



COLON SPECIFIC DRUG DELIVERY SYSTEMS: A REVIEW ON PRIMARY AND NOVEL APPROACHES

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ABSTRACT

Colon specific drug delivery has gained increased importance not just for delivery of the drugs in the treatment associated with the colon, but also as a potential site for the systemic delivery of therapeutic peptides and proteins. 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. 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 in vivo site specificity, and feasibility of manufacturing process.

Keywords: Colon Specific Drug Delivery, Novel Approaches, pH dependent system, CODESTM, Drug Targeting.

INTRODUCTION

Colon delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). The site specific delivery of the of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction^{1,2}. It has also gained increased importance not just for the delivery of drugs for the treatment of local diseases³, but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivery by injections. The colon is a "friendlier" environment for proteins and peptides compared to the upper part of GI tract. Clinically relevant bioavailability may be achieved if the peptide can be protected from acid and enzymes in the stomach and upper intestine.

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 optimal⁴. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies, and this helps in efficient vaccine delivery. The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about first six meters of the small intestine^{5,6}. 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 capacity⁷.

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. glycosides⁸. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon- targeted drug delivery of peptide based macromolecules such as insulin by oral administration. Target sites, colonic disease conditions, and drugs used for treatment are shown in Table 1.⁹

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 agents¹⁰. Administration of glucocorticoids namely dexamethasone and methyl Prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppressant, cushinoid symptoms, and bone resorption¹¹. 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 doses¹².



Table 1: Colon targeting diseases, drugs and sites⁹.

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,
Local action	Pancreatotomy and cystic fibrosis, Colorectal cancer	Digestive enzyme supplements 5-Flourouracil.
Systemic action	To prevent gastric irritation To prevent first pass metabolism of orally ingested drugs Oral delivery of peptides Oral delivery of vaccines	NSAIDS Steroids Insulin Typhoid

FACTORS TO BE AFFECTED IN THE DESIGN OF COLON - TARGETED DRUG DELIVERY SYSTEM

Anatomy and Physiology of Colon¹³

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon and the values were shown in table 2. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus¹⁴.

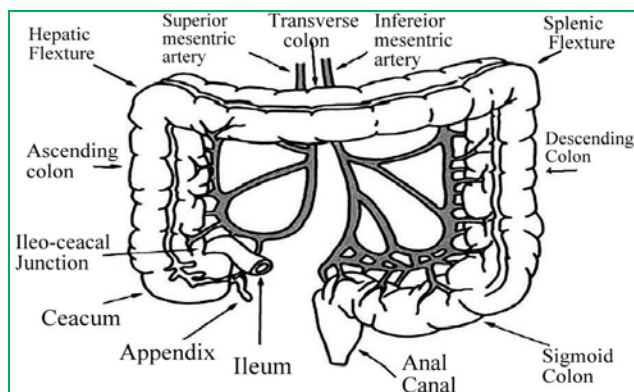


Figure 1: Anatomy of parts of the colon.

Table 2: Measures of different parts of colon¹⁴

Large intestine	Length (cm)
Ceceum	6-9
Ascending colon	20-25
Descending colon	10-15
Transverse colon	40-45
Sigmoid colon	35-40
Rectum	12
Anal canal	3

pH in the colon

The pH of the GI tract is subject to both inter and intra subject variations. Diet, diseased state, and food intake influences the pH of the gastrointestinal fluid. The changes in the pH along the gastrointestinal tract have been used as a means for targeted colon drug delivery¹⁵. Radio telemetry shows the highest pH (7.5±0.5) in the terminal ileum. On entry into the colon, the pH drops to 6.4±0.6. The pH in the mid colon is 6.6±0.8 and in the left colon 7.0±0.7¹⁶. 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 5.0¹⁷.

Colonic Microflora and Enzymes

A large number of anaerobic and aerobic bacteria are present in the entire length of the human GI tract. Intestinal enzymes are used to trigger drug release in various parts of the GI tract. Usually, these enzymes are derived from gut microflora residing in high numbers in the colon. 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 bacteroids¹⁸. The concentration of bacteria in the human colon is around 1000 CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, and Peptostreptococcus, Ruminococcus, Clostridium¹⁹.

Transit of Material in the Colon

The presence of food 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 hours²⁰⁻²². Small intestinal transit is surprisingly constant at 3-4hours and appears to be independent of the type of dosage form and whether the subject is in the fasted or fed state²³.

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 drugs²⁴. 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 electrolytes²⁵.

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 takes¹⁸.

Table 3: gastrointestinal transit time of contents²³

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

The poor paracellular absorption of many drugs in the colon is due to the fact that epithelial cell junctions are very tight²⁶. The slow rate of transit in colon lets the drug stay in contact with the mucosa for a longer period than in small intestine which compensates the much lower surface area. The colonic contents become more viscous with progressive absorption of water as one travels further through the colon. This causes a reduced dissolution rate, slow diffusion of dissolved drug through the mucosa.

Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum. Recent studies have

shown that some drugs (e.g. Theophylline and Metoprolol Oxiprenolol)²⁷.

The oral absorption of the 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.

CRITERIA FOR SELECTION OF DRUGS FOR CDDS

The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery.

The criteria for selection of drugs for CDDS are summarized in Table 4²⁸⁻³⁰.

Table 4: Criteria for selection of drugs for CDDS²⁸⁻³⁰

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in Colon against GIT diseases	Anti-inflammatory drugs Nifedipine	Oxyprenolol, Metoprolol,	Amylin, Antisense Oligonucleotide
Drugs poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Isosorbides, Theophylline Ibuprofen,	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, Salatonin
Drugs for targeting	Antiarthritic and antiasthmatic drugs	Prednisolone, hydrocortisone,	Somatropin, Urotolithin

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. 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 systems³¹.

GENERAL CONSIDERATIONS FOR DESIGN OF COLONIC FORMULATIONS

Formulations for colonic delivery are, in general, delayed-release dosage forms which may be designed either to provide a 'burst release' or a sustained/ prolonged release once they reach the colon³². The proper selection of a formulation approach is dependent upon several important factors which are listed below.

- Pathology and pattern of the disease, especially the affected parts of the lower GI tract or physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment.



- Physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery.
- The desired released profile of the active ingredient.

The most common physiological factor considered in the design of delayed release colonic formulations is pH gradient of the GI tract. Some reports suggest that alteration in GI pH profiles may occur in patients with inflammatory bowel disease (IBD), which should be considered in the development of delayed release formulations³³.

Formulation of the drugs for colonic delivery also requires careful consideration of drug dissolution and/or release rate in the colonic fluids. The poor dissolution and release rate may in turn lead to lower systemic availability of drugs. These issues could be more problematic when the drug candidate is poorly water soluble and/or require higher doses for therapy. Consequently, such drugs need to be delivered in a presolubilized form, or formulation should be targeted for proximal colon, which has more fluid than in the distal colon³⁴.

PHARMACEUTICAL APPROACHES FOR COLON SPECIFIC DRUG DELIVERY (CDDS)

pH sensitive polymer coated drug delivery

This approach is based on the pH-dependent release of the drug from the system. In this case the pH differential between the upper and terminal parts of GI tract is exploited to effectively deliver drugs to the colon. One should not forget that the pH in the intestine and colon depends on many factors such as diet, food intake, and intestinal motility and disease states. This makes it more challenging for the specialists working in this field to design a delivery system that would be robust enough to withstand the variability in the gastric pH as it moves from the stomach to the small intestine. By combining knowledge of polymers and their solubility at different pH environments, delivery systems have been designed to deliver the drug at the target site³⁵. Commonly used copolymers of methacrylic acid and methyl methacrylate have been extensively investigated for colonic drug delivery systems. In vitro evaluation of Eudragit® S and Eudragit® FS was performed and it was found that the latter would be more appropriate for drug delivery to the ileocolonic region³⁶.

Several factors, such as combinations of different polymers, pH of the media, coating level of the tablets and presence of plasticizers, influence the dissolution rate of Eudragit®³⁷.

Inter and intra-subject variability, electrolyte concentration and transit time are some of the key variables impacting success through this route. In spite of these limitations, pH-based systems are commercially available for mesalazine (5 ASA) (Asacol® and Salofalk®) and budesonide (Budenofalk® and Entrocort®) for the

treatment of ulcerative colitis and Crohn's disease, respectively.

Table 5: Enteric polymers used in the development of Modified Release Formulations for CDDS

Enteric polymers	Optimum pH for dissolution
Polyvinyl acetate phthalate (PVAP)	5.0
Methacrylic acid copolymer, Type A	≥6.0
Eudragit FS30D	>7.0
Hydroxypropylmethylcellulose phthalate (HPMCP)	≥5.5
Cellulose acetate trimelitate (CAT)	5.5
Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	≥6.0
Shellac (MarCoat 125 & 125N)	7.0
Methacrylic acid copolymer, Type B	≥7.0

Time dependent delivery system

Time dependent/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 colonic availability³⁸.

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 hr⁴⁴. 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)³⁸. 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 layer (HPC), (Fig. 2).

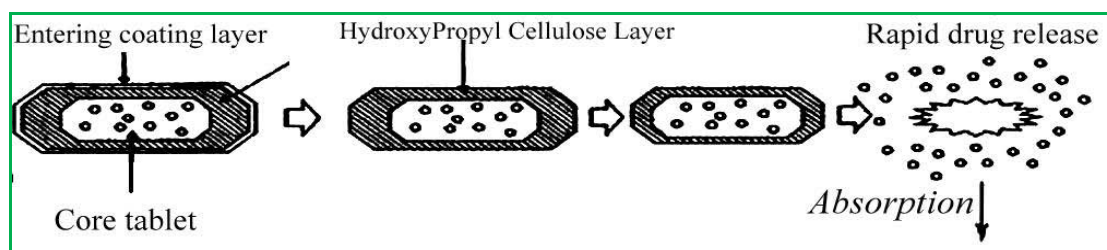


Figure 2: Design of enteric coated timed-release press coated tablet (ETP Tablet)³⁸

Microbially triggered drug delivery system

The microflora of the colon is in the range of 10¹¹-10¹² CFU/ml consisting mainly of anaerobic bacteria, e.g. Bacteroides Bifidobacterium, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc³⁹. This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc^{40,41}. For this fermentation, the microflora produces a vast number of enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatease, deaminase, and urea dehydroxylase⁴². 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. 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^{43,44}. They are then unable to hold the drug entity any longer⁴⁵.

The use of GI microflora as a mechanism of drug release in the colonic region has been of great interest to researchers in recent times. The majority of bacteria are present in the distal gut although they are distributed throughout the GI tract. Endogenous and exogenous substrates, such as carbohydrates and proteins, escape digestion in the upper GI tract but are metabolised by the enzymes secreted by colonic bacteria⁴⁶. Sulphasalazine, a prodrug consisting of the active ingredient mesalazine, was the first bacteria-sensitive delivery system designed to deliver the drug to the colon⁴⁷. Use of polysaccharides offers an alternative substrate for the bacterial enzymes present in the colon. Most of the polymers are used in pharmaceutical compositions and are considered generally regarded as safe (GRAS) excipients. Pectin alone and in combination with other polymers has been studied for colon-specific drug delivery. Pectin, when used alone, was needed in large quantities to control the release of the drug through the core. A coating composition of a mixture of pectin, chitosan and hydroxypropyl methylcellulose was proven to be very efficient as the tablets coated with this composition passed intact through the stomach and small intestine and broke in the colon⁴⁸.

Prodrug Approach for Drug Delivery to Colon

A prodrug is a pharmacologically inactive derivative of a parent molecule that requires some form of transformation in vivo to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. The type of linkage that is formed between the drug and carrier would decide the triggering mechanism for the release of the drug in the colon.

This biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon. The enzymes that are mainly targeted for colon drug delivery include azoreducatease-galactosidase, β -xylosidase, nitroreductase, glycosidase deaminase, etc. Generally, a prodrug is successful as a colon drug carrier if it is hydrophilic and bulky, to minimize absorption from the upper GI tract and, once in the colon, it is converted into a more lipophilic drug molecule that is then available for absorption. Certain drugs can be conjugated to different sugar moieties to form glycosides. Because they are bulky and hydrophilic, these do not penetrate the biological membranes upon ingestion. They break down upon action of glycosidase, releasing the drug part from the sugar. Glycosidase activity of the GI tract is derived from anaerobic microflora in the large bowel or exfoliated cells of the small intestine^{49,50}. Friend and Chang prepared dexamethasone-2- β -glucoside and prednisolone-2- β -glucoside for delivery of these steroids to the colon⁵¹. When free steroids were administered orally, they were almost absorbed in the small intestine and less than 1% of the oral dose reached the colon. Nakamura et al. studied the conjugation of drug molecule to the polar amino acids and prepared prodrugs for colon drug delivery⁵². Proteins and their basic units, i.e. the amino acids, have polar groups like -NH₂ and -COOH. These polar groups are hydrophilic and reduce the membrane permeability of amino acids and proteins. Various non-essential amino acids such as glycine, tyrosine, methionine, and glutamic acid were conjugated to salicylic acid.

The conjugate showed minimal absorption and degradation in the upper GI tract and showed more enzymatic specificity for hydrolysis by colonic enzymes⁵³. Glucuronide and sulphate conjugation is the major mechanism for the inactivation and preparation for clearance of many drugs. Bacteria of the lower GI tract, however, secrete β -glucuronidase and can

deglucuronidate a variety of drugs in the intestine⁵⁴. The azo linkage exhibits a wide range of thermal, chemical, photochemical and pharmaceutical properties. The azo compounds are extensively metabolised by the intestinal bacteria, both by intracellular enzymatic components and extracellular reduction⁵⁵.

The use of these azo compounds for colon targeting has been in the form of hydrogels as a coating material for coating the drug cores, and as prodrugs⁵⁶. Sulphasalazine, which was used for the treatment of rheumatoid arthritis, was later known to have potential in the treatment of inflammatory bowel disease (IBD). This compound has an azo bond between 5-ASA and sulphapyridine⁵⁷. Numerous drugs have been described that form complexes with β -cyclodextrins, enhancing the drug stability and/or absorption performance^{58,59}. The β -cyclodextrins are practically resistant to gastric acid and salivary and pancreatic amylases. A clinical study has shown clear evidence that β -cyclodextrins are poorly digested in the small intestine but are almost completely degraded by the colonic microflora⁶⁰. A number of prod rugs have been outlined in Table 6.

Table 6: Prodrugs evaluated for colon-specific drug delivery

Drug investigated	Carrier	Linkage hydrolysed
5-ASA	Azo conjugates Sulphapyridine(SP)	Azo-linkage
5-ASA	Azo conjugates p-Aminohippurate	Azo-linkage
5-ASA	Azo conjugates Glycine	Amide linkage
Naproxane	Dextran conjugates	Ester linkage
Dexamethasone	Dextran conjugates	Using spacer
Byphenyl acetic acid	Cyclodextrin conjugates	Ester/amide
5-ASA	Sulphanilamido ethylene polymer	Azo linkage
Dexamethasone	Polymeric prodrugs Poly-L-aspartic acid	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 moiety⁶¹. 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 azoreductase in the large bowel. Coating of peptide capsules with polymers cross linked with azoaromatic 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 released⁶². A number of azo-polymeric prodrugs are outlined in Table 7.

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 monosaccharides are found in abundance, have wide availability are inexpensive and are available in a variety of 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, chondroitin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccharides can be broken down by the colonic microflora to simple saccharides^{37,63}. Therefore, they fall into the category of "generally regarded as safe" (GRAS). Chitosan is a high molecular weight cationic polysaccharide, poly (N-glucosamine), derived from chitin in crab and shrimp shells by deacetylation. It is degraded by the rich colonic microflora. Chitosan has been evaluated for colon specific drug delivery mainly in the form of a capsule forming material. Pectin is another non-starch linear polysaccharides with mainly α -(1-4)-linked Dgalacturonic acid residues interrupted by 1, 2-linked L-rhamnose residues. A number of polysaccharide-based delivery systems have been outlined in Table 8.

Combination of pH and Polysaccharides

The polysaccharide delivery vehicles may be layered with an enteric blocking agent. The purpose of such a coating is to protect the delivery vehicle from degradation by stomach acids and proximal intestinal enzymes. David and Sergio (1997) patented controlled release vehicles like nonporous microspheres, microcapsules and liposomes for delivery of drugs to colon. Budesonide delivery system and pectin admixture was compressed into tablets. These matrices were coated with Eudragit S100 yielded enteric release characteristics⁶⁴. Tablets made from microscopic beads containing beclomethasone/ budesonide entrapped in Microsponge were compressed in a matrix formed by pectin. Matrices of these drugs were also prepared by admixing with acrylate copolymers. These matrices were filled into capsules and coated with Eudragit S100. In another investigation, the concentration of 14C hydrocortisone was measured in both urine and ileal effluents for 3-5 days after ingestion of porous microscopic beads loaded capsule. It was observed in all the subjects that 14C was excreted mostly by ileal route. It was also observed that almost all excretion occurred within 24 hr of ingestion of the capsule. Overall, the results indicated that the active ingredient was released primarily in the colon. The detection of 14C hydrocortisone in considerable concentration in faeces within 24 hr of ingestion suggests that pectin matrices loaded in Eudragit S100 coated capsules could also be used to deliver in sufficient quantity of drugs in the colon for treatment of IBD⁶⁵.

Table 7: Some azo polymer-based drug delivery systems evaluated for colon-specific drug delivery with summary of results obtained⁶².

Azo polymer	Dosage form prepared	Drug investigated	In-vitro/ in-vivo model	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.
Hydrogels prepared by copolymerization of 2-hydroxyethyl 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.
Segmented polyurethane	Coating over pellet	Budesonide	Rat	These azopolymer-coated pellets were useful for colon-specific delivery of budesonide to bring healing in induced colites.
Aromatic azo bond containing urethane analogues	Degradable films	5-ASA	In vitro degradation of films in presence of lactobacillus	These films were degraded by azoreductase. The permeability of 5-ASA from lactobacillus treated films was significantly higher than that of control.

Table 8: Polysaccharides investigated for colon-specific drug delivery³⁷

Drug moiety used	Polysaccharide investigated	Dosage form prepared
Diclofenac Sodium	Chitosan	Enteric coated chitosan microspheres
Insulin	Chitosan	Enteric coated chitosan capsules
Indomethacin	Pectin (used as Calcium salt)	Matrices
Paracetamol	Amidated pectin	Matrix tablets
Indomethacin	Amidated pectin	Chitosan-coated amidated pectin beads
Ropivacaine	Amidated pectin	Matrix tablets
Dexamethasone	Guar gum	Matrix tablets
Bovine serum albumin- BSA	pH-sensitive dextran	As hydrogels
Indomethacin	Chondroitin sulphate	Matrix tablet
Radioactive tracer	Starch	Enteric coated capsules
5-ASA	Alginate as calcium salt	Double coated swellable beads
Theophylline	Locust bean gum	Film
Theophylline	Dextran fatty acid esters	As films

Combination of pH and Time Dependent Delivery Systems

The transit time through the small intestine is independent of the formulation. But, the time taken by the formulation to leave the stomach varies greatly. Hence, the time of arrival of a formulation in the colon cannot be accurately predicted. However, the effects of variation in gastric residence time can be minimised by

using systems that prevent drug release until 3-4 hr after leaving the stomach.

Savastano et al. (1997) patented an osmotic delivery device for release of the active ingredient to preselected region of gastrointestinal tract. The delivery system consisted of solid core containing active agent, delay jacket coated over the core (e.g. dextrates, sodium alginate), followed by a semipermeable membrane (cellulose acetate, CAP) and finally, an enteric coat. Metoprolol fumarate core tablets were compression coated with dextrate followed by film coating with cellulose acetate and finally with Eudragit (enteric polymer). The amount of metoprolol released was negligible till 5 hr and 82.7% till 24 hr when dissolution studies were carried out in 0.1N HCl for 0-2 hr followed by phosphate buffer (pH7.5) for 2-24 hr⁶⁶.

NEWLY DEVELOPED APPROACHES FOR CDDS

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 water⁶⁷. 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^{68,69}. 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 liquid⁷⁰. Lag times of three to five hours in relation to drug



absorption were noted when pressure-controlled capsules were administered to humans.

Novel Colon Targeted Delivery System (CODESTM)

CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems^{71,72}. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon (Fig. 3). The system consists of a traditional tablet core containing lactulose, which is over coated with an 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 intestine⁷³. 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 release⁷⁴.

Osmotic Controlled Drug Delivery (OROS-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 unattainable⁷⁵. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, (Fig. 4)⁷⁶. 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 ($\text{pH} > 7$), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable 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. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon⁷⁷⁻⁸⁰. Various in vitro / in vivo evaluation techniques have been developed

and proposed to test the performance and stability of CDDS.

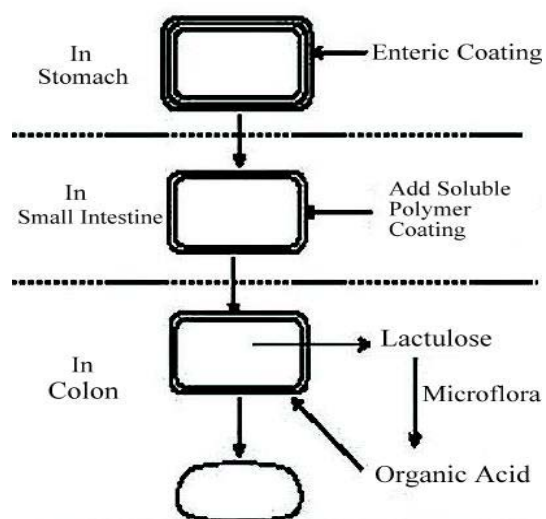


Figure 3: Schematics of the conceptual design of CODESTM⁷⁴

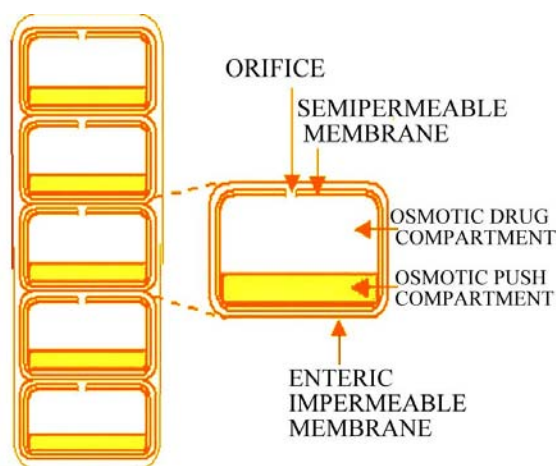


Figure 4: Cross-Section of the OROS-CT colon targeted drug delivery system⁷⁷⁻⁸⁰

LIMITATIONS AND CHALLENGES IN COLON TARGETED DRUG DELIVERY

One challenge in the development of colon-specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system in-vitro. This is due to the rationale after a colon specific drug delivery system is quite diverse.

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 in the distal part of the alimentary canal, the colon is particularly difficult to access. In addition to that the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.

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.

In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a nonspecific way to dietary residues, intestinal secretions, mucus or fecal 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.

SUMMARY

The concept of targeting the delivery of specific drugs to colon is quite self explanatory and sufficient scientific rationale is available to support the justification. Various approaches are being researched in attempts to understand and achieve the desired goal of targeting the delivery to a specific organ, the colon. All the available approaches have their own limitations and advantages and extensive research is being focused on these to improve further. Time-dependant systems are not a very practical solution due to variable GI tract transit times but may have a potential role in diseases that are subject to circadian rhythm. On the other hand, pressure-controlled systems hold some promise but currently little is known about the luminal pressures of different regions of GI tract, and at present the commercial manufacturing methods have some unresolved issues to be addressed. The only system available as of today is based on pH but these systems can possibly deliver the drug at the duodenum or may not deliver the drug at all. Further research is ongoing in different labs and it is quite likely that a day is not far off when new, improved polymers will replace the existing available polymers with improved performance. The bacterially activated systems seem to have the greatest potential as of today as the levels of bacterial enzyme activity is most unique and exploitable in this region. The amylase-based COLAL is the leading product in the later phases of clinical evaluation and has promise for commercial manufacturing. Another area that still needs to be understood is human physiology and inter-/intra-subject variability. Once this aspect of the human system is understood, the gained knowledge can be applied to focus research on identifying suitable analytical tools that can predict the in vivo performance of the developed system. At the end of the day the need of today's business and patient community is to identify the appropriate approach that can result in the delivery of drugs in a safe, effective and less expensive manner with minimum fluctuation in terms of release of drugs at target site. If so, the overall cost of development of such a

technology will be practically feasible and commercially viable.

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