Review Article

AN OVERVIEW ON COLON TARGETED DRUG DELIVERY SYSTEM

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Abstract: Colon drug delivery system is gaining importance in most of the days because colon is a site where in both local and systemic delivery of drugs can take place. Targeting drugs directly to the colon is advantageous in the treatment of colonic disease such as ulcerative colitis, crohn's disease and inflammatory bowel disease. This review mainly comprises the anatomy of the colon, and various approaches to target drugs to the colon.
Key words: Colon, Targeted drug delivery, Colonic Micro flora

Introduction

Colonic delivery refers to targeted delivery of drugs into the colon. Targeted drug delivery in to the colon is highly desirable for local treatment of a several colonic diseases such as ulcerative colitis, crohn's disease and colonic cancer.

Now days, various routes of administration have been explored for the effective delivery of the drug to the colon. The oral route is considered to be most convenient for the administration of drugs to patients. Rectal administration offers the shortest route for targeting the drug to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less. Hence oral route is preferred route of drug administration[12].

Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastro intestinal tract presents several barriers to drug delivery. On oral administration of conventional dosage forms drug normally dissolves in the gastro intestinal fluids and is absorbed from these regions of the gastrointestinal tract (GIT) which depends upon the physicochemical properties of the drug. It is a serious drawback in condition where localized delivery of drugs in the colon is required or in conditions where drug needs to be protected from the hostile environment of upper GIT[11].

To achieve successful colonic delivery, a drug needs to be protected from absorption and or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon targeted delivery of drugs[11]. The colon is rich in lymphoid tissue. Uptake of antigens in to the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.

Advantages of Colon targeted delivery

Dosage forms that deliver drugs into the colon rather than upper GIT offers number of advantages[9].

1. Reducing the adverse effects in the treatment of colonic diseases.
2. By producing the friendlier environment for peptides and proteins when compared to upper GIT.
3. Minimizing extensive first pass metabolism of steroids.
4. Preventing the gastric irritation produced by oral administration of NSAIDS.
5. Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.
6. Administration of glucocarticoids (e.g.Dexamethasone and methyl prednisolone) by the oral and i.v. routes produces systemic side effects including adenosuppression, immunosuppression, cushinoid symptoms and bone re-absorption, thus the selective drug delivery to colon could lower the required dose and hence reduce the systemic side effects.

Anatomy and Physiology of Colon

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocaecal junction to the anus

is divided into three main parts. These are the colon, the rectum and the anal canal. The location of the parts of the colon is either in the abdominal cavity or behind it in the retro-peritoneum.

The colon is made up of caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon. It is about 1.5 m long. The transverse colon being the longest and most mobile part and has a average diameter of about 6.5 cm. However, it varies in diameter from approx.9.0 cm, in caecam to 2cm in sigmoid colon. Unlike the small intestine, the colon does not have any villi but due the presence of plicae semilunares, which are cresentic folds, the intestinal surface of the colon is increased to 1300cm2. The wall of the colon is made of four layers, serosa, muscularis externa, sub mucosa and mucosa[11].

The physiology of the proximal and distal colon differs in several aspects that can have an effect on absorption at each site. The physical properties of the Luminal content of colon also change from liquid in the cecum to semi solid in the distal colon. The main features of the colon shown in Figure No1.
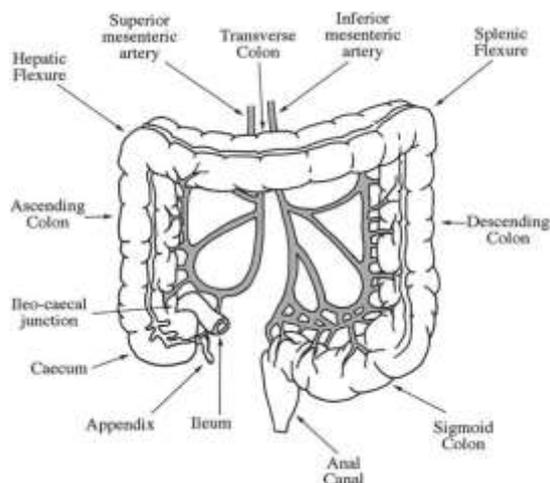

Figure No.1: Main features of the Colon

Major Functions of the Colon

1. The absorptive capacity of colon is very high; each day about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed.
2. Creation of suitable environment for the growth of colonic microorganisms such as bacteroids, eubacterium and enterobacteriaceae.
3. Expulsion of the contents of the colons at an appropriate time.
4. Absorption of water and Na+ from the lumen, concentrating the fecal content and secretion of K+ and $(HCO_3)^{-2}$.

Drugs Suitable for Colonic Drug Delivery

1. Drugs used to treat irritable bowel disease (IBD) require local delivery of drug to colon, eg.-sulfasalazine, osalazine, mesalazine, steroids, like fludrocortisones, budenoside, prednisolone and dexamethasone.
2. Drugs to treat colonic cancer require local delivery. Eg.,5-fluorouracil,doxorubicin,and methotrexate.
3. Drugs that degrade in stomach and small intestine require local delivery – eg., Protein and peptide drugs like insulin, interleukin, interferon, erythropoietin.
4. To treat infectious diseases (amoebiasis & helminthiasis)-require site specific delivery eg., metronidazole, mebendazole, and albendazole.
5. To treat rumatoid arthritis (NSAIDS), nocturnal asthma, angina requires delay in absorption due to circadian rhythms.
6. Drugs showing more selective absorption in colon than small intestine due to small extent of paracellular transport eg.- Glibenclamide, Diclofenac, theophylline, Ibuprofen, Metoprolol and Oxyprenolol.
7. The colon is also a good site for the absorption of drugs that are not stable in the acidic environment of the stomach, cause gastric irritation (e.g. aspirin, iron supplements) or those degraded by small intestinal enzymes[9].

Colonic Absorption of Drugs

Drugs are absorbed passively either paracellular or transcellular route. Transcellular absorption involves the passage of drugs through cells and this is the route most liphophilic drugs takes, where paracellular absorption involves the transport of drug through the tight junction between cells and is the route most hydrophilic drugs takes. Drugs shown to be well absorbed include glibenclamide, diclofenac, theophylline ibuprofen, metoprolol, and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide, buflomedil, atenolol, cimetidine, lithium, and ciprofloxacin[9].

Factors to be Considered in the Design of Colon Specific Drug Delivery System

Colonic Drug Delivery System primarily dependent on the following physiological factors they are transit time, pH level, colonic microflora. These parameters can vary from one individual to the next and also according to the pathological condition and diet.

Transit through GIT

The drug delivery systems first enter into stomach and small intestine via mouth and then reach colon. The nature and pH of gastric secretion and gastric mucus influence the drug release and absorption. Gastrointestinal transit varies from 1 hr to 3 hrs depending upon the condition (fasting or non-fasting). Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hrs to reach the ileocecal junction and the time period is consistent. During this period the dosage form is exposed to enzymes present in small intestine. Compared to the other region of GIT, movement of material through the colon is slow. Total time for transit tends to be highly variable and influenced by number of factors such as diet particularly dietary fiber content, mobility, stress, disease condition and drugs. Gastro intestinal transit times were shown in Table 1.

Table 1: Transit times of Dosage form in GIT[11]

Organ	Trnsit time(hr)
Stomach	<1(fasting) >1(fed)
Small intestine	3-4
Large intestine	20-30

Stomach and Intestinal pH:

Generally, the release and absorption of orally administered drugs are influenced by the GI pH. The pH gradient in the GIT is not in an increasing order. In stomach the pH is 1.5-2. The acidic pH is responsible for the degradation of various pH sensitive drugs and enteric coating may prevent it. In small intestine, the pH increases slightly from 6.6-7.5. Highest pH level (7.5±0.5) in the terminal ileum. On entry into the colon, the pH drop 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 Since there is minimal variation in the pH from ileum to colon, apparently pH dependent polymer drug delivery may not be much selective. However, possible exploitation of pH variation in GIT leads to successful development of various colon specific drug delivery systems.

Colonic Microflora:

A large number of anaerobic and aerobic bacteria are present through out the entire length of human GIT. The upper region of the GIT has very small number of bacteria and predominantly consists of gram-positive facultative bacteria. The concentration of bacteria in the human colon is 10^{11}-10^{12} CFU/ml. The bacterial flora of colon is predominantly anaerobic and composed of more

than 400 strains. The most important anaerobic bacteria are Bacteriod, Bifidobacterium, Eubacterium, Eeptococcus, Peptostreptococcus. Ruminococcus,clostridium and propionibacterium. The important facultative bacteria in large intestine are E. coli, and lacto bacillus. The principle source of nutrition for colonic microorganisms are carbohydrates, arriving in intestinal chime, including starch, non starch polysaccharides such as cellulose, hemi cellulose, guargum, pectin, ispagola, sugar, and oligosaccharides, such as lactose, sorbitol, and xylitol. It is evident that colonic bacterial population will have a significant impact, both negative and positive, on colonic delivery[10].

Approaches to Colon-Specific Drug Delivery

Several approaches are used for site specific drug delivery. These include:

1. pH-dependent system
2. Time controlled release system
3. Microflora activated system
4. Prodrug approach

pH-Dependent Systems

The basic principle in this method is the coating of the tablets or pellets with various pH sensitive polymers, which will produce delayed release and also give protection from gastric fluids. Selection of polymers is important thing. The selected polymers to colon targeting should be able to withstand the pH of the stomach and small intestine. Methyacrylic and esters most commonly used polymers for colon targeting because they are soluble at above pH 6 The ideal polymer should be able to withstand the lower pH of the stomach and of the proximal part of the small intestine but able to disintegrate at neutral or shortly alkaline pH of the terminal ileum and preferably at ileocecal junction. Eudragit L & Eudragit S are widely used in the colon targeting because Eudragit L is soluble at pH 6 or above and Eudragit S is soluble at a pH7 or above and the combination of these polymers give the desirable release rates[9].

Colon targeted drug delivery systems based on methacrylic resins has described for insulin, prednisolone, quinolones, cyclosporine beclomethasone dipropionate and naproxane. pH-sensitive delivery systems are commercially available for mesalazine (5-aminosalicylic acid) (Asacol® and Salofalk®) and budesonide (Budenofalk® and Entocort®) for the treatment of ulcerative colitis and Crohn's disease, respectively. The threshold pH of commonly employed pH-sensitive polymers is shown in Table 2.

Table 2: Threshold pH of commonly used polymers

Polymer	Threshold pH
Eudragit® L100	6.0
Eudragit® S100	7.0
Eudragit® L 30D	5.6
Eudragit® FS 30D	6.8
Eudragit® L100-55	5.5
PVAP	5.0
HPMCP	4.5-4.8
HPMCP 50	5.2
HPMCP 55	5.4
CAP	5.0

PVAP = Polyvinyl acetate phthalate; HPMCP = Hydroxypropylmethylcellulose phthalate; CAP= Cellulose acetate phthalate.

Time-Controlled Release Systems

The basic principle involved in the system is the release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at right time and in the right amount. Colon targeting could be achieved by incorporating a lag time into formulation equivalent to the mouth to colon transit time. A nominal lag time of five hours is usually considered sufficient to achieve colon targeting. In this method the solid dosage form coated with different sets of polymers and the thickness of the outer layer determines the time required disperse in aqueous environment[11].

Time-controlled release systems (TCRS) such as sustained or delayed release dosage forms are also very promising drug release system. Due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability. The dosage forms by prolonging the lag time of about 5 to 6 h, however, the disadvantages of this system are[11]:

1. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
2. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastro intestinal transit of the drug.
3. 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.
4. Therefore time dependent systems are not ideal to deliver

drugs to the colon specifically for the treatment of colon related diseases.

Microflora Activated System

These systems are based on exploitation of specific enzymatic activity of the microflora present in the colon. The colonic bacteria anaerobic in nature and secrete enzymes that are capable of metabolizing substrates carbohydrates, proteins that escapes the digestion in the upper GIT.

The basic principle involved in this method is degradation of polymers coated on the drug delivery system by microflora present in colon and there by release of drug load in colonic region because the bio-environment inside the human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms. In this method drugs and/or dosage forms are coated with the biodegradable polymers i.e., the polymers degrade due to influence of colonic microorganisms. When the dosage form passes through the GIT, it remain intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating[25]. Microbial degrade polymers used for colonic delivery shown in Table3.

Table.3 Microbially degrade polymers used for colonic delivery[6]

Class	Example
Disaccharides	Lactose Maltose
Oligosaccharide	Cyclodextrins Raffinose
Polysaccharide	Alginates Amylase Chitoson Chondroitin sulfate Galactomnan (Guargum, Locust bean gum) Xanthan gum Pectin Starch

Prodrug Approach

A prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous enzymatic transformation in vivo to release the active drug. In this method the prodrugs are designed to undergo minimum absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the carrier[9].

This principle has been exploited commercially to deliver 5-aminosalicylic acid to the colon by way of a prodrug carrier. The prodrug sulphasalazine consists of two separate moieties, sulphapyridine and 5-aminosalicylic acid, linked by an azo-bond. The prodrug passes through the upper gut intact, but, once in the colon, the azo-bond is cleaved by the host bacteria, liberating the carrier molecule sulphapyridine and the pharmacologically active agent 5-aminosalicylic acid. This concept has led to the development of novel azo-bond-based polymers (azo-polymers) for the purpose of obtaining universal carrier systems.

Different types of conjugates were used to prepare 5-ASA prodrugs, which are succeed in releasing the 5-ASA in colonic region. They are biodegradable poly (ether-ester) azo polymers, azo-linked polymeric prodrugs, acrylic type polymeric prodrugs and cyclodextrin prodrugs. Glucuronide prodrugs were developed for corticosteroid to deliver the drug to the large intestine of colitic rats.

Newly developed approaches for colon specific drug delivery system:
Pressure Controlled Drug Release Systems
GI pressure is another mechanism that is utilized to initiate the release of the drug in the distal part of the gut. Viscosity of the luminal contents within the colon is greater than at other sites within the G.I tract, due to the reabsorption of water from the large intestine. This change in viscosity leads to an increase in pressure resulting from the peristaltic forces. This pressure change can be used to trigger drug release[12].

Novel Colon Targeted Delivery System
It is a unique system that was designed to avoid the inherent problem associated with pH or dependent systems. It is combined approach of pH dependent and microbially triggered system. It has been developed by utilizing unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon[12].

The system consists of a traditional tablet core containing lactulose which is over coated with 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 passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the Bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to effect the dissolution of the acid soluble coating and subsequent drug release.

Osmotically controlled drug delivery system:
Osmotically controlled system can be used to target the drug locally to the colon for the treatment of diseases or to achieve systemic absorption that is otherwise unattainable. This system can be single osmotic unit or may incorporated as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule[12].

Each bilayer push-pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. The semipermeable membrane is permeable to the inward entry of water or aqueous GI fluids and is impermeable to the outward exit of the drug.

An orifice is drilled through the semipermeable membrane next to the drug layer. The outside surface of the semipermeable membrane is then coated by Eudragit® S-100 (approx. 0.076 mm thickness) to delay the drug release from the device during its transit through the stomach. Upon arrival in the small intestine, the coating dissolves at pH >7. As a result, water enters the unit causing the osmotic push compartment to swell and concominantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate of water transport through the semi permeable membrane. For treating the 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 upto 24 hours in the colon or can deliver the drug over a period as short as four hours. The design of OROS-CT colon targeted drug delivery system shown in Figure 2.
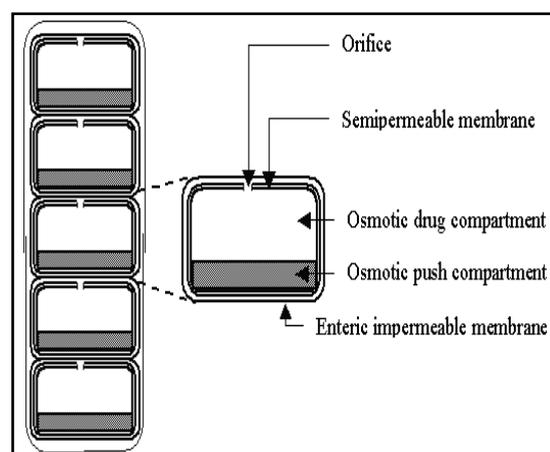

Figure 2: Cross section of the OROS-CT colon targeted drug delivery system

Conclusion

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Colon targeted drug delivery offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Different approaches are designed to develop colonic drug delivery system. The release of drug load in colon region is depend on the pH of the GIT, gastro intestinal transit time and microbial flora and their enzymes to degrade coated polymers and breaking bonds between carrier molecule and drug molecule.

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