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Colon targeted drug delivery systems: A review on primary and novel approaches

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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: Inflammatory bowel disease, CDDS (Colon Targeted Drug Delivery System), pH sensitive drug delivery system

1. Introduction

Currently, a novel oral colon-specific drug delivery system (CDDS) has been developing as one of the site specific drug delivery systems. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the
Gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration. CDDS specifically delivering drug to the colon, a lot of benefits would be acquired in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases. Targeted delivery ensures the direct treatment at the disease site, thus lower dosing, & reduction in side effects [1, 2, 3]

It has also gained increased importance not just for the delivery of drugs for the treatment of local diseases[4], but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon.

These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most, and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the GIT, namely stomach and small intestine[4].

Colon targeted drug delivery would ensures direct treatment at the disease site, lower dosing and less systemic side effects. In addition to restricted therapy, the colon can also be utilized as a portal for the entry of drugs into the systemic circulation. For example, molecules that are degraded/poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon.

Overall, there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs. In such instances, the drug may need to be delivered in a pre-solubilised form, or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon. Aside from drug solubility, the stability of the drug in the colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general faecal matter, thereby reducing the concentration of free drug. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug [5, 6].

1.1 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 Figure 1.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 [7]. (Fig: 1)

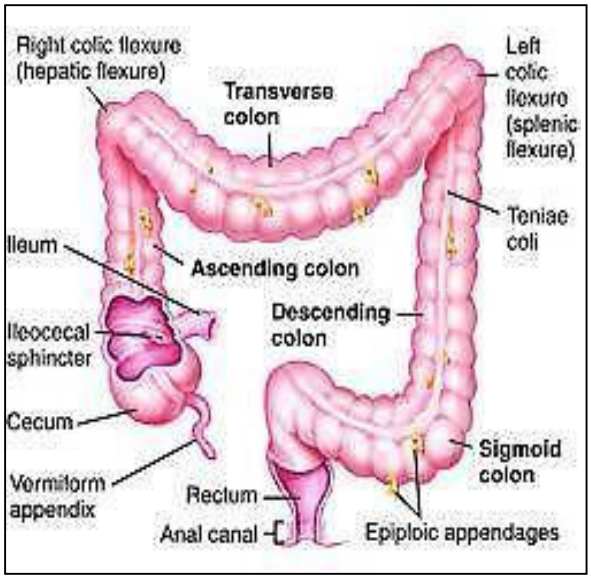

Fig 1: Anatomy of colon [7]

1.2 Advantages of colon targeting

- Patient compliance
- Reduction of doses
- Avoidance of side effects
- Reduction of dosage frequency
- Delivery of drug that are destroyed by stomach acid
- Improvement of bioavailability of protein and peptide drugs

Limitations of colon targeting

- Low fluid content
- Difficult to access
- Long transient time
- Degradation of drug by microflora

Table 1: Colon targeting diseases, drugs and sites [7]

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

Table 2: Criteria for the selection of drugs for the CRDDS [7]

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amyline, Antisense, Oligonucleotide
Drug poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen, Isisorbide, Theophylline	Cyclosporine, Desmopressin
Drug for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagone
Drug that degrade in stomach and small intestine	Peptides and proteins	Bromophenaramine, 5-flourouracil, Doxorubicine	Gonadoreline, Insuline, Interferones
Drug that undergo extensive first pass metabolism	Nitroglycerin and Corticosteroids	Bleomycin, Nicotine	Protirelin, Sermorelin, Saloatonine
Drugs for targeting	Antiarthiritic and antiasthamatic drugs	Predenisolone, Hydrocortisone, 5-Amino-Salicylic acid	Somatropine, Urotoilitin

1.3 Approaches for colon targeting

Solid formulations intended for targeted drug release into the lower gastrointestinal (GI) tract are beneficial for the localized treatment of several diseases and conditions, mainly inflammatory bowel diseases, irritable bowel syndrome and colon cancer. Also, because of their natural potential to delay or avoid systemic absorption of drug from the small intestine, colonic formulations can be utilized for chronotherapy of diseases which are affected by circadian biorhythms (e.g., asthma, hypertension and arthritis), and to achieve clinically significant bioavailability of drugs that are poorly absorbed from the upper parts of the gastrointestinal tract because of their

polar nature and/or vulnerability to chemical and enzymatic degradation in the small intestine (e.g., peptides and proteins). The recent patent literature pertaining to various modified release (MR) formulation methods that are claimed to provide colonic delivery for a wide range of therapeutic agents. A variety of approaches have been used and systems have been developed for the purpose of achieving colonic targeting. These include [8]:

1.4 Primary Approaches for CDDS

I- pH-controlled (or delayed-release) system:-This approach is based on the pH-dependent release of the drug from the system. In this case the pH differential between the upper and terminal parts of GI tract is exploited to effectively deliver drugs to the colon[9]. The pH in the terminal ileum and colon (except ascending colon) is higher than in any other region of the GI tract. Thus a dosage form that disintegrates preferentially at high pH levels has good potential for site-specific delivery into this region [10].

II-Time-controlled (or time-dependent) system: 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. Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time-based [11, 12].

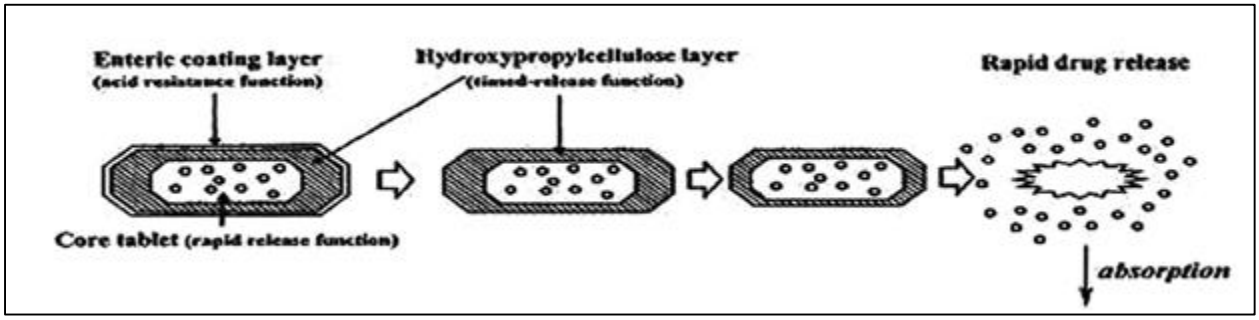

Fig 2: design, of enteric coated timed-release press coated tablet (E T P tablet)

III- Enzyme -controlled system: Microflora activated delivery systems are considered to be preferable and promising since the abrupt increase of the bacteria population and associated enzymatic activities in ascending colon represents a non-continuous event independent of GI transit time and pH [13].

IV- Microbially triggered drug delivery to colon

The microflora of colon is in the range of 1011 -1012 CFU/mL [14], consisting mainly of anaerobic bacteria, e.g**.** Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and trisaccharides, polysaccharides etc [15]. For this fermentation the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase [16].

IV-Covalent linkage of drug with carrier

a) Prodrug approach

Prodrugs are designed to undergo minimal absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon, releasing the active drug moiety from the carrier.

Table 3: Prodrugs used in the colon specific drug delivery system [7]

Azo polymer	Dosage form prepared	Drug investigated	In-vitro/in-vivo model used	Summary of the results obtained
Copolymers of styrene with 2-hydroxyethyl methacrylate	Coating over capsules	Vasopressin insulin	Rats, dogs	These capsule showed biological response characteristics of these peptide hormone in dog though it varied quantitatively
Hydrogel prepared by copolymerization of 2-hydroxyethyl metharylate with 4-methacryloyloxy azobenzene	Hydrogel	5-Fluorouracil	In-vitro	Drug release was faster and greater in human fecal media compared to simulated gastric and intestinal fluids.
Segmented polynurethanes	Coating over pellets	Budesonide	Rat	These azopolymer-coated pellets were useful for colon specific delivery of budesonide to bring healing in induced colites
Aromatic azo bond containing urethane analogues	Degradable films	5-ASA	*In vitro* degradation of films in presence of lactobacillus	These films were degraded by azoreductase. The permeability of 5-ASA from lactobacillus treated films was significantly higher than that of control

b) Polysaccharide Based Approach

These systems are based on the exploitation of the specific enzymatic activity of the microflora (enterobacteria) present in the colon. The colonic bacteria are predominately anaerobic in nature and secrete enzymes that are capable of metabolizing substrates such as carbohydrates and proteins that escape the digestion in the upper GI tract [1, 7].

Table 4: Polysaccharides investigated for colon specific drug delivery system [7]

Polysaccharide investigated	Drug moiety used	Dosage form prepared	In-vitro/in-vivo model used	Performance of the system
Chitosan	5-(6) carboxy fluorescein (CF)	Enteric-coated chitosan capsules	In-vitro	Little release of CF in upper GIT conditions and 100% drug release in 33% cecal content within 4 h of dissolution
Derivative Chitosan Succinate Chitosan Phthalate	Sodium diclofenac	As matrices	In-vitro	Reduced drug release was seen in acidic conditions and improved dissolution under basic conditions
Pectin (used as calcium salt)	Indomethacin	Matrices	In-vitro	In the presence of rat cecal content drug release was 60.8±15.7% as compared to 4.9±1.1 in control
Amidated pectin	Paracetamol	Matrix tablets	In-vitro	These matrices were not suitable for drug delivery in colon
Amidated pectin/calcium pectinate	Ropivacain	Matrix tablets with ethyl cellulose as drug matrix additive	In-vitro	Amidated pectin were more susceptible to pectinolytic enzyme as compared to calcium pectinate. Addition of ethyl cellulose increased the tablet strength and dissolution rate coating this formulation with Eudragit L100 reduced drug release in upper GIT conditions without affecting enzyme degradability
Chondroitin, sulphate Crosslinked chondroitin	Indomethacin	Matrix tablets	In-vitro	Drug release increase in presence of rat cecal content. Also it was observed that as crosslinking increased, drug release decrease
Alginates As calcium salt	5-ASA	Double coated swellable beads	In-vitro	In basic media enteric-coated dissolved and beeds swell to exceed the strength of aquacoat film which then burst releasing the drug

1.5 Newly Developed Approaches for CDDS

I-Pressure-controlled system: Prodrugs are designed to undergo minimal absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon; releasing the active drug moiety from the carrier [7]. A prodrug is a pharmacologically inactive derivative of a parent molecule that requires spontaneous or enzymatic transformation within the body to release the active drug moiety. For targeting drugs to the colon, drug is to be protected from the hostile environments of the stomach and small intestine. This protection in the upper GIT is affected by conjugation with carrier moieties, forming prodrugs. These prodrugs undergo enzymatic cleavage in the colon and regenerate the drug [17, 18].

II-Novel colon targeted delivery system (CODESTM)

CODESTM is an unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems [19, 20]. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon, (Fig. 3). The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passage through the alkaline pH of the small intestine [21]. Once the tablet arrives in the colon the bacteria will enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release [22].

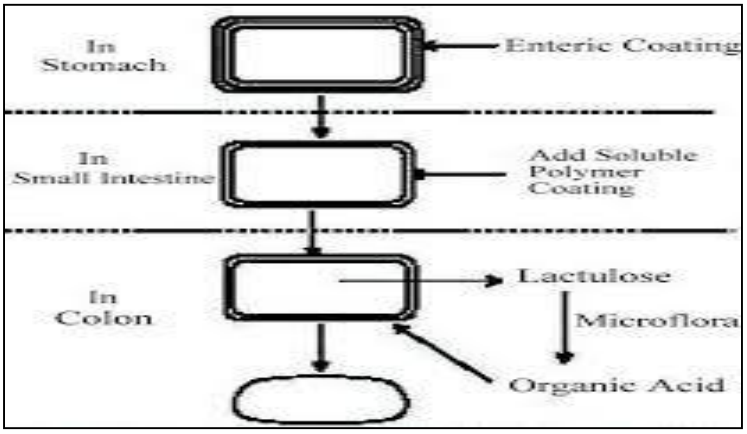

Fig 3: Schematics of the conceptual design of CODESTM

III-Osmotically controlled colon targeted drug delivery system

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable [23]. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, (Fig. 4) [24].

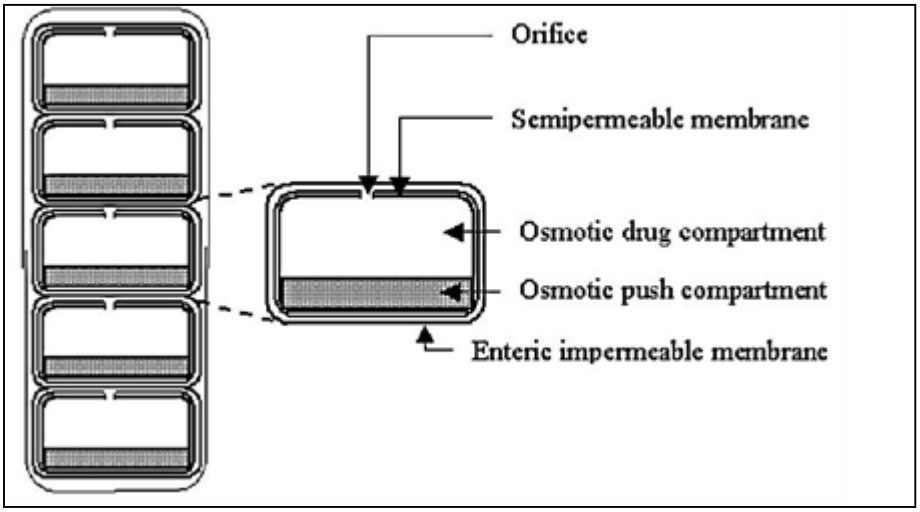

Fig 4: Osmotically controlled CDDs

IV-Pulsatile colon targeted drug delivery

i) Pulsincap system

In this system (Figure No.5) 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 [25].

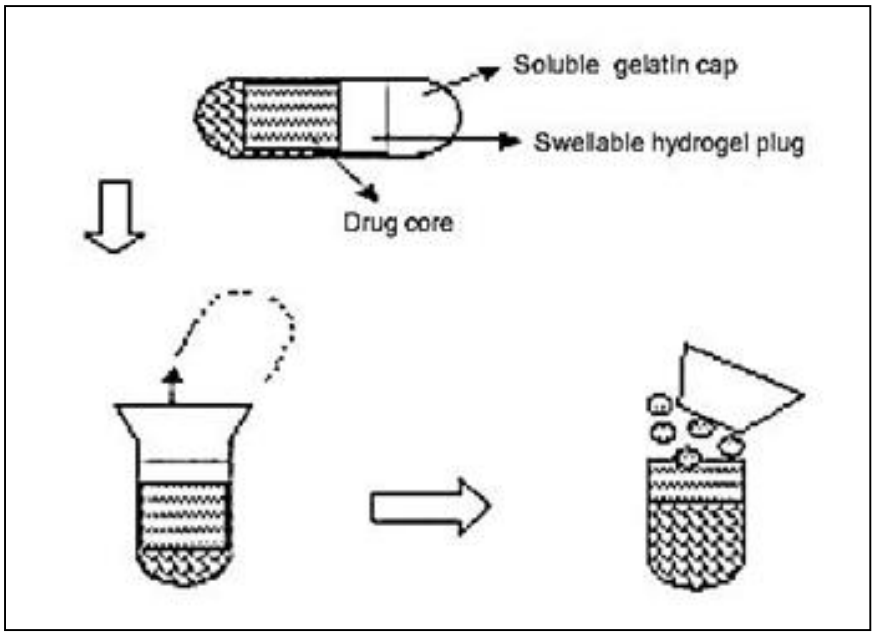

Fig 5: Pulsincap system

ii) Port system

In this system (Fig. 6) 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 [26].

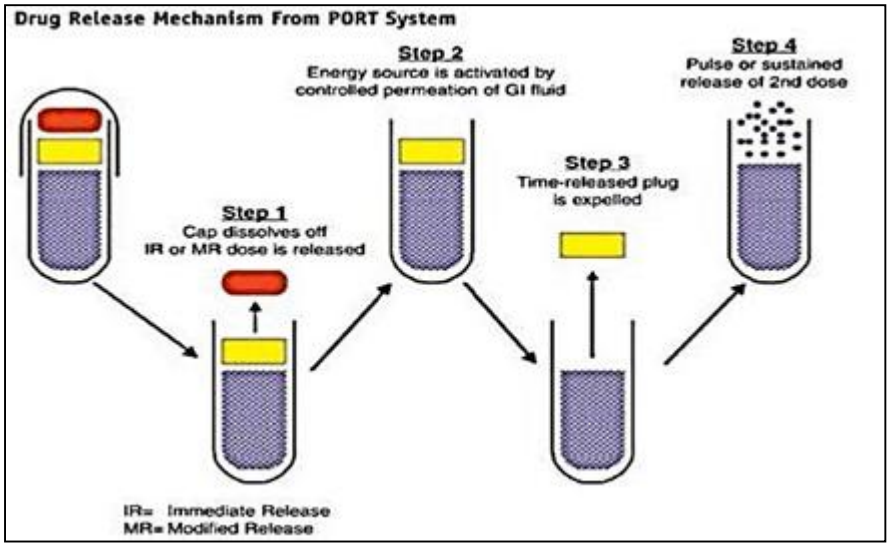

Fig 6:.Drug release mechanism of port system

V-pH-controlled (or delayed-release) system [27-29]

Different pH in the GIT

On entry in to the colon, the pH dropped to 6.4 ± 0.5. The pH in the mid colon is found 6.6 ± 1 and in the left colon, 7.0 ± 1 and the values are shown in this table [30].

Table 5: Different pH in the GIT

Location	pH
1. Stomach	1.5 – 2.0
Fasted condition	3.0 – 5.0
Fed condition	5.0 – 6.5
2. Small intestine	6.0 – 7.5
Jejunum	6.4
Ileum	6.7 – 7.3

1.6 pH sensitive delivery system

The use of pH-dependent systems is one of the leading formulation approaches for the site-specific colon delivery of drugs in the oral treatment of IBD. The residence time of currently existing colon delivery devices like enteric coated tablets, pellets, and granules is less due to diarrhoea which is the common symptom of the IBD [31-33]. Another problem associated with pH dependent polymer is that if the drug release in the small intestine is earlier then therapeutic efficacy decreases due to variability of gut pH [34]. Therefore, a pressing needs for the development of a drug delivery system that is able to target selectively the inflamed tissue of the colon as well as have enhanced residence time. This type of system could maximize the therapeutic efficacy and reduce the systemic side-effects associated with the anti-inflammatory drugs. The pH-sensitive polymers e.g.: Eudragit dissolve in aqueous medium at specific pH, equivalent to drug release to the distal ileum. If we consider the case of ulcerative colitis which mainly affects the distal parts of the colon, an early drug loss with non-flamed tissue of the upper colon may reduce the adverse effects [35-37].

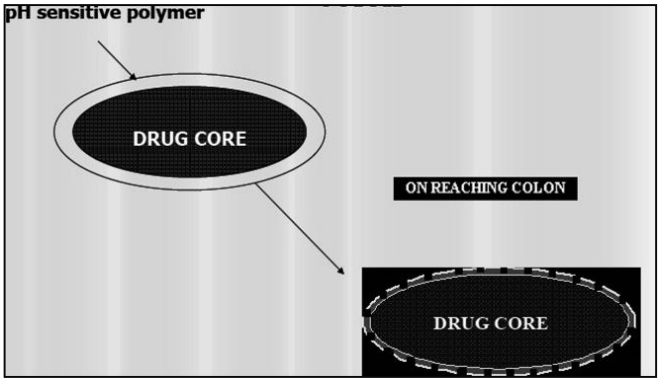

Fig 7: Mechanism of action of a pH dependent system for targeted drug delivery to the colon

1.7 pH sensitive polymers

Drug enclosed in a pH sensitive polymeric microsphere provide delayed release and protect the active drug from gastric fluid. The polymer used for colon targeting, 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. Basically formulation which is coated with enteric polymer releases drug when pH moves towards alkaline range.

Table 6: List of pH sensitive polymers [1, 38, 10]

pH dependent polymers	Threshold pH
Polyvinyl acetate phthalate (PVAP) (Coateric®)	5.0
Cellulose acetate phthalate (CAP) (Aquateric®) 6.0	6.0
Cellulose acetate trimellitate (CAT) 5.5	5.5
Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	
LF Grade	≥5.5
MF Grade	≥6.0
HF Grade	≥6.8

Hydroxypropyl methylcellulose phthalate (HPMCP) HP-50 HP-55 and HP-55	≥5.0 ≥5.5
Shellac (MarCoat 125 & 125N) 7.0	7.0
Eudragit® FS 30D ≥7.0	7.0
Methacrylic acid copolymer, Type A (Eudragit®L-100 and Eudragit® L12,5)	≥6.0
Methacrylic acid copolymer, Type B (Eudragit®S-100 and Eudragit® S12, 5)	≥7.0
Methacrylic acid copolymer, Type C (Eudragit® L100-55)	≥5.5
Methacrylic acid copolymer dispersion (Eudragit® L30D)	5.6

1.8 pH sensitive & biodegradable polymer

The bioenviornment inside the human GIT is characterised by the presence of complex microflora especially the colon that is rich in microorganisms that are involved in the process of reduction of dietary component or other material. Drugs that are enclosed with the polymers, which are showing degradability due to the influence of colonic microorganisms, can be exploited in designing drugs for colon targeting. If we talk about the drug release then the drug which is enclosed with the biodegradable polymer released following degradation of the polymer due to colonic bacteria.

1.9 List of biodegradable polymers

- Chitosan
- Pectin
- Guar gum
- Chondroitin sulphate
- Dextran
- Almond gum
- Locust bean gum
- Cyclodextrins
- Inulin
- Boswellia gum
- Amylose

1.10 Evaluation test of Colon Drug Delivery System

***In vitro* evaluation**

No standardized evaluation technique is available for evaluation of CDDS as an ideal *in-vitro* 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 and physical stress. The *in-vitro* evaluation of colon targeted drug delivery systems includes the *in-vitro* dissolution study and *in-vitro* enzymatic test.

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 behavior 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 [39].

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 [40].

3. *In- vivo* evaluation

The *in-vivo* evaluation of the CDDS is done in dogs, guinea pigs, rats and pigs as they resemble the anatomic and physiological conditions, micro flora of human GIT. The distribution of various enzymes in GIT of rat and rabbit is comparable to that in human [41].

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