INTRODUCTION

Targeted drug delivery to the colon is highly desirable for local treatment of 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. Colon targeting is apparently useful for systemic action of protein – peptide drugs such as insulin, calcitonin and metenkaphalin and even for other nonpeptide drugs such as cardiovascular and antiasthmatic agents describes approaches used for colon targeting. The colonic delivery is also beneficial in the systemic absorption of drugs like nifedipine, theophylline, isosorbide, etc. The successful delivery of drugs to the colon via the gastrointestinal tract requires the protection of a drug from being released in stomach and small intestine. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coating or extremely slow releasing matrices.\(^1\) There are various methods or techniques through which colon drug targeting can be achieved for example, formation of prodrug, coating with pH sensitive polymers, designing formulations using polysaccharides, coating with biodegradable polymers, timed released systems, osmotic pressure controlled systems. Coating of the pH – sensitive polymers provides simple approach for colon – specific drug delivery.\(^2\)

ANATOMY AND PHYSIOLOGY OF COLON

The gastrointestinal tract is divided into stomach, small intestine and large intestine. The large intestine extending from ileocecal junction to the anus is divided into three main parts. These are colon, the rectum and anal canal. The entire colon is about 5 feet long and is divided into five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consist of the cecum, ascending colon,
hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The human colon were shown in following figure. The major function of the colon is the creation of suitable environment for the growth of colonic microorganism, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of fluid is absorbed. [4]

- **ADVANTAGES OF COLON TARGETING DRUG DELIVERY SYSTEM**
  1. Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
  2. Local treatment has the advantages of requiring smaller drug quantities
  3. Reduces dosage frequency. Hence lower cost of expensive drugs.
  4. Bypass initial first pass metabolism.
  5. The colon is an attractive site where poorly absorbed drug molecules may have and improved bioavailability.
  6. Improve patient compliance.
  7. Targeted drug delivery system. [1,2,3,4]

**WHY COLON TARGETED DRUG DELIVERY NEEDED**
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.\cite{4,5}

**Criteria for Selection of Drug for CTDDS**

CTDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are prominent for local colon delivery

Drugs used for local effects in colon against GIT diseases
- Drugs poorly absorbed from upper GIT
- Drugs for colon cancer
- Drugs that degrade in stomach and small intestine
- Drugs that undergo extensive first pass metabolism
- Drugs poorly absorbed from upper GIT
- Drugs for targeting.\cite{5,6}

**FACTORS TO BE AFFECTED IN THE DESIGN OF COLON - TARGETED DRUG DELIVERY SYSTEM**

- **Anatomy and Physiology of Colon**
  The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided into five main segments. These are the colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long, and is divided into five major segments. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon and the values were shown in table. The left colon contains the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus.

- **pH in the colon**
  The pH of the GI tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influences the pH of the gastrointestinal fluid. The changes in the pH along the gastrointestinal tract have been used as a means for targeted colon drug delivery. Radio telemetry shows the highest pH (7.5±0.5) in the terminal ileum. On entry into the...
colon, the pH drops to 6.4±0.6. The pH in the mid colon is 6.6±0.8 and in the left colon 7.0±0.7. There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by the colonic bacteria to produce large amounts of lactic acid resulting in pH drop to about 5.0.\cite{7}

- **Colonic Microflora and Enzymes**
  A large number of anaerobic and aerobic bacteria are present in the entire length of the human GI tract. Intestinal enzymes are used to trigger drug release in various parts of the GI tract. Usually, these enzymes are derived from gut micro flora residing in high numbers in the colon. These enzymes are used to degrade coatings or matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug). Over 400 distinct bacterial species have been found 20-30% of which are of the genus bacteroids. The concentration of bacteria in the human colon is around 1000 CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, and Peptostreptococcus, Ruminococcus, Clostridium.

- **Drug absorption in the colon**
  Drugs are absorbed passively by either paracellular or transcellular route. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, where paracellular absorption involves the transport of drug through the tight junction between cells and is the route most hydrophilic drug takes. The poor paracellular absorption of many drugs in the colon is due to the fact that epithelial cell junctions are very tight. The slow rate of transit in colon lets the drug stay in contact with the mucosa for a longer period than in small intestine which compensates the much lower surface area. The colonic contents become more viscous with progressive absorption of water as one travels further through the colon. This causes a reduced dissolution rate, slow diffusion of dissolved drug through the mucosa. Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum. The oral absorption of the majority of peptide and protein drugs is limited because of following reasons: Degradation in the acidic environment of the stomach. Enzymatic degradation in the small and large intestine. Rapid small intestine transit. Low mucosal permeability. Extensive first pass metabolism by the absorbing membrane and the liver.\cite{8,9}
APPROACHES FOR COLONIC DRUG DELIVERY

A. Covalent Linkage of Drug with Carrier

**Prodrug approaches**

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine and after reached in the colon, enzymatic cleavage regenerate the drug.[6]

**Azo bond conjugate:** 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 (S.P). In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier SP.[5]

- **Glycoside conjugation**

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Certain drugs can be conjugated to different sugar moieties to form glycosides. The drug part forms the aglycone and is linked to the sugar part, which forms the glycone part of the glycoside. Because they are bulky and
hydrophilic, these glycosides do not penetrate the biological membranes upon ingestion. They breakdown upon action of glycosidase, releasing the drug part from the sugar. The presence of glycosidase activity in the small intestine could pose a problem in delivery of these conjugates to the large bowel, because some hydrolysis of the conjugate can be expected in the small intestine. However, the small intestinal transit time, when compared to the large intestinal transit time, is short and moreover, considering the time required for the hydrolysis of glycosidic bond, these conjugates can be expected to be good colon specific drug carriers. The major glycosidase enzymes produced by the intestinal microflora are β-D-galactosidase, α-L-arabinofuranosidase, β-D-xylopyranosidase and β-D-glucosidase. These glycosidase enzymes are located at the brush border and hence are accessible to substrate easily. Example: lucosides, galactosides and celllobiosides of dexamethasone, prednisolone, hydrocortisone and fludrocortisone. Dexamethasone-21-β-glucoside, Prednisolone-21-β-glucoside.\[9\]

**Glucoronide conjugates**

Bacteria of the lower GIT secrete β-glucuronidase and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption. Example: Opiates, when taken for the relief of pain, cause severe constipation by inhibiting GIT motility and secretions. Narcotic antagonists, when given as antidotes for GIT side effects, immediately relieve constipation but precipitate acute withdrawal. This is because these narcotic antagonists are not selective and they not only affect the GIT activity, but also the central nervous system (CNS). A novel approach would be to target these antagonists to the lower bowel so that they are not absorbed systemically. With this purpose, naloxone and nalmefene glucuronide prodrugs were prepared to target these drugs to the colon. When given orally to morphine dependent rats these prodrugs showed increased GIT motility and secretion in the large bowel results in a diarrhea and The resultant diarrhea flushed out the drug/prodrug from the colon thereby preventing the systemic absorption of the antagonist, which in-turn caused absence of withdrawal symptoms. Budesonide-β-glucuronide prodrug also found to be superior to budesonide itself for the treatment of colitis in the rat.\[8\]

**Cyclodextrin conjugate**

Cyclodextrins are cyclic oligosaccharides consisted of six to eight glucose units through -1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as
solubility, stability and bioavailability. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules. They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine however, Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextranase activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed. This susceptibility to degradation specifically by colonic micro flora together with their property to form inclusion complexes with various drugs makes them particularly useful in carrying drug moieties to the colon. The α- and β-cyclodextrins are practically resistant to gastric acid, salivary and pancreatic amylases. A clinical study has shown clear evidence that β-cyclodextrin is poorly digested in the small intestine but is almost completely degraded by the colonic microflora.[9]

**Dextran conjugate**

Dextran is a polysaccharide of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolyzed by moulds, bacteria, and mammalian cells. The enzyme responsible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, where as high dextranase activity is shown by anaerobic gram-negative bacteria, especially the Bacteroides, which are present in a concentration as high as 1011 per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon.[22] In the colon, dextran’s glycosidic bonds are hydrolyzed by dextranases to give shorter prodrug oligomers, which are further split by the colonic esterases to release the drug free in the lumen of the colon. Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function (−COOH). NASIDS were directly coupled to dextran by using carboxylic groups of drugs. Example is Naproxen-dextran conjugate. Glucocorticoids do not possess −COOH group so these are linked to dextran using spacer molecule. e.g. glucocorticoid- dextran conjugates.

**Amino acid conjugation:** Due to the hydrophilic nature of polar groups like -NH2 and - COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme.[8]
Polymeric prodrugs: Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Subsynthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety.

**B. Approaches to deliver intact molecule to colon pH dependent approach**

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

The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon. The drug core includes tablets, capsules, pellets, granules, microparticles or nanoparticles. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. The majority of enteric and colon targeted delivery systems are based on the coating of tablets or pellets, which are filled into conventional hard gelatin capsules. The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide and other fermentation products. Moreover, there is considerable difference in inter- and intra-individual gastrointestinal tract pH and this causes a major problem in reproducible drug delivery to the large intestine Eudragit-L dissolves at a pH level above 5.6 and is used for enteric coating, whereas Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0 (attributable to the presence of higher amounts of esterified groups in relation to carboxylic groups), which results in premature drug release from the system. Problem of premature drug release can be overcome by the use of Eudragit FS.[10]

<table>
<thead>
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<th>Table 4. Various pH dependent coating polymers</th>
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<tr>
<td><strong>Polymer</strong></td>
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<tr>
<td>Eudragit L 100</td>
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<tr>
<td>Eudragit S 100</td>
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</table>
Embedding in pH-sensitive matrices
The drug molecules are embedded in the polymer matrix. Extrusion spheronization technique can be used to prepare uniform-size sturdy pellets for colon targeted drug delivery when it is not possible to obtain mechanically strong granules by other methods. Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increased the pellet size and influenced pellet roundness. Citric acid promoted the pelletization process resulting in a narrower area distribution. However, EudragitS100 could not cause statistically significant delay in the drug release at lower pH.[10]

Time dependent delivery
It also known as pulsatile release, delayed or sigmoidal release system. This approach is based on the principle of delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the which release of drug take place. The lag time in this case is the time requires to transit from the mouth to colon. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms.[9]

This system has some disadvantages as follows
- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>pH</th>
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<tbody>
<tr>
<td>Eudragit® L-30D</td>
<td>5.6</td>
</tr>
<tr>
<td>Eudragit® FS 30D</td>
<td>6.8</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose phthalate 50</td>
<td>5.2</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose phthalate 55</td>
<td>5.4</td>
</tr>
<tr>
<td>Cellulose acetate trimellate</td>
<td>4.8</td>
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</tbody>
</table>
Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea and the ulcerative colitis. Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon.

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

**b) Colon-Targeted Delivery Capsule based on pH sensitivity and time-release principles:** The system contains an organic acid that is filled in a hard gelatin capsule as a pH-adjusting agent together with the drug substance. This capsule is then coated with a three-layered film consisting of an acid-soluble layer, a hydrophilic layer and an enteric layer (Figure 6). After ingestion of the capsule, these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid, upon which the enclosed drug is quickly released. Therefore, the onset time of drug release is controlled by the thickness of the acid-soluble layer.[11]

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Evaluation Parameter

- **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:

- **In vitro dissolution test**

Dissolution of controlled-release formulations used for colon- specific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon- specific
formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine and pH 7.2 to simulate the ileal segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. In vitro test for intactness of coatings and carriers in simulated conditions of stomach and intestine Drug release study in 0.1 N HCl for 2 hours (mean gastric emptying time) Drug release study in phosphate buffer for 3 hours (mean small intestine transit time).[15]

- **In vitro enzymatic test: For this there are 2 tests**
  1. Incubate carrier drug system in fermenter containing suitable medium for bacteria (Streptococcus faccium or B.ovatus) amount of drug released at different time intervals determined.
  2. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

- **In Vivo Evaluation**
  A number of animals such as dogs, guinea pigs, rats and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Eg. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS a novel model has been proposed. In this model the human fetal bowel is transplanted into a subcutaneous 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.[13]

- **Clinical Evaluation**
  Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems. High frequency capsule: Smooth plastic capsule containing small latex balloon, drug and radiotracer taken orally. Triggering system is high frequency generator. Release of drug & radiotracer triggered by an impulse, the release is
monitored in different parts of GIT by radiological localization. It checks the absorption properties of drug in colon. □ Gamma scintigraphy: By means of gammascintigraphic imaging, information can be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine and disintegration. Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained. Gammascintigraphic studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphic studies (pharmacoscintigraphy).[7,11,16,17,18]

REFERENCES


