Review Article

NOVEL APPROACHES FOR 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. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially 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 which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process.

Keywords: Colon drug delivery systems; Primary approaches; newly developed approaches; evaluation of colon targeted drug delivery systems.

INTRODUCTION

Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, crohan's disease amebiosis, colonic cancer, and for local treatment of local colonic pathologies, and the systemic delivery of protein and peptide drugs [1].

Dosage forms that deliver drugs in the colon rather than upper GIT has number of advantages. Oral delivery of drugs in the colon is valuable in the treatment of diseases of colon where by high local concentration can be achieved while minimizing side effects. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability because the colon has a long retention time and appears highly responsible to agents that enhance the absorption of poorly absorbed drugs. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coating or extremely slow releasing matrices [2]. There are various

methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pHsensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems. Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery [3].

Anatomy and Physiology of Colon

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon

contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus. The human colon were shown in Figure1.The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed [4].(Fig: 1)
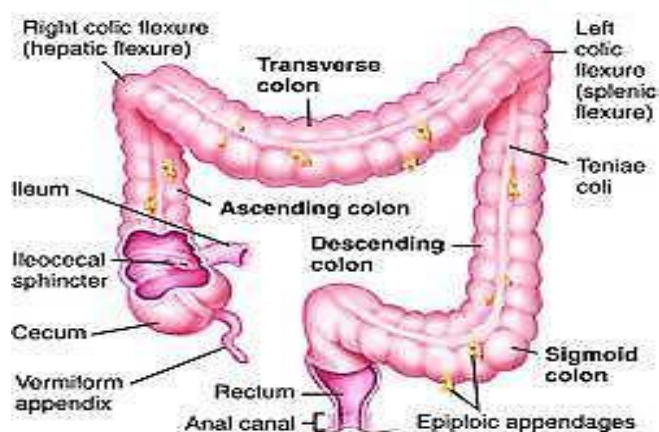

Fig 1: Anatomy of colon

Advantages of colon targeting drug

Delivery system [5]:

1. Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
2. Local treatment has the advantage of requiring smaller drug quantities.
3. Reduces dosage frequency. Hence lower cost of expensive drugs.
4. The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
5. Bypass initial first pass metabolism.
6. It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
7. Possibly leading to a reducedincidence of side effects and drug interactions.
8. Improve patient compliance.
9. Targeted drug delivery system.

Limitations and challenges in Colon Targeted Drug Delivery [6]

1. The targeting of drugs to the colon is very complicated. Due to its location in the distal part of the alimentary canal, the colon is particularly difficult to access. In addition to that the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.
2. In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
3. The resident microflora could also affect colonic performance via metabolic degradation of the drug. Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict the drug transport across the mucosa and into the systemic circulation.
4. One challenge in the development of colon-specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system *in-vitro*. This is due to the rationale after a colon specific drug delivery system is quite diverse.
5. Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.

Factors affecting colon targeted drug delivery [7]

1. Physiological factors
2. Pharmaceutical factors

1. Physiological factors

a. Gastric emptying

Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times. (Table: 1)

Table 1: Transit time of different parts of GIT

Part of GIT	Transit time
Fasted state	10min – 2hr
Fed state	>2hr
Small intestine transit	3-4hr
Colon transit	20-35hr

b. pH of colon

The pH of GIT varies between different individuals.The food intakes, diseased state, etc.influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site. (Table: 2)

Table 2: pH in different parts of Colon

Part of GIT	pH
Stomach	Fasted state 1.5-2 Fed state 2-6
Small intestine	6.6- 7.5
Colon Ascending colon Transverse colon Descending colon	 6.4 6.6 7.0

c. Colonic microflora and enzymes

The GIT contains a variety ofmicroorganisms that produces many enzymes need for metabolism. Growth of this microflora is controlled by the GIT contents and peristaltic movements. The enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT. (Table: 3)

Table 3: Different microflora, enzymes released and action

Microorganism	Enzyme	Metabolic reaction
E.coli, Bacteroids	Nitroreductase	Reduces aromatic & heterocyclic nitro compounds
Clostridia, Lactobacilli	Hydrogenase	Reduces carbonyl groups & aliphatic double bonds
Clostridia, Eubacteria	Glucosidase	Cleavage of bglycosidase of alcohols & phenols
Eubacteria, Clostridia, Streptococci	Sulfatase	Cleavage of Osulphates & Sulfamates

2. Pharmaceutical factors

a. Drug candidates

Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.

b. Drug carriers

The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. The various physicochemical factors of drug that effect the carrier selection includes chemical nature, stability, partition coefficient, functional groups of drug molecule etc.

Polymers Used in Colon Targeting

Polymer contain a large number of structural unit joined by same type linkage, form into a chain like structure. These are nowadays used in formulating various pharmaceutical products. Naturally found polymer, which include gummy exudates, proteins, enzymes, muscle fibre, polysaccharides. In olden days natural polymers are widely used in pharmacy but a variety of synthetic polymer are used nowadays for pharmaceutical and cosmetic development, using these polymer many therapeutic system of body namely controlled drug delivery systems, are achieved [8,9].

Natural polymer

Guar gum, Inulin, Pectin, Cyclodextrin, Dextran, Amylase, Chitosan, Chondrotin sulphate, Locust bean gum.

Synthetic polymer

Shellac, Ethyl cellulose, Cellulosw acetate phthalate, Hydroxy propyl methyl cellulose, Eudragit, Poly vinyl acetate phthalate.

Approaches used for site specific drug delivery to Colon (CDDS)

[A] Primary Approaches for CDDS

a) pH sensitive polymer coated drug delivery to colon

In the stomach pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. From the ileum to the colon pH declines significantly. It is about 6.4 in the ceacum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6, in the descending colon 7.0. Use of pH-dependent polymers is

based on these differences in pH levels. The polymers described as pH-dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH-dependent polymer can protect a formulation in the stomach and proximal small intestine, it may start to dissolve even in the lower small intestine, and the site-specificity of formulations can be poor [10]. The decline in pH from the end of the small intestine to the colon can also result in problems Lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon can also result in poor site-specificity of enteric-coated single-unit formulations [11].

b) Delayed (Time controlled release system) release drug delivery to colon

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising. However due to potentially large variation of gastric emptying time of dosage forms in humans, in this approach colon arrival time of dosage forms can not accurately predicted, resulting in poor colonical availability. The dosage forms may also applicable as colon targeting dosage forms by prolonging the lag time of about 5.5 hours (range 5 to 6 hours). Disadvantages of this system are- (i) Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.(ii) Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug. (iii) Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea 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. That is since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hour. The time-release function (or timer function) should work more efficiently in the small intestine as compared the stomach. In the small intestine drug carrier will be delivered to the target side and drug release will begin at a predetermined time point after gastric emptying. On the other hand in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time [12].

Enteric-coated time-release press coated tablets

ETP tablets are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer, time release function) and an enteric coating layer (acid resistance function). Tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins slowly erode the press coated polymer (HPC) layer and when the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time there is no drug release period (lag phase) after gastric emptying [13]. The duration of lag phase controlled either by the weight or composition of the polymer (HPC) layer (Fig: 2).
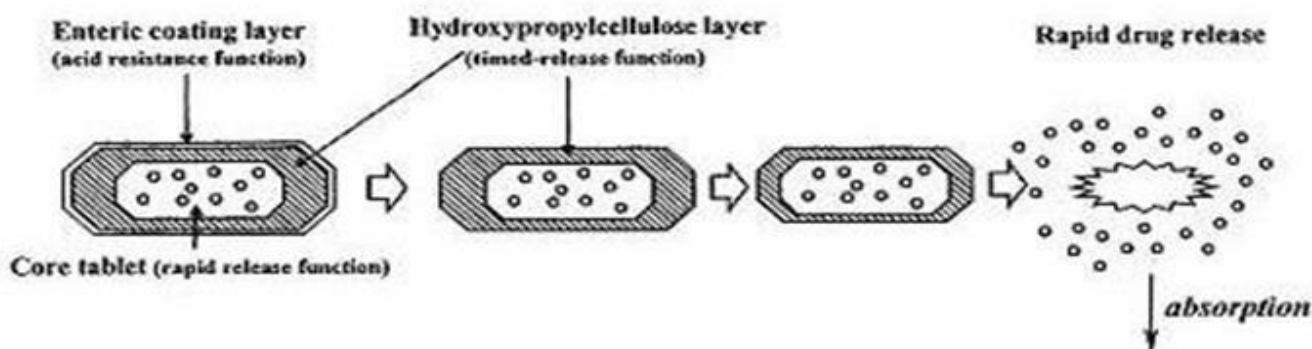

Fig 2: Design of Enteric coated-timed release press coated tablets (ETP tablets).

c) Microbial triggered drug delivery system

The various microflora of the colon are Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus, etc. This microflora of gut depends on fermentation of undigested materials in the small intestine for their energy requirements. The microflora performs fermentation by producing a large number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, and deaminase and urea dehydroxylase. These biodegradable enzymes are capable of degrading the polymers used for targeting the drug delivery to colon. Different polymers are used for preventing the release of drug in the stomach and small intestine. When the coated formulations reach the intestine the biodegradable polymers gets degraded by the enzymes produced by the microbial flora and the drug gets released in the targeted region.

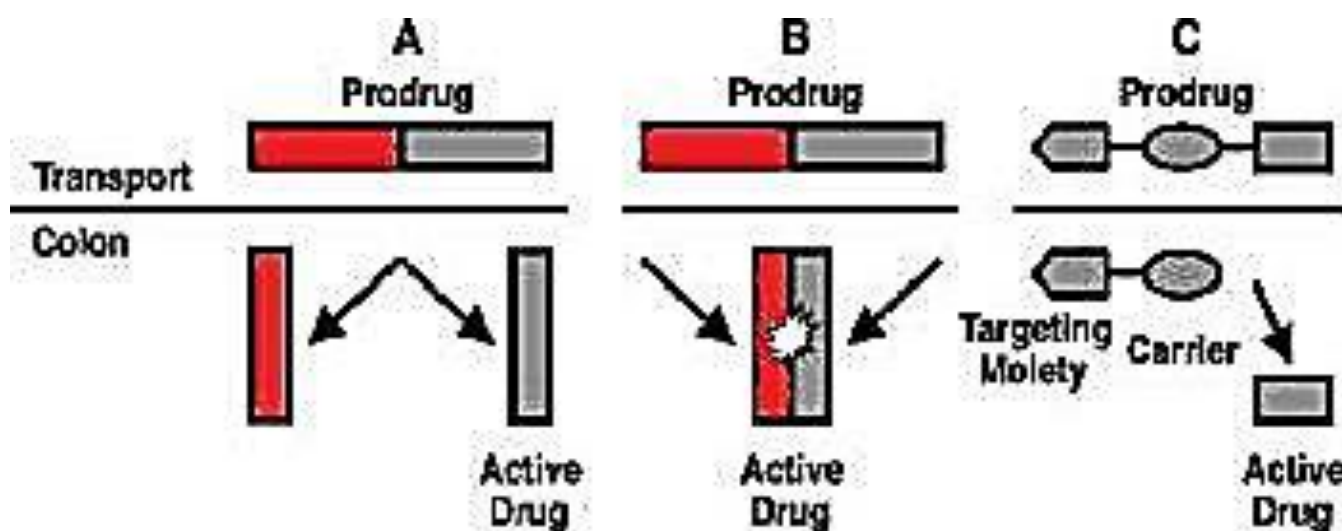## (i) Prodrug approach for drug delivery to colon

Prodrug is the main approach of microbial triggered drug delivery system in which the drug release from the formulation is triggered by the microflora present in the gut. Prodrug is the inactive form of an active parent drug that undergoes enzymatic transformation to release the active drug. The produrgs are prepared by linking the active drug with hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose, etc.

These prodrug molecules get hydrolysed in the presence of the enzymes released by the microflora. The main drawback of this approach is that the formulation depends on the functional groups available on drug moiety for chemical linkage.

The prodrugs formed upon linkage results in the formation of new chemical entities that need a lot of evaluation before using them as carriers. The most widely used prodrug approach is the metabolism of azo compounds by intestinal bacteria. (Table: 4) (Fig: 3)

Table 4: Examples of Prodrug system for CDDS

Drug	Carrier	Linkage hydrolysed
5-ASA	Azo Conjugates	Azo linkage
Dexamethasone	Saccharide Carriers	Glycosidic Linkage
Prednisolone, hydrocortisone, fludrocortisones	Glucose, Galactose	Glycosidic Linkage
Salicylic acid	Amino acid conjugates, glycine	Amide Linkage

Fig 3: Prodrug approach for CDDS

(ii) Polysaccharide based delivery systems

Polysaccharide based delivery system is the other form of microbial triggered drug delivery system. Naturally occurring polysaccharides like guar gum, xanthan gum, chitosan, alginates, etc. are used in targeting the drug delivery. These are broken down by the colonic microflora to simple saccharides [14]. (Table: 5)

[B] Newly developed approaches for CDDS

a) Pressure-controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. (1995) have developed pressure controlled colon-delivery capsules prepared using an ethylcellulose, which is insoluble in water. In such systems drug release occurs following disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for disintegration of the formulation [15]. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure-controlled ethylcellulose 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 [16].

b) Pulsatile colon targeted drug delivery

i) Pulsincap system

In this system the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body [17]. (Fig: 4)
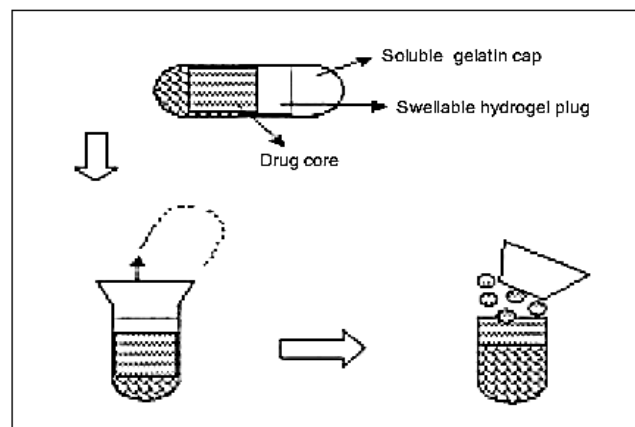
ii) Port system

In this system the capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation. When the capsule comes in contact with the dissolution fluid the semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals [18]. (Fig: 5)

c) Osmotically controlled colon targeted drug delivery system

This system consists of osmotic units. The osmotic units are used either singly or as many as 5-6 push pull units that are encapsulated in a hard gelatin capsule. The push pull units are bilayered with outer enteric impermeable membrane and inner semi permeable membrane. The internal or central part of the push pull consists of the drug layer and push layer. The semipermeable membrane which is present next to the drug layer consists of an orifice through which the drug contents are expelled during the course of time The capsule body enclosing the push pull units gets dissolved immediately after administration [19]. During the passage of the push pull units through the GIT the enteric impermeable membrane prevents the water absorption into the unit. The coating gets dissolved once it reaches the small intestine due to higher pH (>7). Water enters the unit through the semi permeable membrane causing the push layer to swell. The swelling of the push compartment forces the drug into the surrounding environment through the orifice. These osmotic controlled drug delivery systems deliver the drug at a constant rate for up to 24hr [20]. (Fig: 6)
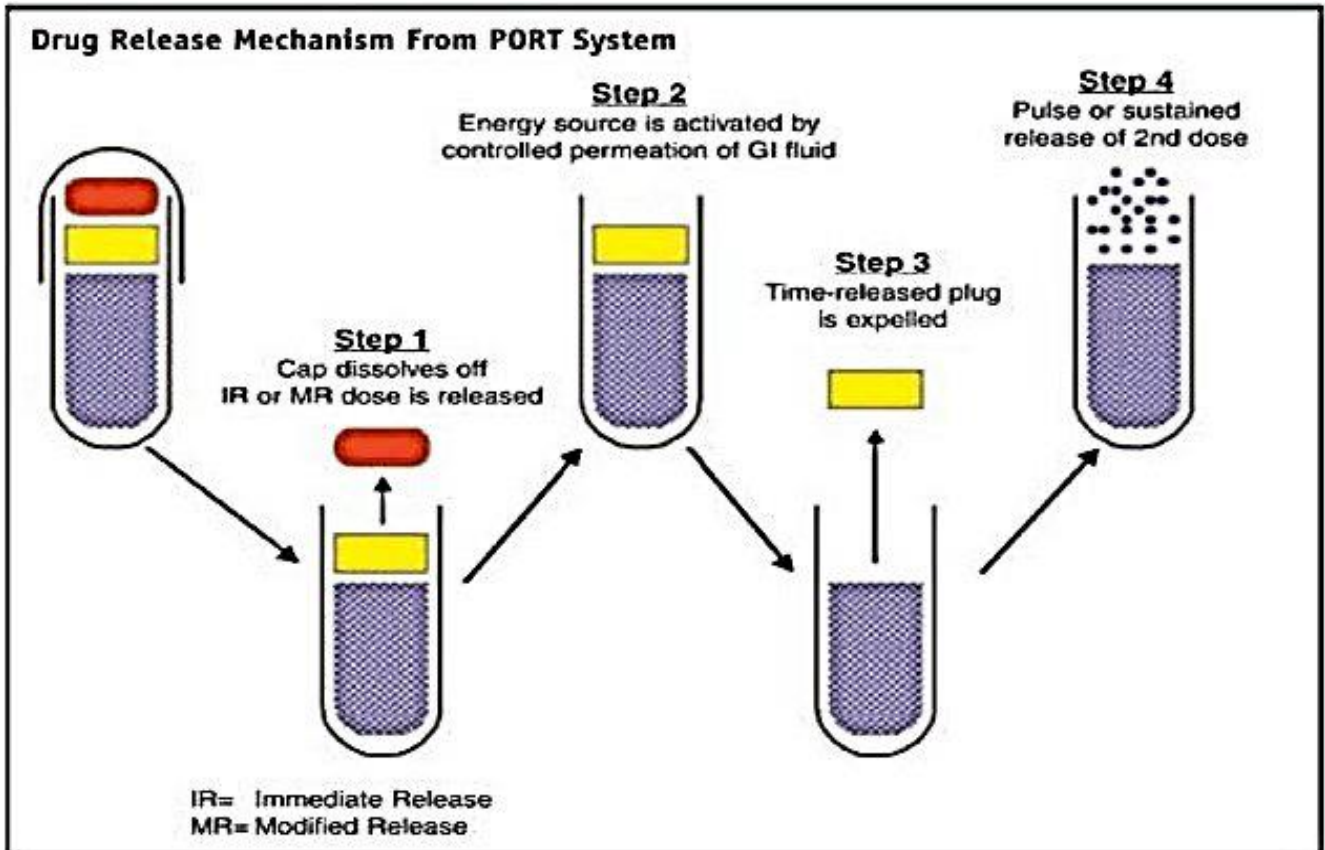

Fig 4: Pulsincap system
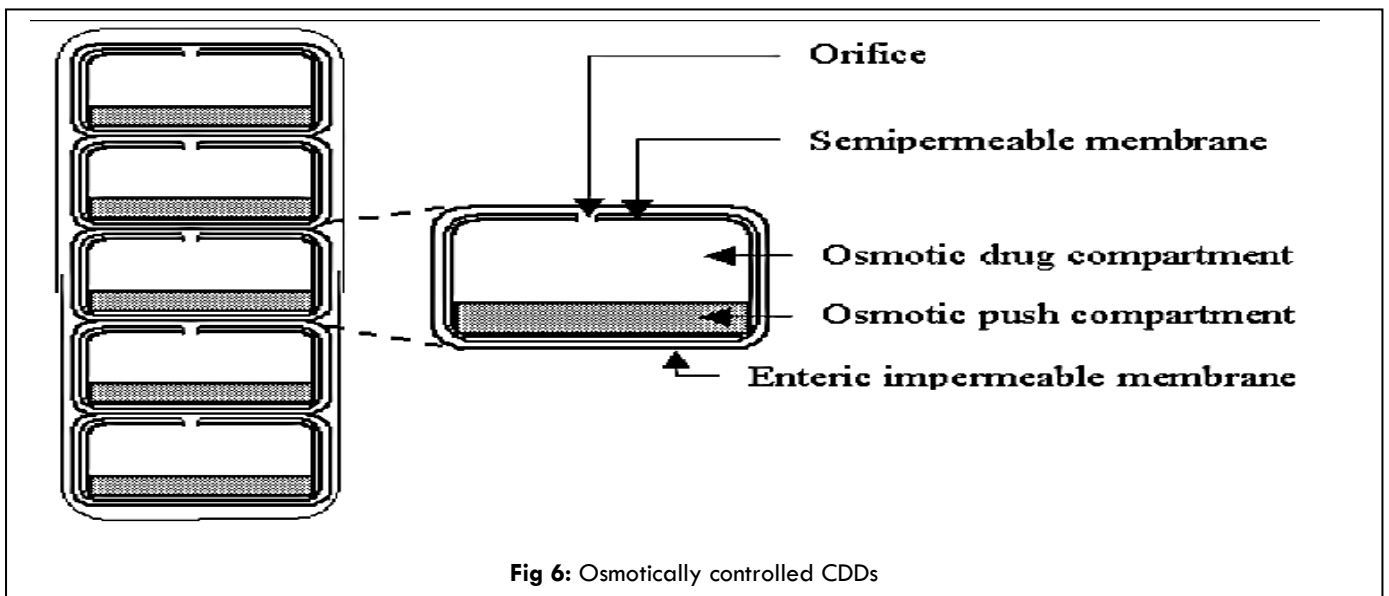
Fig 5: Drug release mechanism of port system

Fig 6: Osmotically controlled CDDs

d) CODES technology

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine.

This system consists of a core tablet coated with three layers of polymer coatings. The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes though the pyloric and duodenum and exposes the next coating. The next coating is composed of Eudragit E.

This layer allows the release of lactulose present in the inner core. This released lactulose gets metabolized into short chain fatty acids that lower the surrounding pH where the Eudragit E layer dissolves. The dissolving of Eudragit E results in the exposure of the drug. The other polysaccharides that are used along with the drug in the core tablet are mannitol, maltose, etc. The bacteria present in the colon are responsible for the degradation of polysaccharides that are released from the core tablet. The degradation of polysaccharides results in organic acids formation that lowers the pH of the contents surrounding the tablet. (Fig: 7)
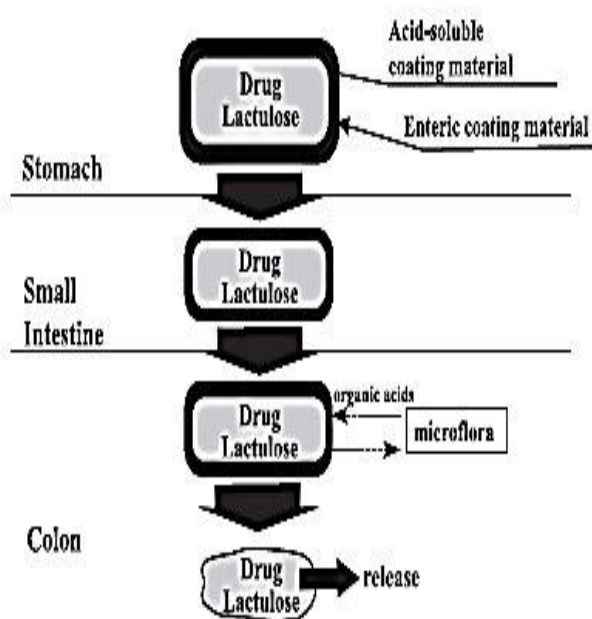

Fig 7: CODES system

h) Multi particulate system based drug delivery

The various advantages of multiparticulate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The various multiparticulate approaches include pellets, microparticles, granules and nanoparticles. Multiparticulates systems are preferred over single unit dosage forms as the multiparticulate systems enables the drug to reach the colon quickly and retained in colon for long period of time. These systems pass through the GIT easily due to their smaller size. Multiparticulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption.

Nanoparticles The preparation of nanoparticles is simple and these are capable of protecting the protein and peptide drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium. The polymeric nanoparticles are prepared by various techniques like polymerization, nanoprecipitation, inverse microemulsion. The methods involve the use of organic solvents, heat and agitation. The drawback of these methods is that the heat, agitation is harmful to proteins and peptide drugs. Ionic gelation technique is the most widely used method for proteins and peptide drugs [21].

Evaluation Test of Colon Drug Delivery System:

In-vitro evaluation

No standardized evaluation technique is available for evaluation of CDDSas an ideal invitro model should possess in-vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and components of food. These conditions are influenced by diet & physical stress. The invitro evaluation of colon targeted drug delivery systems includes the in-vitro dissolution study & in-vitro enzymatic test [22]

1. In-vitro dissolution test

The dissolution testing is done using the conventional basket method. The dissolution testing is done in different buffers to characterize the behaviour of formulations at different pH levels. The different media that are used for the dissolution testing of colon targeted drug delivery are pH 1.2 to simulate gastric fluid, pH 6.8 to simulate small intestine, pH 7.4 to simulate large intestine. The colon targeted drug delivery systems are tested for 2hr in 0.1N HCl, 3hr in pH 6.8 phosphate buffer and finally at pH 7.4 phosphate buffer. Buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems [23].

2. In-vitro enzymatic test:

There are 2 tests for the in-vitro enzymatic test.

☐ The carrier drug system is incubated in fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals is determined.

☐ Drug release study is performed in buffer medium containing enzymes pectinase, dextranase or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is directly proportional to rate of degradation of polymer carrier [24].

In- vivo evaluation

The in-vivo evaluation of the CDDS is done in dogs, guinea pigs, rats & pigs as they resemble the anatomic and physiological conditions, microflora of human GIT. The distribution of various enzymes in GIT of rat and rabbit is comparable to that in human [25].

CONCLUSION

Colon targeted drug delivery system offers benefits of local and systemic effects. The main advantage of CDDS is that the colon offers near neutral pH, a long transit time, reduced enzymatic activity and increased responsiveness to absorption enhancers. The novel approaches are more specific compared to the primary approaches. The biodegradable polymers are used for the colon specific delivery of the drug. For the invitro evaluation of the system the current dissolution techniques are not suitable. Research is going on to develop suitable dissolution methods to evaluate the colon targeted drug delivery systems.

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