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NOVEL APPROACHES OF COLON TARGETED DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

The colon is believed to be a suitable absorption site for peptides and protein drugs for the reasons like less diversity and intensity of digestive enzymes, less proteolytic activity of colon mucosa leading to better protection from hydrolysis and enzymatic degradation in duodenum and jejunum, greater systemic bioavailability and long colon residence time (5 days) and high responsiveness to absorption enhancers. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. Colon target drug delivery system (CDDS) is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiasis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process.

KEYWORDS: Colon Drug Delivery, Polymer coated, Prodrug, Osmotic pressure.

INTRODUCTION

Targeted drug delivery into the colon is 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. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability.4 And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.[1-4]

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

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 azo-reduction and enzymatic cleavage i.e. glycosides.[5-7] These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration. Target sites, colonic disease conditions, and drugs used for treatment are shown in Table 1.

Table 1: Colon targeting diseases, drugs and sites.

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

Advantages of CDDS over Conventional Drug Delivery

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

Criteria for Selection of Drug for CDDS

The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery.[8-10]

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 systems.[11-12]

Table 2: Criteria for selection of drugs for CDDS.

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

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

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

1) Primary Approaches for CDDS

a. pH Sensitive Polymer Coated Drug Delivery to the Colon

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers.[13-15] The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor. 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.[16-18]

b. Delayed (Time Controlled Release System) Release Drug Delivery to Colon

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h. However, the disadvantages of this system are:

i. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
ii. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
iii. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea, and the ulcerative colitis.

Therefore, time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hr. 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). 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.[19-22]

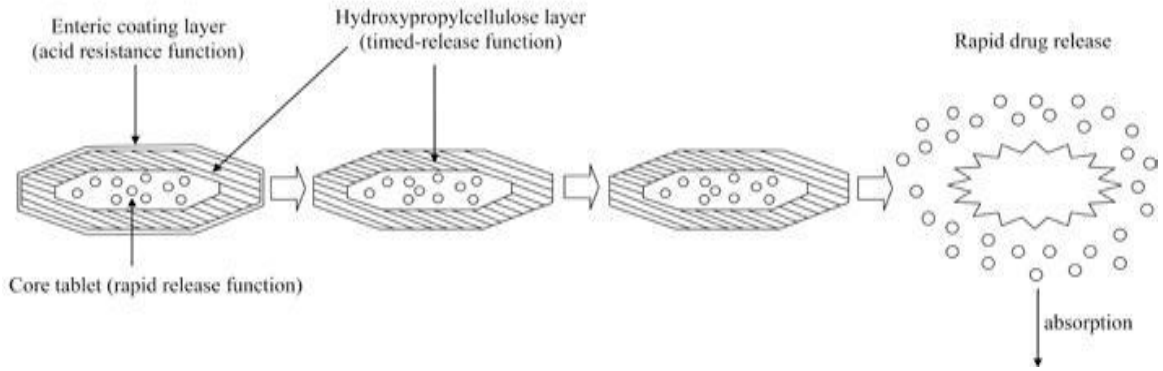

Figure 1: Design of enteric coated timed-release press coated tablet (ETP Tablet)

The duration of lag phase is controlled either by the weight or composition of the polymer (HPC) layer. (Fig. 1)

c. Microbial Triggered Drug Delivery to Colon

The microflora of the colon is in the range of 1011 -1012 CFU/ mL, consisting mainly of anaerobic bacteria, e.g.

bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc. 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. For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to 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. They are then unable to hold the drug entity any longer.[23-24]

i) Prodrug Approach for Drug Delivery to Colon

Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery, the prodrug is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes.[25-26]

Furthermore, prodrugs are new chemical entities, and need a lot of evaluation before being used as carriers. A number of prodrugs have been outlined in Table 3.

Table 3: Prodrugs evaluated for colon specific drug delivery with there in vitro/in vivo performance.

Carrier	**Drug investigated**	**Linkage hydrolyzed**	**In vitro/in vivo model used**	**Performance of the Prodrug/conjugates**
Azo conjugates	5-ASA	Azo linkage	Human	Site specific with a lot of side effects40
Suphapyridine (SP)				associated with SP
5-ASA	5-ASA	Azo linkage	Human	Delivers 2 molecules of 5-ASA as compared to
				suphasalazine41
Amino acid conjugates	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized
glycine				by microflora of large intestine42
Tyrosine/methionine	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized
				by microflora of large intestine43
L – Alanin/D-	Salicylic acid	Amid linkage	In vitro	Salicylic acid-l-alanine was hydrolysed to
Alanine				salicylic acid by intestinal microorganism but salicylic acid-D-alanine showed negligible hydrolysis thereby showing enantiospecific hydrolysis44
Glycine	5-ASA	Amid linkage	In vitro	Prodrug was stable in upper GIT and was
				hydrolysed by cecal content to release 5-ASA45
Saccharide carriers	Dexamethasone/	Glycosidic	Rat	Dexamethasone prodrug was site specific and
	prednisolone	linkage		60% of oral dose reached the cecum. Only 15% of prednisolone prodrug reached the cecum17

(ii) Azo-Polymeric Prodrugs

Newer approaches are aimed at the use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers have been used for this purpose. Sub synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety. These have been evaluated for CDDS. Various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreducatase in the large bowel. Coating of peptide capsules with polymers cross linked with azoaromatic group have been found to protect the drug from digestion in the stomach and small intestine. In the colon, the azo bonds are reduced, and the drug is released.[27-29]

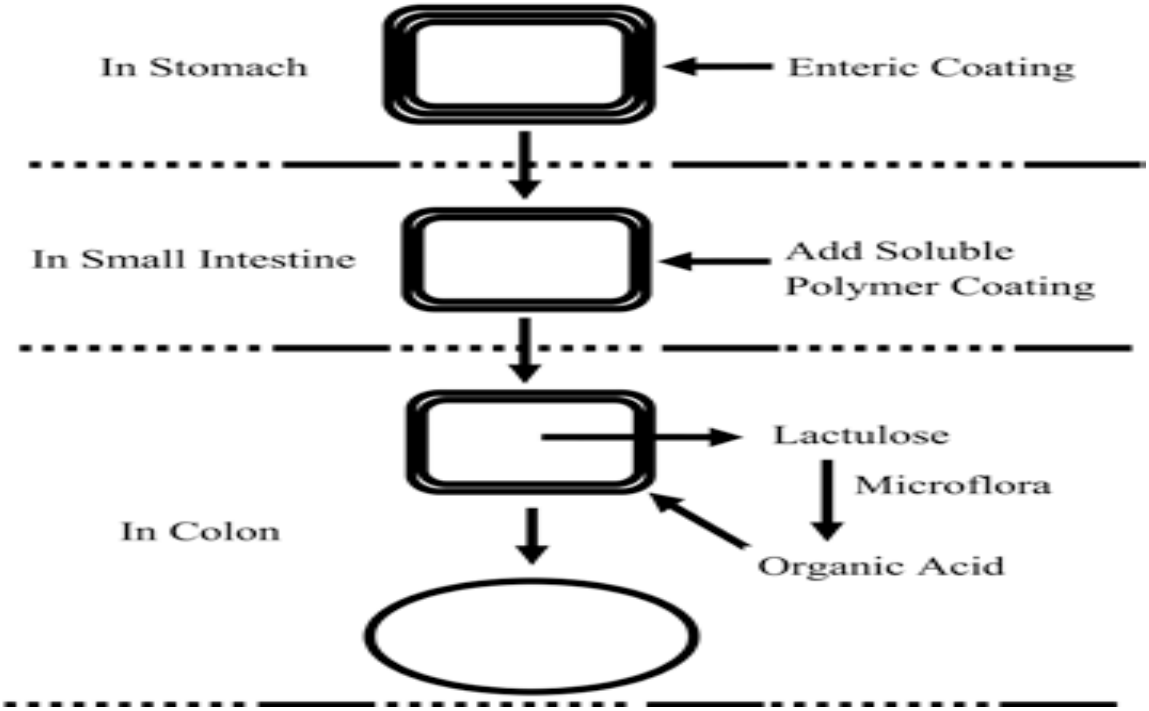

Figure 2: Schematics of the conceptual design of CODES.

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. The OROSCT 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. 3). 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 OROSCT 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 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 colon. Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.[30-33]

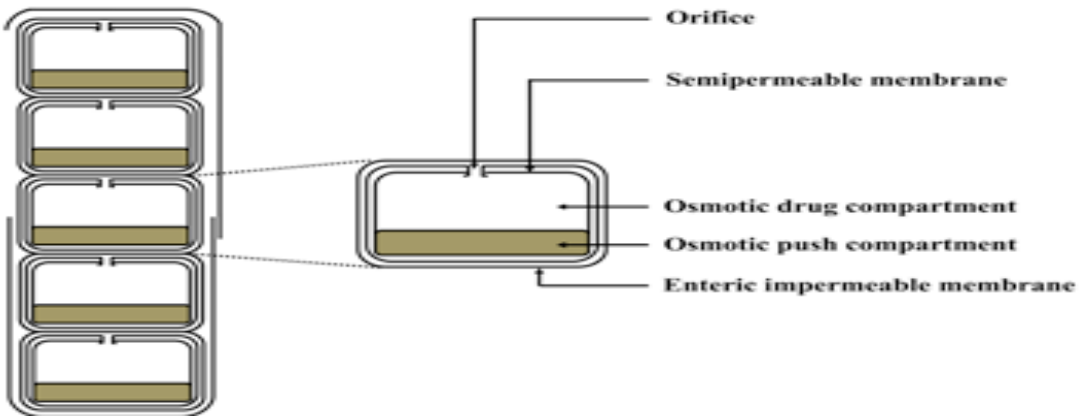

Figure 3: Cross-Section of the OROS-CT colon targeted drug delivery system.

For in vitro evaluation, not any standardized evaluation technique is available for evaluation of CDDS because an ideal in vitro model should posses the in-vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity, and other components of food. Generally, these conditions are influenced by the diet, physical stress, and these factors make it difficult to design a slandered in-vitro model. In vitro models used for CDDS are:

a) In vitro dissolution test

Dissolution of controlled-release formulations used for colon specific drug delivery are usually complex, and the dissolution methods described in the USP cannot fully mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract have been studied. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileum segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4.

b) In vitro enzymatic tests

Incubate carrier drug system in fermenter containing suitable medium for bacteria (strectococcus faccium and B. Ovatus). The amount of drug released at different time intervals are determined.

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

c) In vivo evaluation

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azo-reductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS, a novel model has been proposed. In this model, the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which bascularizes within four weeks, matures, and becomes capable of developing of mucosal immune system from the host.[34-35]

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

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

CONCLUSION

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon-specific drug delivery systems, and the uncertainty of current dissolution methods in establishing possible in-vitro/in-vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

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