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Review Article

Colon Targeted Drug Delivery System – A Review.

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ABSTRACT

Conventional drug therapies till date have proved its advantage for treating different diseases. But still it has certain limitations such as non targeted drug delivery, high dose, high dosing frequency, systemic side effects and decreased bioavailability. These drawbacks suggested need for development of Novel Drug Delivery System. To overcome these hurdles Colon Specific Drug Systems have been developed. Certain diseases are specific to colon and require localized treatment. Also certain drugs which have got variable drug release in upper GIT can be given in colon. The main aim of this delivery system is to achieve targeted drug delivery, improve systemic bioavailability of drug and to reduce potential side effects. Different approaches are designed to achieve colonic drug delivery of dosage form which include pH dependent drug delivery, Time controlled approach, Microbial triggered approach, Pressure controlled drug delivery, Osmotic controlled drug delivery, Multiparticulate approach and Novel colon targeted drug delivery. This article gives an overview on anatomy and physiology of the colon and approaches utilized for colon specific drug delivery. This article also discusses advantages & limitations of the different approaches & evaluation for site specific drug delivery to colon.

KEYWORDS

Colon specific drug delivery system, Advantages, Approaches.

1. INTRODUCTION

The oral aspect is considered to be most convenient for administration of drugs to Patients. Normally dissolves in stomach field as intestinal fluid and absorb from these regions of GIT. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as drugs needs to be protected from the hostile environment of upper GIT. Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowl diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, and colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in stomach as well as 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[1]. Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and / or susceptible to chemical and enzymatic degradation in upper GIT; in particular, therapeutic proteins and peptides are suitable for colonic deliveries [2-4]. Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systematically via colonic absorption. Other examples include novel peptides such as cytokine inhibitors and antibiotics, which are useful in treatment of IBD and GI infections respectively.

Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. A colonic targeted approach found to be effected in minimizing uncertain side effects [5]

The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.

Oral route is the most convenient and preferred route but other routes for CDDS may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal.[6] Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and Prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been

shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity. [7]

Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides.[8] These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration.

Table 1: Colon Targeting Diseases, Drugs and Sites

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

1.2 Advantages of CDDS over Conventional Drug Delivery

Chronic colitis, namely ulcerative colitis, and Crohn's disease are currently treated with glucocorticoids, and other anti-inflammatory agents.[10] Administration of glucocorticoids namely Dexamethasone and methyl Prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppressant, cushioned symptoms, and bone resorption.[11] Thus selective delivery of drugs to the colon could not only lower the required dose but also reduce the systemic side effects caused by high doses.[12]

1.3 Criteria for Selection of Drug for CDDS

The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. Drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. [13] the criteria for selection of drugs for CDDS is summarized in Table 2.[14-16]

Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule.[17]For example; aniline or nitro groups on a drug may be used to link it to another benzene group through an Azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.[13]

Table 2: Criteria for Selection of Drugs for CDDS

Criteria	**Pharmacological class**	**Non-peptide drugs**	**Peptide drugs**
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amylin, Antisense oligonucleotide
Drugs poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen, Isosorbides, Theophylline	Cyclosporine, Desmopressin
Drugs for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Peptides and proteins	Bromophenaramine, 5-Flourouracil, Doxorubicin	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive first pass metabolism	Nitroglycerin and corticosteroids	Bleomycin, Nicotine	Protirelin,sermorelin, Saloatonin
Drugs for targeting	Antiarthritic and antiasthamatic drugs	Prednisolone, hydrocortisone, 5-Amino-salicylic acid	Somatropin,Urotoilitin

1.4 Factors to Be Considered In the Design of Colon-Specific Drug Delivery System

1) Anatomy and Physiology of Colon

The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5 m long. [6] The colon is upper five feet of the large intestine and mainly situated in the abdomen.

The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 2-3 inches in diameter [7]. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal

(Figure 1) [8]. The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.

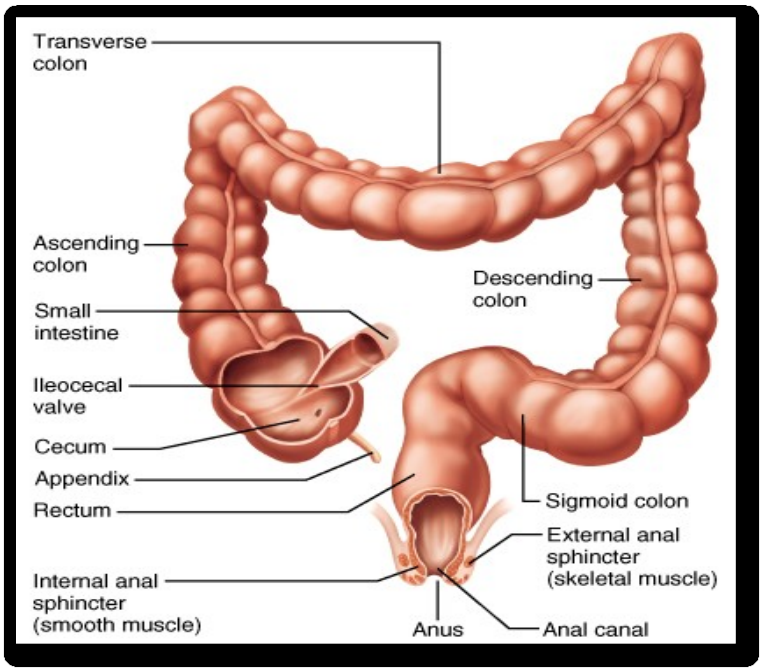

Figure 1: Anatomy of Colon

Functions:

1) Extracts water and salt from solid wastes before they are eliminated from the body. Absorb water, potassium and some fat soluble vitamins

2) Flora-aided (largely bacteria) fermentation of unabsorbed material occurs

2) Pathological conditions related to colon drug delivery

The colon, especially the first part of the lower intestine, can be liable to numerous pathological conditions, such as

1) Constipation,

2) Crohn´s disease, Irritable Bowel Syndrome

3) Ulcerative colitis, Inflammatory Bowel Diseases

4) Colorectal Cancer & Carcinomas and Infections.

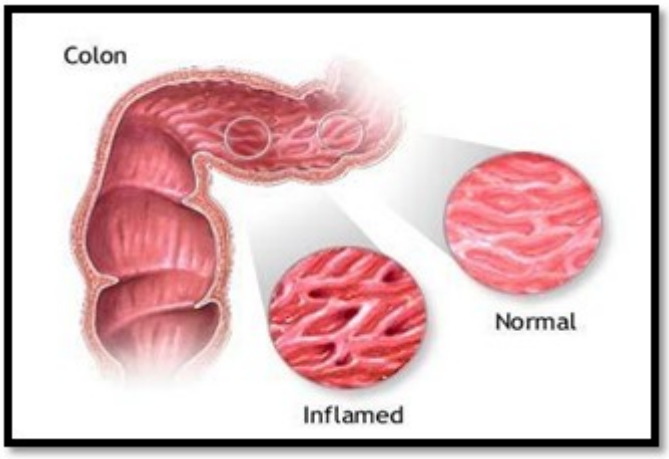

Figure 2: Inflammatory bowels disease

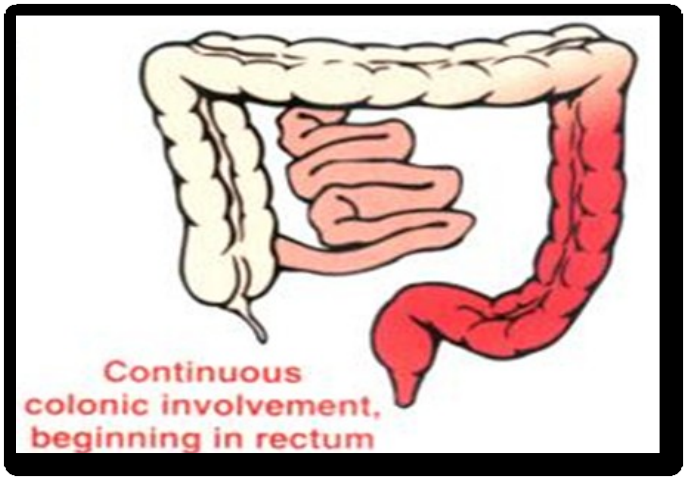

Figure 3: Ulcerative colitis

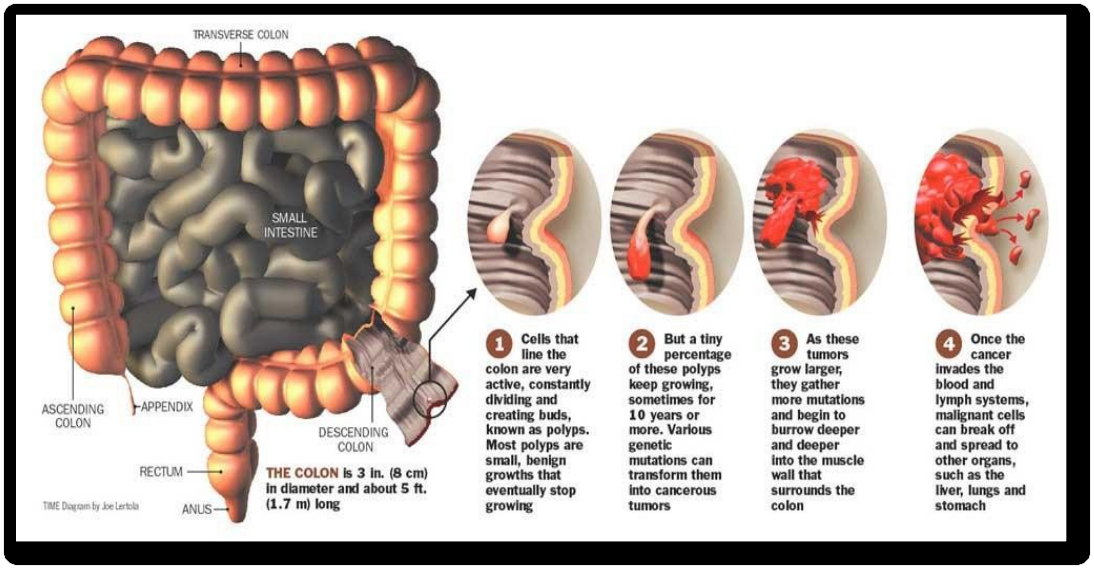

Figure 4: Colon Cancer

3) pH in the Colon

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery [9]. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine **(Table 3)**. The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

4) Transit of material in the colon

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestinal transit time. The transit times of small oral dosage forms in GIT are given in **Table 4.**

Table 3: pH of Various Parts in Gastrointestinal Tract

Sr. No.	**Location**	**pH**
1	**Stomach**	
	Fasted condition	1.5 - 2.0
	Fed condition	3.0 - 5.0
2	**Small intestine**	5.0 - 6.5
	Jejunum	6.0 - 7.5
	Ileum	6.4
3	**Large intestine**	
	Right colon	6.7 – 7.3
	Mid colon &	6.4
	Left colon	6.0 - 7

Table 4: The Transit Time of Dosage form in GIT

Organ	**Transit time (hr)**
Stomach	<1 (Fasting) >3 (Fed)
Small intestine	3-4
Large intestine	20-30

The movement of materials through the colon is slow and tends to be highly variable and influenced by a number of factors such as diet, dietary fiber content, mobility, stress, disease and

drugs. In healthy young and adult males, dosage forms such as capsules and tablets pass through the colon in approximately 20-30 hours, although the transit time of a few hours to more than 2 days can occur. Diseases affecting colonic transit have important implications for drug delivery: diarrhea increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant

5) Colonic micro flora and their enzymes

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut micro flora residing in high number in the colon. These enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a Prodrug. Over 400 distinct bacterial species have been found, 20-30% of which are of the genus Bacteroides [10, 11]. The upper region of the GIT has very small number of bacteria and predominantly consists of Gram-positive facultative bacteria. The concentration of bacteria in the human colon is 1011- 1012 CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptostreptococcus, peptococcus, Ruminococcus and clostridiums [12]. Summary of the most important metabolic reaction carried out by intestinal bacteria are given in Table 5.

Table 5: Drug Metabolizing Enzymes in the Colon that Catalyze Reactions

Enzymes	**Microorganism**	**Metabolic reaction catalyzed**
Nitroreductase	*E. coli*, Bacteroides	Reduce aromatic and heterocyclic nitro compounds
Azareductase	Clostridia, Lactobacilli, *E. coli*	Reductive cleavage of Azo compounds
Esterase and amidases	*E. coli, P. vulgaris, B. subtilis, B. mycoides*	Cleavage of esters or amidases of carboxylic acids
Glycosidase	Clostridia, Eubacterium	Cleavage of β-glycosidase of alcohols and phenols
Glucuronidase	*E. coli, A. aerogenes*	Cleavage of β-glucuronidases of alcohols and phenols

6) Colonic Absorption

The surface area of the colon is much less compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 hours). Different factors affecting colonic absorption were reported Passes through colonocytes (Tran cellular transport). Passes between adjacent colonocytes (Para cellular transport). Tran cellular absorption involves the passage of drugs through cells and thus the route for most lipophilic

drugs takes, where as par cellular absorption involves the transport of drug through the tight junctions between the cells and is the route of most hydrophilic drugs. Drugs shown to be well absorbed include glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide, buflomedil, atenolol

Factors affecting colonic absorption:

- Physical properties of drug such as pKa and degree of ionization.
- Colonic residence time as commanded by GIT motility.
- Degradation by bacterial enzymes and metabolite products.
- Local physiological action of drug.
- Selective and non-selective binding to mucus.
- Disease state.
- Transit through GIT.

Advantages:

- Reduction in dose size.
- Improve bioavailability.
- Flexibility in design.
- Reduced dose frequency.
- Improved patient compliance.
- Delivery of drug in its intact form as close as possible to the target sites.
- Reduced incidence of adverse side effects improved tolerability.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.
- Lower daily cost to patient due to fewer dosage units are required by the patient.

Disadvantages:

- Low dose loading
- Higher need of excipients
- Lack of manufacturing Reproducibility and efficacy
- Multiple formulation steps
- Large number of process variables
- Need of advanced technology.
- Skilled personal needed for Manufacturing of colonic drug delivery system.

1.5 Need of colon targeted drug delivery12, 13:

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.

- Colon-specific drug delivery system is considered to be 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 (targeted).
- 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 are 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.

1.6 Limitations13, 14:

- As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers. However, the targeting of drugs to the colon is very complicated.
- Due to its location at the distal portion of the alimentary canal, the colon is particularly difficult to access.
- In addition, the wide range of pH values and different enzymes present throughout the GI tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.
- 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.
- The drug could potentially bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or faecal matter. The resident micro flora 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 drug transport across the mucosa and into the systemic circulation.

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

Several approaches are used for site-specific drug delivery. Among the primary approaches for CDDS, These include:

1.7.1 Primary Approaches for CDDS

A) pH Sensitive Polymer Coated Drug Delivery to the Colon

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. [21] The pH is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine. [22] From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH

values as low as 5.7 have been measured in the ascending colon in healthy volunteers.[23] The pH in the transverse colon is 6.6 and 7.0 in the descending colon. 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.[24] Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor.[25] 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 which can also result in poor site-specificity of enteric-coated single-unit formulations.[24]

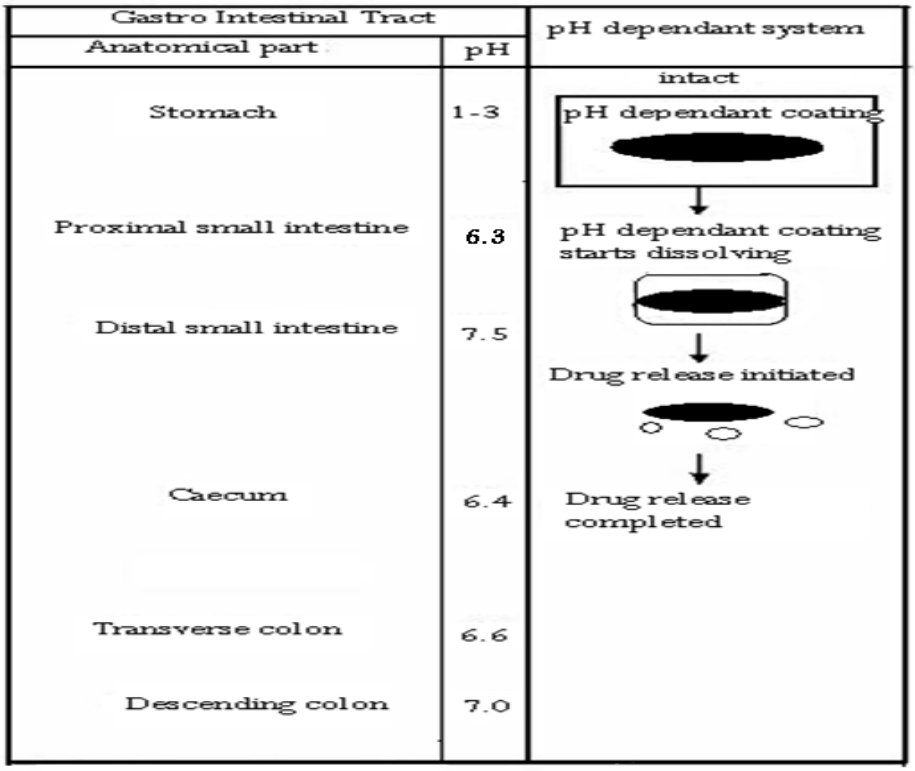

Figure 5: pH Sensitive Polymer Coating Drug Delivery to Colon

Coating is one of the simplest formulation technologies used for colon-specific delivery. Coating agents used in colon specific drug delivery are pH sensitive polymers. The dissolution performance of these polymers is influenced by pH. The polymer which contains ionizable phthalic acid group dissolves much faster at a lower pH than those with acrylic or methacrylic acid groups. The dissolution rate of Eudragit® is influenced in the presence of plasticizer [32] and the nature of the salt in the dissolution medium [33-35]. The advantage of coated formulation is in terms of cost and ease of manufacturing. The coated formulations can be either a single-layered or a multi-layered product. The coating of single-layered product may be

composed of a single enteric polymer that has a pH-dependent solubility or a mixture of two polymers one of which has pH-dependent while other have a pH independent solubility. For multi-layer products, the coating is applied in successive layers which could be either based on two enteric polymers that have different pH-dependent solubility profiles [36].

GI residence time of the dosage form is another important parameter for pH dependent colon targeted drug delivery systems and is influenced by many physiological and other factors [37, 38]. There are standard GI residence values for various parts of the GIT [39]. Most commonly used pH-dependent coating polymers are methacrylic acid copolymers. These polymers dissolve above pH 5.5 by forming salts and disperse in water to form latex and use of organic solvents in the coating process can be avoided. Eudragit® L100-55 is prepared in Eudragit® L30D-55 for a ready to use aqueous dispersion. The water solubility of the Eudragit® S depends on the ratio of free carboxyl groups to the esterifies groups.

Polymers and Threshold pH

1. Eudragit® L 100 (6.0)
2. Eudragit® S 100 (7.0)
3. Eudragit® L-30D (5.6)
4. Eudragit® FS 30D (6.8)
5. Eudragit® L 100-55 (5.5)
6. Polyvinyl Acetate Phthalate (5)
7. Hydroxypropyl Methylcellulose Phthalate (4.5- 4.8)
8. Hydroxypropyl Methylcellulose Phthalate 50 (5.2)
9. Hydroxypropyl Methylcellulose Phthalate 55 (5.4)
10. Cellulose Acetate Phthalate (4.8)
11. Cellulose Acetate Trimellate (5.0)

Table 6: pH Sensitive Polymer and Marketed Formulations

Drug	Trade Name	Coating Polymer / Formulation
Budesonide	Entocort® Budenofalk®	Eudragit® L 100-55, Ethylcellulose (pH-6) Eudragit® S (pH-7)

Mesalazine	Claversal®	Eudragit® L100	(pH-6)
	Asacolitin®	Eudragit® S	(pH-7)
	Salofalk®	Eudragit® S	(pH-7)
	Pentasa®	Ethyl cellulose coated pellets	
	Mesazal®	Eudragit® L100	(pH-6)
	Calitofalk®	Eudragit® L100	(pH-6)
	Asacol ®	Eudragit® S	(pH-7)
Sulfasalazine	Azulfidine®	Cellulose acetate phthalate	(pH- 6.2-6.5)
	Colo-Pleon®	Eudragit ® L100-55	(pH-5.5)

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 drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability. [26] The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h. However, the 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. [27]

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. [9, 28, 29]

Therefore, time dependent systems are not ideal to deliver drugs to the 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. Since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hr. [30] 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. Enteric coated time-release press coated (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 (HPC), time release function) and an enteric coating layer (acid resistance function). [26, 31] The 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 to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. The duration of lag phase is controlled either by the weight or composition of the polymer (HPC) layer. (Figure 6)

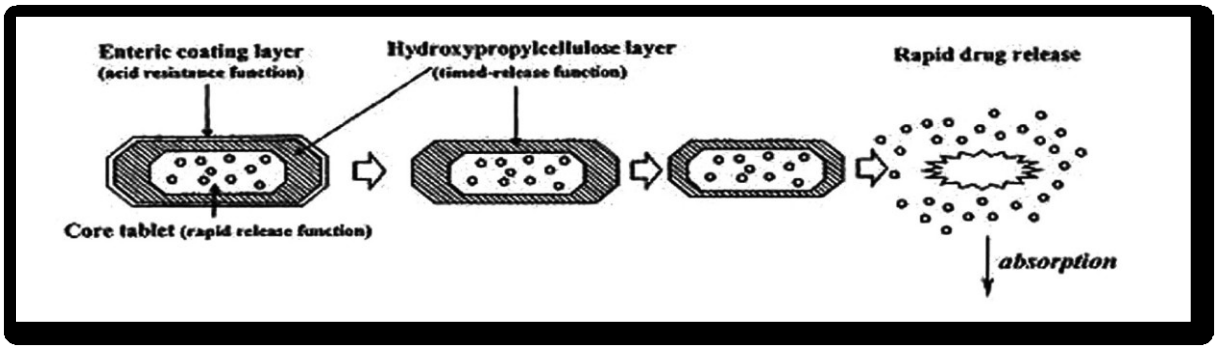

Figure 6: Design of Enteric Coated Timed-Release Press Coated Tablet (ETP Tablet)

ii) Pulsincap (Figure 7):

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. 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 (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (eg, saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (eg, pectin).

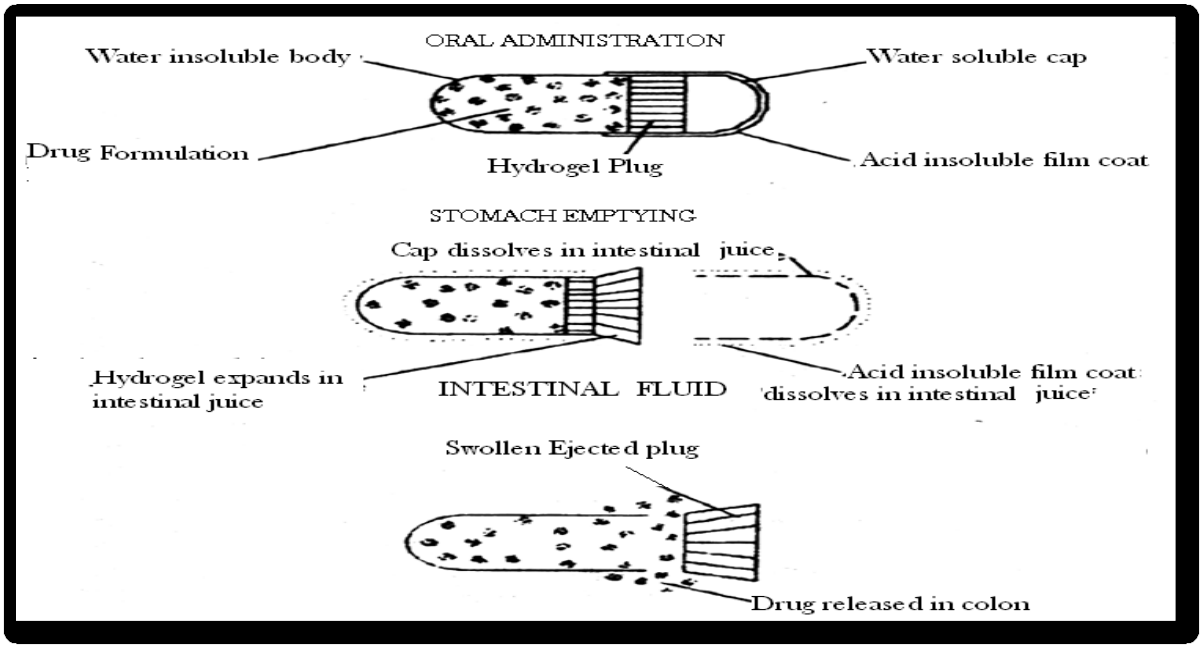

Figure 7: Design of Pulsincap system

ii) 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 **(Figure 8)**. 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.

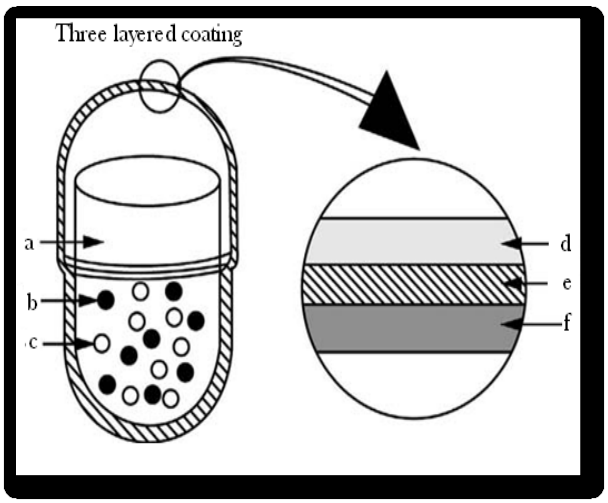

Figure 8: a) gelatin capsule; b) active ingredient; c) organic acid; d) enteric layer; e) hydrophilic layer; and f) acid-soluble layer**.**

C) Microbially Triggered Drug Delivery to Colon

The micro flora of the colon is in the range of 1011 -1012 CFU/ mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc.[28] This vast micro flora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc. For this fermentation, the micro flora produces a vast number of enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareductase, deaminases, and urea dehydroxylase. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to e a more site-specific approach as compared to other approaches. These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer.

i) Prodrug Approach for Drug Delivery to Colon

Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery, the Prodrug is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier. Metabolism of Azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic process.41 A number of other linkages susceptible to bacterial hydrolysis specially in the colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose etc. Limitations of the prodrug approach is that it is not a very versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities, and need a lot of evaluation before being used as carriers. [42] A number of prodrugs have been outlined in Table 7.

Table 7: Prodrugs evaluated for colon specific drug delivery with there in vitro/in vivo performance

Carrier	Drug investigated	Linkage hydrolyzed	In vitro/in vivo model used	Performance of the Prodrug/conjugates
Azo conjugates	5-ASA	Azo linkage	Human	Site specific with a lot of side effects [59] associated with SP
Suphapyridine (SP)	5-ASA	Azo linkage	Human	Delivers 2 molecules of 5-ASA as compared to sulphasalazine [60]
5-ASA				
Amino acid conjugates	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized by micro flora of

glycine				large intestine [61]
Tyrosine/methionine	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized by micro flora of large intestine [62]
L – Alanin/D-Alanine	Salicylic acid	Amid linkage	In vitro	Salicylic acid-l-alanine was hydrolysed to salicylic acid by intestinal microorganism but salicylic acid-D-alanine showed negligible hydrolysis thereby showing enantiospecific hydrolysis [63]
Glycine	5-ASA	Amid linkage	In vitro	Prodrug was stable in upper GIT and was hydrolysed by ceacal content to release 5-ASA [64]
Saccharide carriers	Dexamethasone/ prednisolone	Glycosidic linkage	Rat	Dexamethasone Prodrug was site specific and 60% of oral dose reached the cecum. Only 15% of prednisolone Prodrug reached the cecum [17]
Glucose/galactose/ cellobioside	Dexamethasone; prednisolone hydrocortisone,	Glycosidic linkage	In vitro	Less hydrolysis of the Prodrug was seen in contents of stomach and proximal small intestine (PSI).hydrolysis increased in contents of distal small intestine (DSI) and was maximum in ceacal content homogenates. galactosidase hydrolyzed faster than glycosides which hydrolyzed faster than the corresponding cellobioside [41]
Glucuronide conjugates glucuronic acid	Naloxone/ nalmefene	Glucuronide linkage	Rat	When given to morphine dependent rats, these reversed the GIT side effects caused by morphine without causing CNS withdrawal symptom because of activation in large intestine followed by a resultant diarrheas which excreted the Prodrug drug [65]

(ii) Azo-Polymeric Prodrugs

Newer approaches are aimed at the use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers have been used for this purpose. Sub synthetic polymers have been used to form polymeric prodrug with Azo linkage between the polymer and drug moiety. These have been evaluated for CDDS. Various Azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreducatase in the large bowel. Coating of peptide capsules with polymers cross linked with azoaromatic group have been found to protect the drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced, and the drug is released. A number of azo-polymeric prodrugs are outlined in Table 8.

Table 8: Some Azo Polymer-Based Drug Delivery Systems Evaluated for Colon-Specific Drug Delivery with Summary of Results Obtained

Azo polymer	Dosage from 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 capsules showed biological response characteristics of these peptide hormones in dog though it varied quantitatively [67-69]
Hydrogels prepared by copolymerization of 2-hydroxyethy1 methacrylate with 4-methacryloyloxy) azobenzene	Hydrogen	5-fluorouracil	In vitro	Drug release was faster and greater in human fecal media compared to simulated gastric and intestinal fluids [70]
Segmented polyurethanes	Coating over pellets	Budesonide	Rat	These azopolymer-coated pellets were useful for colon-specific delivery of Budesonide to bring healing in induced colites [71]
Aromatic Azo bond containing urethane analogues	Degradable films	5-ASA	In vitro degradation of films in presence of lactobacillus	These films were degraded by azareductase. The permeability of 5-ASA from lactobacillus treated films was significantly

	higher than that of control [72]

iii) Polysaccharide Based Delivery Systems

The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharide's are found in abundance, have wide availability are inexpensive and are available in a verity of a structures with varied properties. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccrides can be broken down by the colonic microflora to simple saccharides. [24] Therefore, they fall into the category of "generally regarded as safe" (GRAS). A number of polysaccharide-based delivery systems have been outlined in Table 9.

Table 9: Polysaccharide Based Colon Drug Delivery System

Drug	Polysaccharide	Dosage form
Diclofenac Sodium	Chitosan	Enteric coated chitosan microspheres
Paracetamol	Amidated pectin	Matrix tablet
Bovine serum albumin	pH sensitive dextran	Hydrogel
Dexamethasone	Guar gum	Matrix tablet
Indomethacin	Chondroitin sulphate	Matrix tablet
Theophylline	Locust bean gum	Film coat

1.7.2 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. developed pressure controlled colon-delivery capsules prepared using ethylcellulose, which is insoluble in water.[43] In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation.[44,45] 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.[46] Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

b. 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.[47,48] 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, **(Figure 9)**. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently over coated 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 passes through the alkaline pH of the small intestine.[49] once the tablet arrives in the colon, the bacteria enzymetically 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.

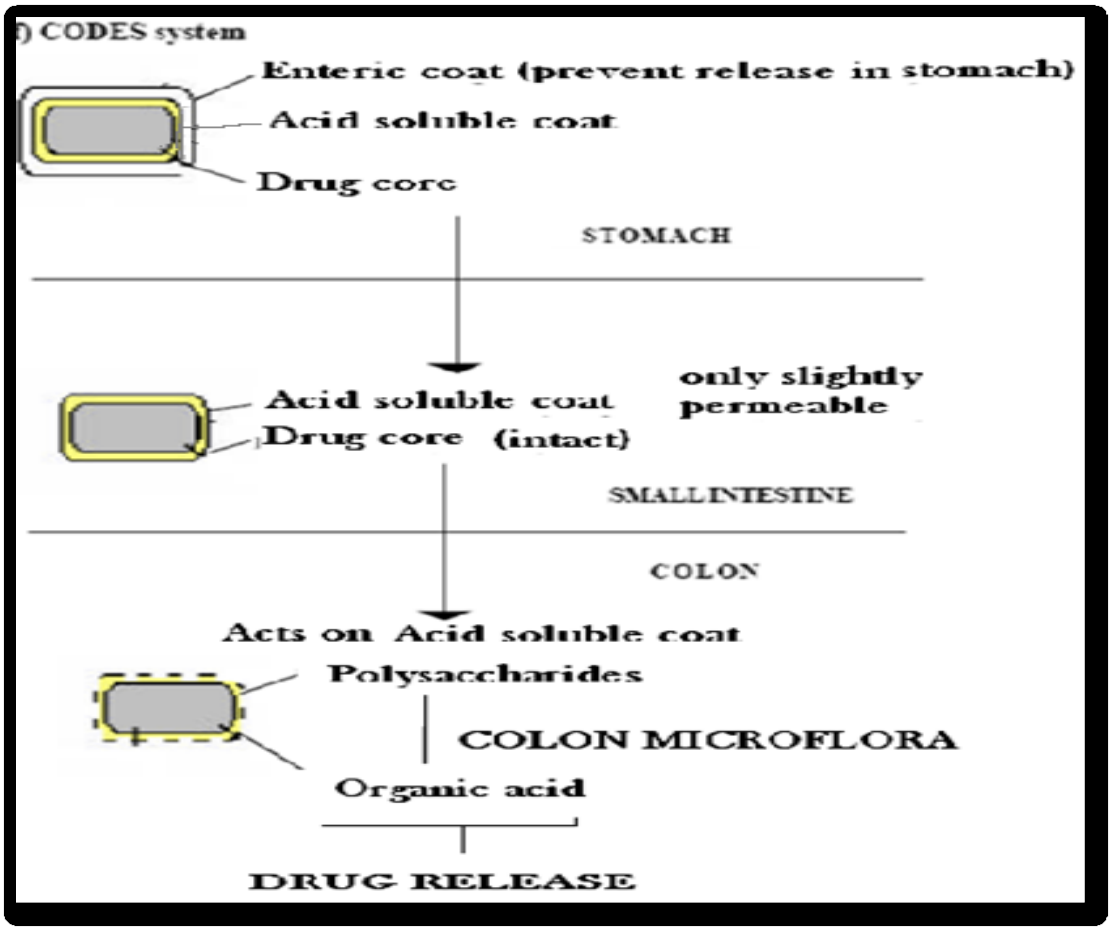

Figure 9: Schematics of the conceptual design of CODES™

c. Osmotic Controlled Drug Delivery (ORDS-CT)

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.[50] 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, **(Figure 10)**.[51] Each

bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flow able gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semi permeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h 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 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon.[52-55] various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

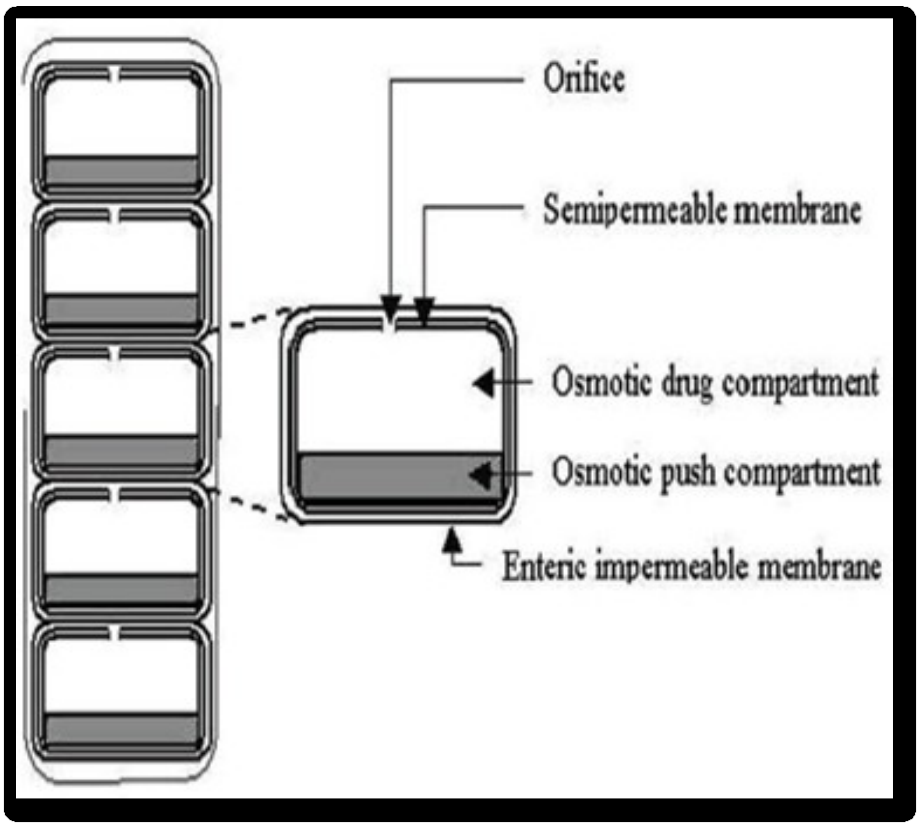

Figure 10: Cross-Section of the OROS-CT Colon Targeted Drug Delivery System

D) Multiparticulate systems:

Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. Report suggests that drug carrier systems larger than 200 µm possess very low gastric transit time due to physiological condition of the bowel in colitis. And for this reason and considering the selective uptake of micron or submicron particles by cancerous and inflamed cells/ tissues a Multiparticulate approach is expected to have better pharmacological effect in the colon. Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like,

- Multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time and hence increased bioavailability.
- Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GI tract easily, leading to less inter- and intra subject variability.
- Moreover, Multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption.
- Reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.

Multiparticulate approaches include formulations in the form of pellets, granules, beads, microparticles and Nanoparticles

E.g. alginate & chitosan beads containing theophylline prepared, followed by coating with Eudragit S100.

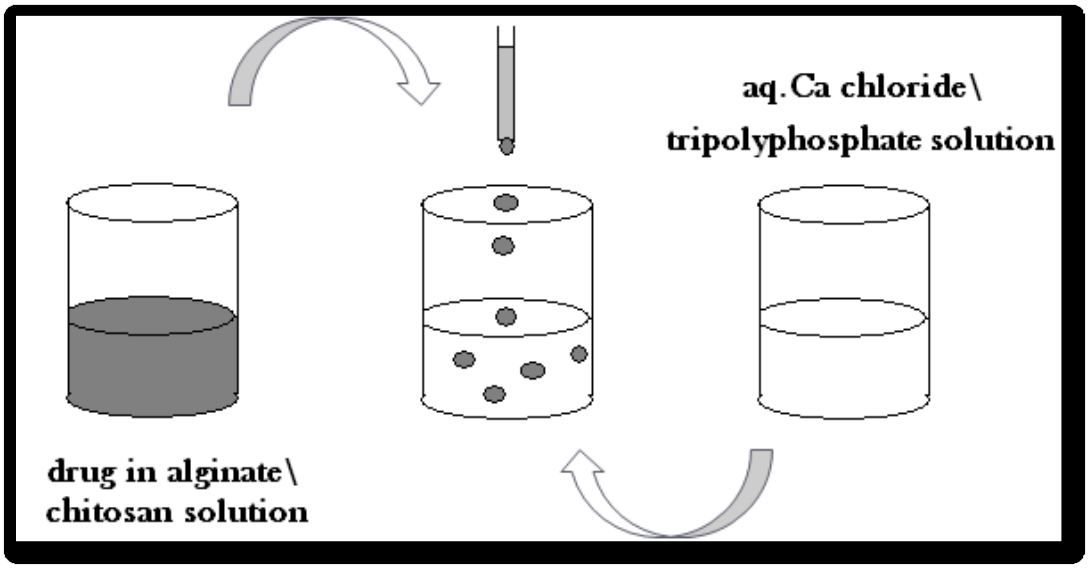

Figure 11: Multiparticulate Drug Deliveries to Colon

1.8 Evaluation

1.8.1 In Vitro Evaluation

No standardized evaluation technique is available for evaluation of CDDS because an ideal *in vitro* model should posses the *in vivo* conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and other components of food. Generally these conditions are influenced by the diet and physical stress and these factors make it difficult to design a slandered in vitro model. *In vitro* model used for CDDS are:

***In vitro* dissolution test:** Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic *in vivo* conditions such as those relating to pH, bacterial environment and mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon- specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileal segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. In vitro test for intactness of coatings and carriers in simulated conditions of stomach and intestine Drug release study in 0.1 N HCl for 2 hours (mean gastric emptying time) Drug release study in phosphate buffer for 3 hours (mean small intestine transit time)

***In vitro* enzymatic test:**

For this there are 2 tests:

1. Incubate carrier drug system in fermented containing suitable medium for bacteria (*Streptococcus faccium* or *B.ovatus*) amount of drug released at different time intervals determined.

2. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit ceacal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

1.8.2 *In Vivo Evaluation*

A number of animals such as dogs, guinea pigs, rats and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the micro flora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Eg. Guinea pigs are commonly used for experimental IBD model. The distribution of azareductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS a novel model has

been proposed. In this model the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which vascularizes within 4 weeks, matures and becomes capable of developing of mucosal immune system from the host.

1.8.3 *Clinical Evaluation*

Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

High frequency capsule: Smooth plastic capsule containing small latex balloon, drug and radiotracer taken orally. Triggering system is high frequency generator.Release of drug & radiotracer triggered by an impulse, the release is monitored in different parts of GIT by radiological localization.It checks the absorption properties of drug in colon.

Gammascintigraphy: By means of gammascintigraphic imaging, information can be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine, and disintegration. Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained. Gammascintigraphic studies can also provide information about regional permeability in the colon. Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphic studies (pharmacoscintigraphy).

Drug Delivery Index (DDI) and Clinical Evaluation of Colon- Specific Drug Delivery Systems

DDI is a calculated pharmacokinetic parameter, following single or multiple dose of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery. Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently, gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

1.9 Limitations and Challenges in Colon Targeted Drug Delivery system

- To establish an appropriate dissolution testing method to evaluate the designed system *in-vitro*
- 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.
- The colon is particularly difficult to access. the targeting of drugs to the colon is very complicated
- The drug may potentially bind in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
- Lower surface area and relative ‘tightness’ of the junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation.

1.10 Current and Future Developments:

Currently, there are several modified release solid formulation technologies available for colonic delivery. These technologies rely on GI pH, transit times, enterobacteria and luminal pressure for site-specific delivery. Each of these technologies represents a unique system in terms of design but has certain shortcomings, which are often related to degree of sites specificity, toxicity, cost and ease of scale up/manufacturing. It appears that Microbially controlled systems based on natural polymers have the greatest potential for colonic delivery, particularly in terms of site specificity and safety. In this regard, formulations that employ a film coating system based on the combination of a polysaccharide and a suitable film forming polymer represents a significant technological advancement. Further developments in this area require means to improve the co processing of the polymeric blend of a polysaccharide(s) and a film forming material while maintaining the propensity of the composition to microbial degradation in the colon [42, 43].

1.11 Opportunities in Colon Targeted Drug Delivery:

- In the area of targeted delivery, the colonic region of the GI tract is the one that has been embraced by scientists and is being extensively investigated over the past two decades. Targeted delivery to the colon is being explored not only for local colonic pathologies, thus avoiding systemic effects of drugs or inconvenient and painful transcolonic administration of drugs, but also for systemic delivery of drugs like proteins and peptides, which are otherwise degraded and/or poorly absorbed in the stomach and small intestine but may be better absorbed from the more benign environment of the colon.
- This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis. Moreover, there is an urgent need for delivery of drugs to the colon that reported to be absorbable in the colon, such as steroids, which would increase efficiency and enable reduction of the required effective dose.
- The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Crohn's disease and other colon diseases, where it is necessary to attain a high concentration of the active agent, may be efficiently achieved by colon-specific delivery.
- The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract is one of the greatest challenges for oral peptide delivery.
- The bioavailability of protein drugs delivered at the colon site needs to be addressed.
- More research is focused on the specificity of drug uptake at the colon site is necessary. Such studies would significant in advancing the cause of colon targeted drug delivery in future.

Table 10: Marketed Drug Products for Treatment of Various Diseases of Colon

SR. No	MARKETED NAME	COMPANY NAME	DISEASE	DRUG
1	Mesacol tablet	Sun pharma, India	Ulcerative colitis	**Mesalamine**

2	Mesacol enema	Sun pharma, India	Ulcerative colitis	**Mesalamine**
3	Asacol	Win-medicare, India	Ulcerative colitis, crohn's disease	**Mesalamine**
4	SAZO	Wallace, India	Ulcerative colitis, crohn's disease	**Sulphasalazine**
5	Intazide	Intas, India	Ulcerative colitis	**Balsalazide**
6	Lomotil	RPG Life, India	Mild ulcerative colitis	**atropine sulphate**
7	Buscopan	German Remedies, India	Colonic motility disorder	**Hyoscine butylbromide**
8	Colospa	Solvay, India	Irritable colon syndrome	**Mebeverine**
9	Cyclomino L	Neol, India	Irritable colon syndrome	**Diclomine**
10	Eldicet	Solvay, India	Irritable colon syndrome, Spastic colon	**Pinaverium bromide**
11	Equirex	Jagsonpal Pharmaceutical , India	Irritable colon syndrome	**Clordiazepoxide**
12	Normaxin	Systopic labs, India	Irritable colon syndrome	**Clidinium bromide**
13	Pro-banthine	RPG Life, India	Irritable colon syndrome	**Propenthline bromide**
14	**Entofoam**	**Cipla, India**	**Ulcerative colitis**	**Hydrocortisone acetate**

1.12 Patents

1) Oral Pharmaceutical Preparation For Colon-Specific Delivery (US 2010/0209520 A1)

1. Core : p'ceutically acceptable vehicle e.g. magnesium alumino silicate, HPMC
2. Drug; +(coating agents; plasticizers, binding inhibitor)
3. Cationic polymer soluble or swellable at pH NMT 6.6 e.g. Eudragit E 100
4. Anionic polymer soluble at pH NLT 7 e.g. Eudragit S 100

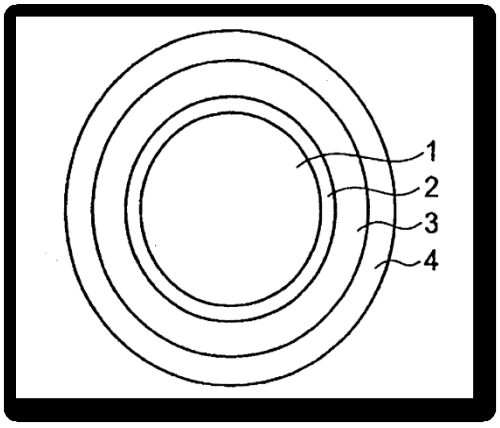

Figure 12: Oral Pharmaceutical Preparation for Colon Specific Drug Delivery

2) System for the Colon Delivery of Drugs Subject to Enzyme Degradation and/or Poorly Absorbed In Git (WO 2010/007515 A2)

a. Core containing drug susceptible to enzymatic degradation\ poor absorption in GIT

b. Inner layer consisting of polymer which swell/dissolve/ degraded in contact with biological fluid in GIT

c. Intermediate layer consisting of protease inhibitor\absorption enhancer

d. Outer layer consisting of polymer which swell/dissolve/ degraded in contact with biological fluid in GIT

e. Optionally external layer consisting of gastro-resistant polymer.

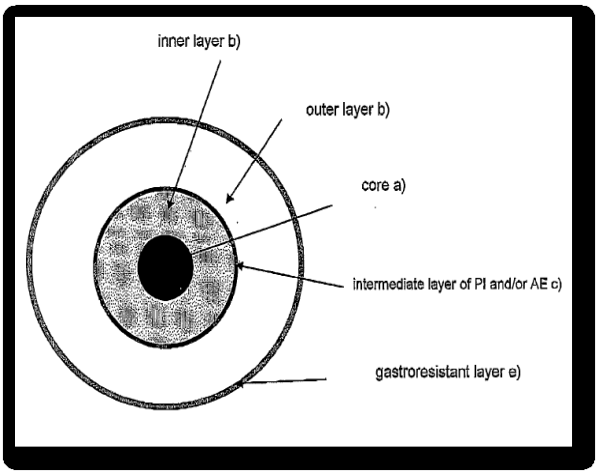

Figure 13: Systems for the Colon Delivery of Drugs Subject to Enzyme Degradation and/or Poorly Absorbed In Git

2. CONCLUSION

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon-specific drug delivery systems, and the uncertainty of current dissolution methods in

establishing possible in-vitro/in-vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

3. CONFLICT OF INTEREST

The authors reported no conflict of interest. The authors alone are responsible for the content and writing of the paper and no funding has been received on this work.

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