A Review Article on Colonic Targeted Drug Delivery System

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Colon targeted drug delivery system (CTDDS) delivered as both local and systemic delivery of drugs. Local delivery could, for example, allow topical treatment of inflammatory bowel disease (IBD). Treatment could be enhanced when drug delivered to the target site on the colon. Systemic side effects could also be reduced. Colon specific systems is most important delivery of those drug which are normally inactivated in the upper parts of the gastrointestinal tract (GIT). Primary approaches for CTDDS (Colon targeted Drug Delivery System), which includes prodrugs, pH and time dependent systems, Bacterial enzyme dependent colonic DDS and pH and bacterial enzyme dependent colonic DDS. The novel approach of CTDDS, which includes pressure controlled colonic delivery capsules (PCDCS), CODES and osmotic controlled drug delivery are specific technique.

Keyword: CTDDS, Novel approaches, evaluation of colon targeted drug delivery systems

INTRODUCTION:

1.1-Colon targeted Drug Delivery system (CTDDS)

Colon targeted Drug Delivery system (CTDDS) may be follow the concept of sustained or controlled drug delivery system, for CTDDS oral route of administration has received most attention. This is because of the flexibility in dosage form designed for oral than parenteral route because

I. Patient acceptance for the oral administration of the drug is quite high.
II. It is relatively safe route of drug administration compared with parenteral route and potential damage at site of administration is minimal.

Most of the conventional drug delivery systems for treating the colonic disorder such as Inflammatory bowel diseases i.e. Ulcerative colitis, Cohn’s diseases, Colon cancer and Amoebiasis are failing as drug do not reach the site of action in appropriate concentration. For effective and safe therapy of these colonic...
disorders, colon specific drug delivery is necessary. Today, colon specific drug delivery is challenging task to pharmaceutical technologists. Therapeutic advantages of targeting drug to the diseased organ include.

Therapeutic advantages of targeting drug to the diseased organ includes\(^1,2\)

a) The ability to cut down the conventional dose
b) Reduced the incidence of adverse site effects
c) Delivery of drug in its intact form as close as possible to the target sites.

Colon specific drug delivery systems are also gaining importance for the delivery of protein and peptides due to several reasons as follow

a) Rapid development of biotechnology and genetic engineering resulting into the availability of protein and peptide drugs at reasonable cost.
b) Proteins and peptide drugs are destroyed and inactivated in acidic environment of the stomach or by pancreatic enzymes in small intestine.
c) Parental route is expensive and inconvenient.
d) Longer residence time, less peptidase activity and natural absorptive characteristics make the colon as promising site for the delivery of protein and peptide drug for systemic absorption.
e) Less diversity, and intensity of digestive enzymes.
f) Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability.

1.2- Advantages of CTDDS over Conventional Drug Delivery:
Chronic colitis, namely ulcerative colitis, and Crohn’s disease are currently treated with glucocorticoids, and other anti-inflammatory agents. Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppression, cushinoid symptoms, and bone resorption. 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\(^ 2\).

1.3- Criteria for Selection of Drug for CDDS\(^3,4\): 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

1.4- FACTORS TO BE AFFECTED IN THE DESIGN OF COLON - TARGETED DRUG DELIVERY SYSTEM\(^2,3,4\)

1.4.1-Anatomy and Physiology of Colon
The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileoceleal junction to the anus is divided in to 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 in to 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 contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus.
1.4.2- 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.

1.4.3-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 bacteroides. 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.

1.4.5-Transit of Material in the Colon
The presence of food material generally increases gastric residence and in some cases with regular feeding, dosage forms have been shown to reside in the stomach for periods in excess of 12 hours. Small intestinal transit is surprisingly constant at 3-4 hours and appears to be independent of the type of dosage form and whether the subject is in the fasted or fed state. Compared to other regions of the gastrointestinal tract, movement of materials through the colon is slow. 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 hours. 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.

1.4.6-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 take, 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 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. 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.
1.5-APPROACHES OF COLONIC DRUG DELIVERY SYSTEM

In general, seven primary approaches have been proposed for targeted colon delivery, namely,

1.5.1-Transit time dependent colonic DDS
1.5.2-pH Dependent colonic DDS
1.5.3-pH- and time-dependent colonic DDS
1.5.4-Bacterial enzyme dependent colonic DDS
   1.5.4.1-Prodrug based system
   1.5.4.1.1- Azo Prodrugs
   1.5.4.1.2- Polymeric/Saccharide Prodrugs
   1.5.4.1.3- Amino acid Prodrugs
1.5.4.1-Coating and matrices Based system
1.5.5-pH and bacterial enzyme dependent colonic DDS
1.5.6-Colonic pressure controlled DDS
1.5.7-and Osmotic pressure controlled colonic DDS
   1.5.7.1-Osmet Pump
   1.5.7.2-OROS CT

1.5.1-Transit time dependent colonic DDS

Transit time dependent colonic DDS such as sustained or delayed release dosage forms are one of important drug release systems. However, 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 colonal availability. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h. However, the disadvantages of this system area.

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.

1.5.2-pH Dependent colonic DDS

The pH-dependent CTDDS exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum. 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, how- ever, 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. These processes distribute the drug throughout the large intestine and improve the potential of colon targeted delivery systems. While this release pattern can be studied in-vitro, there is no real substitute for confirming reliable performance in vivo in man. The technique of gamma scintigraphy has...
become the most popular method to investigate the gastrointestinal performance of pharmaceutical dosage forms. The threshold pH commonly employed pH-sensitive polymers. Table: Optimum pH of commonly used polymers.

1.5.3-pH- and time-dependent colonic DDS
The transit time through the small intestine is independent of the formulation. But, the time taken by the formulation to leave the stomach varies greatly. Hence, the time of arrival of a formulation in the colon cannot be accurately predicted. However, the effects of variation in gastric residence time can be minimized by using systems that prevent drug release until 3-4 hr after leaving the stomach. A multiple coated oral dosage form consisting of core coated with three polymeric layers has developed, a novel oral time based drug release system for colon-specific delivery.

The system designed to exploit the relatively constant small intestinal transit time of dosage forms consists of drug-containing cores coated with three polymeric layers. The outer layer dissolves at pH > 5, then the intermediate swellable layer, made of an enteric material. The system provides the expected delayed release pattern, as also indicated by the preliminary in vivo studies on rats. Several other drug delivery systems have developed that rely upon the relatively constant transit time of small intestine.

A novel delivery system was developed for delivering drugs to the colon by selecting polymethacrylates with appropriate pH dissolution characteristics for the distal end of the small intestine. Pellets were prepared by powder layering of 5-ASA on nonpareils (0.5-0.6 mm) in a conventional coating pan. Drug-layered pellets were coated with an inner layer of a combination of two pH-independent polymers Eudragit RL and RS (2:8), and an outer layer of a pH-dependent polymer, Eudragit® FS.

In another method, an organic acid (succinic acid) was filled into the body of a hard gelatine capsule as a pH-adjusting agent together with the drug substance. The joint of the capsule was sealed using an ethanolic solution of ethyl cellulose. The capsule was first coated with an acid soluble polymer (Eudragit E), then with a hydrophilic polymer HPMC and finally enterically coated with Eudragit L. After ingestion of the capsule, the outermost enteric layer of the coating prevents drug release in the stomach. Enteric layer and hydrophilic layers dissolve quickly after gastric emptying and water starts entering the capsule. When the environmental pH inside the capsule decreases by the dissolution of organic acid, the acid soluble layer dissolves and the enclosed drug is quickly released. Therefore, the onset time of drug releases in the intestine can be controlled by the thickness of acid soluble layer.

Drug targeting to colon would be prove useful where intentional delayed drug absorption is desired from therapeutic point of view in treatment of circadian diseases that have peak...
symptoms in the early morning such as nocturnal asthma, angina pectoris and rheumatoid arthritis. Colon specific drug delivery systems are gaining the importance for systemic as well as local effect. Colon specific drug delivery system is popular for treatment of inflammatory bowel diseases (IBD), delivery of protein and peptide drugs, for circadian diseases and also for improving the systemic absorption of the some drugs, additionally following chart help in selection of drug candidate for colon specific drug delivery (Table)\textsuperscript{1,2,3}

1.5.4-Bacterial enzyme dependent colonic DDS\textsuperscript{1,6,7,8}

The micro flora of the colon is in the range of 10\textsuperscript{11}-10\textsuperscript{12} CFU/ml consisting mainly of anaerobic bacteria, e.g. Bacteroides Bifid bacterium, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. These microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, like di- and trisaccharides, polysaccharides etc. For this fermentation, the micro flora produces a vast number of enzymes like glucuronidase, 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.

The majority of bacteria are present in the colon they are distributed throughout the GI tract. Endogenous and exogenous substrates, such as carbohydrates and proteins, escape digestion in the upper GI tract but are metabolized by the enzymes secreted by colonic bacteria. Sulphasalazine, a Prodrug consisting of the active ingredient mesalazine, was the first bacteria-sensitive delivery system designed to deliver the drug to the colon. Use of polysaccharides offers an alternative substrate for the bacterial enzymes present in the colon. Most of the polymers are used in pharmaceutical compositions and are considered generally regarded as safe (GRAS) recipients

1.5.4.1-Prodrug based system

A Prodrug is a pharmacologically inactive derivative of a parent molecule that requires some form of transformation in vivo 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. The type of linkage that is formed between the drug and carrier would decide the triggering mechanism for the release of the drug in the colon.

This biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon. The enzymes that are mainly targeted for colon drug delivery include azoreducatase-galactosidase, $\beta$-xylosidase, nitroreductase, glycosidase deaminase, etc. Generally, a prodrug is successful as a colon
drug carrier if it is hydrophilic and bulky, to minimize absorption from the upper GI tract and, once in the colon, it is converted into a more lipophilic drug molecule that is then available for absorption. They break down upon action of glycosidase, releasing the drug part form the sugar. Glycosidase activity of the GI tract is derived from anaerobic microflora in the large bowel or exfoliated cells of the small intestine. When free steroids were administered orally, they were almost absorbed in the small intestine and less than 1% of the oral dose reached the colon.

1.5.4.1.1- Azo Prodrugs

The azo linkage exhibits a wide range of thermal, chemical, photochemical and pharmaceutical properties. The azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic components 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 prodrugs. Sulphasalazine, which was used for the treatment of rheumatoid arthritis, was later known to have potential in the treatment of inflammatory bowel disease (IBD). This compound has an azo bond between 5-ASA and sulphapyridine.

1.5.4.1.2- Polymeric /Saccharide Prodrug

The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of mono saccharides 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, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondroitin sulphate), algal (alginites) or microbial (dextran) origin. The polysaccharides can be broken down by the colonic microflora to simple saccharides. Therefore, they fall into the category of “generally regarded as safe” (GRAS). Chitosan is a high molecular weight cationic polysaccharide, poly (N-glucosamine), derived from chitin in crab and shrimp shells by deacetylation. It is degraded by the rich colonic microflora. Chitosan has been evaluated for colon specific drug delivery mainly in the form of a capsule forming material. Pectin is another non-starch linear polysaccharides with mainly α-(1-4)- linked Dgalacturonic acid residues interrupted by 1, 2- linked Lrhamnose.

**Polymeric Prodrugs**

Azo-linked polymeric prodrugs of 5-ASA were prepared and evaluated in simulated human intestinal microbial eco- system. Polyamides containing azo groups in the backbone were prepared and tested in vitro in a reductive buffer or in the bioreactor medium. It was demonstrated that for the hydrophobic polymer, reduction stops

<table>
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<tr>
<th>Drug moiety used</th>
<th>Polysaccharide Conjugation</th>
<th>Dosage form prepared</th>
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<tbody>
<tr>
<td>Diclofenac Sodium</td>
<td>Enteric coated chitosan microspheres</td>
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<tr>
<td>Insulin</td>
<td>Chitosan</td>
<td>Enteric coated chitosan</td>
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Table: Polysaccharides investigated for colon-specific drug delivery
at the hydrazine stage whereas for a hydrophilic analogue reduction with formation of amine occurred. The amount of the drug released depends on the nature of the polymer and can approach that of low molecular weight prodrugs.

**1.5.4.1.3- Amino acid Prodrug**

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.

Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to SA. The prodrug was absorbed into the systemic circulation from the upper GIT and hence it was proved unsuitable for delivery of drugs to the colon. By increasing the hydrophilicity and chain length of the carrier amino acid and decreasing the membrane permeability of conjugate Nakamura et al. prepared salicylic glutamic acid conjugates. This conjugate showed splendid results with minimal absorption and degradation in the upper GIT and proved suitable for colon targeted delivery of SA. Glycine and glutamic acid conjugates of salicylic acid. (a) Salicyluric acid. (b) Salicyl Glutamic acid conjugate.

**1.5.5-pH and bacterial enzyme dependent colonic DDS (CODES SYSTEM)**

CODES system is a unique CTDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODES system is a combined approach of pH dependent and microbiobally triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts
1.5.6-Colonic pressure controlled DDS (PCDC SYSTEM)

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Developed pressure controlled colon-delivery capsules prepared using ethylcellulose, which is insoluble in water. In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation. 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 humans.

1.5.7-and Osmotic pressure controlled colonic DDS

1.5.7.1-Osmet Pump (ALZET)

ALZET® Osmotic Pumps are miniature, infusion pumps for the continuous dosing of unrestrained laboratory animals as small as mice and young rats.
These minipumps provide researchers with a convenient, reliable, and cost-effective method for controlled delivery of agents. ALZET mini-osmotic pumps require no external connections or researcher intervention during the entire delivery period. Their unique design helps researchers save critical time by eliminating the need for frequent animal handling and repetitive injection schedules. These dependable drug delivery systems ensure that constant levels of compounds be maintained at therapeutic levels, thus avoiding potentially toxic or misleading side effects. An assortment of sizes, flow rates and durations is available to meet a variety of research needs. A single ALZET pump provides up to 6 weeks of continuous infusion.

1.5.7.2-OROS CT

The OROS-CT 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 4mm 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 semipermeable membrane. An orifice is drilled through the membrane next to the drug layer.

Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach and hence no drug is delivered. As the unit enter the small intestine, the coating dissolve in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 h in the colon or can deliver drug over an internal as short as 4 hour.

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