A PROSPECTIVE OF PRIMARY AND NOVEL APPROACHES TO THE COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT: In the recent years there is new development in field of colon specific drug delivery system. The colon is the terminal part of the GIT which has gained as a potential site for delivery of various novel therapeutic drugs. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease, Crohn's disease, ulcerative colitis, etc. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. It also plays vital role in systemic antihypertensive drugs and anti-diabetic agents. This review article discusses introduction of colon, need and Primary approaches for CDDS (Colon Specific Drug Delivery), which includes prodrugs, pH and time dependent systems and microbially triggered drug delivery system. Newly developed CDDS, which includes pressure controlled colonic delivery capsules (PCDCS), CODE and osmotic controlled drug delivery and also focuses on evaluations of Colon targeted drug delivery in general.

INTRODUCTION:

Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as (ulcerative colitis, crohn's disease) amebiosis, colonic cancer, and for local treatment of local colonic pathologies, and the systemic delivery of protein and peptide drugs [1]. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine and bioactive agent should not be degraded and to allow drug release only in the colon [2].

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 Colon targeted drug delivery system increases the absorption of poorly absorbable drug due to high retention time of the colon.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.[3] And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.[4]

Advantages: [5]

1. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn's disease, etc.

2. Decreases the side effects in the treatment of colon diseases.
3. Prevents gastric irritation resulting due to the administration of NSAIDs.
4. Minimizes first pass metabolism.
5. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
6. Increased patient compliance.
7. Decreased frequency of administration. Hence decreased cost of drugs.
8. High retention time thus increasing the bioavailability of poorly absorbable drugs.

Limitations of colon target DDS:
Difficult to access colon:

1. Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
2. Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.[6]

Need for colon targeting drug delivery:

1. Targeted drug delivery to the colon to ensure that direct treatment at the disease site (local delivery), at lower dosing and fewer systemic side effects [7].
2. Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery [8].
3. Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases [8].
4. The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine [9].
5. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon [10].
6. Formulations for colonic delivery are also suitable for delivery of drugs which are 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 [10].

Criteria for Selection of Drug for CDDS:
The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD (Inflammatory Bowel Disease), ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery [11]. The criteria for selection of drugs for CDDS is summarized in **Table 1**.[12 13]

TABLE 1: CRITERIA FOR SELECTION OF DRUGS FOR CDDS

Criteria	Pharmacological Class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in Colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amyline, Antisense, Oligonucleotide
Drugs poorly absorbed from upper GIT	Antihypertensive and Antianginal drugs	Ibuprofen, Isosorbides, Theophylline	Cyclosporin, Desmopressin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrin	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Peptides and proteins	Bromophenaramine, 5-Flourouracil, Doxorubicin	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Bleomycin, Nicotine	Protirelin Sermorelin, Saloatonin

Drug Carrier is another factor which influences CDDS. The selection of carrier 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 coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule [14]. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems [15].

Approaches for colon targeted drug delivery: [16]

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)

1. Primary Approaches for CDDS:

a. pH sensitive polymer coated drug delivery system:

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating.[17] The pH is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine.[18] From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers.[19] The pH in the transverse colon is 6.6 and 7.0 in 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.[20]

Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor.[21] 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 which can also result in poor site-specificity of enteric-coated single-unit formulations.[20]

b. Delayed or time controlled release drug delivery system:

Time controlled drug delivery system [22] includes sustained or delayed release systems. In this system the delayed release or colon targeted drug delivery is attained by prolonging the lag time. The transit time varies in different parts of gastrointestinal tract. This transit time is responsible for the delayed release of drug. The main drawbacks of this delivery system are that the transit time varies from one person to other and amount of food intake.

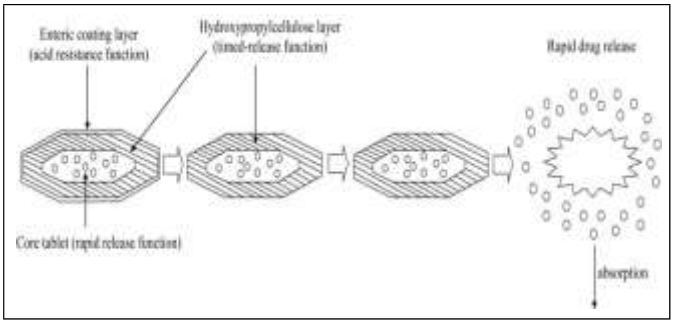

FIG.1: DESIGN OF ENTERIC COATED TIMED-RELEASE PRESS COATED TABLET (ETP TABLET)

Enteric coated time-release press coated (ETP) tablets, are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function). The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying,

the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer.

c. Microbially triggered drug delivery system:

The microflora of colon is in the range of 10^{11} -10^{12} CFU/mL[23], consisting mainly of anaerobic bacteria, e.g. Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri- saccharides, polysaccharides etc [24]. For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase [25]. 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 [26].

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 [27-31]. They are then unable to hold the drug entity any longer. [32]

TABLE 2: EXAMPLES OF PRODRUG SYSTEM FOR CDDS

Drug	Carrier	Linkage hydrolysed
5-ASA	Azo conjugates	Azo linkage
Dexamethasone	Saccharide carriers	Glycosidic linkage
Prednisolone, hydrocortisone, fludrocortisone	Glucose, galactose	Glycosidic linkage
Salicylic acid	Amino acid conjugates, glycine	Amide linkage

Prodrug [33] 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. 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. 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.

TABLE 3: DIFFERENT POLYMERS USED FOR CDDS BASED ON MICROBIAL DRUG DELIVERY SYSTEM [33]

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

2. New approaches for colon targeted drug delivery:

a. Pressure controlled drug delivery system:

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. The peristaltic movement of intestine is responsible for the passage of bolus from one part of GIT to the next part. The peristaltic movement of ascending colon transfers the bolus to transverse colon called as mass peristalsis. These peristaltic

movements occur in limited number i.e. three to four times a day. These peristaltic movements of intestine results in an increase in the luminal pressure. This increase in luminal pressure is the key point in the development of pressure controlled drug delivery system.

The pressure controlled drug delivery system [34] consists of a capsule in which the drug is present. These gelatin capsules are coated with water insoluble polymer like ethyl cellulose on their inner side. The drug is introduced into the capsule along with suppository base. The thickness of ethyl cellulose coating determines the disintegration capacity of the capsule. After administration the suppository base dissolves at body temperature. The water from intestinal contents is absorbed resulting in increased viscosity which leads to an increase in the pressure in the capsule. The pressure in the capsule expels the drug into the colon.

b. CODES:

CODES is a unique CDDS technology that was designed to avoid the inherent problems associated with pH-or time –dependent systems [35, 36]. CODES 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, (**Fig. 2**).

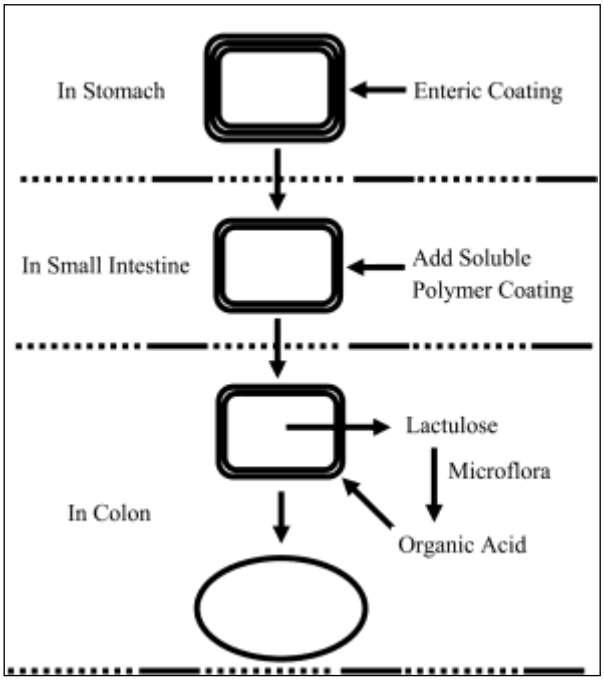

FIG. 2: SCHEMATICS OF THE CONCEPTUAL DESIGN OF CODES™

The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated 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.[37]

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.[38]

c. Osmotic controlled drug delivery system (OROS-CT):

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable.[39] The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter,encapsulated within a hard gelatin capsule, (**Fig. 3**).[40] 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 unitsdissolves.

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 enters the small intestine, the coating dissolves 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 pushpull 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.[41-44] Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

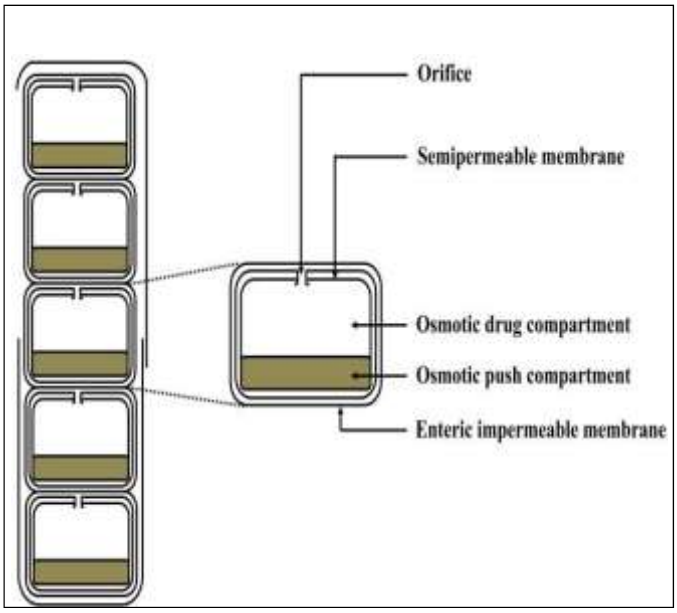

FIG.3: CROSS-SECTION OF THE OROS-CT COLON TARGETED DRUG DELIVERY SYSTEM

For in vitro evaluation, not any standardized evaluation technique is available for evaluation of CDDS because an ideal in vitro model should posses the in-vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity, and other components of food. Generally, these conditions are influenced by the diet, physical stress, and these factors make it difficult to design a slandered in-vitro model. In vitro models used for CDDS are:

a) *In vitro* dissolution test:

Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot fully mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces.[45] Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon-specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract have been studied.[46] The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileum segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4.[47]

b) *In vitro* enzymatic test:

For this there are 2 tests:

a. Incubate carrier drug system in fermenter containing suitable medium for bacteria (*Streptococcus faccium* or *B.ovatus*) amount of drug released at different time intervals determined.

b. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier [48].

c) *In vivo* evaluation:

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the micro flora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human.[49] For rapid evaluation of CDDS, a novel model has been proposed. In this model, the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which bascularizes within four weeks, matures, and becomes capable of developing of mucosal immune system from the host.

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.[50]

CONCLUSION: The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Colon targeted drug delivery system offers benefits of both local as well as systemic effects**.** Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. The main advantage of CDDS is that the colon offers near neutral pH, a long transit time, reduced enzymatic activity and increased responsiveness to absorption enhancers. The novel approaches are more specific compared to the primary approaches. The biodegradable polymers are used for the colon specific delivery of the drug. For the *in vitro* evaluation of the system the current dissolution techniques are not suitable. Research is going on to develop suitable dissolution methods to evaluate the colon targeted drug delivery systems.

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