Novel Approaches to Colon Targeted Drug Delivery System: A Review.

Nemade Mahesh S*, Chaudhari Rajesh Y, and Patil Vijay R.

TVES’s HLMC College of Pharmacy, Faizpur, India.

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*For Correspondence
TVES’s HLMC College of
Pharmacy, Faizpur, India.

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ABSTRACT

Targeted drug delivery to the colon is being explored not only for local colonic pathologies, but also for systemic delivery of drugs like proteins and peptides. Local delivery could allow topical treatment of inflammatory bowel disease. Treatment could be made more effective for drugs to be targeted directly on the colon site and systemic side effects could be reduced. Colon specific systems might also allow oral administration of peptide and protein drugs, which are normally degraded in the upper parts of the gastrointestinal tract. The treatment of disorders of the large intestine (colon), such as Colon cancer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) i.e. Ulcerative colitis and Crohn’s disease, Diverticulitis and other colon diseases, where it is necessary to attain a high concentration of active therapeutic agent, may be efficiently achieved by colon specific delivery. This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina, hypertension and arthritis. Primary approaches for colon specific drug delivery (CDDS), which includes prodrugs, pH and time dependent systems and microbially triggered drug delivery systems achieved limited success and having limitations. Newly developed CDDS, which includes pressure controlled colonic delivery capsules (PCDCS) and osmotic controlled drug delivery are unique in terms of achieving in-vivo site specificity and feasibility of manufacturing process. The focus of this review is to provide detailed insight into the various colon diseases, approaches used to target the therapeutic agents specifically to the colon.

INTRODUCTION

Oral route is the most preferred route for drug administration, especially for chronic therapies where repeated administration is required. The oral route is not amenable to the administration of drug for lower gastrointestinal (GI) diseases due to their release at upper GI tract, which leads to their limited availability at the lower GI tract. To overcome this obstacle, new strategies of drug delivery have been developed. Among them, colon specific drug delivery systems have been extensively explored. Different delivery vehicles from synthetic as well as natural polymers have been exploited for colon specific drug delivery. However, the design of oral drug delivery vehicles that effectively carry drugs to the colon site is challenging as it requires fulfilling the criteria like a) they need to remain intact when traveling through the upper GI tract in order to prevent the release as well as chemical and enzymatic degradation of the incorporated drug. b) they should be able to release the incorporated drugs immediately upon arriving in the colonic region. The efficiency of these formulations is estimated by the difference between the drug released at the colon site and the initial dosage of the drug. The smaller in this difference, the better will be the delivery system [1].

The colon is a site where both local and systemic drug delivery can take place. A local means of drug delivery could allow topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn’s disease. The treatment might be more effective if the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and systemic side effects might be reduced. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted on the colon [2] (Table No.1.). Site specific means of drug delivery to colon could also allow oral administration of peptide and protein drugs, which normally become degraded in the upper parts of the gastrointestinal tract, for
example vaccines, insulin and growth hormone. However, the permeability of the epithelium of the colon to peptide and protein drugs is fairly poor and bioavailabilities are usually very low\(^3\)\(^,\)\(^4\)\(^,\)\(^5\).

Colon specific systems could also be used in conditions in which a circadian rhythm is evident, e.g. asthma, rheumatic disease, ulcer disease and ischemic heart disease. During the early hours of the morning the incidence of asthmatic attacks is greatest. Because dosage forms remain longer in the large intestine than in the small intestine, colon specific formulations could be used to prolong drug delivery\(^5\).

<table>
<thead>
<tr>
<th>Target Site</th>
<th>Disease Condition</th>
<th>Symptoms</th>
<th>Drugs and Active Agents</th>
<th>Marketed Formulations(^24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Action</td>
<td>Ulcerative Colitis</td>
<td>Fulminant Colitis, Pancolitis, Ulcerative proctitis.</td>
<td>Metasulfobenzoate, Tixocortol pivalate, Fluticasone propionate</td>
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<tr>
<td></td>
<td></td>
<td>Abdominal pain or cramping, bloated feeling, flatulence, diarrhea or constipation people with IBS may also experience alternating bouts of constipation &amp; diarrhea, mucus in stool</td>
<td>Prednisolone, Beclomethasone, Dicyclomine, Hydrocortisone, Propantheline, Cimetropium, Tegaserod</td>
<td>---</td>
</tr>
<tr>
<td>Topical/Local action</td>
<td>Irritable Bowel Syndrome</td>
<td>Abdominal pain or cramping, bloated feeling, flatulence, diarrhea or constipation people with IBS may also experience alternating bouts of constipation &amp; diarrhea, mucus in stool</td>
<td>Mesalamine, Sulfasalazine, Mercaptopurine, Beclomethasone, Propantheline</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Ulcerative Colitis</td>
<td>Inflammation in the rectum, rectal bleeding, rectal pain</td>
<td>Mesalamine, Sulfasalazine, Mercaptopurine, Balsalazide</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Colorectal Cancer</td>
<td>A change in bowel habits, narrow stools, rectal bleeding or blood in stool, persistent abdominal discomfort, such as cramps, gas or pain, abdominal pain with a bowel movement, unexplained weight loss</td>
<td>5-Flourouracil, Leucovorin, Cetuximab</td>
<td>Florac Inj.</td>
</tr>
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<td></td>
<td>Diverticulitis</td>
<td>Formation of pouches (diverticula) on the outside of the colon due to bacterial infection</td>
<td>Metronidazole, Clindamycin</td>
<td>Flygyl Tab.</td>
</tr>
<tr>
<td></td>
<td>Antibiotic Associated Colitis</td>
<td>Overgrowth of Clostridium Difficile and its subsequent Toxin production</td>
<td>Broadspectrum penicillins (e.g., ampicillin, amoxicillin)</td>
<td>Almox Tab.</td>
</tr>
</tbody>
</table>

**Table 1: Drugs used in Colon Associated Disease Conditions\(^2\)**

**Rationale For Colon Targeting**

The challenge of targeting drugs to the colon part of the GI tract has been embraced by scientists over the past two decades\(^6\). The research on colon targeting has been driven primarily by the need to improve the treatment of the colonic pathologies. These disease states range in severity from constipation and diarrhoea, to irritable bowel syndrome, ulcerative colitis and Crohn’s disease, through to infection and colon carcinoma. While some of these disorders are fairly innocuous, the majorities are debilitating and life threatening (e.g. colorectal cancer is the third most common cause of cancer related death in human being)\(^7\).

Generally, surgical intervention is required in some patients as the current pharmacotherapy for colonic disorders is generally inefficient. Hence, the introduction of new therapeutic agents would no doubt improve the current treatment. Furthermore, the new and improved delivery strategies for targeting the drugs specifically to the colon would provide significant clinical benefits. This would ensure direct treatment at the disease site. In addition, there will be a great possibility of reduction in the administered dose and associated systemic adverse effects. These are the benefits that can be obtained from the perspective of colonic drug delivery. Additional interest in colon targeted drug delivery system has generated from the potential of the colonic site for the entry of some drugs into the systemic circulation. The colonic region is believed to contain lower levels of luminal and mucosal digestive enzymes in comparison with stomach and small intestine\(^8\).
Colonic region therefore can be a preferred site for the systemic absorption of many drugs, especially peptides and proteins that are degraded and/or poorly absorbed in the upper gut [9].

Factors to Be Considered In the Design of Colon Specific Drug Delivery System

Anatomy and Physiology of GIT

The GIT is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided into three main parts. 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 [10].

Colon pH

The pH of the GIT 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 [11,12].

Gastro Intestine Transit

The movement of materials through the colon is slow than other regions of the gastrointestinal tract. The total time for transit tends to be highly variable and influenced by a number of factors such as diet, in particular dietary fiber content, mobility, stress, disease and drugs. Colonic transit times ranged from 50 to 70 h. Stool weights increased significantly with the presence of active disease presumably due to exudates form inflamed epithelium, increased mucus secretion and reduction in reabsorption of fluid and electrolytes [13].

Colonic Microflora and Enzymes

A large number of anaerobic and aerobic bacteria are present in the entire length of the human GIT. Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut microflora 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 bacteroides. The concentration of bacteria in the human colon is around 1000 CFU / mL. The most important anaerobic bacteria are bacteroides, bifidobacterium, eubacterium, peptococcus, peptostreptococcus, ruminococcus and clostridium [14].

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 slow rate if 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 [15]. Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppressant, cushinoid symptoms and bone resorption [16]. Thus selective delivery of drugs to the colon could not only lower the required dose but also reduce the systemic side effects caused by high doses [17].

Factors Affected In the Design of Colon Specific Drug Delivery System

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 [18].
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 absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule \(^{19}\), 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 \(^{20}\).

**Approaches for Colon Targeting**

Approaches used for site-specific drug delivery are:

**Primary approaches for CDDS \(^{18}\)**

- pH sensitive polymer coated drug delivery to colon.
- Delayed (Time controlled release system) release drug delivery to colon.
- Microbially triggered drug delivery to colon.
  - Prodrug approach for drug delivery to colon.
  - Azo-polymeric approach for drug delivery to colon.
  - Polysaccharide based approach for drug delivery to colon.

**Newly developed approaches for CDDS \(^{21}\)**

- Pressure controlled drug delivery system (PCDCS).
- Osmotic controlled drug delivery to colon (OROS-CT).

**Primary Approaches for CDDS**

**pH Sensitive Polymer Coated Drug Delivery to 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 caecum. 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, 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. 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 also result in poor site-specificity of enteric-coated single-unit formulations.

**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, 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 h (range 5 to 6 h).

Disadvantages of this system are

- 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.
- Accelerated transit through different regions of the colon has been observed in patients with the IBD.
- 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 h. The time-release function (or timer function) should work more efficiently in the small intestine as compared the stomach. In the small
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). 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.

Microbially Triggered Drug Delivery To Colon

The microflora of colon is in the range of 10^{11}-10^{12} 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.

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 in the upper GIT undergo enzymatic transformation 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. 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. Furthermore prodrugs are new chemical entities and need a lot of evaluation before being used as carriers.

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. 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 Azo-reductase in the large bowel. Coating of peptide capsules with polymers cross linked with Azo-aromatic 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.

Polysaccharide Based Delivery System

Use of naturally occurring polysaccharides is attracting lot of attention for drug targeting to the colon since these polymers of monosaccharide are found in abundance, have wide availability are inexpensive and are available in a verity of a structures with varied properties. 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, chondrotin sulphate) algal (alginites) or microbial (dextran) origin. These are broken down by the colonic microflora to simple saccharides.
Newly Developed Approaches for CDDS

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. 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 [22]. 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 [23].

Osmotic Controlled Drug Delivery (OROS-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. The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4-mm in diameter, encapsulated within a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a 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 controled by the rate of water transport through the semi-permeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h 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. Various in-vitro/in-vivo evaluation techniques has been developed and proposed to test the performance and stability of CDDS.

CONCLUSIONS

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Drug targeting to the diseased colon is advantageous in reducing the systemic side effects, lowering dose of a drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site. All the approaches of colon drug delivery provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs. The wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, makes the reliability, delivery efficiency of formulation and targeting to colon complicated.

REFERENCES