COLON TARGETED DRUG DELIVERY – A REVIEW ON PRIMARY AND NOVEL APPROACHES

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ABSTRACT

Drug targeting through various delivery systems to the colon of the gastrointestinal tract has been topic of research and interest since many years. Need for better treatment of local disorders of colonic region such as inflammatory bowel disease such as ulcerative colitis and Crohn’s disease, irritable bowel syndrome (IBS) and cancer has driven the scientific research. The colon has also been explored for direct entry of drugs in systemic circulation and avoid first pass metabolism. Several different delivery systems have been explored and researched for colon targeting which mostly depend on exploiting at least one of the gastrointestinal features: difference in pH, transit time, intestinal pressure and intestinal microflora. Evaluation of colonic drug delivery is a major task and involves different approaches such in vitro dissolution test, fermentation studies, in vitro enzymatic test, in vivo evaluation test with appropriate animal models.

KEYWORD: Drug targeting with appropriate animal models.

INTRODUCTION

The treatment by most of the conventional drug delivery system remains inadequate because the drugs are not able to reach the site of action in an appropriate concentration.1 Local treatment of bowel diseases such as constipation, diarrhoea, ulcerative colitis, Crohn’s disease, amebiosis or colon carcinoma or even systemic delivery of proteins and peptides, colon targeted drug delivery have shown better prospects.1,2 This is expressed by the fact that over past two decades the scientists embraced the challenge to target the drugs to the
colonic part of the gastrointestinal tract (GIT).\textsuperscript{[3-8]} Though some of the disorders are not dangerous, most of them such as colorectal cancer are life threatening and most common cause of death in both women and men.\textsuperscript{[9]}

Some additional advantages of targeting drug delivery in colon includes prevention of side effects of drugs prone to gastric irritation and also minimizing first pass metabolism. However, the drawbacks include individual variations in terms of pH thereby reducing site specificity, altered microflora depending on diet and diseased state and variation in gastric retention time all of which can result in inconsistent drug delivery and subject variations.\textsuperscript{[10]}

**Anatomy and Physiology of Colon and Its Implication For Drug Delivery System**

The GIT is a tubular organ and performs key functions like absorption of nutrients and eliminates wastage by physiological processes such as absorption, secretion, digestion and excretion. The function and morphology of the GIT would provide us the basis to divide it into six distinct portions: mouth, pharynx, oesophagus, stomach, small and large intestine. The large intestine that is approx. 150 cm in length and stretches from ileocaecal junction to anus, is divided into main four regions: colon, caecum, rectum and anal canal. The colon has further subdivisions which include the ascending colon, traverse colon, descending colon and sigmoid regions followed by rectum which is the last anatomic segment before anus. The colonic microbiota plays an important role in fermentation of proteins and polysaccharides, absorption of electrolytes and water and formation, storage and elimination of faecal matter.\textsuperscript{[11,12]}

Generally, the colonic environment is viscous in nature and rapid absorption of water in ascending colon making the contents of distal colon more and more viscous.\textsuperscript{[13,14,15]}

![Figure 1](image_url)
The pH of the GIT is subject to both inter and intra subject variations. Various factors influence the pH of the GIT fluid like diet, food intake and disease state. Changes in the pH along with the GIT have been used to target colonic drug delivery. Radio telemetry shows the highest pH (7.5±0.5) in the terminal ileum. Upon entry into the colon, the pH drops to 6.4±0.6 due to the presence of short chain fatty acids arising from the 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. The pH of the mid colon is 6.6±0.8 and that of left colon is 7.0±0.7.\[16\]

Moreover, a large number of aerobic and anaerobic bacteria are present in the entire length of the human GIT. Over 400 distinct bacterial species have been found and 20 to 30% of which are the genus bacteroids. The concentration of bacteria in the colon of a human is around 1000 CFU/ml. The most important anaerobic bacteria are Bacteroides, Eubacterium, Bifidobacterium, Peptococcus, Ruminococcus, Peptostreptococcus and Clostridium.

Colon as a site of drug delivery has its own limitations such as surface area is significantly smaller than small intestine and a tighter paracellular pathway and elevated levels of efflux transporter PgP(glycoprotein) which limits drug transport across the epithelium.\[17,18,19,20\] However, longer residence time in excess of 24 hours and lower activity of drug metabolizing enzymes in the mucosa of distal bowel do help to overcome some of the constraints of this region.\[21,22\]

Intestinal enzymes are used to trigger drug release in different parts of the GIT. Usually, these enzymes are derived from the gut microflora residing in high numbers in the colon. These enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (i.e. release of a drug from a prodrug).\[23\]

Colon surface mucus is a gel that is highly adhesive, viscoelastic, and thick.\[24\] The mucus traps and removes bacteria, viruses and drug particles. The principal components of mucus are lipids, mucins and mucopolysaccharides. The trapping effects of the mucus may be mediated by electrostatic and/or hydrophobic interactions.\[25\] The viscosity of the mucus network is typically 1000 - 10,000-fold higher than that of water at low shear rates.\[26\] Constant turnover of an adherent layer serves to remove potentially damaging compounds and organisms. Mucus undergoes some changes depending on diseased conditions. In those with Crohn’s Disease, the mucus is thicker than what is commonly observed in healthy
individuals, whereas, in Ulcerative Colitis patients, they mucus layer is abnormally thin and the mucin content of adherent mucus significantly decrease. Biochemical abnormalities in mucins such as variations in protein length and extent of glycosylation have been observed in the patients with Inflammatory bowel disease which may result in decrease in the viscosity and binding property of mucus, which facilitates the mucus penetration of drug formulations. TFF3 peptide, secreted by goblet cells, protects the epithelium. However, biochemical modifications to mucins may impair the ability of such proteins to interact with TFF3 and may further decrease the protective ability of the mucosa.

**Rational For Cdds**

The challenge of targeting drugs to the colonic region of the GIT is one that has been accepted by scientists over the past two decades. Work in this area has been driven to improve the treatment of pathologies of the colon. These disease states range in severity from constipation and diarrhoea, to irritable bowel syndrome (IBS) and inflammatory bowel disease (like Crohn’s disease and ulcerative colitis), through to infection and colon carcinoma. While some of these disorders are fairly harmless, the majority of them are debilitating and life threatening disorders. For example, colorectal cancer is the third most common cause of form a cancer related death in both men and women. Current pharmacotherapy for colonic disorders is generally inefficient, requiring the need for surgical intervention in some patients. While the introduction of new therapeutic agents would no doubt improve therapy, there is much that can be done from the perspective of drug delivery. The targeting of drugs specifically to the colon using new and improved delivery strategies would provide significant clinical benefits. This would ensure direct treatment at the disease site and a possible reduction in the administered dose and associated systemic adverse effects.

Additional interest to target the colon has stemmed from the potential of this region as a site for the entry of drugs into the systemic circulation. Compared with the stomach and small intestine, the colon is believed to contain lower levels of luminal and mucosal digestive enzymes. Molecules that are degraded and/or poorly absorbed in the upper gut, such as proteins and peptides, could therefore be bioavailable via the colon. Moreover, drug delivery to the colon could be beneficial when an intentional time delay in absorption is required for the treatment of diseases that are sensitive to circadian rhythms (chronotherapy) such as asthma, angina pectoris or arthritis or administration of protein-based drugs such as insulin and calcitonin and arthritis.
Various Colonic Diseases\textsuperscript{[34]}

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
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<tr>
<td>Inflammatory bowel disease (IBD)</td>
<td>Chronic inflammatory disease of the GIT; characterized by a granulomatous inflammation affecting any part of the tract, normally form fistulae.</td>
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<tr>
<td>Ulcerative colitis</td>
<td>Chronic inflammatory disorder of colon which is limited to the large intestine as against the case with Crohn's Disease where any part of the alimentary tract may be involved. The condition usually results in the form of inflammation of the rectum extending further-up to colon. The inflammation may be restricted to the left-hand side of the colon or extend to entire colon.</td>
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<tr>
<td>Colonic Cancer</td>
<td>The large intestine may show benign tumours called polyps and malignant tumours called cancers. They are not life -threatening as they do not spread to other parts of the body and can be easily removed during colonoscopy. However, if not removed, then they may become cancerous over period of time.</td>
</tr>
<tr>
<td>Polyps</td>
<td>Spread of colon cancer to distant organs, the occurrence of metastasis makes complete cure of cancer unlikely.</td>
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Factors Affecting on Cdds\textsuperscript{[37]}

<table>
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<tr>
<th>Physiological factors</th>
<th>Pharmaceutical factors</th>
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<tr>
<td>Gastric emptying</td>
<td>Drug candidate</td>
</tr>
<tr>
<td>pH of colon</td>
<td>Drug carrier</td>
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<tr>
<td>Colonic microflora and enzymes</td>
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Advantages and Disadvantages of Cdds\textsuperscript{[37]}

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, Crohn’s disease etc.)</td>
<td>Difficult to access colon.</td>
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<tr>
<td>Provides suitable environment for the peptides and the proteins that are sensitive to GIT fluid and digestive enzymes.</td>
<td>Successful delivery requires that the drug to be in solution before it arrives at the colon, but the fluid content of the colon is lower and more viscous than in upper GIT, which is the limiting factor especially for the poorly soluble drugs.</td>
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<tr>
<td>Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.</td>
<td>Lower surface area and relative tightness of the tight junctions in the colon can restrict the transport of the drug across the mucosa in to the systemic circulation</td>
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<td>Minimizing extensive first pass metabolism of steroids.</td>
<td>Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.</td>
</tr>
<tr>
<td>Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, Crohn’s disease, etc.</td>
<td>Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, mucus or fecal matter</td>
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<tr>
<td>Prevents gastric irritation that results due to the administration of various NSAIDs.</td>
<td>Multiple manufacturing steps. The resident microflora could also affect colonic performance via metabolic degradation of the drug</td>
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Selection of Drug and Carrier For Cdds\textsuperscript{[36]}

**Drug Candidate**

Drug that shows poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drugs used in the treatment of IBD, diarrhoea, ulcerative colitis and colon cancer are ideal candidates for local colon delivery.

**Drug Carrier**

The selection of carrier for the particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Various factors such as chemical nature, stability and partition co-efficient of the drug and the type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule\textsuperscript{[19]}, for example, aniline or nitro groups on a drug may be used to link it with the 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.

**Various Approaches To Cdds\textsuperscript{[20]}**

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<tr>
<th>Approach</th>
<th>Comment</th>
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<td>pH-based systems</td>
<td>In the stomach, pH ranges between 1 and 2 during fasting, but increases after eating. The pH is of about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. The pH declines significantly from the ileum to the colon. It is of 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 of about 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in the levels of pH. The polymers described as pH dependent in colon specific drug delivery are generally insoluble at lower pH levels but become increasingly soluble at higher pH. 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. Application of polymers (e.g. Acrylic polymers from the Eudragit\textsuperset{®}) with pH-dependent solubility properties that dissolve in the elevated pH conditions of the distal gut pH is higher in the distal small intestine than in the colon hence potential for premature drug release. The pH of colon is significantly lower in patients with inflammatory bowel disease, hence potential for incomplete drug release. Unreliable mechanism of release; however, products for the treatment of inflammatory bowel disease are commercially available (e.g. of Asacol. Asacol HD, Salofac\textsuperset{[34]}, Claversal\textsuperset{[34]} &amp; Entocort\textsuperset{[34]})</td>
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<tr>
<td>Time Based System</td>
<td>Time controlled release system (TCRS) such as delayed or sustained</td>
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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, colon arrival time of dosage forms cannot be accurately predicted, results in poor colon availability. Drug release is initiated after a predetermined lag time, which is assumed to be equivalent to the colonic arrival time. A nominal lag time of 5 or 6 hours is usually incorporated into the system on the belief that this is the time for the dosage form to reach the colon. Example of this type of drug delivery system. Somehow complex in design (e.g Pulsincap™), the device consists of an impermeable capsule sealed at one end with a hydrogel plug. The variability in gastric emptying and small intestinal transit times in healthy volunteers and patients with GIT disease limits the importance and usefulness of this approach. Transit is also influenced by circadian rhythms.

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<th>Pressure-based System</th>
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<td>Rupture of dosage forms in response to the raised luminal pressure in the distal gut. Pressure-controlled colon delivery capsule (PCDC) is composed of a drug, dispersed in a suppository base which is coated with the water-insoluble polymer ethylcellulose. When swallowed, the temperature of the body causes the suppository base to melt and increase in volume and the system resembles a liquid filled ethylcellulose balloon. The system is able to withstand the luminal pressures of the stomach and small intestine resulting from muscular contraction of the gut wall, since there is sufficient fluid present in the lumen to dissipate this pressure. Limited data on luminal pressures in various regions of the human GIT. Influence of gastrointestinal disease on product performance yet to be established. Potential issues with the ease and cost of manufacture of the systems.</td>
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<th>Microflora-based system</th>
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<td>Colonic bacteria are predominantly anaerobic in nature and secrete enzymes that are capable of metabolising endogenous and exogenous substrates such as carbohydrates and proteins, which escape digestion in the upper GIT. Such materials that are susceptible to bacterial fermentation in the colon, while remaining unchanged to the conditions in the stomach and small intestine, could therefore be utilised as carriers for drug delivery to the colon. The distal gut is populated with substantial numbers of bacteria that secrete a diverse array of enzymes. Two concepts have been proposed: Prodrugs: There is an enzymatic cleavage of the bond between the drug and the carrier moiety (e.g. colonic delivery was sulfasalazine) The prodrug approach provides site specificity. Marketed products for the treatment of inflammatory bowel disease are commercially available. However, a prodrug is considered a new chemical entity from a regulatory perspective. Universal systems: fermentation of starch and non starch polysaccharides in the form of a film coating or matrix (e.g. CODEST™) The universal approach extends the utility of the prodrug concept by ‘carrying’ any drug to the colon. Some polysaccharides take considerable time to ferment, and there are potential issues with the impact of diet and disease on the microflora population.</td>
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Evaluation of CDDS$^{[35]}$  

> **In-vitro dissolution test**

One of the major tasks to evaluate the colonic drug delivery system *in-vitro* is to develop an appropriate dissolution testing method. A number of alternative or unconventional approaches have been reported to evaluate the performance of colon targeted delivery system *in-vitro*. Conventional basket method was used for dissolution testing of colon delivery systems at different pH buffers for diverse periods of time to simulate the GIT pH and transit time of GIT *in-vivo*. The dissolution study for colon targeted drug delivery is also reported by paddle method reported in the 13th edition of pharmacopeia of Japan. The two fluids of pH 1.2 and 6.8 were reported as dissolution media. The dissolution test can also be performed using continuous-flow apparatus in a pH progression medium at 37$^\circ$C, simulating gastrointestinal conditions. Jean Paul Ramón has reported reciprocating cylinder method (Type 3 USP apparatus) for enteric coated pellet with changing pH. Liquid i.e. simulated gastric fluid for 60 min; followed by 3-6 hrs in simulated intestinal fluid has also been utilized. Jinhe Li et al demonstrated apparatus III (Reciprocating cylinder) as suitable and competent as compare to type II apparatus. Akhgari A. and Sadoghi F. demonstrated USP XXIII dissolution apparatus with simulating condition of gastrointestinal tract in media of pH 1.2 with 0.1 N HCl and, pH 6.5, 6.8, 7.2 with phosphate buffer for time and pH dependent approach. Lee F. Siew, 2003 developed an *in-vitro* dissolution test method with enzyme-based fermentation system and compared with conventional technique with human fecal bacteria and shown potential of system for in vitro assessment.

> **Fermentation studies**

Formulations in which polymers are specially degraded by the enzymes and bacteria present in the colon, the dissolution study is carried out using the rat fecal matter or slurries of human fecal or multi stage culture. Information about coating’s digestibility or permeability within the colonic environment is difficult to obtain by general dissolution testing methodology which is possible by batch culture fermentation system. The rat fecal contents were favoured because of the easy availability of rats and presence of viable count of bacteriodes and bifidobacteria involved in polysaccharide degradation. Anesthetized rats were used for this purpose and there caecal contents were exteriorized for collecting the contents which was further diluted with phosphate buffered saline. The human fresh fecal slurries have also been commonly reported to explore fermentation of non-starch polysaccharides. Fecal bacteria represent the large intestine and hence this is used in dissolution medium. As the ascending
colon is inaccessible the multistage culture system is used. This scheme consists of glass fermentation vessels arranged in series with working volume of 200 ml, and 280 ml, respectively magnetically stirred and kept at 37°C under atmospheric carbon dioxide; pH adjusted at 5.5, 6.2, 6.8, for 1, 2, 3 vessels respectively represents proximal, transverse and distal colon.

- **In-vitro enzymatic test**
  Incubate carrier drug system in fermenter containing suitable medium for bacteria (streptococcus faccium and B. Ovatus). The amount of drug released at different time intervals are determined. Drug release study is done in buffer medium containing enzymes (ezypectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

- **In-vivo evaluation test**
  When the system design is conceived and prototype formulation has acceptable in vitro character, the site specificity of drug release and pharmacokinetics information of the drug delivery system was studied by in vivo studies. Although animal models have obvious advantages in assessing colonic drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems with γ-scintigraphy imaging. Sangalli M.E. et al in their research work have given the in vitro in vivo correlation of colon specific delivery system using human volunteers and antipyrine as a model drug, by testing pharmacokinetic data of the drug and gamma scintigraphic analysis. For, CODESTM CSDDS Gamma scintigraphic studies revealed to achieve target release in the colon despite of the ingestion of food.

**Animal model**
Animal models (Rats58, mice59, pigs43 and dogs14) were reported for colon targeted drug delivery systems. For simulating the human physiological environment of the colon, appropriate animal model selection depends on its approach and design of system. For example, guinea pigs have glycosidase and glucuronidase activities in the colon and digestive anatomy and physiology is similar to that of human, so they are appropriate in evaluating prodrugs containing glucoside and glucuronate conjugated for colonic delivery. Techniques, which are used for monitoring the in-vivo behaviour of colon targeted drug delivery, are string technique, endoscopy, radiotelemetry, roentegenography and gamma scintigraphy.
Drug Delivery Index (DDI) and Clinical Evaluation of Colon-Specific Drug Delivery Systems: DDI is a calculated pharmacokinetic parameter, following single or multiple dose 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. 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.

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