Review Article

Colon Targeted Drug Delivery System

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ABSTRACT

The colon is a site where both local and systemic delivery of drugs can take place. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, etc. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in the upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon. This review mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbial triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery (ORDS-CT) which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process. Treatment could be more effective if it is possible for drug to be directly delivered to colon. This article also discusses advantages & limitations of the different approaches & evaluation for site specific drug delivery to colon.

Keywords: Colon specific drug delivery system, crohn's disease, drug carrier, pH dependent approach, time dependent delivery.

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INTRODUCTION

The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S. and these systems have more advantages due to patient acceptance and ease of administration [1, 2]. During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents [3,4]. There are various methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems [5-7]. Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery.

Advantages of colon targeting drug delivery system [8-10]

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.

- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Bypass initial first pass metabolism.
- Extended daytime or night-time activity.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route [11].

Limitations of colon targeting drug delivery system

- Multiple manufacturing steps.
- The resident microflora could also affect colonic performance via metabolic degradation of the drug.
- Incomplete release of drug Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. Normal in patients with ulcerative colitis [12, 13].
- Limitations of prodrug approach is that it is not very versatile approach as it's formulation depends upon the functional group available on the drug moiety for chemical linkage [14].

Need of colon targeted drug delivery system

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. 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. 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. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

Criteria for selection of drug for colonic drug delivery

Drug candidate

Drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. The drug used in treatment of IBD, ulcerative colitis, diarrhoea and Colon cancers are ideal candidates for local colon delivery [15].

Drug carrier

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of drug molecule [16]. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems [17].

Approaches for colonic drug delivery

1) Covalent linkage of drug with carrier

1.1) Prodrug approaches [18]

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon

oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.

1.2) Azo bond conjugate [19]

These azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. The use of these azo compounds for colon-targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrug. In the latter approach the drug is attached via an azo bond to a carrier**.** This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora. Sulphasalazine, used for the treatment of IBD has an azo bond between 5-ASA and sulphapyridine (SP). In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier SP which shown in (**Figure 1**).

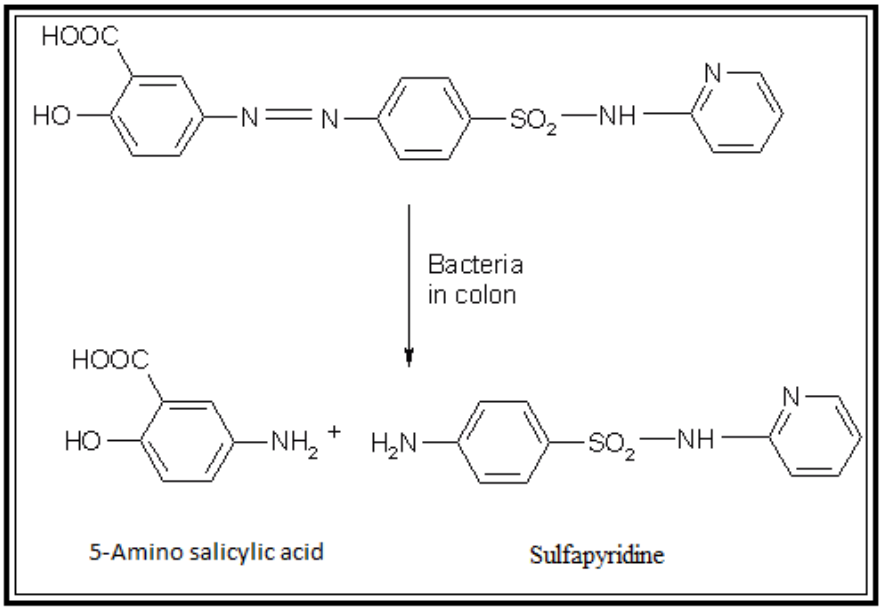

Figure1: Hydrolysis of Sulphasalazine

1.3) Glycoside conjugation:

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Certain drugs can be conjugated to different sugar moieties to form glycosides. The drug part forms the aglycone and is linked to the sugar part, which forms the glycone part of the glycoside. Because they are bulky and hydrophilic, these glycosides do not penetrate the biological membranes upon ingestion. They breakdown upon action of glycosidase, releasing the drug part from the sugar. The presence of glycosidase activity in the small intestine could pose a problem in delivery of these conjugates to the large bowel, because some hydrolysis of the conjugate can be expected in the small intestine. However, the small intestinal transit time, when compared to the large intestinal transit time, is short, and moreover, considering the time required for the hydrolysis of glycosidic bond, these conjugates can be expected to be good colon specific drug carriers. The major glycosidase enzymes produced by the intestinal microflora are β -D-galactosidase, α -L-arabinofuranosidase, β -D-xylopyranosidase, and β –D glucosidase. These glycosidase enzymes are located at the brush border and hence are accessible to substrate easily. Example: lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone.

1.4) Glucoronide conjugates [20]

Bacteria of the lower GIT secrete b-glucuronidase and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption. Example: Opiates, when

taken for the relief of pain, cause severe constipation by inhibiting GIT motility and secretions. Narcotic antagonists, when given as antidotes for GIT side effects, immediately relieve constipation but precipitate acute withdrawal. This is because these narcotic antagonists are not selective and they not only affect the GIT activity, but also the central nervous system (CNS). A novel approach would be to target these antagonists to the lower bowel so that they are not absorbed systemically. With this purpose, naloxone and nalmefene glucuronide prodrugs were prepared to target these drugs to the colon. When given orally to morphine dependent rats these prodrugs showed increased GIT motility and secretion in the large bowel results in a diarrhoea and The resultant diarrhoea flushed out the drug / prodrug from the colon thereby preventing the systemic absorption of the antagonist, which in-turn caused absence of withdrawal symptoms. Budesonide-b- glucuronide prodrug also found to be superior to budesonide itself for the treatment of colitis in the rat.

1.5) Cyclodextrin conjugate [22]

Cyclodextrins are cyclic oligosaccharides consisted of six to eight glucose units through -1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules. They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine however, Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextranase activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed. This susceptibility to degradation specifically by colonic micro flora together with their property to form inclusion complexes with various drugs makes them particularly useful in carrying drug moieties to the colon .The a- and b-cyclodextrins are practically resistant to gastric acid, salivary, and pancreatic amylases. A clinical study has shown clear evidence that b-cyclodextrin is poorly digested in the small intestine but is almost completely degraded by the colonic microflora.

1.6) Dextran conjugates [23]

Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolyzed by moulds, bacteria, and mammalian cells. The enzyme responsible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, where as high dextranase activity is shown by anaerobic gram-negative bacteria, especially the bacteroides, which are present in a concentration as high as 1011 per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon. In the colon, dextran's glycosidic bonds are hydrolyzed by dextranases to give shorter prodrug oligomers, which are further split by the colonic esterases to release the drug free in the lumen of the colon. Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function (−COOH).NASIDS ware directly coupled to dextran by using carboxylic groups of drugs. Example is Naproxen-dextran conjugate. Glucocorticoids do not possess −COOH group so these are linked to dextran using spacer molecule. E.g. glucocorticoid-dextran conjugates.

1.7) Amino acid conjugation:-

Due to the hydrophilic nature of polar groups like -NH2 and -COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme [25].

1.8) Polymeric prodrugs [26]

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Subsynthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety.

2. Approaches to deliver intact molecule to colon

2.1) pH dependent approach [27]

This approach utilizes the existence of pH gradient in the git that increases progressively from the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0).By combining the knowledge of the polymers and their solubility at different pH environments, delivery systems can be designed to deliver drugs at the target site. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose.

2.2) Coating of the drug core with pH sensitive polymers:-

The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon. The drug core includes tablets, capsules, pellets, granules, microparticles or nanoparticles. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. The majority of enteric and colon targeted delivery systems are based on the coating of tablets or pellets, which are filled into conventional hard gelatin capsules. The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products. Moreover, there is considerable difference in inter and intra individual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the large intestine Eudragit-L dissolves at a pH level above 5.6 and is used for enteric coating, whereas Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0 (attributable to the presence of higher amounts of esterified groups in relation to carboxylic groups), which results in premature drug release from the system. Problem of premature drug release can be overcome by the use of Eudragit FS. Various example of polymer and their pH are shown in (**Table 1**).

Polymer	Threshold pH
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit® L-30D	5.6
Eudragit® FS 30	6.8
Hydroxypropylmethylcellulose phthalate 50	5.2
Hydroxypropylmethylcellulose phthalate 55	5.4
Cellulose acetate trimellate	4.8

Table 1: Example of various pH dependent coating polymers

2.3) Embedding in pH-sensitive matrices:

The drug molecules are embedded in the polymer matrix. Extrusion spheronization technique can be used to prepare uniform-size sturdy pellets for colon targeted drug delivery when it is not possible to obtain mechanically strong granules by other methods. Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increased the pellet size and influenced pellet roundness. Citric acid promoted the pelletization process resulting in a narrower area distribution. However, EudragitS100 could not cause statistically significant delay in the drug release at lower pH.

2.4) Time dependent delivery:

It also known as pulsatile release or sigmoidal release system. This approach is based on the principle of delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit

variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place. The lag time in this case is the time requires to transit from the mouth to colon. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered. Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms.

Disadvantages:

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
- Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhoea and the ulcerative colitis.

Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon.

2.4.1) Pulsincap

The first formulation introduced based on this principle was Pulsincap® developed by R.R. Scherer International Corporation, Michigan, US. It consists of non disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug starts to swell. The length of the plug and its point of insertion into the capsule controlled the lag time. Diagram of pulsincap are shown in figure no.2. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin).

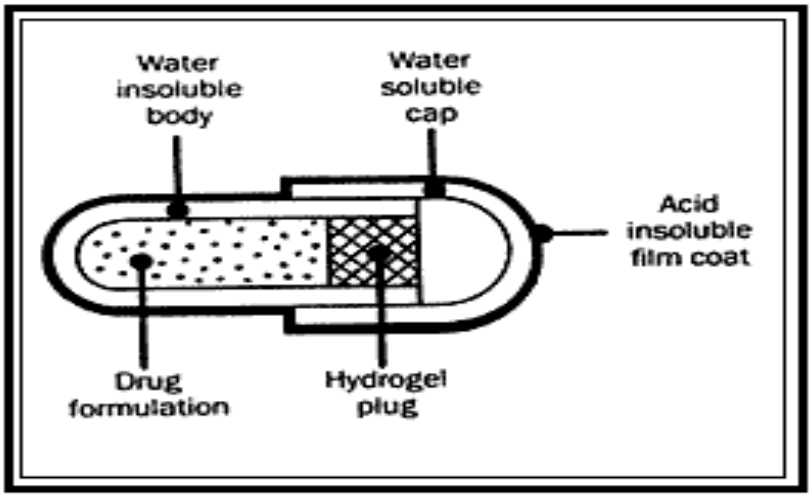

Figure 2: Design of Pulsincap system

2.5) Colon-Targeted Delivery Capsule based on pH sensitivity and time-release principles:

The system contains an organic acid that is filled in a hard gelatin capsule as a pH-adjusting agent together with the drug substance. This capsule is then coated with a three-layered film consisting of an acid-soluble layer, a hydrophilic layer, and an enteric layer. After ingestion of the capsule, these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid, upon which the enclosed drug is quickly released. Therefore, the onset time of drug release is controlled by the thickness of the acid-soluble layer. CTDC are shown in (**Figure 3**).

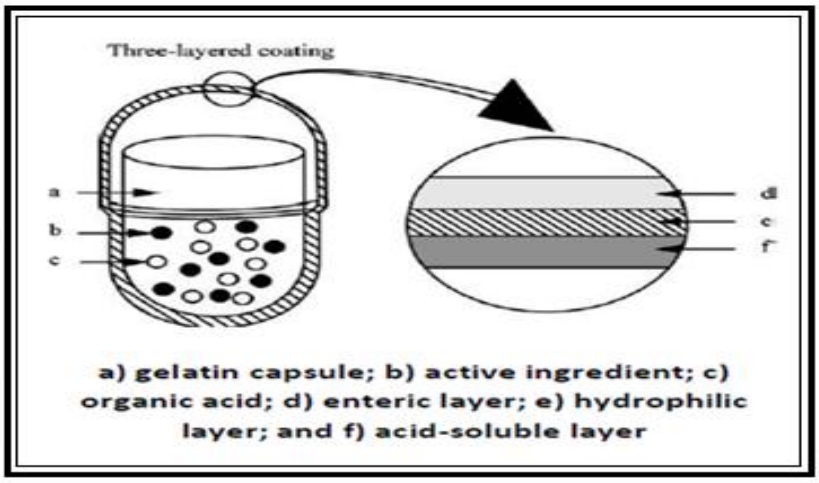

Figure 3: Design of the colon targeted delivery capsule

2.6) Chronotropic system [28]

The Chronotropic system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. The system is suitable for both tablets and capsules. (**Figure 4**) represents the chronotropic system.

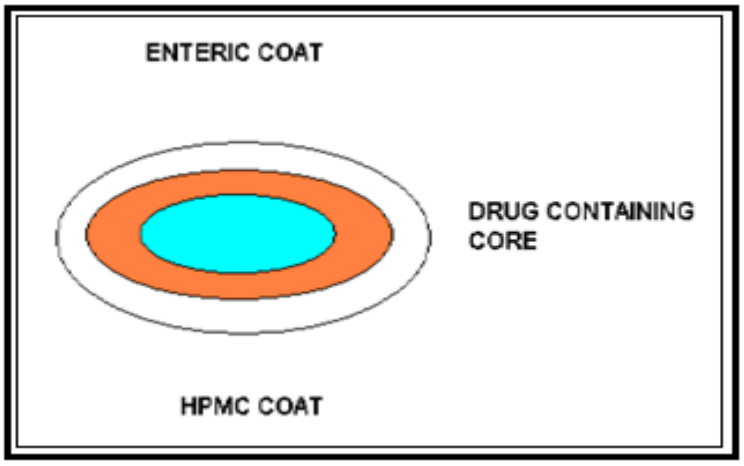

Figure 4: Design of Chronotropic system

3) Microbially triggered drug delivery to colon: The microflora of colon is in the range of 1011- 1012 CFU/ml. Consisting mainly of anaerobic bacteria e.g.

bacteroides, bifidobacteria, eubacteria, clostridia, and enterococci**,** enterobacteria and pnemiococcus etc., thus vast microflora fulfills its energy needs by various types of substrates that have been left undigested in small intestine e.g., di & tri saccharides, polysaccharides etc. for this fermentation the microflora, produces a vast number of enzymes like glucoridase, xylosidase, arabinosidase, galactosidase, nucleoreductase, azoreductases, deaminase and urea dehydroxylase, Because of the presence of biodegradable enzymes only in the colon, the use of biodegradable polymers for colon specific drug delivery seems to be more site specific approach as compared to other approaches. These polymer shield the drug from the environment of stomach and small intestine and are able to deliver the drug to the colon on reacting the colon, they undergo assimilation by micro organism as degradation by enzyme as breakdown of polymer back bone leading to subsequent reduction in their molecular weight and thereby loss of mechanical strength.

4) Bioadhesive systems [29]

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Bioadhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers have been investigated as materials for Bioadhesive systems .Bioadhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery systems.

5) Pressure controlled system:

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of faeces. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. Takaya et al. (1995) have developed pressure controlled colon delivery capsules prepared using an ethyl cellulose, which is insoluble in water. In such systems drug release occurs following disintegration of water insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. The preferred thickness of the capsule wall is about 35-60 μm. The system also appeared to depend on capsule size and density. In pressure-controlled ethyl cellulose single- unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

6) Osmotic controlled drug delivery [30]

The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units are shown in figure no.5. Each 4mm in diameter, encapsulated within a hard gelatin capsule. Each push-pull unit

is bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. In principle semipermeable membrane is permeable to the inward entry of water and aqueous GI fluids and is impermeable to the outward exit of the drug. An orifice is drilled into the semipermeable membrane to the drug layer. The outside surface of the semipermeable membrane is then coated by eudragit®S100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at pH≤7. As a result water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour 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 h in the colon.

CONCLUSION

The concept of targeting the delivery of specific drugs to colon is quite self explanatory and sufficient scientific rationale is available to support the justification. Various approaches are being researched in attempts to understand and achieve the desired goal of targeting the delivery to a specific organ, the colon. All the available approaches have their own limitations and advantages. The need of today's business and patient community is to identify the appropriate approach that can result in the delivery of drugs in a safe, effective and less expensive manner with minimum fluctuation in terms of release of drugs at target site.

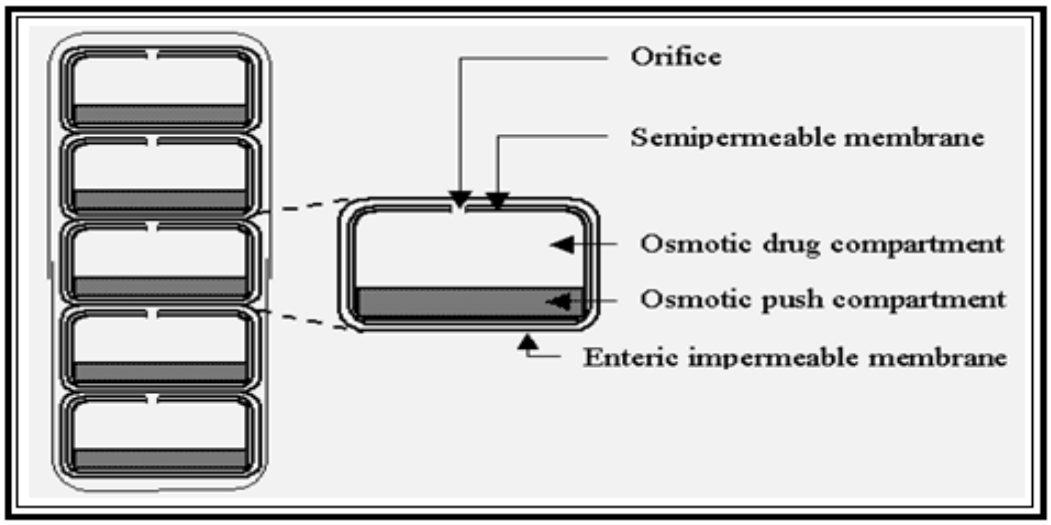

Figure 5: Cross section of the OROS-CT colon targeted drug delivery system

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