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Colon targeted drug delivery system - a review

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ABSTRACT

The Colon is a site where both local and systemic delivery of a drug can take place. Targeted drug delivery implies selective and effective localization of drug, into the target at therapeutic concentration with limited actions at non- target sites. Colonic drug delivery has gained increased importance not just for the delivery of the drug, but also for treatment of local diseases associated with colon like Crohn's disease, Ulcerative colitis etc., but also for the systemic delivery of proteins, therapeutic peptide, anti-asthmatic drug , anti - hypersensitive drug and anti-diabetic drugs. Local delivery allows tropical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon. Thereby reducing the systemic side effects. Colon specific system might also allow oral administration of peptide and protein drugs which are normally inactivated in the upper portion of the GIT. Newly developed CDDS, which includes Pressure Control Colonic Delivery Capsules (PCDSC), CODESTM and osmotic controlled drug delivery as specific technology. This review mainly compares the primary approaches for CDDS namely; prodrugs, PH and time dependent system and microbially triggered system, which achieved limited success and accepting limitations. Colon targeting holds a great potential and still need more innovative work. This article highlights introduction to colon, factors influencing colon-specific drug delivery and colonic drug bioavailability and limitations associated with CDDS. Further, the review provides a systemic discussion of various conventional, as well as relatively newer formulations approaches / technologies currently being utilized for the development of CDDS.

Keywords: Colon Targeting System, CODESTM, Prodrug, PCDSC, Crohn's disease.

INTRODUCTION

Colon targeted drug delivery system (CTDDS)

The goal of Targeted Drug Delivery is to deliver the drug to the specific organ. Colon Targeted Drug Delivery is used to deliver the substances that are degraded by the digestive enzymes in stomach such as proteins and peptides. Colon Drug Delivery System is beneficial not only for oral delivery of proteins and peptide drugs but also for the delivery of the low molecular weight compounds used to treat diseases associated with the colon such as ulcerative colitis, diarrhea and colon cancer. The Colon Targeted Drug Delivery System (CTDDS) may follow the concept of sustained or controlled drug delivery system for CTDDS oral route of administration. In addition to local therapy the colon

can also be utilized as a site for entry of drug into systemic circulation. Systemic absorption from colon can also be used as a means of achieving chronotherapy for diseases that are sensitive to circadian rhythms. The colon is believed to a suitable absorption site for peptide and protein drugs for following reasons.

- Less diversity and intensity of digestive enzymes.
- Comparative proteolytic activity of colon mucosa is much less than that observed in small intestine.

Successful colonic drug delivery requires careful consideration of properties of drug, the type of delivery system and its interaction with healthy or diseased gut. The colon is having high water absorption capacity, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. Colon Targeted Drug Delivery System increases the absorption of poorly absorbable drugs due to high retention time of colon. CDDS protects peptide drugs from hydrolysis, enzymatic degradation in duodenum, jejunum and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability.

Advantages

- Targeted drug delivery to the colon in the treatment of colonic disease ensures direct treatment at the affected area with lower dose and less systemic side effects.
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- Administration of glucocorticoids namely dexamethasone and methyl prednisolon by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppression, cushinoid symptoms and bone resorption.
- Possibly thus leading to reduced incidence of side effects and drug interactions.
- Reduce gastric irritation caused by many drugs. (example: NSAIDS- Non Steroidal Anti-inflammatory Drugs such as Ibuprofen.)
- It has a longer retension time and appears highly responsive to the agents that enhance the absorption of poorly absorbed drugs.
- Improves patient compliance.
- Extended day time and night time activity.
- It has low hostile environment, less peptidase activity, so peptides, oral vaccines, insulin, growth hormones can be given through this route.

Limitations

- The resident microflora could also affect colonic performance via metabolic degradation of the drug.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- An important limitation for PH sensitive coating technique is uncertainty of the location and environment in which the coat starts to dissolve.
- Limitations of the prodrug approach is that, it is not very versatile approach as its formulation depends upon functional group available for the drug moiety for the chemical linkage.
- Incomplete release of drug.

Criteria for CDDS

CTDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drug used in the treatment of IBO, ulcerative colitis, diarrhea and colonic cancers are the ideal candidates for local colonic delivery. The drugs used for the local effects in colon against GIT diseases-

- Drugs poorly absorbed from upper GIT.
- Drugs for targeting.
- Drugs that undergo extensive first pass metabolism.

The selection of drug carrier for particular drug candidate depends on the physiochemical nature of the drug as well as diseases for which the systems is to be used. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the system.

Anatomy and physiology of colon

The colon is also called the large intestine. The ileum (last part of the small intestine) connects to the cecum (first part of the colon) in lower right abdomen. The colon removes water, salt, and some nutrients forming stool. Over all in humans, the large intestine is about 1.5 meters (5ft.) long which is one fifth of the whole length of GIT. The colon is cylindrical tube which is lined by moist, soft, pink lining called mucosa. The colon and rectum have an anatomic blood supply. Lymph nodes are also present

with blood vessels. In humans, the large intestine begins in the right iliac region of the pelvis, where it is joined to the end of the small intestine at cecum, via the ileocecal valve. It then continues as the colon ascending the abdomen and as transverse colon and then descending to rectum and endpoint at the anal canal. The rest of the colon is divided into four parts:

- The ascending colon travels up the right side of the abdomen.
- The transverse colon runs across the abdomen.
- The descending colon travels down the left abdomen.
- The sigmoid colon is a short curving of the colon just before the rectum.

Segmenting movements, caused by the circular muscle and causing the appearance of the sac like haustra, pre dominate and results in mixing of the luminal contents.

Functions of colon

- It creates suitable environment for growth of the colonic microbes.
- Fecal contents storage reservoir.
- Eviction of contents of the colon.
- To secrete K+ and HCO_3^-

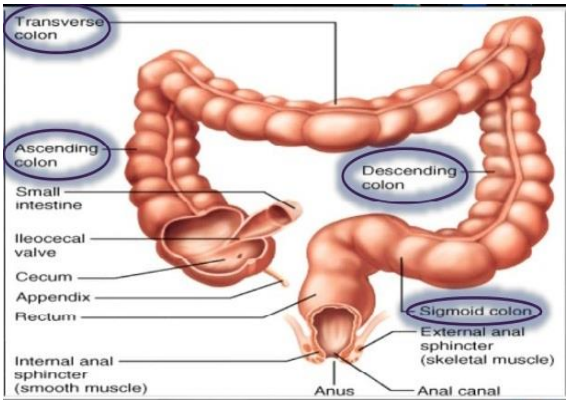


Fig1: Diagram of various regions in Gastrointestinal Tract

DRUG ABSORPTION IN COLON

Recent advances in controlled release techniques have allowed the delivery of the drugs to the colon that is the lower part of Gastro Intestinal Tract. The colon is more selective site for drug absorption as compared to small intestine because of small extent of paracellular transport. Due to its morphological and functional aspects related to drug absorption if notably has several carrier mediated transport systems which might be used as drug targets and are permeable to some lipophilic drugs. The transport pathways of the colon allow rapid and specific active bi- directional transport of ions. The drugs reported to the well absorbed through colon include glibenclamide, theophylline, diclofenec, ibuprofen. Drugs shown to be less absorbed are piretamied, buftomedil and ciprofloxacin.

Colonic Ph

PH in different parts of GIT is the basis for the development of Colon Drug Delivery System. Diet, diseased state and food intake influences the PH of gastro intestinal fluid on the entry into colon, the PH drops to 6.4±0.6. The PH in the mid colon is 6.6 ± 0.8 and in left colon 7.0±0.7. This fall of PH is due to presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

Colonic microflora and enzymes

A large number of aerobic and anaerobic bacteria are present in the entire length of the human GIT. Which provides many enzymes need for metabolism. Over 400 distinct bacterial species have been found 20-30% of which are of the genus bacteriods. Growth of this microflora is controlled by GIT contents and peristaltic movements.

Table 1: **Different microflora, enzymes released and action.**

Microorganism	Enzyme	Metabolic reaction
E.coli, Bacteroids	Nitroreductase	Reduces aromatic & heterocyclic nitro compounds
Clostridia, Lactobacilli	Hydrogenase	Reduces carbonyl groups & aliphatic double bonds
Clostridia, Eubacteria	Glucosidase	Cleavage of b-glycosidase of alcohols & phenols
Eubacteria, Clostridia, Streptococci	Sulfatase	Cleavage of O-sulphates & sulfamates

Approaches for CTDDS

An oral colonic delivery system should retard drug release in the stomach and small intestine but allow complete release in the colon. A variety of strategies has been used and systems have been developed for the purpose of achieving colonic targeting.

Primary approaches for colon targeted drug delivery

a. PH sensitive polymer coated drug delivery system.
b. Delayed release drug delivery system.
c. Microbially triggered drug delivery system.
    1. Prodrug.
    2. Polysaccharide based delivery.

New approaches for CTDD

a. Pressure controlled drug delivery system.
b. CODESTM.
c. Osmotic controlled drug delivery system.
d. Pulsative
    1. Pulsincap system.
    2. Port system.
    3. Azohydrogels.
    4. Multi particulate system based drug delivery.

Primary approaches for colon targeted drug delivery

Coating with PH dependent polymers

The underlying principle of the approach has been employment of polymers that are able to withstand the lower PH values of the stomach, but that disintegrate and release the drug as the PH in the small bowel increases .Selection of enteric polymer dissolving at PH 7 is likely to cause drug release in terminal small bowel.

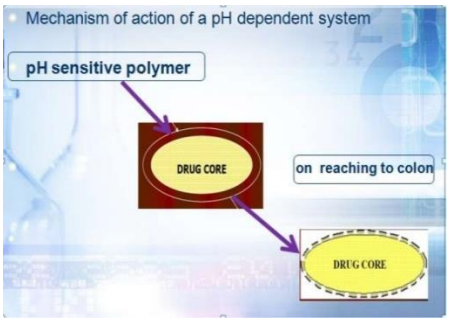
- The PH in transverse colon is 6.6 and 7.0 on the descending colon. Use of PH dependent polymers is based on these differences in PH levels.
- The polymers described as PH dependent in Colon Specific Drug Delivery are insoluble at low pH levels but become increasingly soluble as pH rises.
- These processes distribute the drug through out the large intestine and improve the potential of Colon Targeted Delivery System.

TABLE 2: PH dependent

Polymer	Threshold PH
Eudragit® L 100	6.0
Eudragit®S 100	7.0
Eudragit® L-30D	5.6
Eudragit® FS 30D	6.8
Eudragit®L 100-55	5.5
Polyvinyl acetate phthalate	5.0

Hydroxypropyl methylcellulose phthalate	4.5-4.8
Hydroxy propyl methyl cellulose phthalate 50	5.2
HPMC 55	5.4
Cellulose acetate trimelliate	4.8
Cellulose acetate phthalate	5.0

Mechanism of action of a ph dependent system



Delayed release drug delivery system

- Non-biodegradable polymers are used.
- They are generally non specific with respect to PH solubility characteristics and the employment of these polymers as carrier matrices for colonic delivery often utilizes a time dependent mechanism.
- This provides an initial lag phase of low or no release during transit through the upper GIT.
- The lag time usually starts after gastric emptying because most of the time controlled formulations are enteric coated.
- The enteric polymer coat prevents the drug release in the stomach.
- The drug release from these systems is not pH dependent.
- Various polymers used are: Polyacrylates, methyl cellulose, HPMC, CMC.
- This system consists of three main parts: an outer enteric coat, inner semipermeable polymer membrane, and a central core having swelling excipients and an active component.
- The outer enteric coating prevents drug release until the tablet reaches the small intestine.
- In the small intestine, the enteric coating dissolves allowing gastrointestinal fluids to diffuse through the semipermeable membrane into the core.
- The core swells until after a period of 4-6hrs, when it bursts, and releases the active component in the colon.

Microbially triggered drug delivery system

- The microflora of the colon is in the range of 1011-1012 CFU/mL, consisting mainly of anaerobic bacteria.(eg. Bacteroids, Bifidobacteria, Clostridia, Enterococci etc..)
- Microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase and ureadehydroxylase.
- Presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon specific drug delivery.
- These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon.

Prodrug

Prodrug is a pharmacologically inactive derivative of a parent molecule that require some form of transformation invivo to release the active drug at the target site.

- This approach involves covalent linkage between the drug and its carrier.
- 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 azoreductase-galactosidase,β-xylosidase, nitroreductase, glycosidase, deaminase, etc.)
- For colonic delivery, prodrug is
- Designed to undergo minimal hydrolysis in the upper tracts of GIT and undergo enzymatic

hydrolysis in colon thereby releasing the active drug moiety.

- Metabolism of azo compounds by intestinal bacteria is one of most extensively studied bacterial metabolic process.

TABLE 3: Examples of prodrug system for CDDS

Drug	Carrier	Linkage hydrolysed
5-ASA	Azo conjugates	Azo linkage
Dexamethasone	Saccharide cariers	Glycosidic linkage
Prednisone, Hydrocortisone, fludocortisone	Glucose, galactose	Glycosidic linkage
Salicylic acid	Amino acid,conjugates, glycine	Amide linkage

Polysaccharide based drug delivery system

Polysaccharides offer an alternative substrate for the bacterial enzymes present in the colon. Most of them are hydrophilic in nature. Natural polysaccharides are either modified or mixed with water insoluble polymers.

Polysaccharidesas carriers

- The colonic microflora secretes a number of enzymes that are capable of hydrolytic cleavage of glycosidic bonds.
- These include β-d-glucosidase,β-d-galactosidase,amylase,pectinase,xylanase,α-d-xylosidase and dextranases.
- Natural polysaccharides like pectin and inulin are not digested in stomach and small intestine but are degraded in colon by resident bacteria.
- The bacteria converts polysaccharides to gases such as methane, carbon dioxide, hydrogen and to short chain fatty acids.
- These polysaccharides thus have the potential as non-toxic carriers for colon specific drug delivery.

Polysaccharides used for colon drug delivery

- Chitosan
- Pectin
- Guargum
- Chondroitin sulphate
- Dextran
- Cyclodextrins
- Almond gum
- Locust bean gum
- Inulin
- Boswellia gum
- Karaya gum

New approaches for colon targeted drug delivery

Pressure controlled drug delivery system (PCDDS)

Digestion mainly occurs due to contractility of stomach and peristaltic movement of the intestine. The contractility of the stomach leads to the digestion or breakdown of larger particles to smaller ones which are then transferred to intestine. The peristaltic movement of the intestine is responsible for the passage of bolus from one part of GIT to the next part. In this type the pressure is generated by the peristaltic movements of the intestine which results in the increase in the luminal pressure which is the key point in the development of PCDDS. The molecules of drug travels fastely due to the contraction of the muscles which also increase in the gastrointestinal motility. So in short time the drug is reached to the colon and show effect. For this purpose capsule shell are prepared of water insoluble polymer ethylcellulose.

Codestm

This method is developed to minimize the problems associated with PH and time dependent drug delivery system. In this system the PH sensitive polymers are used along with the polysaccharide that are degraded only by specific enterobacteria present in the intestine. It consists of a core tablets coated with three layers of polymer coatings. The first

coating is an acid soluble polymer (Eudragit-L) and the outer layer is enteric with a HPMC barrier layer in between to prevent any possible interaction between the oppositely charged particle. The core tablet is comprised of active ingredient and one or more polysaccharide. During the transit through GIT the enteric barrier dissolves in small intestine (PH>6). Because Eudragit E dissolves at PH 5 the inner coating swells slightly in the small intestine. Upon entry into colon the bacteria enzymatically degrade the polysaccharide into organic acid.

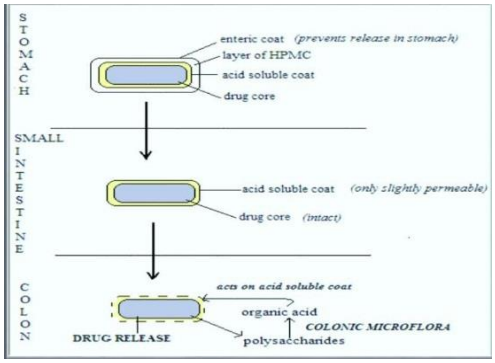


FIG2: CODESTM

Osmotic controlled drug delivery system (OROS-CT)

Immediately after ingestion ,hard gelatin capsule shell dissolves the push &pull unit is prevented from absorbing water in acidic medium of stomach by enteric coating .The osmotic pumping action results when the coating dissolves in the drug is delivered out of the orifice at a rate controlled by rate of water transport across the membrane.

The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push –pull units. It can be used to target the drug locally to the colon for the treatment of disease or to achieve systematic absorption that is otherwise is unattainable. In principle, the outer surface of the semi-permeable membrane is coated by Eudragit-S100 which leads to the delay release of the drug from the device during is transit through the stomach .Upon arrival on the small intestine the coating dissolves at PH≤7.As a result water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into the colon.

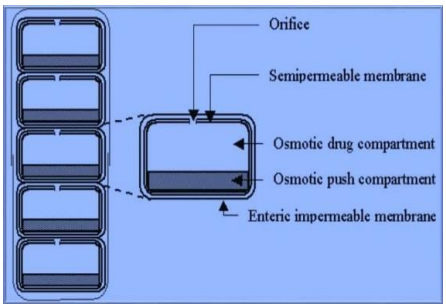


FIG 3: OROS-CT

Pulsative

Pulsincap system

Time dependent system are not always ideal for delivering drugs to the colon due to variability in gastric emptying time and the changes in the GI transit due to peristalsis or disorders such as IBS. In this system the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swell able hydrogels are used to seal the drug contents. Polymers such as HPMC, poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. When the capsule comes in contact with the dissolution fluid its swells up there by the plug gets pushed off from the capsule after a lag time thus the drug is released into the colon.

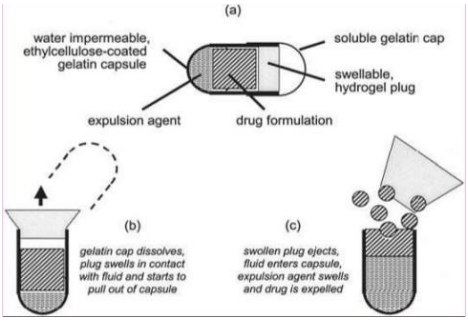


FIG 4: Pulsincap system

Port system

It consist of a gelatin capsule coated with a semi-permeable membrane (eg: cellulose acetate), housing and insoluble plug (eg: lipidic) & osmotically active agent along with drug formulation. When the capsule comes in contact with the dissolution fluid the semi-permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to the release of the drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals.

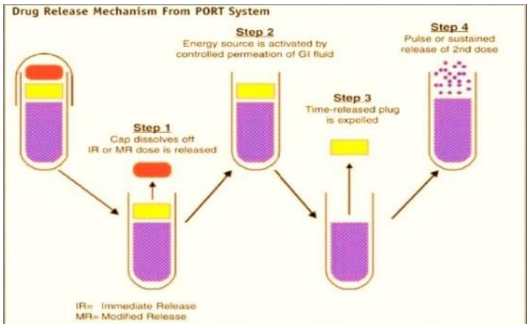


FIG 5: port system

Azohydrogels

The PH sensitive monomers and azo cross liking agents in the hydrogel produce the colon specificity. During their passage through the GIT these hydrogels swell as the PH increases. This swelling of hydrogels cleaves the cross links in the hydrogel network causing the release of drug entrapped in the hydrogel. These hydrogels are prepared by cross linking of polymerization of N-substituted (meth) acrylamides, N-tert-butyl acrylamide and acrylic acid with 4,4-di (methacryloylamino) azobenzene as cross linking agents. The hydrogels are also prepared by cross linking polymeric precursors, polymer-polymer reaction using same polymeric precursor with the corresponding copolymer containing side chains terminating in amine groups. The degradation rate of hydrogel is associated with the degree of swelling and inversely proportional to the cross linking density.

Multiparticulate system

The various advantages of multiparticlate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The various multi particulate approaches include pellets, micro particles, granules and nano particales. Multiparticulates systems are preferred over single unit dosage forms as the multiparticulate systems enable the drug to reach the colon quickly and retained in the colon for longer period of time. These systems pass through the GIT easily due to their smaller size. Multiparticulate systems are dispersed

more uniformly in the GIT resulting in more uniform drug absorption.

Nanoparticles

The preparation of nanoparticles is simple and these are capable of protecting the protein and peptide drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium. The polymeric nanoparticles are prepared by various techniques like polymerization, Nano precipitation, inverse microemulsion. The methods involve the use of organic solvents, heat, agitation.

Colonic diseases

Inflammatory bowel disease

Crohn disease may affect any portion of the gas-trointestinal tract from esophagus to anus but most often involves the ileum. The cause of in-flammatory bowel disease is multi-factorial and it is due to the inflammatory responses, abnormal local immune response against the normal flora of the gut, genetic factors such as multiple genetic factors, candidate genes, chromosome location, infectious agents like Escherichia coli, Measles virus, Cytomegalovirus, etc., dietary factors such as saturated fats, milk products, allergic foods etc. Crohn's disease and ulceration colitis are chronic relapsing inflammation disorder of unknown origin, collectively known as idiopathic inflammatory bowel disease (IBD). The main drugs used in the treatment of ulcerative colitis and Crohn's disease are the amino salicylates and corticosteroids. These diseases and other inflammatory bowel disease have been linked with an increased risk of colo-rectal cancer.

Ulcerative colitis

Ulcerative colitis occurs only in the large intestine. Ulcers form in the inner-lining of the intestine, or mucosa, of the colon or rectum, often resulting in diarrhea, blood, and pus. The inflammation is usually very rigorous in the sigmoid and rectum and usually reduces in the colon.

Crohn's disease

Crohn's disease, also called regional enteritis, is a chronic inflammation of the intestines which is usually confined to the terminal portion of the small intestine, the ileum.

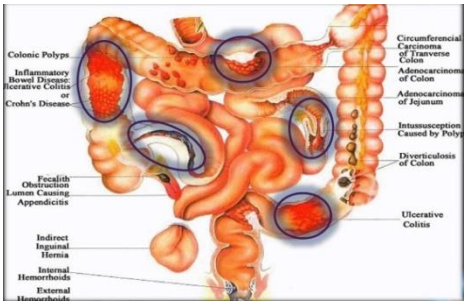


FIG 6: disorders of colon.

CONCLUSION

Colon Targeted Drug Delivery System offers benefits of local and systemic effects. The colonic region of the GIT has become an increasingly important site for drug delivery. Considering the specifications of colon – specific drug delivery systems and the uncertainity of current dissolution methods in establishing possible invitro/ invivo correlation. The challenges remain for pharmaceutical scientist to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in industry setting for the evaluation of CDDS.

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