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Review Article

RECENT ADVANCES IN COLON TARGETED DRUG DELIVERY SYSTEM: AN UPDATE

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ABSTRACT

Colonic drug delivery has gained interest for the delivery of drug for the treatment of local diseases which allows for treatment of inflammatory bowel disease associated with colon and systemic delivery of therapeutic peptides and proteins and its side effects could be reduced. The drug directly delivered to colon then its treatment is more effective. The colon is often a prospective site for the systemic absorption of a handful of drugs for the treatment of non-colonic conditions. Improved drug delivery systems are essential for drugs currently in use to treat localized diseases of the colon. Drugs like proteins and peptides that are identified to degrade in the extreme stomach pH scale, if delivered to the colon intact, can be systemically absorbed by colonic mucosa. In order to attain effective therapeutic results, it is imperative that the designed delivery system specifically targets the drugs into the colon. The various strategies for targeting administered drugs to the colon include coating with pH-sensitive polymers, formulation of timed released systems, bio adhesive systems and osmotic controlled drug delivery systems. The advantages of targeting drugs precisely to the diseased colon are reduced frequency of systemic side effects, lower dose and supply of the drug to the bio-phase only when it is required and maintenance of the drug in its intact form as close as possible to the target site. This study is based on anatomy and physiology of the colon advantages, limitations, and their approaches for targeted delivery at a specific site of the colon.

KEYWORDS: *Colon drug delivery, novel approaches, inflammatory Bowel disease, polymers.*

INTRODUCTION

Colon targeting drug delivery is not only valuable for the oral delivery of peptide and proteins drugs which is degraded by the digestive enzymes of stomach and small intestine but also for low molecular weight compounds for the delivery used to treat diseases related with the colon or large intestine for example ulcerative colitis, diarrhea, and colon cancer [1]. The colon target drug delivery system (CDDS) should be able to protect the drug and route of administration to the colon i.e. release and absorption of drug should not occur in the stomach along with the small intestine, and neither the bioactive agent should be degraded either of the dissolution sites, but only released, absorbed once the system reaches the colon [2]. Coating of the drugs with pH-sensitive polymers provides simple propose for colon-specific drug delivery. Drugs used in colon cancer are: 5-fluorouracil, 9-aminocamptothecin, Capecitabine, Cetuximab, Trinotecan, Levamisole hydrochloride, Oxaliplatin, Trimetrexate, UFT (tegafur and uracil), Bevacizumab, Cisplatin [3, 4].

Drug preparation for intrarectal delivery is delivered as solutions, foam, and suppositories. The intrarectal route is used as both as a means of systemic dosing and for the delivery of active drug topically to the large intestine. Corticosteroids [hydrocortisone and prednisolone] are administered through the rectum for the ulcerative colitis treatment. Even though these drugs absorbed from the large bowel, it is commonly supposed that their efficacy is due mainly to the topical application. The concentration of drug attainment the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been made that it retained especially in the rectum and sigmoid colon while enema solutions have a great spreading capacity [5]. Since the high-aqueous absorption capacity of the colon, the colonic contents are significantly viscous, and their mixing is not well organized, thus the availability of most drugs to the absorptive membrane is low. The human colon has more than 400 distinct species of bacteria as resident flora, Amongst the reactions carried out by the gut flora are enzymatic cleavage namely glycosides [6]. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to the targeted sites of colon peptide-based macromolecules for instance insulin by oral administration.

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Advantages of colon drug delivery:

1. The Colon is an ideal site for the delivery of drugs to treat the local diseases of the colon.
2. The advantage of local treatment is that requiring smaller drug quantities.
3. Dosage frequency reduced and reduces systemic side effects and interactions of the drug, also improved bioavailability.
4. Through CTDDS gastric irritation reduced which caused by many drugs like NSAIDs.
5. Initially bye-pass first-pass metabolism.
6. Day time or nighttime activity extended.
7. Improve patient compliance.
8. It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs [7].
9. It has an aiding environment, least peptidase activity that's why the peptides, oral vaccines, insulin, growth hormones, can be administered through this route [8].

Criteria for Selection of Drug for CDDS:

CTDDS drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are important for local colon delivery drugs used for local effects in colon against GIT diseases [9].

Choice of polymer for CDDs: [10]

Delivery of drugs to the colon leads interest for local and systemic treatment of various colonic diseases because it has various therapeutic advantages of the colon like near neutral and longer transit time. The advantage of delivery of a drug to the colon provides protection of the drug from degradation or release in the stomach which can be achieved by using polymer. The polymer can influence the rate of release and absorption of the drug also plays an important role in formulating CTDDS. Both natural and biodegradable polymers are ideal for drug delivery applications.

The advantage of polymers is-

- Reasonable and obtainable in a variety of structure.
- Biodegradable polymers are broken down in the presence of biologically acceptable molecules that are metabolized and eliminated from the body via a normal metabolic alleyway.
- So, the choice of polymer for the formulation of colon targeted drug delivery system is playing a dynamic role [11, 12].

Table No. 1: Colonic diseases, its sites, and active drug components [13]

Targeted site	Disease	Drug
Topical	Inflammatory bowel diseases Irritable bowel diseases, Amoebiasis	Hydrocortisone, Prednisolone, Metronidazole, Mebendazole, Tinidazole
Systemic	Oral delivery of peptides and vaccines, to prevent gastric irritation, to prevent first-pass metabolism of an orally administered drug	NSAIDs, Steroids, Insulin
Local	Pancreatectomy, Colorectal cancer, cystic fibrosis, chronic pancreatitis	5- Fluorouracil, digestive enzymes

Anatomy and Physiology of Colon:

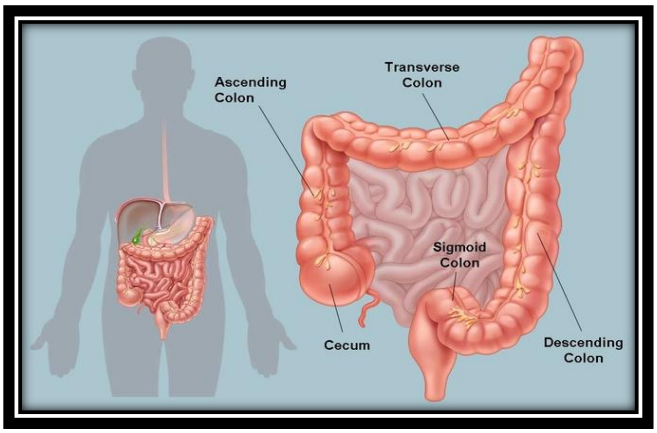

Fig. 1: Anatomy of colon

The GIT is divided into three parts Stomach, Small intestine, and large intestine. The large intestine is 1.5m long and divided into caecum (6-9 cm), appendix, colon, and rectum. The colon is dividing into the ascending, transverse and descending colon. The colon eliminates water, salts and some nutrients from the stools.

The ascending colon 20-25cm in length. It runs through the abdominal cavity upwards in the direction of the transverse colon. It extends from the caecum to the hepatic flexure. Its main purpose is to remove water and nutrients. The waste materials are moving uphill into the transverse colon and this process called peristalsis.

The transverse colon (40-45cm) is the colon part from the hepatic flexure to the splenic flexure.

The descending colon (10-15cm) is the portion of the colon from the splenic flexure to the opening of the sigmoid colon (35-40cm). The descending colon function is to store food

which shrunk into the rectum. Colon including of four different layers is Mucosa, Submucosa, Muscularis externa, and Serosa. The colon and its contents coated by the Billions of bacteria. The main function of the colon is providing a suitable environment to Colonic microflora growth and as storage reservoir of fecal contents and eliminates waste materials from the colon at an apposite time. The absorption capacity of the colon was originated to be very high at approximately 2000ml. The fluid goes in the colon through the ileocecal valve 90% of which is absorbed by the colon. The colon holds almost 220 gm of wet material which is comparable to 35 g of dry matter [14].

Approaches used for Site Specific Drug Delivery to Colon (CDDS):

Numerous approaches are used for specific site drug delivery. The primary approaches of CDDS, these consist of:

1. Primary Approaches for CDDS:

a. pH-Sensitive Polymer Coated Based Delivery to the Colon:

The stomach pH range is 1 to 2 all through fasting but rises after intake [15]. The pH small intestine is about 6.5, and approximately 7.5 in the distal small intestine. pH declines from the ileum to the colon, significantly. The use of pH-dependent polymers is depending on the differences in pH levels. The polymers designated as pH-dependent on colon targeted drug delivery are unsolvable at low pH levels but more soluble when pH rises. [16]A various mechanism has been established to conquer the colon targeting of drugs. Generally used mechanisms is that the formulation coated by using natural or synthetic polymer [17]. The most frequently used pH-dependent polymerase derivatives of acrylic acid and cellulose [18].

Table No. 2: Viewing different PH sensitive polymers and their threshold pH release [19]

S. No.	Polymer	Threshold pH
1	Eudragit S-100	7
2	Eudragit PL-100	6
3	Eudragit Fs30D	>7
4	Hydroxy-propyl-methyl Cellulose phthalate 6	>5.5
5	Shellac	7
6	Eudragit L100-55	5.54

b. Delayed (Time controlled release system) release drug delivery system:

Time-dependent / Controlled release system, for instance, sustained or delayed-release dosage form are also very capable drug release system. Yet due to potentially large differences in gastric emptying time of dosage forms. In these approaches, the Colon entrance time of dosage forms cannot be accurately predicted, subsequent in poor colonial availability [20]. The strategy in designing time-released systems is to resist the acidic environment of the stomach and to undertake a lag time of predetermined duration of time, after which release of the drug have affected the lag time. In this case, the time required to transit from the mouth to colon a lag time of 5 hours is frequently considered enough since small intestine takes about 3-4 hours, which is comparatively constant and scarcely affected by the nature of formulation administered [21]. Enteric-coated time-release press coated tablets, are made of three components, a drug containing core tablet, the press coated swellable hydrophobic polymer layer (Hydroxypropyl cellulose layer, and an enteric coating layer (acid resistance function). [22] The drug does not release from the tablet in the stomach because of the acid resistance of the outer enteric coating layer. Afterwards, gastric emptying, the enteric coating layer rapidly dissolves, and the intestinal fluid initiates to gradually erode the press coated polymer layer. As soon as the erosion front spreads the core tablet, quick drug release occurs later the erosion process takes a long period as there is no lag phase after gastric emptying.

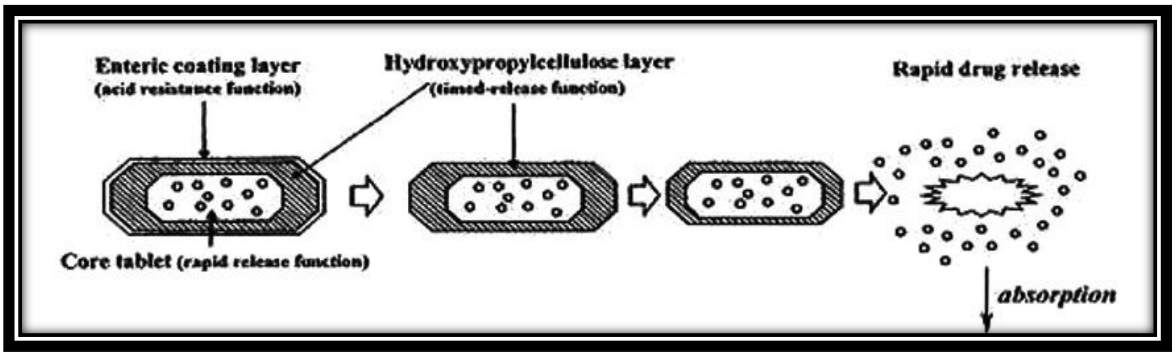

Fig. 2: Design of enteric coated timed-release press coated table

i. Microbially Triggered Drug Delivery to Colon: The microflora of the colon is in the range of 10^{11}-10^{12} CFU/mL, comprising chiefly of anaerobic bacteria e.g. Bacteroides, Eubacteria, Clostridia, Enterobacteria, and Ruminococcus, etc. This vast microflora fulfills its energy needs by fermenting various substrates that have been remained undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides, etc. For fermentation, the microflora produces several enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase. Only the biodegradable enzymes are present in the colon, the biodegradable polymers use for colon-specific drug delivery give the impression to be a more site-specific approach than other approaches. These polymers protect the

drug from the environments of the stomach and small intestine then bring the drug to the colon. When reaching the colon, they endure assimilation by a micro-organism, degradation by enzyme or polymer breakdown leads to molecular weight reduced and thereby they lose its mechanical strength. Then they are unable to hold the drug entity for a longer period [23].

ii. Prodrug Approach for Drug Delivery to Colon: A prodrug is an inactive form of a parent drug molecule that requires spontaneous or enzymatic transformation to release the active drug. The prodrug is designed to endure minimal hydrolysis in the upper regions of GIT and undergo enzymatic hydrolysis in the colon thereby freeing the active drug molecules from the drug carrier. Metabolism of azo compounds by intestinal bacteria is the most widely deliberate bacterial metabolic process. In the colon, the drug is attached to hydrophobic moieties like amino acids, glucuronic acids, glucose, galactose, cellulose, etc. Its limitation is that it is not a very versatile approach because its formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities and require a lot of evaluation before used as carriers [24].

Table No. 3: Pro-drug assessed for colon-specific drug delivery. [25]

Drug investigated	Carrier	Linkage hydrolysed
5-ASA	Azo conjugates, Sulpha pyridine	Azo linkage
Naproxen	Dextran conjugate	Ester linkage
Dexamethasone	Dextran conjugate	Using spacer

c. Azo-Polymeric Prodrugs:

Newer approaches aim to use polymers as drug carriers for delivery of the drug to the colon. Synthetic and naturally occurring polymers are used for this purpose. Polymeric prodrug with Azo linkage between the polymer and drug moiety. These have been originated to be similarly susceptible to cleavage by the Azo reductase in the large bowel. Coating of peptide capsules with polymers cross-linked with Azo-aromatic group has been found to protect the drug from digestion in the stomach and small intestine. In the colon, the Azo bonds are abridged, and the drug is released [22, 27].

Table No. 4: Azo polymers investigated with drug moiety from the dosage form [28, 29]

Azo Polymers	Dosage form	Drugs	Results
Copolymer of styrene + 2 hydroxyethyl methacrylate	Coated capsule	Vasopressin, Insulin	Shows biological response characteristics peptide hormones
Aromatic azo bond containing urethane analoges	Degradable films	5-ASA	Films eroded by azo reductase. The permeability of 5-ASA from lactobacillus when treated films were significantly higher than that of control

d. Polysaccharide Based Delivery System:

Use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting to the colon since these polymers of monosaccharide are found in abundance, have wide availability are inexpensive and are available in a verity of structures with varied properties. They can be easily modified chemically and biochemically and are highly stable, safe, non-toxic, hydrophilic and gel-forming and in addition biodegradable. These include naturally occurring polysaccharides obtained from plant, animal, algal or microbial origin. These are broken down by the colonic microflora to simple saccharides [30].

Table No. 5: Polysaccharides studied for colon drug delivery with their dosage forms [31]

Polysaccharides investigated	Drug used	Dosage form
Chitosan	5-(6) carboxyfluorescein	Enteric-coated chitosan capsules
Amidated pectin	Paracetamol	Matrix tablets
Pectin (used as calcium salt)	Indomethacin	Matrices

2. Newly Developed Approaches for CDDS:

a. Pressure Controlled Drug-Delivery Systems:

Accordingly, of peristalsis, higher pressures are come across in the small intestine by passing through the colon, pressure-controlled capsules prepared using ethyl cellulose, which is insoluble in water for specific colon drug delivery. Drug release by following the disintegration of a water-insoluble polymer capsule through pressure in the colon. The factor of disintegration is depending on the thickness of the ethyl cellulose membrane [32]. The formulation is also depending on the size of the capsule and its density. The viscosity of luminal content in the colon is higher than in the small intestine due to reabsorption of water from the colon. In pressure-controlled single-unit capsules of ethyl cellulose. Lag times of drug absorption are three to five hours when pressure-controlled capsules were taken to human [33].

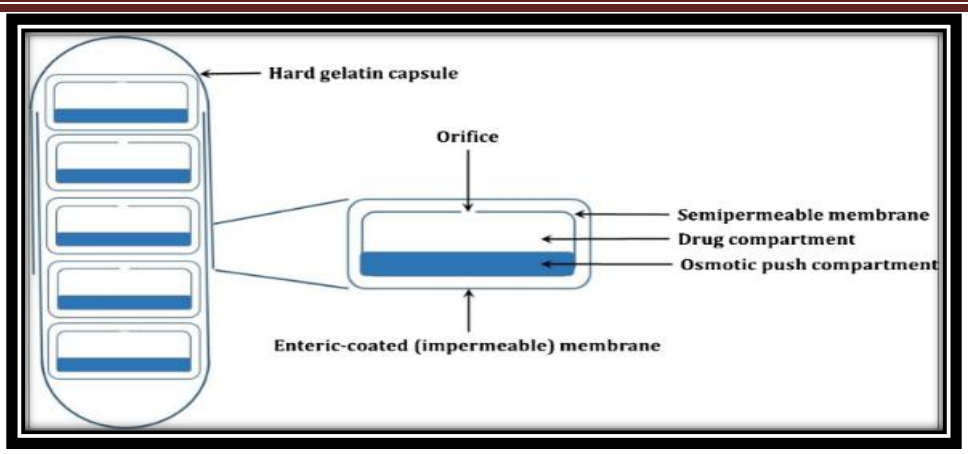

Fig. 2: Schematic diagram of Pressure Controlled Drug-Delivery Systems

b. Pulsatile colon targeted drug delivery:

- Pulsincap system
- Port system

i. Pulsincap System: Pulsincap was formulated in a capsule form invented by R.R. Scherer International Corporation, US. The plug placed inside the capsule which helps to controls the release of the drug. Seal the drug content by using swellable hydrogels. The capsules encounter the dissolution fluid get swelled and the capsule and the drug will be released after a lag time when the plug gets pushed. [34] Polymers, for example, different grades of hydroxyl propyl methyl cellulose, poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is measured by the length and point of intersection of the plugin the capsule body [35].

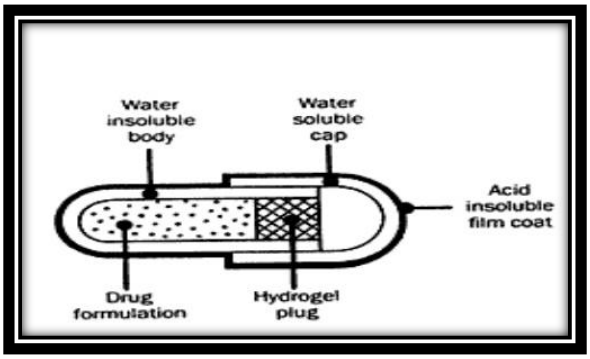

Fig. 3: Schematic diagram of the Pulsincap system

ii. Port System: The port system was developed in the research laboratory of the USA, and it is a capsule-shaped which is coated with a semi-permeable membrane, the insoluble plug is present inside the capsule. The insoluble plug consisting of osmotically active agents and the formulation of the drug [36]. When the capsule is administered then it meets dissolution fluid, the semi-permeable membrane of capsule swelled and make pores which allowed the entry of water, the pressure is developed inside it, the insoluble plug ejected after a lag time. It avoids second time dosing, which was beneficial for children and old peoples during the daytime [37].

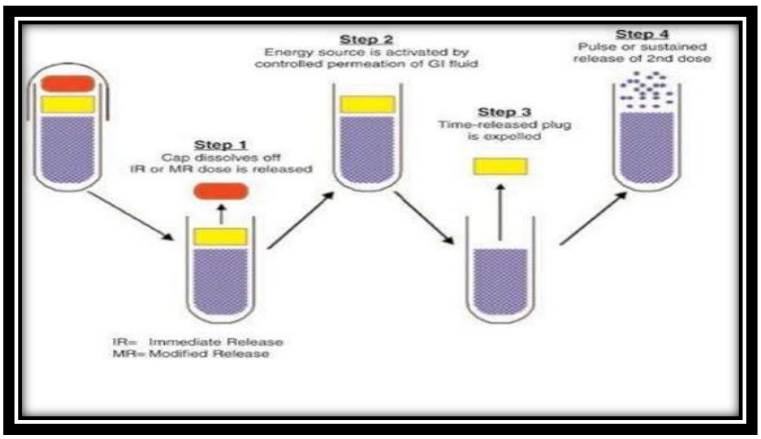

Fig. 4: Schematic diagram of the port system

b. Novel Colon Targeted Delivery System (CODESTM):

CODESTM is an exclusive technology that was intended to avoid the pH or time-dependent problems. [38] It is a joint approach of pH-dependent and microbially triggered colon drug delivery systems. Its mechanism is unique involving lactulose, which releases at its specific site of the colon. The system contains tablet core (lactulose), coated with acid-soluble material, Eudragit E, and then later overcoated with an enteric material, Eudragit L. The principle of the technology is that the enteric coating protects. It dissolves quickly in the stomach following gastric emptying. The acid-soluble material coating protects from the alkaline pH of the small intestine. [39] Once the tablet reaches in the colon, the bacteria enzymatically breakdown the polysaccharide (lactulose) into organic acid. It helps to lower the pH nearby the system enough to affect the dissolution of the acid-soluble coating and succeeding drug release [40].

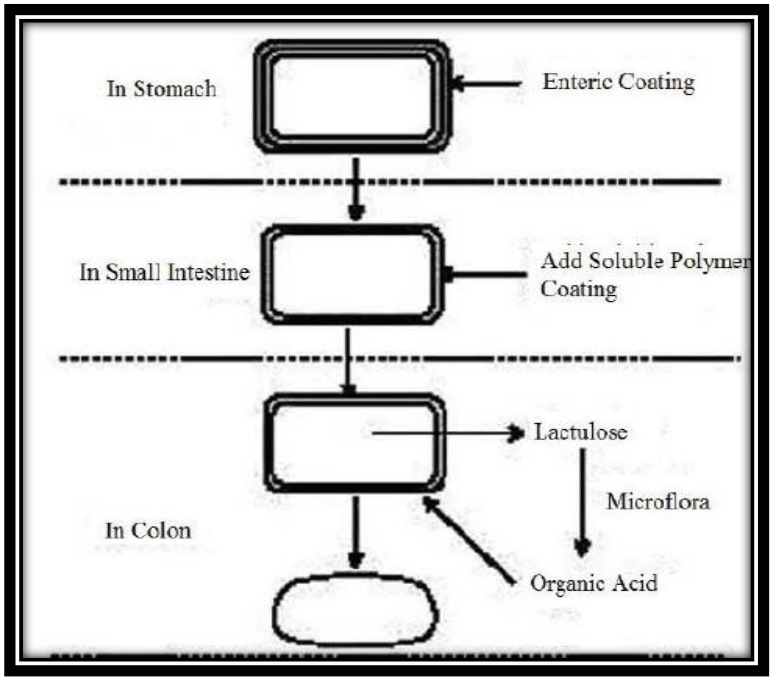

Fig. 5: Schematic diagram of CODES System

c. Osmotic Controlled Drug Delivery:

The osmotic-controlled release oral delivery system is an innovative controlled release drug delivery system in the form of tablet which is hard and its outer membrane is semi-permeable in this small laser holes drilled. When the tablet administered it enter into the body, passes through the body, the semipermeable membrane absorbs the water through osmosis, results osmotic pressure creates and push the active drug through the holes (opening) in the tablet. OROS is a trademarked name owned by ALZA Corporation, which established the use of osmotic pumps for oral drug delivery [41-43].

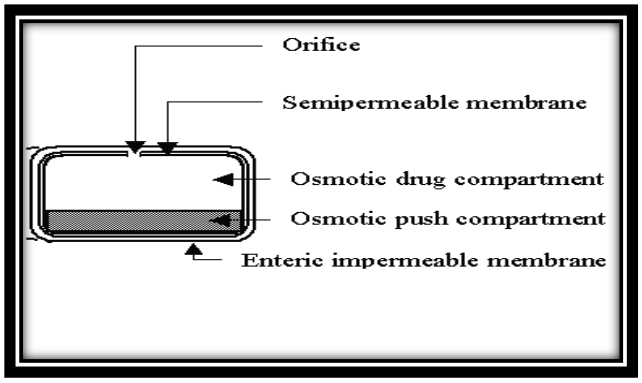

Fig. 6: Schematic diagram of OROS

CONCLUSION

CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. The main advantage of this system is that the colon offers a long transit time, close to neutral pH. It also minimizes enzymatic activity and enhances absorption. The most perilous challenge in CDDS is to preserve the formulation when it passes through the stomach. Various approaches are used for specific site drug delivery. The primary and novel approaches of CDDS are the pulsincap system, port system, CODES are more precise as compared to primary approaches. Both polymers i.e. natural

and biodegradable polymers are used for the formulation of colon targeted delivery of the drug. Today's it is necessary for the patient community is to recognize the appropriate approach that is the delivery of the drug in an effective manner, safe, reduce the side effects and shows minimum fluctuation during the release of drug at the specific targeted site.

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