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Colon Targeted Drug Delivery-Approach and Future Prospect: A Review

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ABSTRACT

The colon is the terminal part of the GIT which has gained increased importance not just for the delivery of the drugs for both local and systemic administration. The delivery of drug for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, etc. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in the upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon and that system refers to delivery of drug in to lower part of the GI tract, mainly large intestine. When this is the most important delivery of those drug which are normally inactivated in the upper parts of the gastrointestinal tract (GIT). This review mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbial triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery (ORDS-CT) which are unique in terms of achieving the *in vivo* site specificity, and feasibility of manufacturing process for the CDDS. These treatments could be more effective if it is possible for drug to be directly delivered to colon. This review article discusses introduction of colon, need and approaches of colonic drug delivery, factor effecting colonic transition, colonic diseases and the novel and emerging technologies for advanced colon targeting for site specific drug delivery to colon. It is a challenging area for future research and holds lots of promises for novel and efficient approach for targeted drug delivery system.

Keywords: Colon targeted drug delivery, newly developed approaches, future prospect for CDDS.

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INTRODUCTION

The major goal of any drug delivery system is to supply a therapeutic amount of drug to a target site in a body so that highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs[1,2]. The deliveries of drugs to the colon via gastrointestinal (GI) tract require the protection of a drug from being released in stomach and 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[3]. Because the colon has a long residence time 72 hours and high water content it favors absorption of poorly absorbed drug molecule may have an improved bioavailability, Drug targeting to specific sites of action offers several advantages over non targeted drugs such as prevention of side effects and reduction of doses. The colon act as a site of drug delivery offers various therapeutic advantages because of its near neutral pH and longer transit time and the drug must be released in the colon from the drug delivery system. The targeted depends on exploiting a unique feature of specific site and protecting the drug until it reaches to the site. This is because of the flexibility in dosage form designed for oral than parenteral route because

- Patient acceptance for the oral administration of the drug is quite high.
- It is relatively safe route of drug administration compared with parenteral route and potential damage at site of administration is minimal. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon. These drug should be reduces the systemic side effect[4]. CDDS has been employ to achieve following objectives

- It should be sustained delivery to reduce dosing frequency.
- It should be Delay delivery of drug to achieve high Concentration in treatment of disease of distal gut.
- It should be to delay than in upper GIT, which is the limiting factor for poorly soluble drugs.
- It should be deliver drug to that region that is less hostile metabolically, drug.
- This is acid and enzyme labile such as proteins.

These sustained releases of drug in to the colon can be useful in the treatment of certain disease. This colonic delivery system is also useful for the systemic absorption of drug like as nifedipine, isosorbide and theophiline. Delivery of drugs via colon offers many therapeutic advantages. Drugs, which are destroyed by the stomach acid and metabolized by pancreatic enzymes, are protected.

Sustained release of drugs into colon can be useful in the treatment of certain diseases. Colon related pathologies range in seriousness from constipation and diarrhoea to the incapacitating inflammatory bowel diseases through to colon cancer, the third most widespread form of cancer in both women and men [5].

Benefit of CSDDS[6]

- Target drug delivery
- Decrease in dose to be administered
- Decreased side effects
- Improved drug utilization
- It is a promising site for a drug which is unstable or poorly absorbed from upper GI tract

Limitation of colon target DDS

- Difficult to access colon.
- Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug.
- Transport across the mucosa in to the systemic circulation[7].

Advantages of Colonic Drug Delivery[6, 8, 9]

- Targeted drug delivery to the colon in treatment of colonic disease ensures direct treatment at the affected area with lower dose and less systemic side effects.
- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Bypass initial first pass metabolism.
- The colonic drug delivery can also be utilized as the threshold entry of the drugs into blood for proteins and peptides which degraded or poorly absorbed in upper GIT.
- Improve patient compliance.
- The colon targeted drug delivery can also be used for chrono therapy for effective treatment of diseases like asthma, angina and arthritis.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).

- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route[10].

Disadvantages of Colonic Drug Delivery[11, 12]

- There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired CSDDS site. The pattern of drug release may differ from person to person which may cause ineffective therapy.
- The pH level in the small intestine and caecum are similar which reduces site specificity of formulation.
- The major disadvantage of colonic delivery of drug is poor site specificity.
- Diet and diseases can affect colonic microflora which can negatively affect drug targeting to colon. Nature of food present in GIT can affect drug pharmacokinetics. In disease conditions pH level of GIT differs from pH level of healthy volunteers which alters the targeted release of formulations which release the drug according to pH of desired site.
- Enzymatic degradation may be excessively slow which can cause interruption in polymer degradation and thus alters the release profile of drugs.
- Substantial variation in gastric retention time may cause drug release at the undesired site in case of time dependent colonic drug delivery system.
- Lack of manufacturing Reproducibility and efficacy
- Need of advanced technology.
- Low dose loading and Higher need of excipients.

Need of colon targeted drug delivery system[13, 14, 15, 16, 17, 18]

- Targeted drug delivery to the colon to would ensure that direct treatment at the disease site (local delivery), at lower dosing and fewer systemic side effects[13].
- It should be Site-specific and targeted drug delivery system should allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery[14].
- It should be considered as beneficial in the treatment of colon diseases [15].
- 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 [16].
- 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 [17].

- It is 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[18].

CRITERIA FOR SELECTION OF DRUG FOR COLONIC DRUG DELIVERY

Drug candidate

These are type of drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. The drug used for treatment of IBD, ulcerative colitis, diarrhoea and Colon cancers are ideal candidates for local colon delivery[19].

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. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule[20,21]. The carriers, which contain additives like polymers (may be used as matrices and hydrogels or coating agents) may influence the release properties and efficacy of the systems[22]. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond.

Drugs used for local effects in colon against GIT diseases

- Drugs poorly absorbed from upper GIT
- Drugs for colon cancer Drugs that degrade in stomach and small intestine
- Drugs that undergo extensive first pass metabolism
- Drugs poorly absorbed from upper GIT
- Drugs for targeting

Table 1 Criteria for selection of drugs

Criteria	Pharmacological class	Non peptide drugs	Peptide drugs
Drugs used for local action in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amylin, Antisense oligonuc leotide
Drugs poorly absorbed from upper GIT	Antihypertensive and Antianginal drugs	Ibuprofen, Isosorbide, 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, Interferon
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

Factors to be affected in the Design of Colon - Targeted Drug Delivery System [23, 24, 25]

Anatomy and Physiology of Colon

The GIT [26, 27] is divided into stomach, small intestine and large intestine. The GIT measures about 5 meters long. The different parts of GIT are divided into upper and lower gastrointestinal tract. The upper GIT includes oesophagus, stomach, and duodenum. The lower GIT includes small intestine and large intestine. The small intestine measures an average of about 6.9 meters to 7.1 meters. It includes duodenum, jejunum and ileum. The main function of small intestine is the absorption of nutrients and minerals from food. The retention time of small intestine is 3-5 hr.

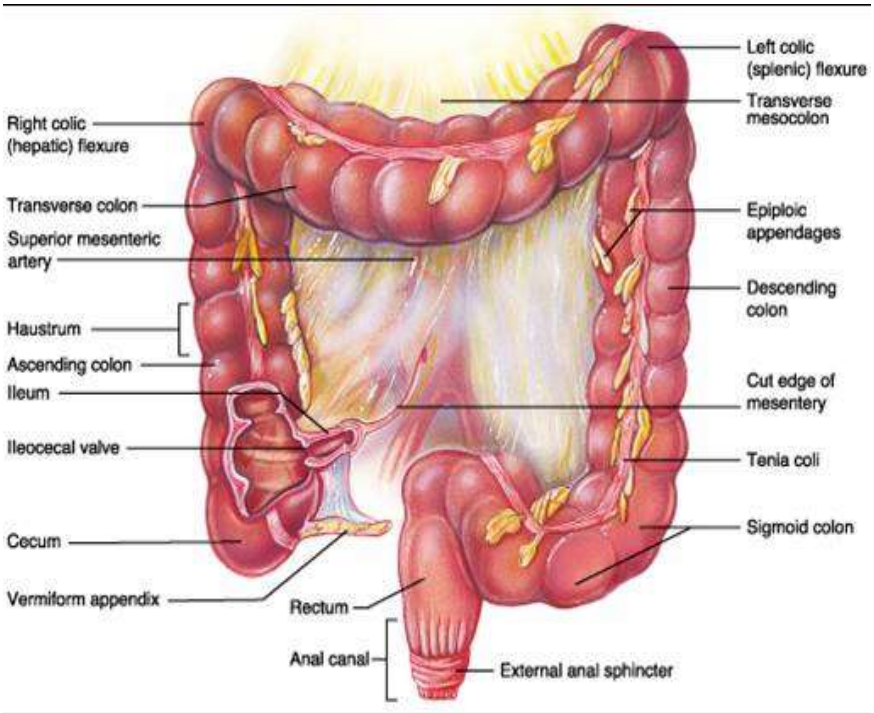

Figure 1: Anatomy of Colon

Table 2: Measures of different parts of GIT

Organ	Length
Small intestine	3m
Duodenum	25cm
Jejunum	1m
Ileum	2m
Large intestine	1.5m
Cecum	6cm
Colon	20-25cm
Ascending colon	10-15cm
Transverse colon	40-45cm
Descending colon	35-40cm
Sigmoid portion	
Rectum	20cm
Anal colon	3cm

The large intestine extending from the ileocecal junction to the anus is divided in to three main parts colon, rectum and anal canal[28]. 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 caecum, 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, spleen flexure and sigmoid. The rectum is the last anatomic segment before the anus.

ANATOMY OF COLON

pH in the colon

The pH of the GI tract is varies to both inter and intra subject variations. Diet, diseased state, and food intake influences the pH of the gastrointestinal fluid. These changes in the pH along the different parts of gastrointestinal tract have been used as a means for targeted colon drug delivery. 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. Researcher taking benefits of these changes in pH for delivering the drug to the colon by using pH sensitive enteric coating polymer in order to achieve both local and systemic effect. There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by the colonic bacteria to produce large amounts of lactic acid resulting in pH drop to about 5.0.

Table 3: Different parts of GIT

Region of Gastrointestinal Tract	pH
Stomach	1.5 in fasting and 2-5 in fed condition
Small intestine	6.6- 7.5
Duodenum	6.1(fasted) 5.4(fed)
Jejunum	5.4
Ileum	7-8
Large intestine	5.5-7
Cecum	5.5-7
Sigmoid colon	7-8
Colon	
Ascending colon	6.4
Transverse colon	6.6
Descending colon	7.0
Rectum	7-8

Transit of material in the colon

The dosage form first enters into stomach and small intestine and then reach colon. The nature and

pH of the stomach affect the drug release and absorption. In order to successfully deliver tablet to colon in an intact form, the drug delivery systems should surpass the barriers in the stomach and small intestine. Small intestinal transit is surprisingly constant at 3-4 hours and appears to be independent of the type of dosage form and whether the subject is in the fasted or fed state. The presence of food material generally increases gastric residence and in some cases with regular feeding, dosage forms have been shown to reside in the stomach for periods in excess of 12 hours. Compared to other regions of the gastrointestinal tract, movement of materials through the colon is slow. The total time for transit tends to be highly variable and influenced by a number of factors such as diet, in particular dietary fiber content, mobility, stress, disease and drugs. Colonic transit times ranged from 50 to 70 hours. Stool weights increased significantly with the presence of active disease presumably due to exudates form inflamed epithelium, increased mucus secretion, and reduction in reabsorption of fluid and electrolytes.

Table 4: Transit time of different parts of GIT[29]

Organ	Transit time (hr)
Stomach	<1(fasting) >3(fed)
Small intestine	3-4
Large intestine	20-30

Colonic microflora and enzymes

The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. Growth of this microflora is controlled by the GIT contents and peristaltic movements. The intestinal enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT. These enzymes are used to degrade coatings or 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 bacteroids. The concentration of bacteria in the human colon is around 1000 CFU/ml. A large number of anaerobic and aerobic bacteria are present in the entire length of the human GI tract. The most important anaerobic bacteria are Bacteroids, Bifidobacterium, Eubacterium, Peptococcus, and Peptostreptococcus, Ruminococcus, Clostridium.

Table 5: colonic microflora and enzymes

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

Drug Absorption in the Colon

Drugs are absorbed passively by either paracellular or transcellular route. Transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, where paracellular absorption involves the transport of drug through the tight junction between cells and is the route most hydrophilic drug takes where as paracellular 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 in the colon include glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol and oxyprenolol. Drugs shown to be less absorbed in the colon include furosemide, pyretanide, buflomedil, atenolol. The colon may not be the best site for drug absorption since the colonic mucosa lacks well defined villi as found in the small intestine.[30] The oral absorption of majority of peptide and protein drugs is limited because of following reasons:

- Degradation in the acidic environment of the stomach.
- Enzymatic degradation in the small and large intestine.
- Rapid small intestine transit.
- Low mucosal permeability.
- Extensive first pass metabolism by the absorbing membrane and the liver.

Approaches for colon targeted drug delivery[31]

- Primary approaches for colon targeted drug delivery
    - pH sensitive polymer coated drug delivery system
    - Delayed release drug delivery system
    - Microbially triggered drug delivery
    - Prodrug approach
    - Polysaccharide based system
- New approaches for colon targeted drug delivery
- Pressure controlled drug delivery system (PCDDDS)
- CODE
- Osmotic controlled drug delivery system (OROS-CT)
- Pulsatile
- Pulsincap system
- Port system
- Azo hydrogels
    - Multiparticulate system based drug delivery

A) Primary approaches of colon specific drug delivery system

a. pH Sensitive Polymer Coated Drug Delivery to the Colon

The pH varies in different parts of the gastrointestinal tract. The pH in stomach ranges between 1 and 2 during fasting. The pH in the proximal part of small intestine is 6.5 and in distal part of small intestine it is 7.5. The pH is 6.4 in caecum, 5.7 in ascending colon, 6.6 in transverse colon and 7.0 in descending colon. The pH dependent drug delivery system is based on the solubility of different polymers at different pH ranges. The polymers are insoluble at lower pH values and get solubilized as the pH increases. As the polymers are insoluble at lower pH values the polymer can protect a formulation in stomach and to some extent in small intestine. In this way by altering the polymers used the release of drug from the formulation can be controlled [30]. 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.[32] The threshold pH employed pH-sensitive polymers.

Table 6: Example of various pH dependent coating polymers

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

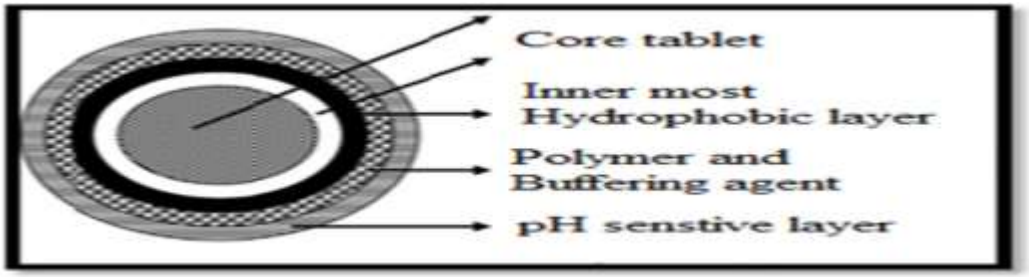

Figure 2: Optimum pH of commonly used polymers

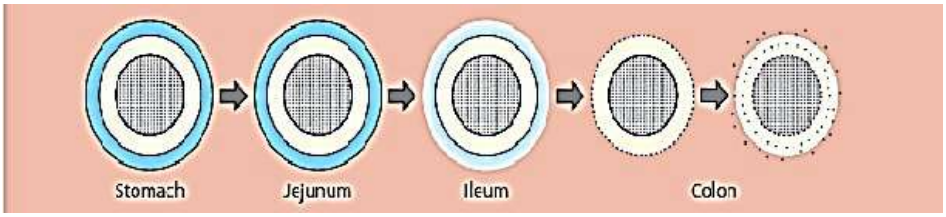

Figure 3: Drug release pattern of a multilayer coated system at different pH conditions in GIT

b) Delayed or time controlled release drug delivery system

Time controlled drug delivery system[33] includes sustained or delayed release systems. In this system the delayed release or colon targeted drug delivery is attained by prolonging the lag time. The transit time varies in different parts of gastrointestinal tract. This transit time is responsible for the delayed release of drug. The main drawbacks of this delivery system are that the transit time varies from one person to other and amount of food intake. 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:

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug[34].
- 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[35,36,37].

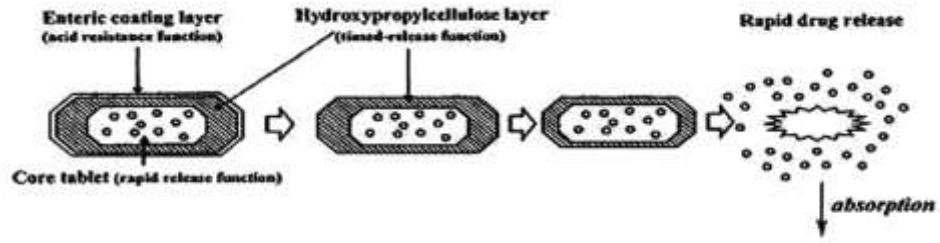

Figure 4: Design of enteric coated timed-release press coated tablet (ETP Tablet)

c) Microbial triggered drug delivery system

The microflora of the colon is in the range of 1011 -1012 CFU/ml, with some 400 different species which are consisting mainly of anaerobic bacteria, e.g. bacteroids, Bifidobacterium, Eubacteria, clostridia, enterococci, enterobacteria and Ruminococcus etc[1]. This vast microflora fulfils 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 microflora produces a vast number of enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareductase, deaminase, and urea dehydroxylase[38]. The enzymes present in the colon are:

Reducing enzymes:

Nitroreductase, Azareductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.

Hydrolytic enzymes:

Esterases, Amidases, Glycosidase, Glucuronidase, Sulfatase etc[39].

Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches[40]. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches[41]. 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[42,43,44,45,46]. They are then unable to hold the drug entity any longer[47].

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.[21,48] 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, glactose, cellulose etc. A limitation 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.[31, 49] A number of prodrug has been showed in table

Table 7: Examples of Prodrug system for CDDS

Drug	Carrier	Linkage Hydrolyzed
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

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.[28, 50] 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 azo reductase in the large bowel. Coating of peptide capsules with polymers cross linked with azo aromatic group has been found to protect the drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced, and the drug is released. [51] A number of azo-polymeric Prodrugs are outlined in the system. Sulphasalazine, used for the treatment of IBD saulphasalazine (5-ASA) is composed of sulphapyridine. This has antibacterial activity and 5-ASA which has anti-inflammatory activity and both drug link with azo bond. In the colon, the azoreductase cleave the azo bond releasing the drug, and the carrier sulphapyridine. [52]

Glycoside Conjugated prodrug

Enzyme Glycosidase produce by various human microflora are -D- galactosidase, Larabino Furanosidase, -D-xylopyranosidase, and -D glucosidase. These glycosidase enzymes are located at the brush border of colon. Natural occurring drug contain glycosides and aglycon part in their structure, after oral administration when they reach in colon glycosidases act on it and release pharmacological active aglycon. Glycosides are hydrophilic and poorly absorb from GIT because of this properties it use as the carrier for delivering drug to colon. Drug targeted by this approach are lucosides, galactosidase, and cellobiosides of dexamethasone, Prednisolone, hydrocortisone, and fludrocortisone. It has been seen that both modified form of steroids reach to the caecum whereas unmodified analog get absorbed in small intestine[21, 53]. The major glycosidases identified in human faeces are:

- D-galactosidase,
- D-glucosidase,
- L-arabinofuranosidase,
- D-xylopyranosidase
- Due to the bulky and hydrophilic nature of these glycosides, they do not penetrate the biological membrane upon ingestion.

Glucuronide Conjugation Prodrug

Glucuronide conjugation is the major metabolic pathway of drug. Glucuronidase secreted from large intestine deglucuronide various drug. This concept of metabolism is use for delivering drug to colon where drug is couple with glucuronid conjugation after oral delivery when it reach in to

colon the conjugation is specifically cleaved by Glucuronidase and release active drug molecule. Colon targeting study has been carry out using glucuronide conjugation of narcotic analogs nalaxone and nalmefene which indicate that such conjugation useful in treatment of constipation cause by opiate.[54]

Cyclodextrin conjugate[55]

Cyclodextrin are cyclic oligosaccharides consisted of six to eight glucose units through -1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine however, Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextrins activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed. A clinical study has shown clear evidence that b-cyclodextrin is poorly digested in the small intestine but is almost completely degraded by the colonic microflora.

Dextran conjugates[56]

Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolyzed by moulds, bacteria, and mammalian cells. The enzyme responsible for the hydrolysis of these linkages is Dextrans. The Dextrans activity is almost absent in the upper GIT, where as high Dextrans activity is shown by anaerobic gram-negative bacteria, especially the Bacteroids, which are present in a concentration as high as 1011 per gram in colon. Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function (−COOH).NASIDS ware directly coupled to dextran by using carboxylic groups of drugs. Example is Naproxen-dextran conjugate. Glucocorticoids do not possess −COOH group so these are linked to dextran using spacer molecule. e.g. glucocorticoid-dextran conjugates.

Amino acid conjugation

Due to the hydrophilic nature of polar groups like -NH2 and -COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme[57].

Polymeric Prodrugs[58]

Azo-linked polymeric prodrug of 5-ASA were prepared and evaluated in simulated human intestinal microbial eco- system. Polyamides containing azo groups in the backbone were prepared

and tested in vitro in a reductive buffer or in the bioreactor medium. Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Sub synthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety.

Polysaccharide based delivery systems

Polysaccharide based delivery system is the other form of microbial triggered drug delivery system. They are easily modified chemically and biochemically and are safe, highly stable, nontoxic, gels forming, hydrophilic and biodegradable. These 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[31, 59].

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, have developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water[60]. 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 ethyl cellulose membrane is the most important factor for disintegration of the formulation[61]. 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 ethyl cellulose single-unit capsules the drug is in a liquid [62]. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human[63].

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. [64, 65] 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 5). 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[66]. 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 effect the dissolution of the acid soluble coating and subsequent drug release[67].

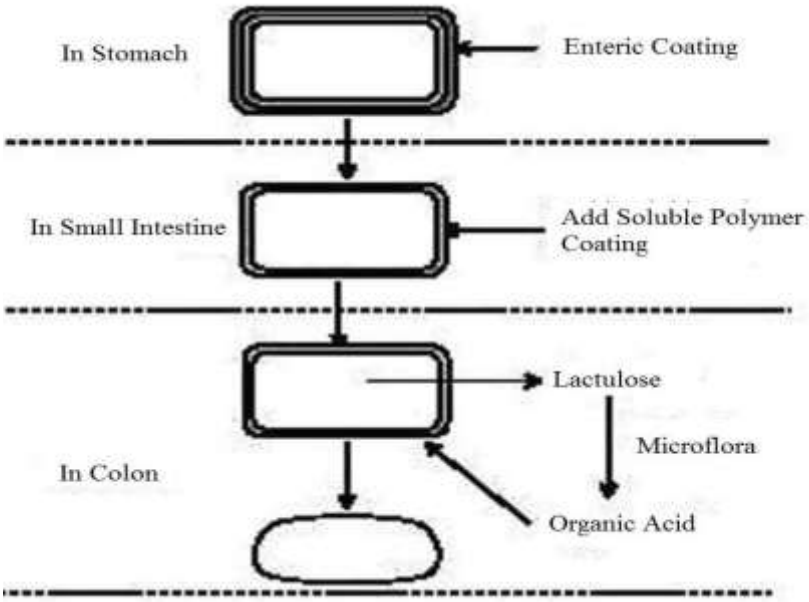

Figure 5: Schematics of the conceptual design of CODES™

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[68]. 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 6)[69]. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable 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 semipermeable 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[70]. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon[71-74]. various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

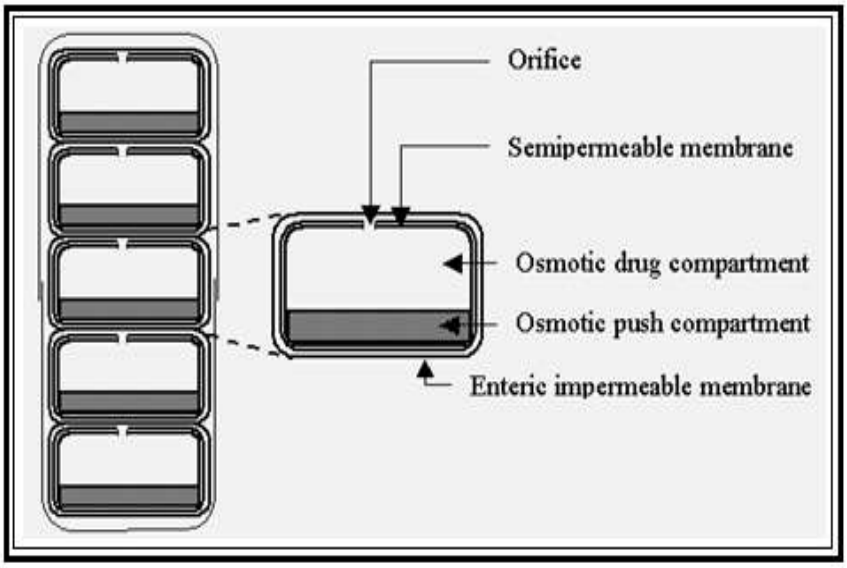

Figure 6: Cross-Section of the OROS-CT colon targeted drug delivery system

Pulsatile drug delivery system

a) Pulsincap System

b) Port System

a) 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 [75] 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. Diagram of Pulsincap are shown in figure For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrates. The plug material consists of insoluble but permeable and Swellable polymers (e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin).

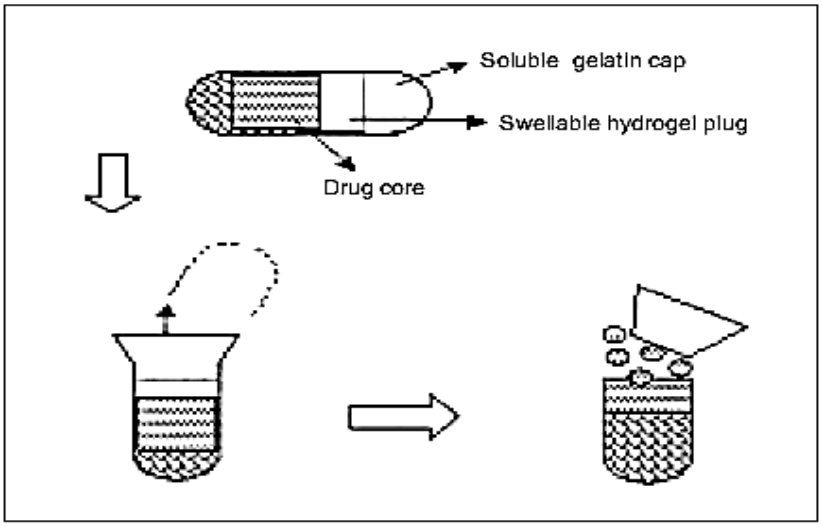

Figure 7: Design of Pulsincap system

b) Port system

The Port® developed by Port Systems, LLC it consists of a hard gelatin capsule which is coated with a cellulosic semi permeable membrane. Inside the capsule there was an insoluble plug and an osmotically active agent along with the drug formulation .When such contact with the aqueous medium, water diffuses across the semi permeable membrane of the device, resulting in increased inner hydrostatic pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness. The drug release pattern of port system is given in Figure 8. The approach of pulsatile drug delivery system is based on the principle of delaying the time of drug release until the system transits from mouth to colon. The transit time of small intestine is about 3-4 hours so lag-time of 5 hours is usually considered, which is relatively constant.

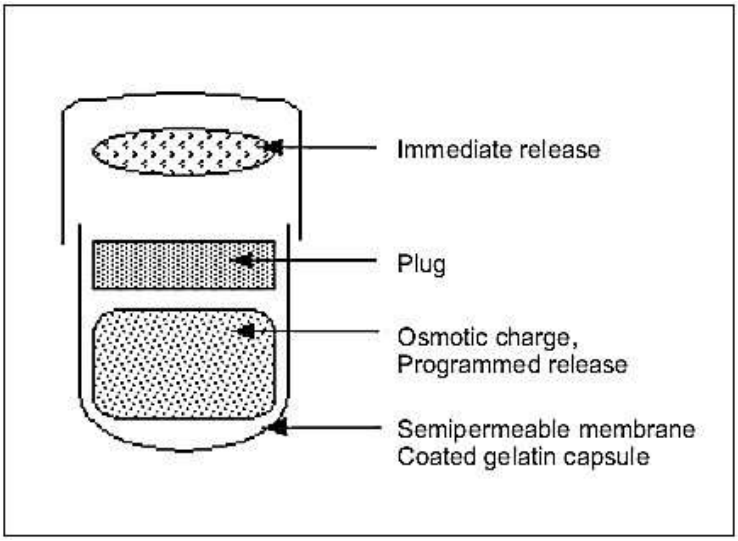

Figure 8: Design of port system

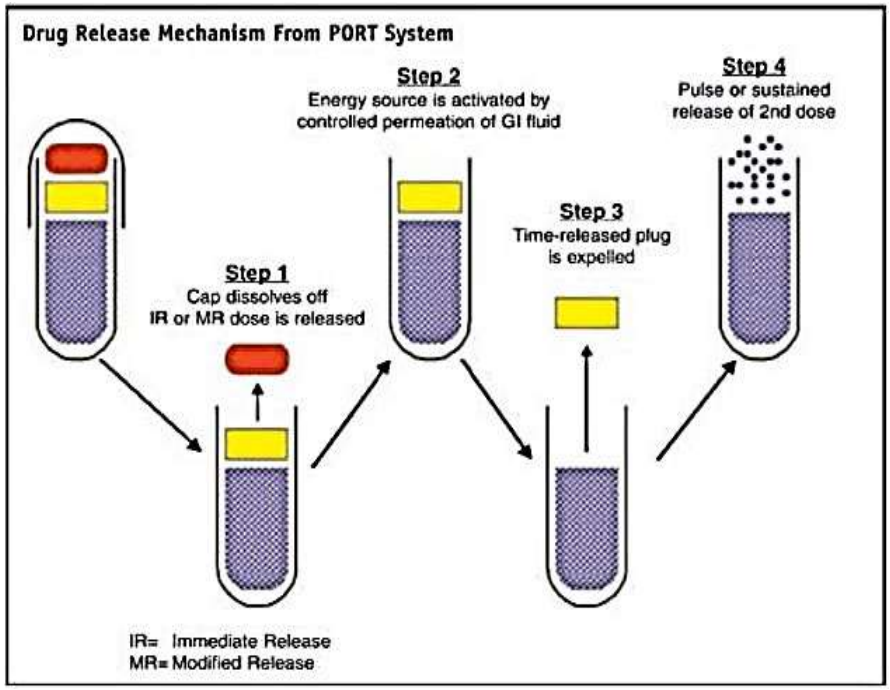

Figure 9: Drug release mechanism of port system

Chronotropic system[76]

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

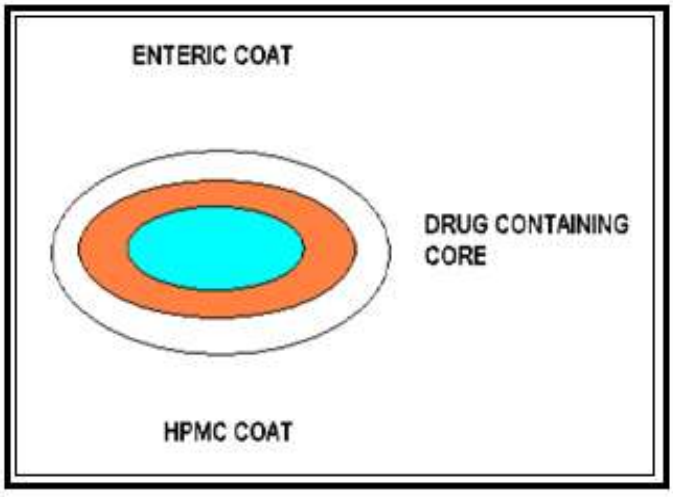

Figure 10: Design of Chronotropic system

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. Multiparticulate 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.

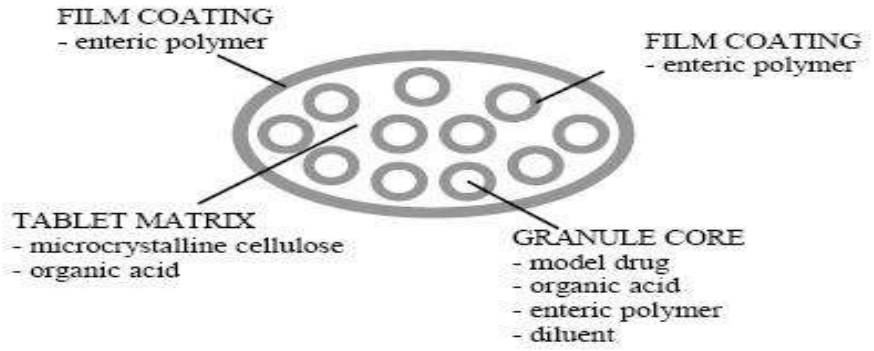

Figure 11: Structure of multiple-unit colon-specific tablet developed

Azo hydrogels

The pH sensitive monomers and azo cross linking agents in the hydrogel produce the colon specificity. During their passage through the GIT these hydrogels swell as the pH increases. This swelling of hydrogels cleaves the cross links in the hydrogel network causing the release of drug entrapped in the hydrogel. These hydrogels are prepared by cross linking polymerization of N-substituted (meth) acrylamides, N- tert- butyl acrylamide and acrylic acid with 4, 4-di (methacryloylamino) azobenzene as cross linking agents. The hydrogels are also prepared by cross linking polymeric precursors, polymer- polymer reaction using same polymeric precursor with the corresponding copolymer containing side chains terminating in NH2 groups. The degradation rate of hydrogel is associated with the degree of swelling and inversely proportional to the cross linking density[77].

EVALUATION OF COLON TARGETED 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 & physical

stress. The *in vitro* evaluation[78] of colon targeted drug delivery systems includes the *in-vitro* dissolution study & *in-vitro* enzymatic test.

***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.

***In-vitro* enzymatic test**

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

- The carrier drug system is incubated in fermented 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, Dextrans 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.

In vitro enzymatic dissolution study of tablet made by natural guar gum and xanthan gum has been carried out in presence of galactose, mannose enzyme and in both present and absence of caecal rate content.[79, 80, 81]

***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 gastro-intestinal tract of rat and rabbit is comparable to that in human.

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.

Saintigraphy

Saintigraphy is an image modality which enables the in vivo performance of drug delivery system to be visualized under normal physiological conditions in a non invasive manner. Through scintigraphy imaging, the following information regarding the performance of a colon specific drug delivery system within human Gastro-intestinal tract can be obtained, the location as a

function of time the time and location of initial and complete system disintegration, the extent of dispersion the colon arrival time, stomach residence and small intestine transit time. Studies has been carried out in human subjects using technetium-99m-DTPA as tracing agent in sodium chloride core tablet and compression coated with guar gum act as protecting coat against upper Gastro-intestinal tract environment, and it has been observed that the tablet remain intact in stomach and intestinal pH but as it enter in ascending colon it get degrade by colonic microflora and the release drug[82].

Roentgenography

This technique involve incorporation of radio opaque material instead of drug such as barium sulfate, which visualized by taking X- rays of abdomen after oral administration. It is possible to observe movement, location and the integrity of the dosages after oral administration by placing the subject under a fluoroscope and taking a series of X-rays at various time intervals[83].

Future advances in colon targeted drug delivery

The design of colon delivery systems has significantly advanced the future for IBD therapy by improving the selective targeting of active agents to sites of inflammation. Contrary to most therapeutic regimens utilizing oral administration, systemic absorption is an undesirable delivery feature for these drugs. Disease localization dictates the need for maximal intestinal tissue drug exposure while systemic delivery should be minimized to avoid unwanted side effects. This drug delivery approach has been shown to increase therapeutic efficacy, lower the therapeutically effective dose, reduce systemic side effects, and has allowed the use of novel compounds with poor physicochemical properties for oral delivery. This has been achieved through specific biodistribution and accumulation in the inflamed intestinal regions. The practicability of designing dosage forms that are both acceptable to humans and efficacious needs to be further explored. Firstly, the safety of the different nano-delivery carriers following uptake need to be explored further. Studies focused on the nanotoxicology of these delivery systems in the human GI tract in IBD have been limited, and is likely to vary according to the nanoparticles material (e.g. polymer, lipids) and nanoparticles size. [84] Secondly, structural stability during GI transit would need to be further optimized to prevent premature release in the stomach and small intestine. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines. The colon segment is designed by nature mainly to expel metabolism products rather than to absorb nutrients. Therefore, more research that is focused on the specificity of drug uptake at the colon site is necessary. Such studies will be significant in advancing the cause of colon targeted livery of therapeutics in future.

in future, therapeutic strategies should be Constructed individually for each patient based on the molecular taxonomy of tumors, which would be lower toxicity, higher therapeutic index, and a weaker tendency to induce resistant phenotypes in tumor cells.

CONCLUSION

In recent years CDDS has gained its importance as a site for delivery of various drugs including novel therapeutic drugs, i.e. peptides. Colon targeted drug delivery system offers benefits of local and systemic effects. Thus the colon is the terminal part of the GIT. The Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. The various strategies for targeting orally administered drugs to the colon includes, coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bio adhesive systems etc. All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs through colon. In future by combining various other strategies, colon targeted drug delivery will find the central place in novel drug delivery. Research is going on to develop suitable dissolution methods to evaluate the colon targeted drug delivery systems.

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