</td>
<td>Friend et al, 1984</td>
</tr>
</tbody>
</table>

(i) Prodrug approach for drug delivery to colon

Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery the prodrug are designed to undergo minimal absorption and hydrolysis in the tracts of upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the drug carrier. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes [19]. A number of other linkages susceptible to bacterial hydrolysis especially in the colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose etc. Limitations of prodrug approach is that it is not
very versatile approach as it’s formulation depends upon the functional group available on the drug moiety for chemical linkage. Further more prodrugs are new chemical entities and need a lot of evaluation before being used as carriers [20]. A number of prodrugs have been outlined in table 3.

(ii) Azo-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 been used to form polymeric prodrug with azo linkage between the polymer and drug moiety [21]. These have been evaluated for CDDS, various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreductase in the large bowel. Coating of peptide capsules with polymers cross linked with azaaromatic group has been found to protect drug from digestion in the stomach and small intestine. In the colon the azo bonds are reduced and the drug is released [22]. A number of azo-polymeric prodrugs have been outlined in table 4.

Table 4. Some Azo polymer-based drug delivery systems evaluated for colon-specific drug delivery with summary of results obtained.

<table>
<thead>
<tr>
<th>Azo polymer</th>
<th>Osage from prepared</th>
<th>Drug investigated</th>
<th>In vitro/in vivo model used</th>
<th>Summary of the results obtained</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copolymers of styrene with 2-hydroxyethyl methacrylate</td>
<td>Coating over capsules</td>
<td>Vasopressin insulin</td>
<td>Rats dogs</td>
<td>These capsules showed biological response characteristics of these peptide hormones in dog though it varied quantitatively.</td>
<td>Saffron et al., 1986, 1988, 1991</td>
</tr>
<tr>
<td>Hydrogels prepared by copolymerization of 2-hydroxyethyl methacrylate with 4-methacryloyloxy) azobenzene</td>
<td>Hydrogen</td>
<td>5-fluorouracil</td>
<td>In vitro</td>
<td>Drug release was faster and greater in human fecal media compared to simulated gastric and intestinal fluids</td>
<td>Shanta et al., 1995</td>
</tr>
<tr>
<td>Segmented polynurethanes</td>
<td>Coating over pellets</td>
<td>Budesonide</td>
<td>Rat</td>
<td>These azopolymer-coated pellets were useful for colon-specific delivery of budesonide to bring healing in induced colitis.</td>
<td>Tozaki et al., 1999</td>
</tr>
<tr>
<td>Aromatic azo bond containing urethane analogues</td>
<td>Degradable films</td>
<td>5-ASA</td>
<td>In vitro degradation of films in presence of lactobacillus</td>
<td>These films were degraded by azoreductase. The permeability of 5-ASA from lactobacillus treated films was significantly higher than that of control</td>
<td>Chavan et al., 2001</td>
</tr>
</tbody>
</table>

(iii) Polysaccharide based delivery systems

Use of naturally occurring polysaccharides is attracting lot of attention for drug targeting to the colon since these polymers of monosaccharides are found in abundance, have wide availability are inexpensive and are available in a variety of structures with varied properties [23]. They can be easily modified chemically and biochemically and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin) animal (chitosan, chondroitin sulphate)
algal (alginites) or microbial (dextran) origin. These are broken down by the colonic microflora to simple saccharides [24]. So these fall into the category of “generally regarded as safe” (GRAS). A number of polysaccharides based delivery systems have been outlined in table 5.

Table 5. Polysaccharides investigated for colon specific drug delivery

<table>
<thead>
<tr>
<th>Polysaccharide investigated</th>
<th>Drug moiety used</th>
<th>Dosage form prepared</th>
<th>In vitro/ in vivo model used</th>
<th>Performance of the system</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan</td>
<td>5-(6) carboxy fluorescein (CF)</td>
<td>Enteric-coated chitosan capsules</td>
<td>In vitro</td>
<td>Little release of CF in upper GIT conditions and 100% drug release in 33% cecal contents within 4 h of dissolution.</td>
<td>Tozaki et al., 1997</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>Enteric-coated chitosan capsules</td>
<td>Rat</td>
<td>Chitosan capsules carried the drug to the colon. Improvement in insulin absorption seen by co-administration of absorption enhancers</td>
<td>Tozaki et al., 1997</td>
</tr>
<tr>
<td>Derivatives</td>
<td>Sodium diclofenace</td>
<td>As matrices</td>
<td>In vitro</td>
<td>Reduced drug release was seen in acidic conditions and improved dissolutions under basic conditions</td>
<td>Aiedeh et al, 1999</td>
</tr>
<tr>
<td>Chitosan succinate</td>
<td>Sodium diclofenace</td>
<td>As matrices</td>
<td>In vitro</td>
<td>In the presence of rat cecal content drug release was 60.8±15.7% as compared to 4.9±1.1% in control.</td>
<td>Rubinstein et al, 1993</td>
</tr>
<tr>
<td>Chitosan phthalate.</td>
<td>Insulin</td>
<td>Compression coated / matrix tablets</td>
<td>In vivo</td>
<td>In the in vivo studies neither of the two types of the tablets could resist an initial leak of the insulin from the tablet and it was suggested that additional protection was required for colon drug delivery.</td>
<td>Rubinstein et al, 1995</td>
</tr>
<tr>
<td>Pectin (used as calcium salt)</td>
<td>Indomethacin</td>
<td>Matrices</td>
<td>In vitro</td>
<td>These matrices were not suitable for drug delivery colon.</td>
<td>Wakerly et al., 1997</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>Compression coated / matrix tablets</td>
<td>In vivo</td>
<td>Amidedated pectin was more susceptible to pectinolytic enzymes as compare to calcium pectinate. Addition of ethyl cellulose increased the tablets strength and dissolution rate coating this formulation with Eudragit L100 reduced drug release in upper GIT conditions without effecting enzyme degradability.</td>
<td>Ahrabi et al., 2000</td>
</tr>
<tr>
<td>Amidedated pectin</td>
<td>Paracetamol</td>
<td>Matrix tablets</td>
<td>In vitro</td>
<td>These matrices were not suitable for drug delivery colon.</td>
<td>Wakerly et al., 1997</td>
</tr>
<tr>
<td>Amidedated pectin / calcium pectinate</td>
<td>Ropivacaine</td>
<td>Matrix tablet with ethyl cellulose as drug matrix additive</td>
<td>In vitro</td>
<td>Amidedated pectin was more susceptible to pectinolytic enzymes as compare to calcium pectinate. Addition of ethyl cellulose increased the tablets strength and dissolution rate coating this formulation with Eudragit L100 reduced drug release in upper GIT conditions without effecting enzyme degradability.</td>
<td>Ahrabi et al., 2000</td>
</tr>
<tr>
<td>Chondroitin sulphate</td>
<td>Indomethacin</td>
<td>Matrix tablet</td>
<td>In vitro</td>
<td>Drug release increases in presence of rat cecal content. Also it was observed that as cross linking increased, drug release decreased</td>
<td>Rubin et al., 1992</td>
</tr>
<tr>
<td>Cross linked chondroitin</td>
<td>Alginates</td>
<td>Double coated swellable beads</td>
<td>In vitro</td>
<td>Drug release increases in presence of rat cecal content. Also it was observed that as cross linking increased, drug release decreased</td>
<td>Rubin et al., 1992</td>
</tr>
</tbody>
</table>

[B] Newly developed approaches for CDDS

a) Pressure-controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. (1995) have developed pressure controlled colon-delivery capsules prepared using an ethylcellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the
ethylcellulose membrane is the most important factor for disintegration of the formulation [25]. 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 human [26].

b) Novel colon targeted delivery system (CODESTM)
CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH-or time –dependent systems. CODESTM is 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 form site specific drug release in the colon. (Figure. 2) the system consists of a traditional tablet core containing lactulose, which is over coated with, and acid soluble material, Eudragit E, and then subsequently over coated 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 passage through the alkaline pH of the small intestine. Once the tablet arrives in the colon the bacteria will 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 (Figure 2) [27].

(c) Osmotic controlled drug delivery (ORDS-CT)
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 [19]. 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 with in a hard gelatin capsule (Figure 3). Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi-permeable 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 enter the small intestine, the coating dissolve 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 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 of colon specific dissolution system. Various in vitro / in vivo evaluation techniques has been developed and proposed to test the performance and stability of CDDS [28].

Figure 2. Schematics of conceptual design of CODESTM.

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

**a) 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 [29]. 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 [25]. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileal segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4 [26].

**b) In vitro enzymatic test**

For this there are 2 tests:

i) 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.

ii) 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 [28].

**In vivo evaluation**

A number of animals such as dogs, guinea pigs, rats and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Eg. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS a novel model has been proposed. In this model the human fetal bowel is transplanted into a subcutaneous 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 [24].

![Figure 3. Cross-section of the OROS-CT colon targeted drug delivery system.](image)

**Drug delivery index (DDI)**

DDI is calculated pharmacokinetic parameters; following single is multiple doses of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery.

**Clinical evaluation of colon-specific drug delivery system**

Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gama scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems [30].

**Conclusion**

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. For colon targeted drug delivery four primary approaches were proposed for CDDS: prodrugs, pH and time dependent systems and micobletriggered drug delivery system. Of these first three approaches is not ideal for CDDS. Novel
approaches developed for CDDS are more specific. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. For in vitro evaluation of a colon-specific drug delivery system, it seems that more than one testing method is necessary to characterize drug release and justify system design rationale. 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


