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VARIOUS APPROACHES FOR TARGETING COLON: A REVIEW

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Abstract

The colonic region of GIT has become an increasingly important site for drug delivery and absorption. This site specific delivery of drug to lower parts of the GIT is advantage for localized treatment of several colonic disease like colon cancer, crohn's disease, ulceratice colitis, IBD, diarrhea etc. colon targeted drug delivery system (CTDDS) ensure direct treatment at the disease site and avoiding the systemic side effects. It is suitable for absorption site for protein and peptide drugs. Cytochrome P450 3A class of drug metabolizing enzyme, have lower activity in colon. This review, mainly compares the primary approaches for (CTDDS) Colon targeted Drug Delivery system namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process.

Keywords: Colon segments, microbial triggered, Cytochrome P450 3A, CTDDS approaches.

INTRODUCTION

Colon Targeted Drug Delivery System (CTDDS) may be following the concept of Controlled or Sustained drug Delivery System. For CTDDS oral route of administration has received most attention. Local delivery allows topical treatment of inflammatory bowel disease. Colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs [1,2]. For effective and safe therapy of these colonic disorders, colon specific drug delivery is necessary i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon [3]. Today, colon specific drug delivery is challenging task to pharmaceutical technologist.

The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons, (i) less diversity, and intensity of digestive enzymes, (ii) 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 [4]. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time [5]. Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery [6]. The bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the reaches the colon. Because the colon has a long residence time 72 hours and high water content it favors absorption of poorly absorbed drug molecule may have an improved bioavailability, CDDS has been employ to achieve following objectives i) Sustained delivery to reduce dosing frequency ii) Delay delivery of drug to achieve high concentration in treatment of disease of distal gut iii) to delay deliver to a time appropriate to treat acute phase of disease iv) Deliver drug to that region that is less hostile metabolically, drug which is acid and enzyme labile such as proteins[7].

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Benefits of Colon Target Drug Delivery System:

a) Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, Crohn's disease etc.)

b) Minimizing extensive first pass metabolism of steroids.
c) Preventing the gastric irritation produced by oral administration of NSAIDS.
d) High retention time thus increasing the bioavailability of poorly absorbable drugs.
e) Increased patient compliance.
f) Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.

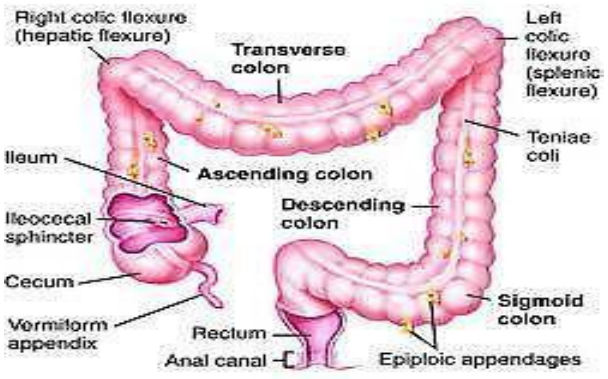

Fig 1: Anatomy of colon

Limitation of Colon Target Drug Delivery System

a) Difficult to access colon.
b) Incomplete release of drug.
c) Multiple manufacturing steps.
d) Parental route is expensive and inconvenient.
e) Lower surface area and relative tightness of the tight junctions in the colon can restrict drug [8]

Need of Colon Targeted Drug Delivery System

The Colonic region of the GIT has Became an increasingly important site for drug delivery and absorption. CDDS offers therapeutic benefits of patients in both local and systemic treatment. Systems utilize natural material that are degraded by colonic bacterial enzyme and have high commercial viability. It ensures direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides. It also provide opportunity to clarify the mechanism of action of some non-steroids anti- inflammatory drugs (NSAID) such as sulfide which get metabolized in the colon to the active moiety and interfere with the proliferation of colon polyps (first stage in colon cancer) probably in local mode. Large intestine is potential site for absorption of protein drugs.

Criteria for Selection of Drug for Colon Targeted Drug Delivery System:

a. Colon Targeted Drug Delivery System which show poor absorption from the stomach or intestine including peptides and protein.
b. The selection of Polymer for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition
c. Coefficient of the drug and type of absorption enhancer chosen influence the carrier selection.
d. Drugs poorly absorbed from upper GIT.
e. Drug for colon cancer drugs that degrade in stomach and small intestine.
f. Drugs that undergo extensive first pass metabolism.

Part of GIT	Transit time
Fasted state	10min – 2hr
Fed state	>2hr
Small intestine transit	3-4hr
Colon transit	20-35hr

Table 1: Transit time of different parts of GIT Anatomy and Physiology of colon

The GIT consists of parts from mouth to anus. It mainly consists of two parts namely stomach, intestine. Intestine is further divided into two small intestine and

large intestine [9]. The large intestine extending from the ileocecal 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. Peritoneal folds called as mesentery .peritoneal is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. 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.

A. Physiological factors

I. Gastric emptying :-

Part of GIT	pH
Stomach	Fasted state 1.5-2 Fed state 2-6
Small Intestine	6.6-7.5
Colon Ascending colon Transverse colon Descending colon	 6.4 6.6 7.0

Table 2: pH in different parts of Colon

Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit time [10].

II. pH of colon

The food intake, diseased state, etc. influences the pH of the GIT. 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±0.7) 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 (7.7±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.

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 β-glycosidase of Alcohols, phenols
Eubacteria, Clostridia, Streptococci	Sulfatase	Cleavageof Osulphates & Sulfamates

Table 3: Different microflora, enzymes released and action

III. 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 GIT. Usually, these enzyme are derived from gut micro flora residing in high numbers in the colon. These enzyme are used to degrade coatings or matrices as well as to break bonds between an inert carrier as 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 bacteroids. 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 , Ruminococcus , Clostridium.

2.Pharmaceutical factors

I. Drug candidates

Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. drugs used for treatment of inflammatory

bowel diseases, etc. are suitable for colon targeted drug delivery system [11].

II. Drug carriers

The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. The various physicochemical factors of drug that affect the carrier selection include chemical nature, stability, partition coefficient, functional groups of drug molecule etc.

COLONIC DISEASES:

- ✓ Acute colitis
- ✓ Adenoma carcinoma of colon
- ✓ Adenoma of colon
- ✓ Collagenous colitis
- ✓ Crohn's disease
- ✓ Diverticulitis
- ✓ Ulcerative colitis
- ✓ Inflammatory bowel disease (IBD)
- ✓ Colonic Cancer

APPROACHES FOR COLON TARGETED DRUG DELIVERY [12]

1. 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
   i. Prodrug approach
   ii. Polysaccharide based system

2. New approaches for colon targeted drug delivery

a. Pressure controlled drug delivery system (PCDDDS)
b. CODE
c. Osmotic controlled drug delivery system (OROS-CT)
d. Pulsatile
   i. Pulsincap system
   ii. Port system
e. Azo hydrogels
f. Multiparticulate system based drug delivery

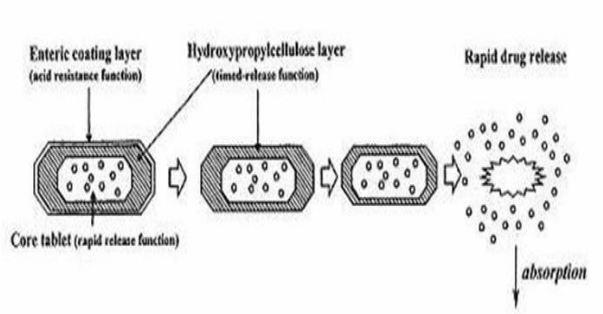

Fig 3: Design of Enteric coated-timed release press coated tablets (ETP tablets).

a) pH sensitive polymer coated drug delivery system:-

The pH varies in different parts of the gastrointestinal tract. The pH in stomach ranges between 1 and 2 during fasting. The pH in the proximal part of small intestine is 6.5 and in distal part of small intestine it is 7.5. The pH is 6.4 in caecum, 5.7 in ascending colon, 6.6 in transverse colon and 7.0 in descending colon. 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.[13]. 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 can also result in poor site-specificity of enteric-coated single-unit formulations [14].

Class	Examples
Disaccharides	Lactose, Maltose
Oligosaccharides	Cyclodextrins, Lactulose, Raffinose, Stachyose
Polysaccharides	Alginates, Amylose, Cellulose, Chitosan, Starch,Chondroitin sulphate, pectin, xanthan gum, etc.

Table.5. Different polymers used for CDDS based on Microbial drug delivery system

b) Delayed (Time controlled release system) release drug delivery to colon

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 colonical 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 are:-1) Gastric emptying time varies markedly between subject 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 gastrointestinal 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. Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. On the other hand in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time. Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases [15].

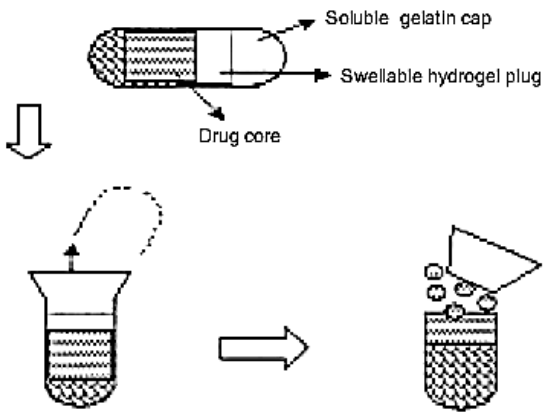

Fig.4 Pulsincap system

c) Microbial triggered drug delivery system

The microflora of the colon is in the range of 1011-1012 Cfu/ml consisting mainly of anaerobic bacteria, e.g. Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcusetc. These microfloras 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 floras produce a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareductase, deaminase, and urea dehydroxylase. Because of the presence of the biodegradable enzyme 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.

(i) Prodrug approach for drug delivery to colon

Prodrug [16] is the main approach of microbial triggered drug delivery system in which the drug release from the formulation is triggered by the microflora present in the gut. Prodrug is the inactive form of an active parent drug that undergoes enzymatic transformation 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. e.g. The produrgs are prepared by linking the active drug with hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose, etc. These Prodrug molecules get hydrolysed in the presence of the enzymes released by the microflora. The main drawback of this approach is that the formulation depends on the functional groups available on drug moiety for chemical linkage. The prodrugs formed upon linkage results in the formation of new chemical entities that need a lot of evaluation before using them as carriers. The most widely used prodrug approach is the metabolism of azo compounds by intestinal bacteria like azoreducatase-galactosidase , β – xylosidase, nitroreductase, glycosidase deaminase, etc.

(ii)Polysaccharide based delivery systems

Polysaccharide based delivery system is the other form of microbial triggered drug delivery system. Naturally occurring polysaccharides like guar gum, xanthan gum, chitosan, alginates, etc. are used in targeting the drug delivery. These are broken down by the colonic microflora to simple saccharides [17]. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable.

[B]NEWLY DEVELOPED APPROACHES FOR CDDS

a)Pressure-controlled drug-delivery systems

Digestion mainly occurs due to the contractility of the stomach and peristaltic movement of the intestine. The contractility movement of stomach leads to the digestion or breakdown of larger particles to smaller ones which are then transferred to intestine. 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 [18]. The system can be modified to withstand and rupture at different pressuresby changing the size of the capsule and thickness of the capsule shell wall.

b) CODES technology:

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon . The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine[19]. 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 [20].

C) Osmotic Controlled Drug Delivery (ORDS-CT)

The OROS-CT system can be a 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 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. 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 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 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon.52-55 Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS[21].

d) Pulsatile colon targeted drug delivery

a)Pulsincap system

It is the capsule formulation. The plug placed in the capsule controls the release of the drug.

Swellable hydrogels are used to seal the drug contents. The capsule [22] gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body.

b) Port system:

The capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and 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 release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals.

c) Azo hydrogels:

The pH sensitive monomers and azo cross linking 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 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 crosslinking polymeric precursors, polymer- polymer reaction using same polymeric precursor with the corresponding copolymer containing side chains terminating in NH2 groups.The degradation rate of hydrogel is associated with the degree of swelling and inversely proportional to the cross linking density.[22]

d) Multi particulate system based drug delivery:-

The various advantages of multiparticulate systems are increased bioavailability, reduced risk of local irritation,reduced risk of systemic toxicity. The various multiparticulate approaches include pellets, microparticles, granules and nanoparticles.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.

Drug Delivery Index (DDI) and Clinical Evaluation of Colon- Specific Drug Delivery Systems

DDI is a calculated pharmacokinetic parameter, following single or multiple dose of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery. Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently, gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems

Advantages of Colonic Drug Delivery

a. Targeted drug delivery to the colon in treatment of colonic disease ensures direct treatment at the affected area with lower dose and less systemic side effects.

b. The colonic drug delivery can also be utilized as the threshold entry of the drugs into blood for proteins and peptides which degraded or poorly absorbed in upper GIT.

c. The colon targeted drug delivery can also be used for chronotherapy for effective treatment of diseases like asthma and angina.

d. Minimizes first pass metabolism.

e. Decreased frequency of administration. Hence decreased cost of drugs

f. High retention time thus increasing the bioavailability of poorly absorbable drugs.

Disadvantages of Colonic Drug Delivery

a. There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired CSDDS site.

b. The pH level in the small intestine and caecum are similar which reduces site specificity of formulation

c. The major disadvantage of colonic delivery of drug is poor site specificity.

d. Diet and diseases can affect colonic micro flora which can negatively affect drug targeting to colon .

e. Nature of food present in GIT can affect drug pharmacokinetics.

f. Enzymatic degradation may be excessively slow which can cause interruption in polymer degradation and thus alters the release profile of drugs .

CONCLUSION

CDDS offers therapeutic benefits to the patient in both local and systemic treatment. System utilize natural material that are degraded by colonic bacterial enzyme and having high commercial viability. For in-vitro evaluation the current dissolution methods are not suitable. For that, Research is going to evaluate better dissolution techniques for CTDDS. Targeted drug delivery system is preferred for having instability, low solubility and short half life, large volume of distribution, poor absorption, low specificity and low therapeutic index. CTDDS provide maximum therapeutic effects.

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