Natural Prodrugs Conjugates And Recent Pharmaceutical Approaches To Colon Targeted Drug Delivery System: A Review

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ABSTRACT

Small intestine is mostly the site for drug absorption but in some cases the drug needs to be targeted to colon due to some factors like local colonic diseases such as IBDs (inflammatory bowel disease, ulcerative colitis, Crohn's disease) amebiosis, colon cancer), degradation related conditions, delayed release of drugs, systemic delivery of protein and peptide drugs etc. 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 controlled release in the proximal colon. Many prodrugs have been evaluated for colon drug delivery. These prodrugs are designed to pass intact and unabsorbed from the upper GIT and undergone biotransformation in the colon releasing the active drug molecule by variety of enzymes, mainly of bacterial origin present in the colon (e.g. azoreductase, glucuronidase, glycosidase, dextranase, esterase, nitroreductase, cyclodextranase etc.). Treatment of these diseases with colon-targeted drug delivery system provides an interesting alternative over systemic drug administration because of lower dosing and fewer systemic side effects. This review will cover various natural prodrug conjugates and recent pharmaceutical approaches to colon targeted drug delivery system.

Keywords: Prodrug, Colon Targeted Drug delivery system, Natural Prodrugs Conjugates

INTRODUCTION

To the date, oral delivery is still the most favorable route of drug administration, especially for chronic therapies where repeated administration of drugs is required. Oral administration offers less pain, good patient convenience and reduced risk of cross infection and needle stick injuries and also oral drug delivery system account half of the market share. [1,2] Despite these advantages, the oral route is not applicable to the administration of protein and polypeptide drugs, due to their high susceptibility to digestive enzymes in the gastrointestinal tract (GIT) and poor absorption. As a result, new strategies of drug delivery have been developed to overcome obstacles encountered by oral delivery. Among these strategies, oral colon targeted delivery has been extensively studied from the last two decades. Targeted drug delivery to the colon, by means of combination of one or more controlled release mechanism, hardly releases drug in the upper part of the GIT but releases in the colon following oral administration. Specifically delivering drug to the colon, a lot of benefits would be acquired in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases [3, 4].

I. Less diversity and intensity of digestive enzymes.

II. Comparatively 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 the duodenum and jejunum and eventually releases drugs in the ileum or colon which leads to greater systemic bioavailability.

III. The colon has along residence time (upto 5 days) and is highly responsive to absorption enhancers [5]

There are some of the diseases and drugs which are generally used for the colon targeting sites as shown in **Table 1**.

Table 1: Colon targeting sites, diseases and drugs [6]

S.no	Targeted Sites	Diseases	Drugs
1.	Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease.Chronic pancreatitis	Hydrocortisone, Budesonide, Prednisolone, Sulfasalazine, Olsalazine, Mesalazine, Balsalazide
2.	Local action	Pancreactomy, cystic fibrosis, colorectal cancer	Digestive enzyme supplements 5-Fluorourocil 5-Flourouracil
3.	Systemic action	To prevent gastric irritation To prevent first pass metabolism of Orally ingested drugs Oral delivery of peptides and vaccines	NSAIDS, Steroids Insulin, Typhoid

Rational for the development of oral colon targeted drug delivery

Rational behind development of oral colon targeted drug delivery is the treatment of local pathologies; chronotherapy (asthma, hypertension, cardiac arrhymias, arthritis or inflammation); greater responsiveness to the absorption enhancers; less enzymatic activity; site for delivery of delicate drugs (proteins and peptides) and oral delivery of vaccines as it is rich in lymphoid tissue[7]. A number of colonic disease such as Inflammatory bowel diseases (IBDs) Crohn's diseases, ulcerative colitis, colorectal cancer and amebiasis are still lacking appropriate medical treatment. The drugs which are given generally have poor bioavailability at the colonic site hence colon targeted prodrugs approach is designed [8].

COLONIC DISEASES:

Inflammatory bowel disease:

Inflammatory bowel disease (IBD) is often localized to specific sites in the gastrointestinal tract (GIT) and comprised of two specific conditions namely Ulcerative colitis (UC) and Crohn's disease (CD).

Ulcerative colitis (UC):

It is an inflammatory destructive disease of the large intestine characterized by motility and secretion disorders such as acute flare-up, diarrhoea, bleeding ulcer, pus discharge etc. It may also be called as colitis or proctitis. It is thought to result from a dysregulated mucosal response in the intestinal wall facilitated by defects in the protective barrier function of the intestinal epithelium and the mucosal immune system [9,10,11].

Crohn's disease (CD):

It differs from ulcerative colitis because it causes deeper inflammation within the intestinal wall. There is discontinuous distribution of lesions and may involve any part of GIT from oral cavity to colon. It is an idiopathic, relapsing chronic inflammatory disease also called as regional enteritis[12,13].

Inflammatory bowel syndrome

It is characterized by a variable combination of unexplained chronic and recurrent symptoms attributed to intestine, abdominal pain, disturbed defecation (urgency, straining, incomplete evacuation, altered stool form and frequency) and bloatedness[14].

Colorectal cancer

It results from an accumulation of mutation in tumor suppressor genes and oncogenes. Colorectal cancer is the second leading cause of cancer death in the United States and progresses through a series of clinical and histopathological stages ranging from single crypt lesions through small

benign tumors (adenomatous polyps). The prodrug approach, a chemical approach using reversible derivatives ,can be useful in the optimization of the clinical application of a drug .The prodrug approach gained attention as a technique for improving drug therapy in the early 1970s[15].

Factors to be considered during design of colon targeted drug delivery system

In order to get a colon targeted drug delivery system it is essential to familiarize with the various factors that influences the targeted drug delivery. These factors are:-

a) Anatomy and physiology of the colon.

b) Parameters influencing bioavailability of drug in colon.

Anatomy and Physiology of Colon

Colon has been considered as the BLACK BOX as most of the drugs are absorbed from the upper part of gastro intestinal tract. Gastrointestinal tract has been divided in to three major parts:

(1) Stomach

(2) Small Intestine

(3) Large Intestine

The large intestine starts from the ileacecal junction to the anus, it includes three parts: Colon, Rectum and Anus. The colon is a cylindrical tube about 5 feet long and 2-3 inches in diameter [16], it lacks villi but due to the presence of pilcaesemilunares (cresetntic folds) it is about 1300 cm (2) in area. Colon has been divided in to five major segments [17]

(1) Caecum

(2) Ascending colon

(3) Transverse colon

(4) Descending colon

(5) Sigmoid colon

Each segment is made up of four layers: Serosa, Muscularisexterna, Sub Mucosa and Mucosa. Activity of colon can be divided in two types [18]

(1) Segmenting movement

(2) Propulsive movement

- Segmenting movement has been caused by circular muscle and causing the appearance of the sac like haustra, predominate and result in mixing of the luminal content.

- Propulsive movement associated with deflection and affected by longitudinal muscle is less common and occurs at an average of three or four times daily.
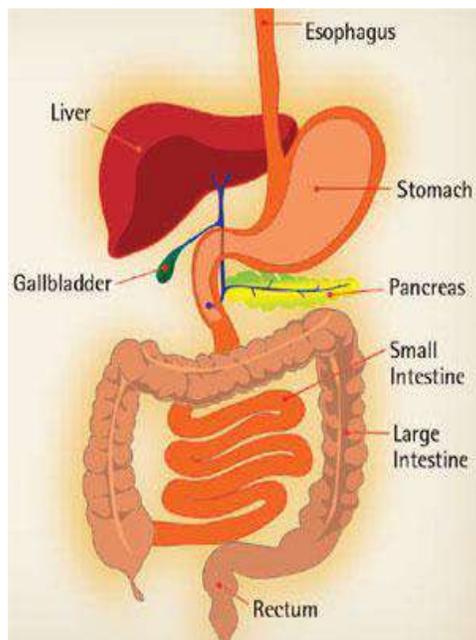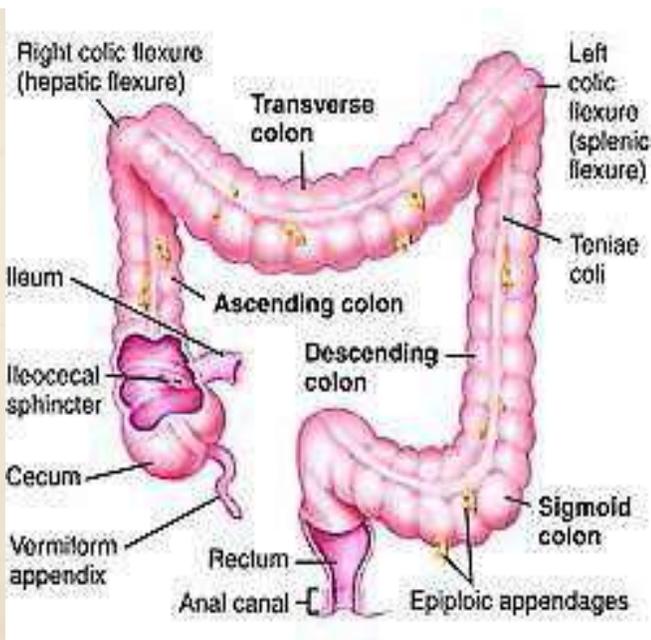
Figure: 1: Human Intestine   Figure: 2: Anatomy of colon

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. On average, it has been estimated that colon contains only about 220 gm of wet material equivalent to just 35 gm of dry matter. The majority of this dry matter is bacteria. The colon tissue contains villi, lymph, muscle, nerves, and vessels [19].

Table 2: Summary of anatomical and physiological features of small intestine and colon [20]

Region of Gastrointestinal Tract	Length (cm)	pH	Internal Diameter (cm)
Stomach	……	1.5(fastened) 2-5(fed)	……
Small intestine		6.1(fasted)	
Duodenum	20-30	5.4(fed)	
Jejunum	150-200	5.4	3.4
Ileum	200-350	7.8	
Large intestine			
Cecum	6-7		
Ascending colon	20	5.5-7	6
Transverse colon	45		
Descending colon	30		
Sigmoid colon	40		
Rectum	12	7-8	
Anal canal	3		

Limitations [21, 22]

- 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 microflora could also affect colonic performance via metabolic degradation of the drug.

- Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation.

Criteria for Selection of Drug for CDDS [23]

- 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: 3 Criteria for selection of drugs for CDDS [24]

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 absorb 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	Peptides and proteins	Bromophenaramine, 5-Flourouracil,	Gonadoreline, Insulin,

intestine			
Drugs that undergo extensive first pass metabolism	Nitroglycerin and Corticosteroids	Doxorubicin Bleomycin, Nicotine	Interferons Protirelin,sermorel in, Saloatonin
Drugs for targeting	Antiarthritic and antiasthmatic Drugs	Prednisolone, hydrocortisone, 5-Aminosalicylic acid	Somatropin, Urotoilitin

Factors affecting colon targeted drug delivery

1. Physiological factors

a. Gastric emptying

Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times [25].

Table 4: Transit time of different parts of GIT

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

pH of colon

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

Table 5: pH in different parts of Colon

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

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

enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT.

Table 6: Different micro flora, enzymes released and action [26]

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 glycosidase of alcohols & phenols
Eubacteria, Clostridia, Streptococci	Sulfatase	Cleavage of Osulphates & Sulfamates

Pharmaceutical factors

a. Drug candidates

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

b. Drug carriers

The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. The various physicochemical factors of drug that effect the carrier selection, includes chemical nature, stability, partition coefficient, functional groups of drug molecule etc [26].

Polymers Used in Colon Targeting

Polymer contain a large number of structural unit joined by same type linkage, form into a chain like structure. These are nowadays used in formulating various pharmaceutical products. Naturally found polymer, which include gummy exudates, proteins, enzymes, muscle fibre, polysaccharides. In olden days natural polymers are widely used in pharmacy but a variety of synthetic polymer are used nowadays for pharmaceutical and cosmetic development, using these polymer many therapeutic system of body namely controlled drug delivery systems, are achieved [27, 28].

Natural polymer: Guar gum, Inulin, Pectin, Cyclodextrin, Dextran, Amylase, Chitosan, Chondrotin etc.

Synthetic polymer: Shellac, Ethyl cellulose, Cellulose acetate phthalate, Hydroxy propyl methyl cellulose, Eudragit, Poly vinyl acetate phthalate[29].

Table 7: Marketed drug products for the treatment of various diseases of colon[30]

S.No.	Marketed name	Company name	Disease	Drug
1.	Mesacol Tablet	Sun Pharma,India	Ulceretive Colitis	Mealamine
2.	Mesacol Enema	Sun Pharma,India	Ulceretive Colitis	Mealamine
3.	Asacol	Win Medicare, India	Ulceretive Colitis, Crohn's Disease	Mealamine

4.	SAZO	Wallace, India	Ulceretive Colitis, Crohn's Disease	Sulphasalazine
5.	Intazide	Intas, India	Ulceretive Colitis	Balsalazide
6.	Lomotil	RPG Life, India	Mild Ulceretive Colitis	Diphenoxylate HCl, Atropine Sulphate
7.	BUSCOPAN	German Remedies, India	Colonic Motility Disorder	Hyoscine Butylbromide
8.	COLOSPA	Solvay, India	Irritable Colon Syndrome	Mebeverine
9.	CYCLOMINOL	Neol, India	Irritable Colon Syndrome	Diclomine
10.	Eldicet	Solvay, India	Irritable Colon Syndrome, Spastic Colon	Pinaverium bromide
11.	Equirex	Jagsonpal Pharma, India	Irritable Colon Syndrome	Chlordiazepoxide
12.	Normaxin	Systopic Labs, India	Irritable Colon Syndrome	Clidinium bromide
13.	Pro-banthine	RPG Life, India	Irritable Colon Syndrome	Propenthaline bromide
14.	Entofoam	Cipla, India	Ulceretive Colitis	Hydrocortisone acetate

Approaches used for site specific Colon drug delivery (CDDS)

1. Natural Prodrugs Conjugates Approaches for colon targeted drug delivery

2. Recent Pharmaceutical Approaches for colon targeted drug delivery

Table 8: Natural Prodrugs Conjugates Approaches for colon targeted drug delivery

S.No.	Approaches	
1	**Natural Prodrug Conjugates**	**Basic Features**
1(a)	Glycosidic conjugates	The drug is conjugated with Glycoside
1(b)	Dextran conjugates	The drug is conjugated with Dextran
1(c)	Glucuronide conjugates	The drug is conjugated with Glucoronide
1(d)	Polymeric conjugates	The drug is conjugated with Polymer
1(e)	Polypeptide conjugates	The drug is conjugated with Polypeptide
1(f)	Cyclodextrin conjugates	The drug is conjugated with Cyclodextrin

Natural Prodrugs Conjugates

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site. In the colon vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatasedeaminase, and urea dehydroxylase are cleved the drug from the carrier. 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 [32].

1 (a) Glycosidic conjugates

Glycosides conjugates and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Due to hydrophilic nature of drug glycosides, they are absorbed from the upper GIT and once such a glycoside reaches the colon it can be hydrolyzed

or acted upon by glycosidase, and subsequent release of free drug takes place which gets absorbed by the mucosa of colon. Naturally found glycosides, e.g. the sennosides, have been utilized for laxative action since ages. These sennosides are activated by colonic microflora to generate rhein anthones, which shows the desired laxative effect [33]. Drugs that can be targeted by this approach are: lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisones, daxamethasone-21-β- glucoside[34].

1 (b)Dextran Conjugates

Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolyzed by moulds, bacteria, and mammalian cells. The enzyme responsible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, where as high dextranase activity is shown by anaerobic gram-negative bacteria, especially the bacteroides, which are present in a concentration as high as 1011 per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon. In the colon, dextran's glycosidic bonds are hydrolyzed by dextranases to give shorter prodrug oligomers, which are further split by the colonic esterases to release the drug free in the lumen of the colon. Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic acid function ($-COOH$).NASIDS ware directly coupled to dextran by using carboxylic groups of drugs. Example is Naproxen-dextran conjugate. Dextran ester prodrugs of metronidazole have been prepared and characterized [35, 36].

1 (c)Glucuronide conjugates

Bacteria of the lower GIT secrete bglucuronidase and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption. Example: Opiates, when taken for the relief of pain, cause severe constipation by inhibiting GIT motility and secretions. Narcotic antagonists, when given as antidotes for GIT side effects, immediately relieve constipation but precipitate acute withdrawal. This is because these narcotic antagonists are not selective and they not only affect the GIT activity, but also the central nervous system (CNS). A novel approach would be to target these antagonists to the lower bowel so that they are not absorbed systemically. With this purpose, naloxone and nalmefene glucuronide prodrugs were prepared to target these drugs to the colon. When given orally to morphine dependent rats these prodrugs showed increased GIT motility and secretion in the large bowel results in a diarrhoea and The resultant diarrhea flushed out the drug / prodrug from the colon thereby preventing the systemic absorption of the antagonist, which in-turn

caused absence of withdrawal symptoms. Budesonide-b- glucuronide prodrug also found to be superior to budesonide itself for the treatment of colitis in the rat [37].

1 (d)Polymeric prodrugs

This approaches has been based upon the principle that polymers have been used as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose [38].

1 (e)Polypeptide conjugates:

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. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids. Non-essential amino acids such as tyrosine, glycine, methionine and glutamic acid were conjugated to salicylic acid (SA) successfully, which show higher hydrophilicity with decrease membrane permeability property. By having these desirable features, these amino acid prodrugs were found to show majestic results with least absorption from the upper gastrointestinal tract and found appropriate for targeted salicylic acid delivery to colon[39].

1 (f)Cyclodextrin conjugate

Cyclodextrins are cyclic oligosaccharides consisted of six to eight glucose units through -1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules. They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine however, Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextranase activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed. This susceptibility to degradation specifically by colonic micro flora together with their property to form inclusion complexes with various drugs makes them particularly useful in carrying drug moieties to the colon .The a- and b-cyclodextrins are practically resistant to gastric acid, salivary, and pancreatic amylases. Ibuprofen prodrugs of α- , β-and γ-Cyclodextrins were investigated [40]. Methotrexate prodrugs of α- and γ-Cyclodextrins were also synthesized and result established the primary aim of masking the ulcerogenic potential of free drug, by using 12-fold dose of the normal dose of methotrexate and equivalent doses of the esters [41].

Table 9: Natural Prodrugs Conjugates for colon-specific drug delivery with their *in vitro*/*in vivo* performance

Carrier	Drug investigated	Linkage/conjugate hydrolysed	In vitro / in vivo/ex vivo model used	Performance of the Prodrug conjugates
Saccharide	Dexamethasone /Prednisolone [42]	Glycosidic linkage	Rat	Dexamethasone prodrug was site specific and 60% of oral dose reached the cecum. Only 15% of prednisolone prodrug reached the cecum.
Glucose/Galactose/ Cellobioside	Dexamethasone[43]Prednisolone Hydrocortisone, Fludrocortisone	Glycosidic linkage	In vitro	Less hydrolysis of the prodrug was seen in contents of stomach and proximal small Intestine
Dextran conjugates	Ketoprofen[44]	Ester linkage	Pig	Selective colon delivery of drugs possessing a carboxylic acid derivatives
Dextran with succinate and glutarate spacer	Dexamethasone[45]	Dextran-drug conjugate	Rat	Glucocorticoid-dextran conjugates as potential prodrugs for colonspecific delivery
Glucuronide Conjugates glucuronic acid	Budesonide [46]	Glucuronide linkage	Rat	Was found to be superior than budesonide itself for treatment of colitis
Chitosan	Metronidazole[47]	Chitosan metronidazole conjugates	In vitro	Targeting delivery to Colon
Amino acid	Celecoxib[48]	Amino acid-drug conjugate	In vitro	Improved therapeutic potency and cardiovascular toxicity for chemoprevention of colorectal adenomas
Cyclodextrin	5-ASA [49]	Cyclodextrin drug conjugate	Rat	CyD-5-ASA conjugates may be used as prodrugs for colon-specific drug delivery system

Table 10: Recent Pharmaceutical approaches for colon targeted drug delivery [50]

2	Approaches	Basic Features
2a	Pressure controlled drug delivery system (PCDDDS)	Based on the strong peristaltic waves that lead to a temporary increase in luminal pressure in colon.
2b	CODE	It is pH sensitive polymers (polysaccharides) and drug is release by specific bacteria present in the intestine.
2c	Novel Colon Targeted Delivery	It has been developed by utilizing a unique mechanism involving lactulose, drug is release by specific

	System(CODESTM)	bacteria present in the intestine.
2d	Osmotic controlled	Drug release through Semi permeable membrane due to osmotic pressure
2e	Time dependent delivery	Drug after a lag time of 3-5 hours that is equivalent to small intestine transit time
2e	Pulsatile system	The barrier swells, erodes, or dissolves after a specific lag period that leads to subsequent release of drug
2e1	Pulsincap	Drug has been encapsulated in a capsular pulsatile system with polymeric plugs
2e2	Port system	It consists of a gelatin capsule coated with a semipermeable membrane
2(f)	Hydrogel approach	Hydrogels are composing of acidic monomer and enzymatically degradable azo aromatic cross-linkers.
2(g)	Multiparticulate approach	Based on microparticles which are absorbed through macrophages present in colon and increase resident time of drug

2. Recent Pharmaceutical Approaches

a. Pressure Controlled Drug-Delivery Systems:

Digestion mainly occurs due to the contractility of the stomach and peristaltic movement of the intestine. The contractility movement of stomach leads to the digestion or breakdown of larger particles to smaller ones which are then transferred to intestine. The peristaltic movement of intestine is responsible for the passage of bolus from one part of GIT to the next part. The peristaltic movement of ascending colon transfers the bolus to transverse colon called as mass peristalsis. These peristaltic movements occur in limited number i.e. three to four times a day. This peristaltic movement of intestine results in an increase in the luminal pressure, this increase in luminal pressure is the key point in the development of pressure controlled drug delivery system.

The pressure controlled drug delivery system consists of a capsule in which the drug is present. These gelatin capsules are coated with water insoluble polymer like ethyl cellulose on their inner side. The drug is introduced into the capsule along with suppository base. The thickness of ethyl cellulose coating determines the disintegration capacity of the capsule. After administration the suppository base dissolves at body temperature. The water from intestinal contents is absorbed resulting in increased viscosity which leads to an increase in the pressure in the capsule. The pressure in the capsule expels the drug into the colon. The intestinal pressure developed varies with the circadian rhythms, state of body, food administration, etc [51].

b. CODES technology

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine. This system consists of a core tablet coated with three layers of polymer coatings. The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes though the pyloric and duodenum and exposes the next coating. The next coating is composed of Eudragit E. This layer allows the release of lactulose present in the inner core. This released lactulose gets metabolized into short chain fatty acids that lower the surrounding pH where the Eudragit E layer dissolves. The dissolving of Eudragit E results in the exposure of the drug. The other polysaccharides that are used along with the drug in the core tablet are mannitol, maltose, etc. The bacteria present in the colon are responsible for the degradation of polysaccharides that are released from the core tablet. The degradation of polysaccharides results in organic acids formation that lowers the pH of the contents surrounding the tablet [52, 53]
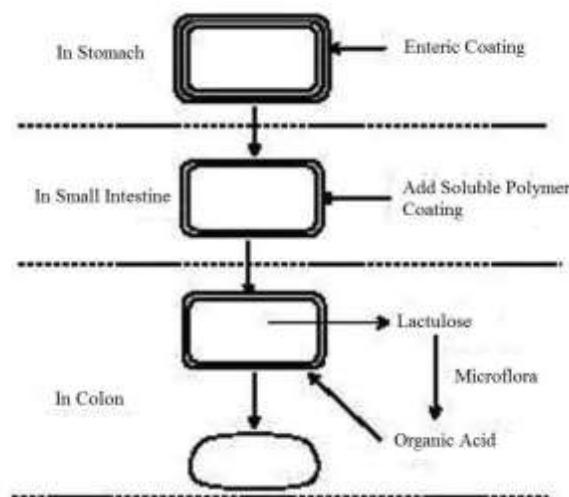
Figure 3: Schematics of the conceptual design of CODES

c. Novel Colon Targeted Delivery System (CODESTM):

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. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymatically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release [54, 55, 56].
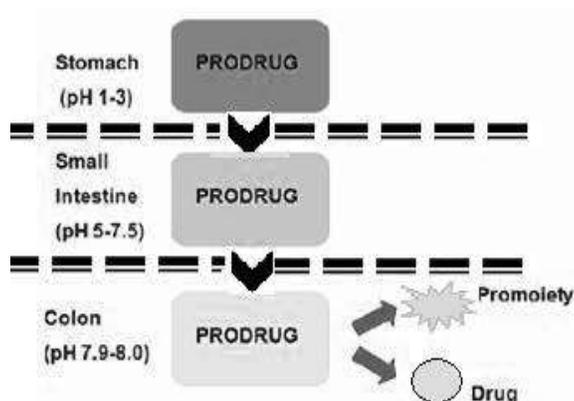

Figure 4: Schematics of Conceptual Design Of CODESTM.

d. Osmotic controlled drug delivery:

This system consists of osmotic units. The osmotic units are used either singly or as many as 5-6 push pull units that are encapsulated in a hard gelatin capsule. The push pull units are bilayered with outer enteric impermeable membrane and inner semi permeable membrane. The internal or central part of the push pull consists of the drug layer and push payer. The semi permeable membrane which is present next to the drug layer consists of an orifice through which the drug contents are expelled during the course of time.

The capsule body enclosing the push pull units gets dissolved immediately after administration. During the passage of the push pull units through the GIT the enteric impermeable membrane prevents the water absorption into the unit. The coating gets dissolved once it reaches the small intestine due to higher pH (>7). Water enters the unit through the semi permeable membrane causing the push layer to swell. The swelling of the push compartment forces the drug into the surrounding environment through the orifice. These osmotic controlled drug delivery systems deliver the drug at a constant rate for up to 24hr [57, 58].
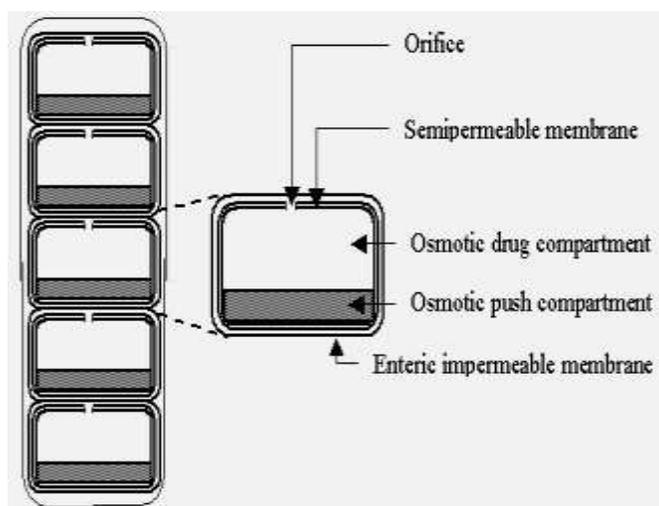

Figure 5: Cross-Section of the OROS-CT Colon Targeted Drug Delivery System.

Table 11: Marketed products of different osmotic systems [59]

Product name	Active	Design	Dose
Acutrim	Phenylpropanolamine	Elementary pump	75 mg
Alpress LP	Prazosin	Push-Pull	2.5-5 mg
Covera HS	Verapamil	Push-Pull with time delay	180, 240 mg
Ditropan CR	Oxybutinin chloride	Push-Pull	5, 10 mg
Dynacire CR	Isradipine	Elementary pump	5, 10 mg
Efidac 24	Pseudoephiderine	Elementary pump	60 mg IR,180 mg CR
Glucotrol	glipizide	Push-Pull	5, 10 mg
Volmax	Salbutamol	Elementary pump	4, 8 mg

e. Pulsatile colon targeted drug delivery (Time dependent delivery)

i) Pulsincap system

Pulsincap® is the first formulation was developed by R.R.Scherer International Corporation, Michigan, US [60]. In this system the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body. eg. Chronomodulated drug delivery system of salbutamol sulphate had been developed for the treatment of nocturnal asthma. The cores containing salbutamol sulphate were prepared by direct compression method use of microcrystalline cellulose and effervescent agent (sodium bicarbonate) and then coated sequentially with an inner swelling layer containing a hydrocolloid (hydroxypropylmethylcellulose E5) and an outer rupturable layer having eudragit RL/RS (1:1)[61].
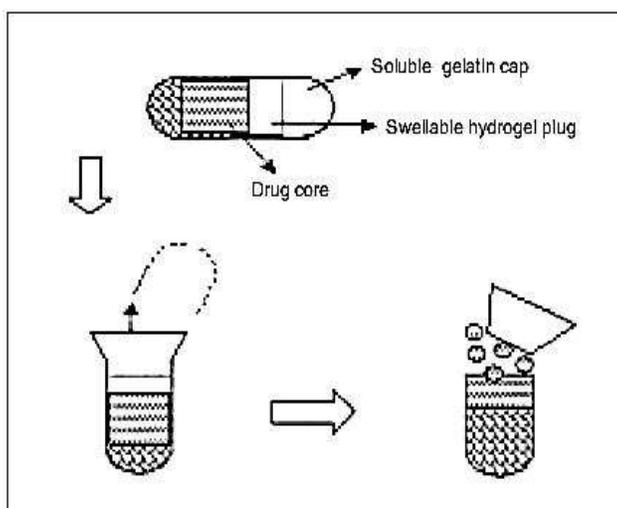

Figure 6: Pulsincap system

ii) Port system

The Port system was developed by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA, and consists of a gelatin capsule coated with a semipermeable membrane. In this system the capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation. When the capsule comes in contact with the dissolution fluid the semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release

of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals [62]. The system proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children [63].
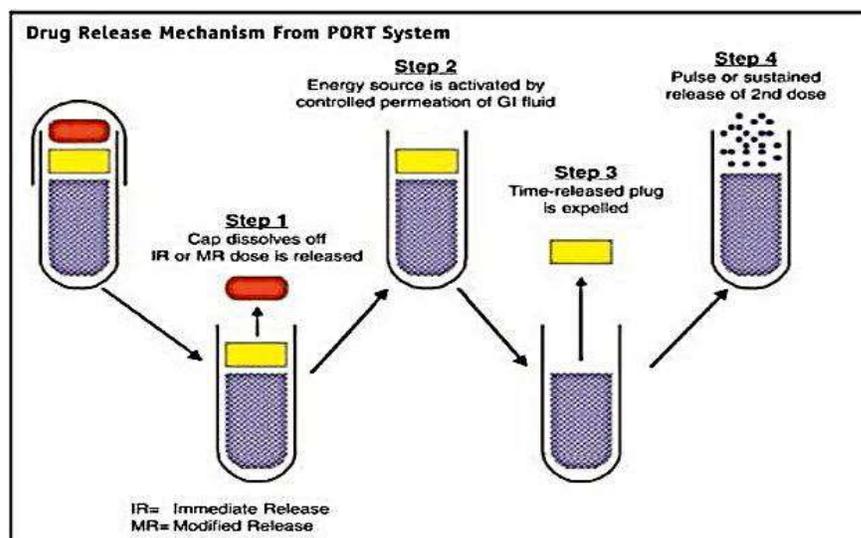

Figure 7: Drug release mechanism of port system

f. Hydrogels

Hydrogels can be used for site specific delivery of peptide and protein drugs through colon. The Hydrogels are composing of acidic monomer and enzymatically degradable azo aromatic cross-linkers. In the acidic pH, gels shows less swelling that protect the drug against degradation in stomach. As the pH of environment increases i.e. become basic, swelling increases. This result is easy access of enzymes like azareducatase, which ultimately release the drug [64,65]. 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 degradation rate of hydrogel is associated with the degree of swelling and inversely proportional to the cross linking density [66].

g) Multi particulate system based drug delivery

Multi particulates systems are preferred over single unit dosage forms it 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. Multi particulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption. The advantages of multi particulate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity [67,68]. The various multi particulate approaches are enlists in table.

Table 12: Different multiparticulate approaches [69]

S.No.	Approaches
1.	Intestinal Protective Drug Absorption System
2.	Programmable Oral Drug Absorption System
3.	Stabilized Pellet Delivery System
4.	Minitabs
5.	Multiparticle Drug Dispersing Shuttle
6.	Delayed release oral polypeptides
7.	Multiparticulate crystalline drug Compositions
8.	Spheroidal oral drug absorption Systems
9.	Diffucaps
10.	Pelletized Delivery System
11.	Pelletized tablet
12.	Layering process for multiparticulate dosage form
13.	Multiparticulate mucoadhesive Formulations
14.	Multiparticulate as NDDS

CONCLUSION

Since two decades, considerable amount of research work has been carried out in the area of colon targeting. CDDS offers potential therapeutic benefits to patients in terms of both local and systemic treatment and also as proteins and peptides drugs. Successful colonic delivery could be achieved by protecting the drug from the upper GIT warriors. The Natural polymer based colon specific drug delivery is relatively easy due to the presence of various derivatizable groups, wide range of molecular weights, varying chemical compositions, low toxicity and high stability. At present there are various approaches are being researched in attempts to understand and achieve the desired goal of targeting the delivery to a specific organ that is colon. The approaches described (Natural Prodrugs Conjugates and Recent Pharmaceutical Approaches) above are quite promising and further improvements are required to achieve the high bioavailability and safe delivery of drugs to the colon.

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