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GENERAL STUDY ON THE DESIGN AND DEVELOPMENT OF COLONIC DRUG DELIVERY SYSTEM

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ABSTRACT

For producing systemic effect, administration of drug through oral route is mostly preferred. But due to the release of drug at upper GI tract and lower accessibility of drug at lower GI tract, oral route sometimes becomes less efficient for drug administration. To surpass this difficulty, colon specific drug delivery system has been analyzed for the last two decades. The colon is a region where both local and systemic delivery of drugs can take place. CDDS are desirable for the treatment of a range of local diseases such as ulcerative colitis, crohn's disease, inflammatory bowel disease, colonic cancer etc. In addition, the colon can be a potential site for systemic absorption of several drugs to treat non-colonic condition as well. In order to gain effective therapeutic outcomes, it is vital that the designed delivery system specifically targets the drug into the colon in a predictable and reproducible manner. This review presents a systematic discussion of various conventional as well as relatively newer formulation technologies currently being utilized for the development of CDDS

Keywords: CDDS approaches, prodrug, conventional and novel approaches,Ph sensitive polymers, delayed release, pulsincap.

INTRODUCTION

Colon targeted drug delivery has been gained important due to its capacity to improve treatment of local diseases affecting the colon and numerous studies are conducted in recent years. The delivery of drugs to the colon without absorbed from the stomach is effective. The concentration of drug in the colon is higher when there is minimum absorption from upper GIT. For improving the treatment of local diseases that affecting colon like crohn's disease, ulcerative colitis, irritable bowel syndrome etc. the important of colon specific drug delivery system design and development come into consideration. Drug which are frequently used for the treatment of diseases affecting colon include sulfasalazine, prednisolone, azathioprine, cyclosporine, mercaptopurine, dicyclomine, amitriptyline and others [1-4].

The delivery of drug to colon either through oral or rectal route, oral route is most preferred route for delivery of colon targeted drugs and it is more convenient for patient. The direct delivery of drugs to colon is not applicable, thus it is available to delivery as targeting a drug to specific sites within colon. By developing suitable dosage form with specific formulation can achieve this goal [5-6].

Several conditions that affecting the drug en route to colon is the acidic pH in stomach, intestinal micro flora, physicochemical properties of drugs, gastric emptying,

enzymes etc. the design of dosage forms is likely to be counteract or nullify the effect and successfully delivering the drug to the colon. Degradation of some drugs in acidic environment of stomach can be minimized by presenting newer techniques like polymer coating that is pH sensitive. More emphasis is put on peptide drugs, which have high chance of degradation in stomach (e.g.: insulin, calcitonin, vasopressin etc). Conventional and newly developed approaches are used for colon targeting. The most critical challenges in CDDS are to preserve the formulation during its passage through stomach and about six meters of small intestine [6].

The colon is to be a suitable absorption site for peptides and protein drugs due to many reasons like the less intensity of digestive enzymes, less proteolytic activity and which helps in increased bioavailability of peptides in colon. To ensure direct treatment at the disease site, to prolong drug delivery, lowering dose and reduce the side effects, that's why the colon targeted drug delivery is needed. Considering the advantages of colon on emphasis to near neutral pH, longer transit time, low enzymatic activity and provide a triggering system to force the release of drug on reaching the colon. Using some strategies having better success than others for developing and designing the CDDS.

The colonic contents are viscous and their mixing

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is not efficient, the proximity and availability of most of the drugs to the absorptive membrane is low. The human colon consists of microbial flora, which is approximately composed of over 400 distinct species of bacteria. The delivery of peptide molecules such as insulin through oral route will responsible for the metabolism by this microbial flora liker azo reduction and enzymatic cleavage, which will be another factor affecting CDDS. Variety of diseases that affecting colon should be treated with anti-inflammatory agents and also glucocorticoids either by oral or iv route shows systemic side effects like immune suppression, cushinoid symptoms, bone resorption and adeno suppression, in this scenario the colon targeted drug delivery is effective and can possible reduce these side effects and lower the required dose [2].

Colon is considered as a BLACK BOX, as most of drugs are absorbed from the upper part of the GIT. Prime objective in the treatment of colon diseases are increase the pharmacological activity, reduce dosing and side effects, prevent drug from degradation, ensure direct treatment at disease site, used to prolong the drug therapy, improved drug utilization. For this, a variety of strategies has been used and systems have been developed for the purpose of achieving colonic targeting, this strategies are either drug specific (prodrug) or formulation specific (coated or matrix preparation), most commonly used targeting mechanisms are pH dependent, time dependent, pressure dependent, bacteria dependent delivery [7-8].

As most of the conventional drug delivery systems for treating colon disorders such as inflammatory bowel diseases, infectious diseases and colon cancer are failing as the drugs don't reach the site of action in appropriate concentration. Thus an effective and safe therapy of these colonic disorders using colonic site specific.

Anatomy of colon

The entire length of the colon is about 5 feet (150 cm) and is divided into five main segments. The rectum is the last anatomical segment before the anus.
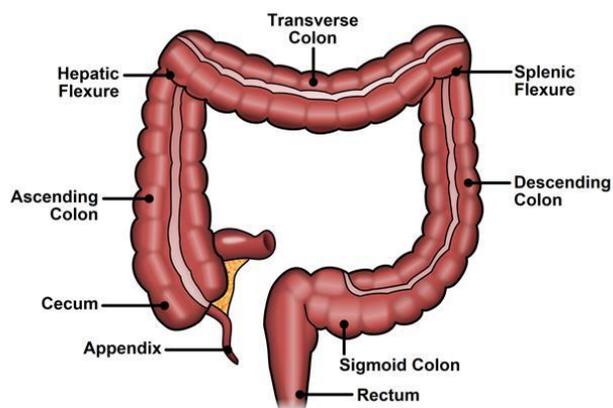
The ascending and descending colons are supported by peritoneal folds called the mesentery. The right colon consists of the cecum, the ascending colon, the flexion of the liver, and the right half of the transverse colon. The left colon consists of the left half of the transverse colon, the flexion of the spleen, the descending colon, and the sigmoid colon [7].

Factors to consider in designing a colon-specific drug delivery system

I. ANATOMICAL FACTORS
II. PHYSIOLOGICAL FACTORS
III. PHARMACEUTICAL FACTORS

Anatomical factors

The large intestine is the part of the digestive tract that starts from the cecum to the anus. It is 1.5 m long and 6-8 cm inside diameter [4].

The function of the colon

❖ Solidification of intestinal contents into feces by absorption of water and electrolytes and storage of feces until excreted from the body.
❖ Provide a favorable environment for colon microbial growth.
❖ Absorption of H_2O and Na^+ from the rumen, and secretion of K^+ and HCO_3.

Physiological factors.

❖ pH
❖ Stomach emptying
❖ Bowel-colon transit time
❖ Colonic flora and its enzymes
❖ Colon fluid volume
❖ Viscosity of the contents of the colon lumen
❖ digestive disorders status

Pharmaceutical factors

❖ Formulation factors
❖ Drug candidates
❖ Drug carriers

CDDS drug selection criteria

o Drugs used for local effects of the colon on GIT disease.
Example: Anti-inflammatory drug
o Drugs that are hardly absorbed from the upper GIT.
Example: Antihypertensive drug
   Antianginal drugs
o Colon cancer drugs.
Example: antitumor drug
o Drugs that break down in the stomach and small intestine.
Example: peptides and proteins
o Drugs that undergo extensive first-pass metabolism.
Example: Nitroglycerin and corticosteroid
o Drugs for targeting
Example: anti-arthritic and anti-asthmatic drugs.

Advantages

- Reduce gastric inflammation caused by many drugs by preventing absorption in the upper GIT (such as NSAIDS).
- Ideal location for delivery of active agents to treat colon diseases (ulcerative colitis, Crohn's disease, amoebiasis, etc.).
- Local treatment requires smaller amounts of drug.
- Bypass first-pass metabolism.
- Fewer side effects and drug interactions.
- Extended day or night activities
- Infrequent administration and cost-effective.
- Long colon retention time, improved bioavailability of poorly absorbed drug molecules (up to 5 days).

Limitation and challenges
- Colon anatomy and physiology.
- Colon is the distal part of the digestive tract, making it difficult to access the colon.
- The lower surface area and the relatively tight junction of the colon limit drug transport across the mucosa to the systemic circulation.
- Drugs bind nonspecifically to intestinal contents (food debris, intestinal secretions, feces) and may reduce the bioavailability of the drug.
- Metabolic degradation of the drug by the resident microflora can also affect colon performance.
- Factors considered in the design of a colon colon-specific drug delivery system
- Lack of adequate dissolution test to evaluate dosage form in dosage tubes.

Drug in solution form required for successful colon delivery or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs.

Approaches used for the design and development of colonic drug delivery system
Primary or conventional approaches
Novel approaches
A. Primary /conventional approaches
1. Covalent linkage of drug with carrier
a) Prodrug approaches
Azo bond conjugates
Cyclodextrin conjugates
1. Glycoside conjugates
2. Glucuronide conjugates
3. Dextran conjugates
4. Polymeric prodrugs
5. amino acid conjugation

2. Approaches to deliver intact molecule to Colon
1. Coating with polymers
2. Coating with pH sensitive polymer system.
3. Coating with biodegradable polymers

b) Embedding in matrices
1. Embedding in biodegradable matrices and hydrogels .

2. Embedding in pH- sensitive matrices
3. Time controlled release system
a) Delayed release drug delivery system
4. Microbial triggered system
5. Polysaccharide based delivery system.

B. Novel approaches
1) Pressure controlled drug delivery
2) Time dependent delivery
a) Pulsatile colon targeted drug delivery
Pulsincap system
Port system
Chronotropic
3) Colon targeted delivery capsule based on Ph sensitivity and time release
4) Osmotic controlled drug delivery (OROS-CT)
5) CODES technology
6) Multiparticulate system based drug delivery
7) Azo hydrogels
8) Probiotic approach
9) Bioadhesives
10) Redox sensitive polymers
11) Coating with micro particles
12) Hydrogels
13) Microspheres
14) Nanoparticles
15) Self-microemulsifying drug delivery system.

Covalent linkage of the drug with a carrier
It involves the formation of a covalent bond between the drug and the carrier in such a way that its parts remain intact in the stomach and small intestine upon oral administration. This approach mainly involves the formation of prodrugs.

A. Prodrug Approaches
Prodrugs are inert derivatives of drug molecules that release the active ingredient when hydrolyzed by enzymes such as those in the colon. It is designed to undergo enzymatic hydrolysis in the colon by undergoing minimal hydrolysis in the upper tract of the GIT and releasing the active drug moiety from the drug carrier [9].

Azo bond conjugates
These azo compounds are extensively metabolized by enterobacteria, both by intracellular enzyme components and extracellular reduction. The use of these azo compounds for colon targeting has been performed in the form of hydrogels as coating materials for coating drug cores and as prodrugs. In the latter approach, the drug is attached to the carrier via an azo bond [19]. This azo bond is stable in the upper GIT and is broken in the colon by azo reductase produced by the microbiota. Sulfasalazine used to treat IBD has an azo bond between 5-ASA and sulfapyridine. In the colon, azoreductase cleaves the azo bond, releasing the drug, 5-ASA, and the carrier SP [6,10].

EXAMPLE
Fig 1. 1]hydrolysis of sulphasalazine [2] 5-amino salicylic acid [3] sulfapyridine

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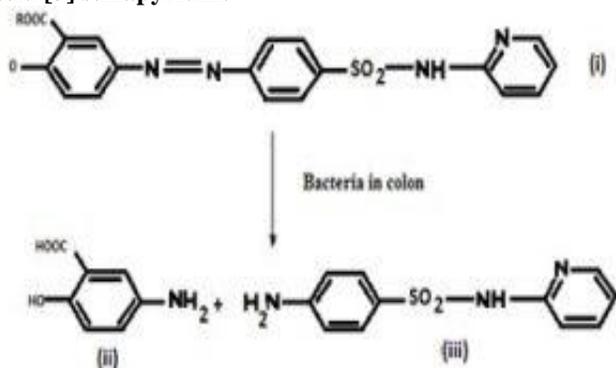
Cyclodextrin conjugate

Cyclodextrins are cyclic oligosaccharides composed of 6 to 8 glucose units via -1,4 glucosidic bonds, to improve certain properties of drugs, such as solubility, stability, bioavailability, etc. They tend to form inclusion complexes with various drug molecules. Although it is known that they are hardly hydrolyzed and only slightly absorbed by passage through the stomach and small intestine, colon bacteria can degrade the carbon source cyclodextrin by stimulating cyclodextranase activity. These form small sugars that are fermented and absorbed by the colon microbiota, but due to their sensitivity to specific degradation by the colon microbiota and the ability to form inclusion complexes with various drugs, It is particularly useful for transporting drug components to the colon.

Glycoside conjugation

The unique glycosidase activity of steroid glycosides and colon microbiota forms the basis for a new colon-targeted drug delivery system. Certain drugs can bind to different sugar moieties to form glycosides. The drug moiety forms an aglycone and is linked to the sugar moiety that forms the glycoside moiety of the glycoside. Because these glycosides are bulky and hydrophilic, they do not penetrate biological membranes when ingested.[6] They break down under the action of glycosidases, releasing the drug moiety from the sugar. The presence of glycosidase activity in the small intestine can cause problems in the delivery of these complexes to the large intestine because of the expected hydrolysis of the complex in the small intestine. Intestines. However, the transit time of the small intestine is short compared to the transit time of the large intestine, and in view of the time required for hydrolysis of glycosidic bonds, these conjugates can be expected to be excellent colon-specific drug carriers. The major glycosidase enzymes produced by the gut flora are β-D-galactosidase, α-L-arabinofuranosidase, β-dixylopyranosidase, and β-D glucosidase. These glycosidase enzymes are [6].

Example: lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone.

Glucoronide conjugates

Bacteria in the lower GIT secrete b-glucuronidase and deglucuronize various drugs in the intestine. Thus, the de-glucuronidation process releases the active drug again, allowing its reabsorption. Example: Opiate, when taken for pain relief, causes severe constipation by inhibiting motility and secretion of GIT. When given as an antidote to GIT side effects, narcotic antagonists immediately relieve constipation, but accelerate acute withdrawal. This is because these narcotic antagonists are not selective and affect not only GIT activity but also the central nervous system (CNS). A novel approach is to target the lower intestine so that these antagonists are not absorbed systemically. For this purpose, glucuronide prodrugs of naloxone and nalmefene have been prepared to direct these drugs to the colon.

Dextran conjugate
Eg: glucocorticoid dextran conjugates.

In the colon, dextran glycosidic bonds are hydrolyzed by dextranase to yield shorter prodrug oligomers, which are further split by colon esterases and release the released drug into the colon lumen. Includes carboxylic acid function (-COOH). NSAIDS ware directly attached to dextran using the carboxyl group of the drug. An example is a naproxen-dextran conjugate. Glucocorticoids do not have a -COOH group, so they bind to dextran using a spacer molecule [6,11].

Amino acid conjugation

Example: Salicylic acid (a glycine conjugate of SA) was found to be metabolized to SA by microorganisms in the intestinal flora of rabbits and dogs. Prodrugs proved to be unsuitable for drug delivery to the colon because they were absorbed into the systemic circulation from the upper GIT. By increasing the hydrophilicity and chain length of the carrier amino acids and decreasing the membrane permeability of the conjugate. The prepared salicylic acid glutamic acid conjugate. This conjugate showed excellent results with minimal absorption and degradation in the upper GIT, demonstrating its suitability for colon targeted delivery of SA [16].

Approaches to deliver the intact molecule to the colon
Coating with polymers
Coating with pH-sensitive polymers

The pH-dependent system is a generally accepted view that the pH of human GIT increases gradually from the stomach (from pH 1-2 to 4 during digestion) and from the small intestine (pH 6-7) at the site of digestion. The coating of tablets, capsules, or pellets with a pH-sensitive polymer provides delayed release and protects the active drug from gastric juices. However, the polymers used for colon targeting can tolerate the low pH values of the proximal stomach and small intestine and are slightly alkaline neutral.These processes distribute the drug throughout the

large intestine, increasing the potential for delivery systems targeted to the colon. The threshold pH generally used a pH sensitive polymer. Coating of tablets or pellets that are filled into traditional hard gelatin capsules.

Polymer	Threshold pH
Eudragit® L100	6.0
Eudragit® S100	7.0
Eudragit® L-30D	5.6
Eudragit® FS 30D	6.8
Eudragit® L100-55	5.5
Poly vinyl acetate pthalate	5.0
Hydroxy propyl methyl cellulose phtalate	4.5-4.8
Hydroxy propyl methyl cellulose phthalate50	5.2
Hydroxy propyl methyl cellulose phthalate55	5.4
Cellulose acetate pthalate	5.0

Coating with biodegradable polymers

Drugs coated with polymers that are degradable by the effects of colonic microorganisms can be used to design drugs for colon targeting. These bacterially degradable polymers, especially azopolymers, have been studied to release orally administered drugs in the colon. Release of the drug from the azopolymer-coated formulation is believed to occur after reduction, thus resulting in degradation of the azo bond by the azoreductase enzyme released by the azo bacteria present in the colonial flora. The bacterial degradation of the polymer coating depends on several other factors, such as dietary fermentation precursors, consumed food types etc [6].

Embedding in biodegradable matrices and hydrogels

Polysaccharides, polymers of monosaccharides, retain their integrity because they are resistant to the digestive effects of gastrointestinal enzymes. The polysaccharide matrix is supposed to remain intact in the physiological environment of the stomach and small intestine, but when it reaches the colon, it is subject to the action of bacterial polysaccharides and causes matrix degradation. It is composed of a large number of derivatizable groups, a wide range of molecular weights, different chemical compositions, and predominantly low-toxicity and biodegradable polymers .

Embedding in pH-sensitive matrices

Extrusion spheronization and pelletization have been used to prepare pH-sensitive matrix pellets for targeted drug delivery to the colon. Ibuprofen was used as a model drug, and Eudragit® S and Aqoat AS-HF were used as enteric polymers to develop a site-specific system that releases the drug in the lower intestine or colon .

Time Controlled Release System

Sustained-release preparations are based on drugs that are released in the colon after a specified time. This approach depends on the time of transit through the small intestine, which is known to vary between three and four hours. Stomach emptying time varies between individuals and varies with food intake. In addition, colon-related disorders, such as irritable bowel syndrome and ulcerative colitis, can affect the time it takes to cross the colon. Colon-specific delivery was achieved using a combination of a pH-sensitive polymer and a sustained release approach. A formulation was developed consisting of a drug-containing core surrounded by three polymer layers (a hydrophilic layer sandwiched between two pH-sensitive layers). In vitro evaluation results revealed sustained drug release due to pH protection and hydrogel formation.

Delayed release system
Principle: Drug release from the dosage form must be after a predetermined lag time. This means delivering the right amount of drug to the right site of action at the right time. Zein has proven to be a potential coating material for delayed release of drugs into the large intestine[1].

Example:
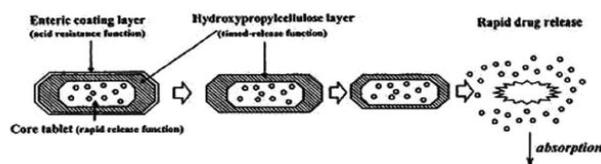Enteric-coated time-release press coated tablets

Figure 1: Design of enteric coated timed-release press coated tablet (ETP Tablet)

2.   Microbially Triggered Drug Delivery to Colon
The colonic flora mainly anaerobic bacteria such as Bacteroides, Bifidobacteria, Eubacteria, Clostridium, Enterococci, For this fermentation, the microbiome produces a vast number of enzymes, such as glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azaredducatase, deaminase, and urea dehydroxylase. These polymers protect the drug from the stomach and small intestine environment and can deliver the drug to the colon. Upon reaching the colon, the molecular weight is reduced through microbial assimilation or enzymatic degradation or degradation of the polymer's spine, thereby reducing mechanical strength [6].

3.   Polysaccharide Based Delivery Systems

Polymers can be easily modified chemically and biochemically, are very stable, safe, non-toxic, hydrophilic, gel-forming and even biodegradable. These include natural polysaccharides from plant (guar gum, inulin), animal (chitosan, chondrotin sulfate), algae (alginate) or microbial (dextran) sources. Polysaccharides are broken down by the colonial flora into simple sugars [2, 12].

NOVEL APPROACHES
1.   Pressure Controlled Drug-Delivery Systems

Takaya has developed a pressure-controlled colon delivery capsule prepared using ethylcellulose that is insoluble in water [2, 13]. In such a system, drug release occurs after disintegration of the water-insoluble polymer capsule due to pressure in the lumen of the colon. Due to the reabsorption of water from the colon, the viscosity of the luminal contents is higher in the colon than in the small intestine. In pressure controlled ethyl cellulose single unit capsules, the drug is in a liquid.
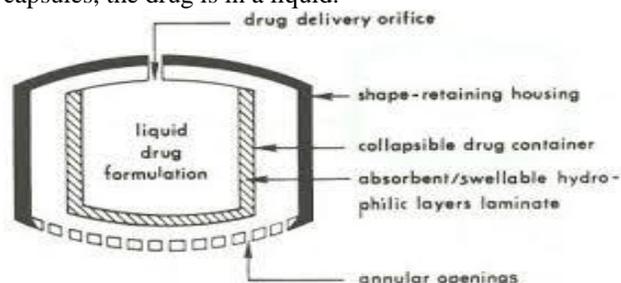

Pulsating Drug Delivery
Pulsincap System

In this system, the formulation is developed in capsule form. A plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the contents of a drug. The capsule expands upon contact with the lysate, and after a lag time the plug is pushed out of the capsule and the drug is released. Polymers such as various grades of hydroxylpropyl methylcellulose (HPMC), polymethyl methacrylate, and polyvinyl acetate are used as hydrogel plugs. The log time is controlled by the length of the plug and the intersection of the capsule body [7].
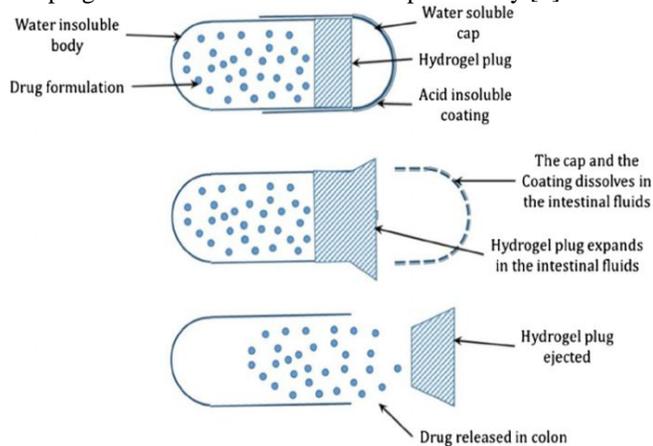

Port System

It consisted of a capsule coated with a semi-permeable membrane, with an insoluble plug of osmotically active agent and formulation inside the capsule. When the capsule came into contact with the lysate, the semi-permeable membrane allowed water to enter, thereby creating pressure and discharging the insoluble plug after the lag time [7].
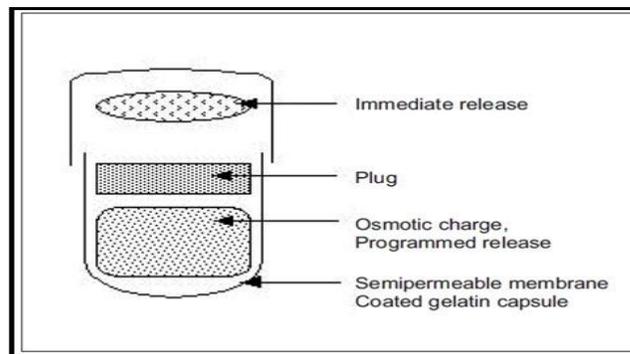
Osmotic Controlled Drug Delivery (ORDS-CT)

OROS-CT can be used to target drugs locally to the colon for treatment of disease. The OROS-CT system can be a single osmotic unit or can incorporate five or six 4 mm diameter push-pull units encapsulated in hard gelatin capsules. Each two-layer push-pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi-permeable membrane. Open an orifice in the membrane next to the drug layer. Immediately after swallowing OROS-CT, the gelatin capsule containing the push-pull unit dissolves. Due to the drug-impermeable enteric coating, each push-pull unit is unable to absorb water in the acidic aqueous environment of the stomach and therefore 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 and swells the osmotic push compartment, while at the same time creating a free flowing gel in the drug compartment . The expansion of the osmotic push compartment forces the drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For the treatment of ulcerative colitis, each push-pull unit is designed after 3-4 hours of gastric delay to prevent drug delivery in the small intestine. When the unit reaches the colon, drug release begins. The OROS-CT unit can maintain a constant release rate in the colon for up to 24 hours or deliver the drug in as little as 4 hours [14].
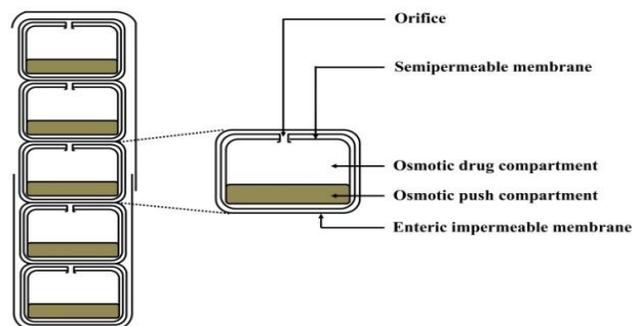
CODESTM

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 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 [2,15]. 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
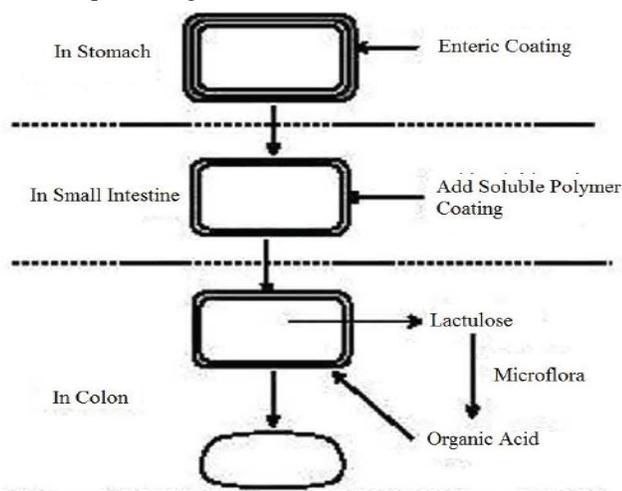

Figure 2: Schematics of the conceptual design of CODES™

Azo hydrogel

The pH-sensitive monomer and azo crosslinker in the hydrogel create colon specificity. As they pass through the GIT, these hydrogels swell as the pH increases. This swelling of the hydrogel breaks the crosslinks in the hydrogel network and causes the release of the drug entrapped in the hydrogel. These hydrogels are prepared by cross-linking polymerization of N-substituted (Meth) acrylamide, N-tert-butyl acrylamide, and acrylic acid with 4,4-di (methacryloylamino) azobenzene as a cross-linking agent. The rate of hydrogen decomposition is related to the degree of swelling and is inversely proportional to the crosslink density [7].

1. Bioadhesive Systems

The bioadhesive system allows the formulation to stay in contact in the organ, in this case the colon, for a long time, helping to absorb poorly absorbable drugs. Some of the polymers that have been considered as bioadhesive components in these systems include polycarbophil, polyurethane, and polyethylene oxide. Bio-adhesive microspheres (BAM) have been developed to target the delivery of metronidazole to the colon using Assambora rice starch. These BAMs found long retention time in the colon and helped to increase the absorption of drugs in the colon.

2. Pro-biotic approach

The probiotic approach is one of the modern methods of colon targeting. In this approach, three components are preferred: a probiotic strain, a microbial digestive carrier, and a trigger temperature. Probiotic stains include inactive flora such as bifidobacteria and lactic acid bacteria. At body temperature, these strains are activated and begin digesting the carrier, eventually releasing the drug where desired. This approach is successful in colon drug delivery systems because these conditions are only available for colon [12, 4].

3. Microspheres

Crosslinked guar gum microspheres containing methotrexate have been developed and characterized for local release in the colon for efficient treatment of colorectal cancer. In this method, glutaraldehyde was used as a crosslinking agent, and guar gum microspheres were developed by an emulsification method.

4. Nanoparticles

Nanoparticles are expected to be drug carriers to achieve oral peptide delivery. Polymer nanoparticles have the advantage of protecting protein and peptide drugs from chemical and enzymatic degradation of GIT, increasing stability and absorption in intestinal epithelium and retaining drug release [9].

Table 1. CDDS drug selection criteria

Pharmacological class	Non-peptide drugs	Peptide drugs
Anti-inflammatory drugs	Oxyprenolol, metaprolol, nifedipine	Amylin, antisense oligonucleotide
Antihypertensive & antianginal drugs	Ibuprofen, isosorbides, theophylline	Cyclosporine, desmopressin
Antineoplastic drugs	pseudoephedrine	Epoetin, glucagon
peptides & proteins	Bromophenaramine, 5-flourouracil, doxorubicin	Gonadoreline, insulin, interferones
Nitroglycerin & corticosteroids	Bleomycin, nicotine	Protirelin, sermorelin, saloatonin
anti-arthritic & anti-asthmatic drugs	Prednisolone, hydrocortisone, 5-amino salicylic acid	Somatropin, urotoilitin

Table 2. Colon targeting diseases, drugs and sites [2]

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease. Chronic pancreatitis	Budenoside,Sulfaselazine, Hydrocortisone, , Prednisolone Olsalazine, Mesalazine, Balsalazide.
Local action	Pancreatactomy and cystic fibrosis, Colorectal cancer	5-Flourouracil, Digestive enzyme supplements.
Systemic action	To prevent gastric irritation To prevent first pass metabolism of orally ingested drugs. Oral delivery of peptides Oral delivery of vaccines	NSAIDS Steroids.Insulin Typhoid

Colon disease/disorder	Drugs	Delivery system
Inflammatory bowel disease Ulcerative colitis Crohn's disease	Mesalazine	
	- Asacol®	DR tablets
	- Pentasa®	TR capsules
	Sulfasalazine	
	- Azulfidine EN-tabs®	DR tablets
	Prednisone	
	- Rayos®	DR tablets
	Budesonide	
	-MMX®	Multi-matrix tablets
	- Uceris®	ER tablets
	- Clipper®	Gastro-resistant prolonged-release tablets
	Prednisolone (Colal-Pred®)	Oral colon-targeted pellets
	Metronidazole (Flagyl® ER)	ER tablets
	Azathioprine (Azasan®)	IR tablets
	Mercaptopurine (Purinethol®)	IR tablets
	Cyclosporine (Gengraf®)	IR capsules, oral solution

CONCLUSION

The colon area of the GIT has become an increasingly important site for drug delivery and absorption. CDDS provides patients with therapeutic benefits in both local and systemic treatments. The system utilizes natural substances that are broken down by colonic bacterial enzymes. The colon provides favorable factors and conditions for the design of the delivery system. High commercial viability. The increase in international patents and research work on this particular mode of drug delivery itself indicates a potential for the pharmaceutical market. The colon area of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers significant therapeutic benefits to patients, both in terms of local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural substances that are broken down by colonic bacterial enzymes. Given the sophistication of colon-specific drug delivery systems and the uncertainty of current lysis methods in establishing potential in vitro / in vivo correlations, pharmaceutical scientists have taken lysis into account with physiological characteristics of the colon Challenges remain for developing and validating the method, which can still be used routinely in the industry environment for CDDS evaluation.

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