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Colon Targeted Drug Delivery:- A Review

T M Litto*, S D Shaiju, S Meenu
M pharm, Department Of Pharmaceutics, Ezhuthachan College Of Pharmaceutical Sciences, Marayamuttom, Neyyatinkara, Trivandrum-695124
Principal, , Department Of Pharmaceutics, Ezhuthachan College Of Pharmaceutical Sciences, Marayamuttom, Neyyatinkara, Trivandrum-695124
M pharm, , Department Of Pharmaceutics, Ezhuthachan College Of Pharmaceutical Sciences, Marayamuttom, Neyyatinkara, Trivandrum-695124

Abstract

The main aim of colon specific drug delivery systems (CDDS) is the treatment of a range of local diseases such as ulcerative colitis, crohn's disease, Irritable bowel syndrome, chronic pancreatitis and colonic cancer. The oral route is not suitable to the administration of the drug for the lower gastro intestinal(GI) diseases, this happened due to their release at upper GI tract (stomach , small intestine) that will further minimizes the accessibility of drugs at lower GI tract. To overcome this difficulty, so many formulation approaches have been developed for targeting the colon. These approaches is mainly formulated according to GI physiology, such as the difference in the pH along the GI tract, the presence of colonic microflora and enzymes. This review discusses about the merits and demerits, factors influencing the colonic transition, novel and emerging approaches in the colon targeted drug delivery and colonic diseases.

Keywords :- Colon specific drug delivery system (CSDDS), GI physiology, Colonic diseases, Formulation approaches

INTRODUCTION

The targeted drug delivery system is defined as a desired drug concentration in the body by delivering a therapeutic amount of drug to a target site. The reasons for targeting a drug into a specific site such as instability, low solubility, short halflife, a large volume of distribution, poor absorption, low specificity and therapeutic index. The advantages of targeted drug delivery is to increase the therapeutic activity of the drug, preventing the degradation of drug, minimize the adverse effect, and to reduce the toxicity of the drugs by reducing dose. [1]

The colon targeted drug delivery of drugs into the lower GI tract, for localized treatment of several colonic disease mainly inflammatory bowel disease (Crohn's disease & ulcerative colitis), irritable bowel syndrome and colon cancer. The colon specific drug delivery system should be capable of protecting the drug en route to the colon ie., drug release and absorption should not occur in the stomach and the small intestine, and neither the bioactive agent should be degraded in either of the dissolution studies but only release and absorbed once the system reaches the colon. The colon is belives to be a suitable absorption site for peptides and protein drugs for the following reasons; less diversity and intensity of digestive enzymes , comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptides drug from hydrolysis and enzymatic degradation in duodenum and jejunum and eventually release the drug into ileum or colon which leads to greater systemic bioavailbility. [3]

The oral route is the most convenient and important method for administration of drugs for systemic effects, but the oral route is not suitable for the administration of the drug for lower GI diseases because the drug release at upper GI tract which further minimizes the accessibility of drug at lower GI tract.

To overcome this difficulty the drugs are formulated with different novel and emerging approaches. According to GI physiology such as the difference in pH, presence of colonic microflora and enzymes.Some factors are to be considered for successful colonic drug delivery, including the properties of the drug, the type of delivery system and its interaction with healthy or disease gut. [There are different types of polymers are used for the colon targeted drug. These include biodegradable polymers, natural polymers and synthetic polymers. The application of these polymers is taste masking, modify drug release characteristics, enhance the drug stability and sustained release of drug. [5]

ADVANTAGES OF COLON TARGETED DRUG DELIVERY

- The site specific drug delivery to lower part of GIT for localized treatment of several colonic diseases (ulcerative colitis, crohn's disease, carcinomas and infections)
- Ensure direct treatment at disease site
- Prevent drug from degradation
- Used to prolong the drug therapy and pharmacological activity
- Improved drug utilization
- Reduce dosing
- Fewer systemic side effects
- Suitable absorption site for protein and peptide drug
- Avoidance of hepatic first pass metabolism
- Minimizing the mucosal irritation
- Dosage frequency is less, so cost effect
- The long retention time of colon, improved bioavailability of poorly absorbed drug molecules (up to 5 days) [1]
- Extended day time or night time activity
- 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 [3]

- The colon is having high water absorption capacity, the colonic contents are considerably viscous and thus availability of most drugs to the absorptive membrane is low [3]
- The metabolic process like azo reduction and enzymatic cleavage are take place in colon which is responsible for the metabolism of many drugs and peptides like insulin [3]
-

DISADVANTAGES:

- A longer residence time of 3-5days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme. [3]
- Single unit colon targeted drug delivery system has the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology. [3]
- Development of colon specific drug is difficult due to many biological barriers. [3]
- Cytochrome (p450) class of drug metabolizing enzyme has lower affinity in the colonic mucosa. [3]
- There is less fluid in colon them in small intestine and hence,dissolution is a problem for water soluble drugs.
- Binding of drug to dietery residues, intestinal secreation etc, reduce concentration of free drugs.
- Some microflora may degrade the drug.
- Small luminal surface area and relative tightness of tight junctions is colon, delay the systemic absorption.
- Onset of action is slow

LIMITATIONS

- Colon offers a near neutral PH , at the site of drug delivery , reduced enzyme activity , along transit time and increased responsiveness to absorption enhancers [3]
- Wide range of PH value and different enzymes present throughout the gastro intestinal tract, through which dosage form has to travel before reaching target site [3]
- For better drug delivery it should br in solution from before it arrives in the colon [3]\
- Fluid content in the colon is much lower and it is more viscous than in the upper part of GI tract [3]
- Stability of drug is also a concern and must be taken in to consideration while designing the delivery system. The drug may potentially bind is a non-specific way to dietary residues , intestinal secretions, mucus or fecal matter [3]

FACTORS TO BE CONSIDERED IN THE DESIGN OF CDDS

1, ANATOMY AND PHYSIOLOGY OF COLON

The GIT is divided into stomach, small intestine and large intestine. The large intestine extending from the ileo-caecal junction to the anus is divided into three main parts. These are the colon, the rectum and the anal canal. The colon itself is made up of the caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descendingand the sigmoid colon. [1] [3]

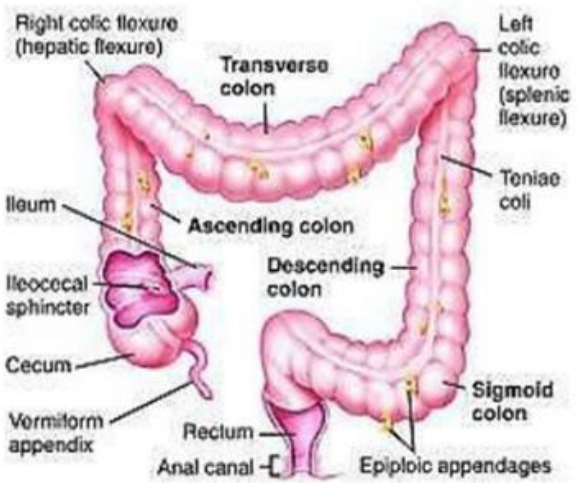

FIG:1 STRUCTURE OF COLON

The colon wall is composed of four layers; the serosa (exterior coat), the muscularis externa, the submucosa and the muvosa. Lining the lumen of the colon, the mucosa is divided into epithelium, lamina propria and muscularis mucosac. The arterial blood supply to the proximal colon is from the superior mesenteric artery and the inferior mesenteric artery supplies the distal colon.

a) Different layers and parts of colon and its description

Layers of colon	Description
serosa	Exterior coat of the large
Muscular external	Major muscular coat of the
Sub mucosa	A layer of connective
Mucosa	The mucosa has three :

Parts of colon	Description
Ascending colon	20- 25 cm long located
Cecum (proximal right	6×9 cm pouch covered with
Transverse colon	Lies anterior in the
Descending colon	10- 15 long located behind
Sigmoid colon	This part describes an s-
Rectum	This is a slightly dilated
Anal canal	This is the short passage

2, INTESTINAL- COLONIC TRANSIT TIME

The intestinal-colonic transit time plays an important role in the colonic bioavailability of drugs. The colonic diseases such as, UC and CD also influenced by the transit time. The transit of dosage forms generally depends on the time of administration, presence/absence of food and the type of dosage form. Small intestinal transit is not influenced by the physical state, size of the dosage form and the presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hrs to reach the ileocecal tunction and the time period is consistent. The colonic transit time is highly influenced the

bioavailability of drugs released from the dosage forms. The factor influence the colonic transit time is gender and size of the dosage form and physiological conditions such as stress, presence of food and diseased state. Solution and small particles are slowly pass through the proximal colon. The women shows shorter colonic transit time compare to men. In adults the colonic transit time of capsule is about 20-35 hrs and the transit time of capsule is independent of the capsule density and volume. [3] [4]

Organ	Transit time (h)
stomach	<1(fasting)
Small intestine	3-4
Large intestine	20-30

3, COLONIC pH

The pH of the GIT is subjected to both inter and intra subject variations. The pH of the colon may be influenced by a carbohydrate rich diet. This is due to the fermentation of polysaccharides by colonic bacteria and subsequent formation of short chain fatty acids. The pHof colon affects the pharmacokinetics and pharmacodynamic behavior of a CDDS by influencing the solubility of the drugs in the colonic fluid. For eg: If the CDDS formulation contain a pH – sensitive coating membrane, then the effect of colonic pH is even pronounced on the drug release. [4]

pH OF GIT PARTS

organ	pH
Stomach	1.5-2(fasted state) 2-6(fed
Small intestine	6.6-7.5
Right colon	6.4
Mid colon	6.0
Left colon	7.6
Rectum	7

4, COLONIC MICROFLORA AND ENZYMES:

The human colon consist of over 400 different species of aerobic and anaerobic micro organisms like Escherichia coli and clostridium species. These bacteria produce several hydrolytic and reductive metabolizing enzymes. These enzymes catalyze a range of reactions,including the metabolism of xenobiotics (eg: drugs) and other biomolecules (eg: bile acid), deactivation of harmful metabolites as well as carbohydrates and protein fermentation. The chitosan, guargum, peptin, etc is a polysaccharides and these are commonly employed as release rate-controlling components in colon targeting dosage forms. These polysaccharides have ability to resist both gastric and intestinal enzymes. But are metabolized by anaerobic bacteria present in the colon. Drugs are also known to be succeptible to biotransformation by colonic enzymes. The metabolism of drugs by the colonic enzymes may result in the formation of metabolities that are pharmacologically active or inactive. The pharmacologically active metabolites by the colonic metabolism of drug is commonly used "prodrug" approach for the colon specific drug delivery system. [4]

Drug metabolizing enzymes and microorganisms

enzymes	Microorganisms
Nitro reductase	E-coli, bacteroides
Azo reductase	Clostridia, lacto bacilli, E-
glycosidase	Clostridia, eubacterium
glycuronidase	E-coli, A.aerogenes

5, COLONIC ABSORPTION

The surface area of the colon is much less compared to small intestine. The colon resident time is about 10-24 hrs. The mechanism of absorption in the colon is divided into two ie;

i. Transcellular transport (passing through colonocytes)
ii. Paracellular transport t(passing through adjacent colonocytes)

The absorption is influenced by the transport of water, electrolytes and ammonia across the mucosa. The absorption of the drug in the colon is enhanced by the use of absorption enhancers and it shows effective absorption through various membranes. The absorption enhancers causes disruption of the intracellular occluding junction complex, opens the paracellular route, modification of epithelial permeability by denaturing membrane proteins and modification of lipid-protein interaction and distruption of the integrity of lipid barrier by colonic electrolytes. The GI diseases such as crohn's disease, constipation, diarrhea and gastro enteritis may affect the release and adsorption properties of colon specific drug delivery systems. [3]

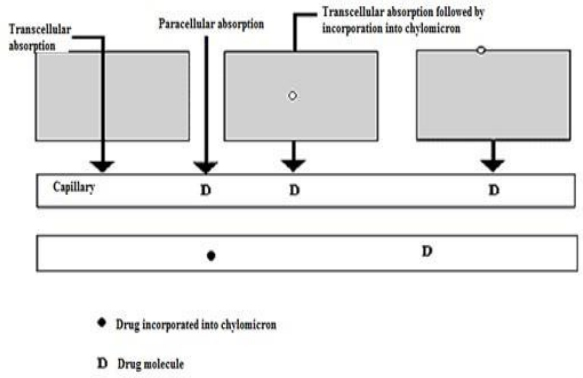

FIG:2 COLONIC ABSORPTION

6, PHARMACEUTICAL FACTORS

a) DRUG CANDIDATES

The drug candidates used in the CDDS must be poorly absorbed from the stomach and small intestine and show compatibility with carrier molecule and show stability at alkaline pH of GIT. These should be widely used for treatment of IBD and other diseases

Eg: sulphasalazine and 5-aminosalicylic acid etc. [1]

b) DRUG CARRIERS

The carrier selection depends on the physicochemical nature of the drug as well as disease for which system is to be used. The chemical nature, stability and partition coefficient of the drug and the type of absorption enhancers chosen influence the carrier selection. [3]

APPROACHES FOR COLON TARGETED DRUG DELIVERY SYSTEM

a) PRIMARY APPROACHES FOR CDDS

i. pH SENSITIVE POLYMER COATED DRUG DELIVERY TO COLON

In this approach, to provide a coating to the dosage form (eg: tablets/pellets) with various pH sensitive polymers and it will produce delayed release formulation and protect it from upper GIT. [1] The pH varies from 1 to 8 throughout GI transit and it declines significantly from the ileum to the colon. The pH sensitive polymers are insoluble in low pH and it increasingly soluble in high pH .Example : eudragit S and eudragit L. some problems associated with this approach, these are;

- Variability in gastrointestinal pH between and within individuals and it is affected by diet, disease conditions
- Poor site- specificity (start to dissolve even in the lower small intestine)

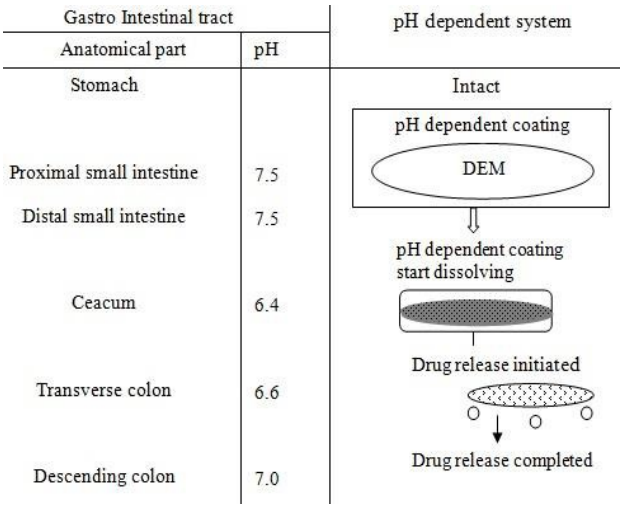

FIG:3 PRESENTATION OF pH DEPENDENT RELEASE

ii. DELAYED (TIME CONTROLLED RELEASE SYSTEM) RELEASE DRUG DELIVERY TO COLON

Time controlled release system formulation are based on the drug released in the colon after a specified amount of time. It depend on the transit time through the small intestine, it vary between 3 and 4 hrs. the gastric emptying time is inconsistent between individuals and also fluctuates depending on food intake. Some diseases associated with the colon such as, irritable bowel syndrome and ulcerative colitis are also influence the transit time through the colon. The gastro intestinal movement, especially peristalsis or contraction in the stomach would result in change in gastro intestinal transit of the drug. The combinations of hydrophilic (HPMC) and hydrophobic polymers have been used as coating for tablets that release drug from a core after a lad time. Time controlled formulations have also been prepared using water insoluble ethylcellulose and swellable polymer. [3]

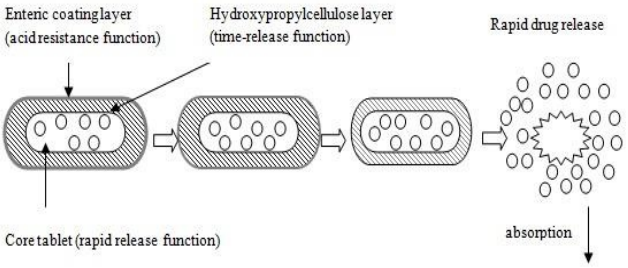

FIG:4 DESIGN OF ENTERIC COATED TIMED-RELEASE PRESS COATEDTABLET

iii. MICROBIALLY TRIGGERED DRUG DELIVERY TO COLON

This approach is based on degradation ofbiodegradable polymer coated on the dosage forms by micro flora present in colon. The colon is rich in micro organisms. These dosage forms protected from upper GIT, because very little microbial degradable activity in upper GIT. The biodegradable polymer coated dosage forms on reaching the colon, they under go assimilation by micro organism or degradation by enzyme or breakdown of the polymer back-bone leading to a subsequent reduction in their molecular weight and there by loss of mechanical strength. They are the unable to hold the drug entity any longer. [2]

1. PRODRUG APPROACH FOR DRUG DELIVERY TO COLON

Prodrug approach is a non specific chemical approach to mask unwanted drug properties such as low bioavailability , less site specifity and chemical instability. In colonic delivery, the prodrug is formulated to undergo minimal hydrolysis in the the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier. The prodrug approach is not very versatile approach because its formulation dependes upon the functional group available on the drug moiety for chemical linkage. So the prodrugs are new chemical entities and need a lot of evalution before being used as carriers. [1] [4]

2. AZO- POLYMERIC APPROACH

It is a newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic and naturally occurring polymers are used for this purpose. Semi-synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety. Various azo polymers have also been evaluated as coating material over drug cores. These have been found to be similarly susceptible to cleavage by the azo reductase in the large bowel. Coating of peptide capsules with polymers corss linked with azo aromatic group has been found to protect drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced and the drug is to be released. [1] [2]

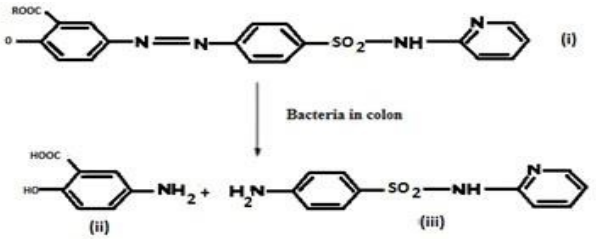

FIG:5 (I) HYDROLYSIS OF SULPHASALAZINE (II) 5-AMINOSALICYLIC ACID (III) SULFAPYRIDINE.

3. POLYSACCHARIDE BASED APPROACH

Polysaccharide based delivery systems is most convenient and have several advantages for design the colon targeted drug delivery systems. Some of the advantages of polysaccharides use include easy availability, easy modifications, stability, safety and biodegradability.[4]

Polysaccharide such as pectin, chitosan ,chondroitin sulfate, galactomannan, amylase are ideal materials for achieving colon specific delivery because they can be degraded by the colonic enzymes and are harmless to the organisms. Pectin is a hydrophilic polysaccharide which can modify drug release due to its gelling ability. An insoluble polymer such as ethyl cellulose is often mixed with the pectin in the coating layer to help reduce water permeability and protect the drug core. [4]

The use of a combination of polysaccharides in CDDS has been found to be more effective for achieving colon specific delivery compared to the use of a single polysaccharide. The polysaccharides are broken down by the colonic microflora to simple sacchrides, so these fall into the category of "generally regarded as safe"(GRAS). [1]

a) NOVEL APPROACHES FOR CDDS

1. PRESSURE CONTROLLED DRUG DELIVERY SYSTEMS (PCDDS)

The pressure controlled systems are designed on the basis of luminar pressure with in the colon. In this delivery, is in the form of capsule which is resistant to the pressure of upper GIT but it is collapsed in the large intestine, due to increased pressure. The digestive process with in GI tract involve contractile activity of the stomach and peristaltic movement for propulsion of intestinal contents. The colon produce strong peristaltic waves with short duration, and it occurring only 3-4 times a day. The capsule shell are fabricated from ethyl cellulose. The collapse time of the capsule in large intestine can be controlled by adjusting the thickness of the capsule shell wall. [3]

In the system drug release occurs following disintegration of a water insoluble polymer capsule as a result of pressure in the lumen of the colon. The pressure controlled system also depend on capsule size and density, because the re-absorption of water from the colon, the viscosity of luminal comtent is higher in the colon than in the small intestine. In pressure controlled ethyl cellulose single unit capsules the drug is in a liquid. The lag time was 3 to 5 hrs in relation to drug absorption were noted when pressure controlled capsules after administered to human. [2]

2. NOVEL COLON TARGETED DRUG DELIVERY SYSTEM (CODES^{TM})

CODES^{TM} is aadvanced and unique CDDS technology, which overcomes the problems associated with PH or time dependent systems. It is a combination of two approaches ie; PH – dependent and microbially trigged CDDS. It is comprises a series of polymers that are combined to protect the drug core until the formulation enters in the colon. CODES^{TM} is developed by utilizing a unique mechanism involving lactulose, which act as a trigger from site specific drug release. The system designed as a traditional tablet core containing lactulose, which is over coated with an acid soluble material, eudragit E and then subsequently over coated with an enteric material,eudragit L . in this technology protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating is then protects the formulation as it passage through the alkaline pH of the small intestine. Once the tablet enters in the colon the bacteria will enzymatically degrade the polysaccharide (lactulose) in to organic acid. This lower the PH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release. [2]

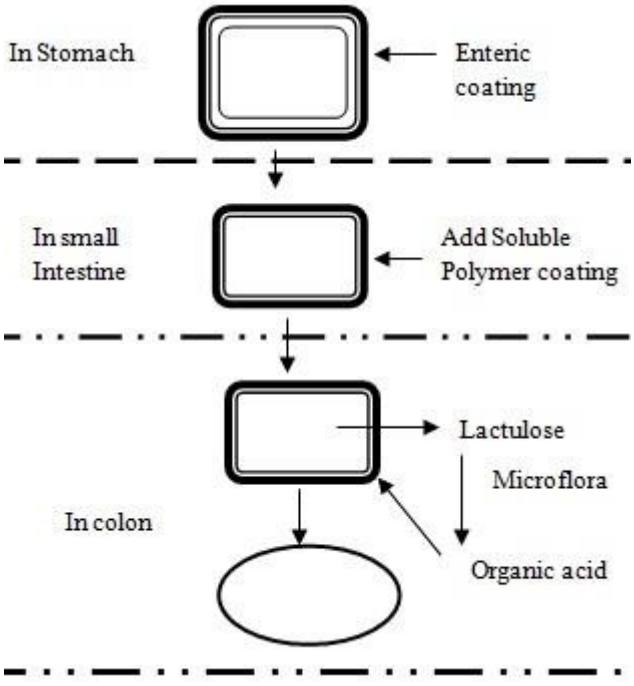

FIG:6 DESIGN OF CODES™

3. OSMOTIC CONTROLLED DRUG DELIVERY TO COLON (ORDS-CT)

The ORDS-CT (Alzacorporation) has been used to target the drug locally to the colon. It deliver the drug, when the unit dosage reached the colon and maintained a constant release rate for up to 24hrs in the colon. The ORDS-CT is an example of a system regulated by osmotic pressure. It contains a hard gelatin capsule which dissolves in the

pH of the small intestine and allows water enters to the unit. Then the system will swell and the drug is forced out with in each capsule there can be as many as 5-6 units and each units is surrounded by a drug impermeable enteric coatings, which prevents water form entering in the acidic environment of the stomach. When it reaches to the higher pH of the small intestine the coating dissolves and the water enters to the system. With in the enteric coating there is a semi permeable membrane which encompasses an osmotic push compartment as well as a drug compartment. When the water enters to the system the push compartment is swell and forms a gel in the drug compartment that is forced out of an orifice through the membrane. The rate at which water enters to system is depends on the rate at which the drug flows out to the system. The drug release in the small intestine is prevented by the system is designed such that there is a lag time between when the enteric coating dissolves and the drug is released. [1] [4]

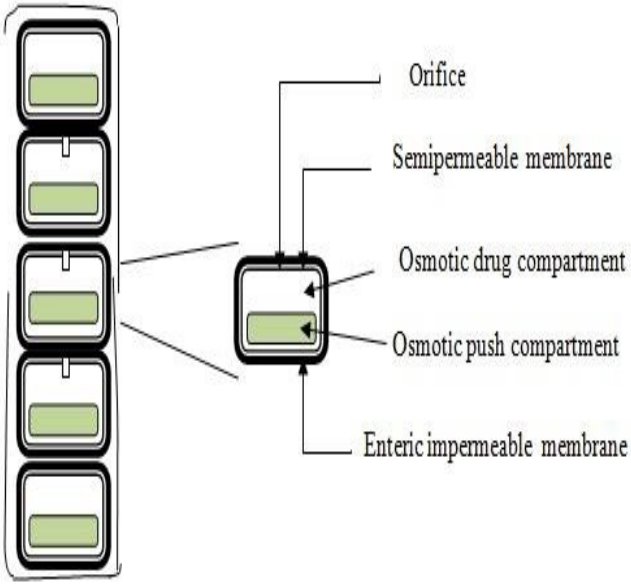

FIG:7 CROSS-SECTION OF THE OROS-CT SYSTEM

b) ADVANCED APPROACHES FOR CDDS

1,MINITABLET APPROACH

These mini-tablet processing includes different techniques of formulation like the use of polymers that release drug in time- dependent manner called core mini- tablet filled with pulsincap. In another method the pH dependent and microsomal enzyme- dependet polymers, that are known as capsules filled with matrix mini- tablets or filled with coated mini- tablets by utilizing pH- dependent polymer. [6]

2, MICROSPHERES

Biodegradable polymers or protein based microsphere having free- flowing properties and the particle size 5200nm, and it have a variety of advantages over conventional drug delivery systems. The microspheres provide a localized, sustained delivery and better stabilization of the sensitive drug. Different kind of matrices used in these microspheres, they are polysaccharide- based microspheres, combination of prodrug approach along with mulitiparticulate system, pectin metronidazole microspheres etc…[6]

3, MUCOADHESIVE APPROACH

The mucoadhesive approach is the one of the advanced technology used for CDDS. In this method, the increasing the residence time of drug and bioavailability. Here the system is formulated with the mucoadhesive polymers. The mucoadhesive polymers aloows better adhersive to the mucus layer of the colon and sustained release of drug in to the colon. Example for mucoadhersive approach is the naproxen sodium mucoadhersive polymer made of sodium alginate and eudragit 100 for the treatment of ulcerative colitis. [6]

CONCLUSION

Drug delivery to the diseased colon are advantages is reducing systemic side effects, lower dose of drug, supply of the drug only when it is required and maintainance of the drug in tis intact form as close as possible to the target site. Better colonic delivery could be achieved by protecting the drug from absorption and the environment of the upper GIT andthen abruptly released in to proximal colon, which is the site for colonic targeted delivery of drugs. All the aooroaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbed drugs. The colon is rich in microflora which can be used to target the drug release in the colon.

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