DIFFERENT APPROACHES TO COLON SPECIFIC DRUG DELIVERY: A REVIEW

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Summary

Colonic drug delivery has gained increased importance as colon is a site where both local and systemic delivery of drugs can take place not just for the delivery of drugs but also for the treatment of local diseases associated with the colon and as a potential site for the systemic delivery of therapeutic peptide and proteins. Different approaches have been designed based on prodrug formulation, pH-sensitivity, time-dependency (lag time), microbial degradation and osmotic pressure, etc to formulate the different dosage forms like tablets, capsules, multiparticulates, etc for colon targeting. The efficiency of this drug delivery system is evaluated using different *in-vitro* and *in-vivo* release studies. This review is aimed at different approaches for formulation including newly developed CDDS, which includes pressure controlled colonic delivery capsules (PCDDS), CODES^{TM} and osmotic controlled drug delivery which are unique in terms of achieving *in-vivo* site specificity and feasibility of manufacturing process.

Keywords: Colon specific drug delivery system, Microbial degradation, Osmotic Pressure, pH-sensitivity, Prodrug

Introduction

Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiosis, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs [1,2]. 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 [3]. 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 protecting 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, since the colon has a long residence time which is up to 5 days thus is highly responsive to absorption enhancers [5].

Oral route is the most convenient and preferred route [6] but other routes for CDDS may also be used. Rectal administration offers the shortest route to targeting drugs on the colon. It can also be uncomfortable for the patients and compliance may be less than optimal [7]. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. The concentration of drug reaching the colon will depend on formulation factors, the extent of retrograde spreading and the retention time.

Advantages of colon specific drug delivery system [8,9,10,11]:

- Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, Crohn's disease, etc.)
- Produces 'friendlier' environment for peptides and proteins when compared to upper gastrointestinal tract.
- Minimizes extensive first pass metabolism of steroids.
- Preventing gastric irritation produced by oral administration of NSAIDs.
- Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.

To achieve successful colon targeting it should overcome the following limitations [12].

- The location at the distal portion of the alimentary canal, the colon is difficult to access.
- Successful delivery requires the drug to be in solution form before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.

The human colon has over 400 distinct species of bacteria as resident flora. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides [13]. 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**[14].

Table 1: Colon Targeting Diseases, Drugs and Target Sites

Target sites	Disease conditions	Drug and active agents
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease. Chronic pancreatitis	Hydrocortisone, Budesonide, Prednisolone, Sulfasalazine, Olsalazine, Mesalazine, Balsalazide.
Local action	Pancreatactomy 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

Criteria For Selection Of Drug For CDDS

Drug Candidate

Drugs which showed poor absorption from the stomach or intestine including peptide are most suitable for CDDS. The drugs used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhoea and colon cancer was ideal candidates for local colon delivery [15]. Criteria for selection of drugs for CDDS are summarized in **Table 2**.

Table 2: Criteria for Selection of Drugs for CDDS

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

Drug Carrier

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used.
Factors which influence the carrier selection are:

- Chemical nature
- Stability
- Partition coefficient of the drug
- Type of absorption enhancer chosen

Moreover, the choice of drug carrier depends on the functional groups of the drug molecule [16]. 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 hydrogels or coating agents) influences the release properties and efficacy of the systems [17].

Approaches Used For Colon Specific Drug Delivery (CDDS)

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

[A] Primary approaches for CDDS [18]

- ❖ pH sensitive polymer coated drug delivery to colon.
- ❖ Delayed (Time controlled release system) release drug delivery to colon
- ❖ Microbially triggered drug delivery to colon
  - Prodrug approach for drug delivery to colon
  - Azo-polymeric approach for drug delivery to colon
  - Polysaccharide based approach for drug delivery to colon

[B] Newly developed approaches for CDDS [19]

- ❖ Pressure controlled drug delivery system (PCDDS)
- ❖ CODES™ (A Novel colon targeted delivery system)
- ❖ Osmotic controlled drug delivery to colon (OROS-CT)

Primary Approaches for CDDS

A) pH Sensitive Polymer Coated Drug Delivery to the Colon

The basic principle in this method is the coating of the tablets/pellets, etc with various pH sensitive polymers which will produce delayed release and also give protection from gastric fluids. Selection of polymers is important thing. The selected polymers to colon targeting should be able to withstand the pH of the stomach and small intestine. Methacrylic acid esters was the most commonly used polymers for colon targeting because they are soluble at above pH 6. The ideal polymer should be able to withstand the lower pH of the stomach and of the proximal part of the small intestine but able to disintegrate at neutral or shortly alkaline pH of the terminal ileum and preferably at ileocecal junction. Eudragit L and Eudragit S are widely used in the colon targeting because Eudragit L is soluble at pH 6 or above and Eudragit S is soluble at pH 7 or above and the combination of these polymers gives the desirable release rates. E.g. 5-fluorouracil granular matrices were designed for the release of drug in the descending colon in a controlled fashion for the treatment of colorectal carcinoma. Glyceryl palmitostearate was used as the retardant material to formulate the controlled release matrices. These matrix granules were introduced into enteric coated capsules so as to be carried to and liberated in the ileum [20]. The hydroxy propyl methylcellulose capsules were enteric coated with Eudragit FS 30D. It showed that these capsules disintegrate in the distal portion of small intestine and proximal colon. Capsules of this type could, therefore ensure spatial delivery of drug preferentially in colon without substantial release in the upper GI tract up to the ileum. The matrices were coated by Eudragit S100 and were then covered by a layer of chitosan HCl and loaded inside these capsules. Upon hydration, the capsule shell dissolves and the chitosan layer forms a gel (internal pH of 4.5), which generates an acidic environment around the Eudragit film so that it does not dissolve in the ascending colon. In the ascending colon, the chitosan HCl gel is degraded by the colonic micro flora, thereby exposing the Eudragit film to the colonic environment. But since the ascending colon is weakly acidic where pH is less than 7.0, the film coat still remains intact. However, on arrival in the descending colon where pH is greater than 7, the Eudragit film coat dissolves and the drug is released in a controlled fashion from the matrices [21].

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 very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches the colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability [21]. The colon targeting dosage forms may also be applicable 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 [22].
iii. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhoea and the ulcerative colitis [23,24,25].

Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. But integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon [26]. In the small intestine, drug carrier will be delivered to the target site 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 [27].
E.g. Colon drug delivery system of diclofencac sodium (DS) was developed using time dependent approach. In this, diclofencac sodium tables were coated with ethylcellulose in ethanol solution cooling diethyl phthalate as a plasticizer and PEG 400 as channeling agent. The lag time of DS release was primarily controlled by thickness of ethylcellulose coating layer. By increasing the thickness of the coating layer, longer the lag time of DS release [28].

C) Microbially Triggered Drug Delivery to Colon

The basic principle involved in this method is degradation of polymers coated on the drug delivery system by microflora present in colon and thereby causing release of drug load in colonic region because the bioenvironment inside the human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms [29]. In this method drugs and/or dosage forms are coated with the biodegradable polymers such as Eudragit L-100, Eudragit S-100, Eudragit L-30 D, Poly Vinyl Acetate Phthalate, Hydroxy Propyl Methyl, Cellulose Phthalate 50, Hydroxy Propyl Methyl Cellulose Phthalate 55, etc. When the dosage form passes through the GIT, it remains intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating. The microflora of colon is in the range of 1011 -1012 CFU/mL [30], consisting mainly of anaerobic bacteria, e.g**.** *Bacteroide*s, *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 [31]. For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareductase, deaminase and urea dehydroxylase [32]. 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 [33] .These polymers protect the drugs 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 [34].

a. 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 GIT tract 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 [35]. A number of other linkages susceptible to bacterial hydrolysis especially in the colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, glactose, cellulose, etc. Limitations of the prodrug approach are that it is not a very versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities, and need a lot of evaluation before being used as carriers [36]. A few prodrugs have been outlined in **Table 3**.

Table 3: Prodrugs Evaluated for Colon Specific Drug Delivery

Carrier	**Drug investigated**	**Linkage hydrolyzed**	***In-vitro*/*In-vivo* model used**	**Performance of the Prodrug/conjugates**
Azo conjugates	5-ASA	Azo linkage	Human	Site specific with a lot of side effects [37] associated with SP
Amino acid conjugates glycine	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized by microflora of large intestine[38]
Glycine	5-ASA	Amid linkage	*In vitro*	Prodrug was stable in upper GIT and was hydrolyzed by ceacal content to release 5-ASA [39]

b. Azo-polymeric prodrugs

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Sub-synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety [40]. 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 azo-aromatic group has been found to protect drug from digestion in the stomach and small intestine. In the colon the azo bonds are reduced and the drug is released [41]. E.g of some azo-polymeric prodrugs has been outlined in **Table 4**.

Table 4: Some Azo Polymer-Based Drug Delivery Systems Evaluated for Colon-Specific Drug Delivery with Summary Of Results Obtained

Azo polymer	Dosage form prepared	Drug Investigated	*In-vitro*/ *In-vivo* model used	Summary of the results obtained
Hydrogels prepared by copolymerization of 2-hydroxyethylmethacrylate with 4-methacryloy loxy) azobenzene	Hydrogen	5-fluorouracil	*In-vitro*	Faster and greater drug release in human fecal media compared to simulated gastric and intestinal fluids[42]
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[43]

c. 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 a structures with varied properties. They can be easily modified chemically, biochemically and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccharides can be broken down by the colonic microflora to simple saccharides [44]. Therefore, they fall into the category of "generally regarded as safe" (GRAS). A number of polysaccharide-based delivery systems have been outlined in **Table 5**.

Table 5: Polysaccharides Investigated for Colon Specific Drug Delivery with their Dosages Forms and Summary Of Results Obtained

Polysaccharide investigated	Drug moiety used	Dosage form prepared	*In-vitro/ In-vivo* model used	Performance of the system
Chitosan	5-(6)carboxy fluorescein (CF)	Enteric-coated chitosan capsules	*In-vitro*	Little release of CF in upper GIT conditions and 100% drug release in 33% ceacal contents within 4 h of dissolution[45]
Derivatives	Sodium	As matrices	*In-vitro*	Reduced drug release

Chitosan succinate Chitosan phthalate.	diclofenac			was seen in acidic conditions and improved dissolutions under basic conditions[46]
Amidated pectin	Paracetamol	Matrix tablets	*In-vitro*	These matrices were not suitable for drug delivery colon[47]

NEWLY DEVELOPED APPROACHES FOR CDDS

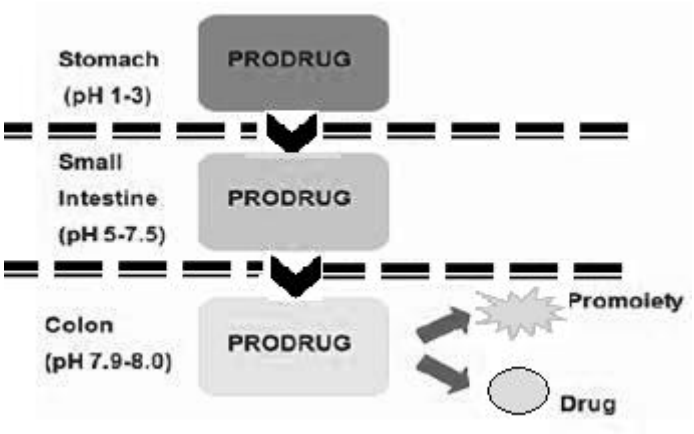
- **Pressure Controlled Drug-Delivery Systems**

This system was developed to target the drugs to the colon. Pressure controlled colon-delivery capsules of ethylcellulose, were prepared by coating the inner surface of gelatin capsule with ethylcellulose which were insoluble in water [48]. In such systems, drug release occurs after the disintegration of a water insoluble polymer capsule because of pressure inside the lumen of the colon. The most important factor for disintegration of the formulation is the thickness of the ethylcellulose membrane [49,50]. This system also depends 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. E.g. In pressure controlled ethylcellulose single unit capsules the drug is in a liquid form [51]. Lag times of 3 to 5 h were noted in relation to drug absorption when pressure-controlled capsules were administered to humans. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems.

- **Novel colon targeted delivery system (CODES^{TM})**

CODES^{TM} was a unique CDDS technology which is a combined approach involving pH dependent and microbially triggered CDDS and was designed to avoid the inherent problems associated with pH or time dependent systems. It was developed by utilizing a unique mechanism involving lactulose, acting as a trigger for site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is coated with acid soluble material Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The final conclusion of this 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 will 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 thus cause subsequent drug release (**Figure 1**) [52].

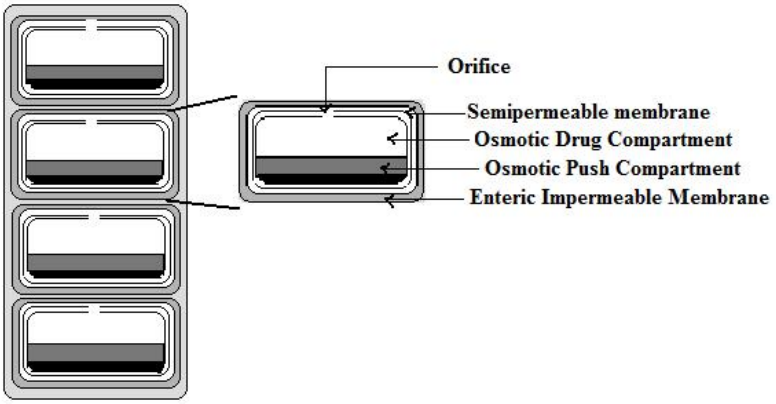
Figure 1: Schematics of Conceptual Design Of CODES^{TM}



- **Osmotic Controlled Drug Delivery (ORDS-CT)**

The OROS-CT was used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable [53]. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 units, each encapsulated within a hard gelatin capsule (**Figure 2**) [54]. Each bilayer unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane thus it is called as a push-pull unit. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Each push-pull unit was prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered because of its drug-impermeable enteric coating. As the unit enters the small intestine, the coating dissolves because of 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 in a rate controlled manner [55-58]. Various *in-vitro*/*in-vivo* evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

Figure 2: Cross-Section of the OROS-CT Colon Targeted Drug Delivery System



Combination of Different Approaches of CDDS

An oral colonic drug delivery system of 5-aminosalicylic acid was developed using combination of pH dependent, time-based and enzyme degradable approaches. The pellets were coated with three functional layers i.e. the outer EudragitL30D-55 layer for protection against GI fluids, the intermediate layer of ethyl cellulose to inhibit the drug release during passage through the small intestine and the inner layer of pectin for swelling and enzyme-degradation. *In-vitro* release studies indicated that the coated pellets completely protected the drug release in 0.1M HCl while the drug release was delayed for 3 to 4 h in pH 6.8 phosphate buffer [59]. Pulsatile device was formulated to achieve time or site specific release of theophylline based on chronopharmaceutical consideration. The basic design consists of an insoluble hard gelatin capsule body filled with Eudragit microcapsules of theophylline and sealed with a hydrogel plug and finally the enteric device was enteric coated. In this approach, pH sensitive and time dependent delivery systems were combined. In this the thickness of enteric coat is a measure of protection from stomach and intestine pH. Different hydrogel polymers were used as plugs to maintain a suitable lag period. The hydrophilic polymer content is a measure of delayed release of theophylline from microcapsules [60].

Hydrogel based CDDS

Hydrogels are usually formed by the covalent crosslinking of linear hydrophilic polymers to form a network of material capable of absorbing water, yet still remaining insoluble [61]. Heterogenous polymer mixture may also be used to form hydrogels without the need for covalent crosslinking [62]. Glutaraldehyde cross-linked dextran capsules were prepared for colon specific delivery. Along with magnesium chloride and PEG 400 in water the capsule caps and bodies were prepared on nylon molding pins. Then the dextran capsules were filled with model drug (Hydrocortisone) and drug release was studied. The drug release pattern was suitable for colon targeting [63]. The hydrogels formed by cross-linked polyvinyl alcohol were suitable for colon specific drug delivery systems. In this method polyvinyl alcohol of different molecular weights was cross-linked with succinyl, adipoyl, or sebacoyl chloride to obtain hydrogel-forming polymers. The hydrophilic drugs like diclofencac sodium, propranolol hydrochloride and vitamin B6 hydrochloride were used as model drugs [64].

Other Novel Drug Delivery Systems

A new microparticulate system containing budesonide was prepared by microencapsulation for colon specific delivery [65]. A novel colon specific drug delivery system containing flurbiprofen microsponges was also designed. Microsponges containing flurbiprofen and Eudragit RS100 were prepared by quasi-emulsion solvent diffusion method and/or flurbiprofen was entrapped in to a commercial microsponge-5640 system using entrapment method. Using these flurbiprofen microsponges the colon specific tablets were prepared using triggering mechanism. The particulate form (microsponges) has been used to provide more uniform distribution of the drug in the colon and help the drug to spread on the colon surface in an appropriate way [66].

Evaluation of CDDS [67]

The drug release in the colonic region from different CDDS is evaluated by different methods of *in-vitro* and *in-vivo* release studies, which showed the success rate of different designs of colon drug delivery systems. Depending upon the method of preparation different evaluation methods were proposed. A successful colon specific drug delivery system is one in which

drug remains intact in the physiological environment of stomach and small intestine, but releases the drug in the colon.

In-vitro Evaluation

In *in-vitro* studies the ability of the coats/carriers to remain intact in the physiological environment of the stomach & small intestine is assessed by drug release studies in 0.1N HCl for 2 h (mean gastric emptying time) and in pH 7.4 phosphate buffer for 3 h (mean small intestine transit time) using USP dissolution apparatus. In case of micro flora activated system dosage form, the release rate of drug is tested *in-vitro* by incubating in a buffer medium in the presence of either enzyme (e.g. pectinase, dextranase). The amount of drug released at different time intervals during the incubation is estimated to find out the degradation of the carrier under study.

In-vivo Evaluation

Like other controlled release delivery systems, the successful development of the CDDS was ultimately determined by its ability to achieve release in colonic region thus exerting its intended therapeutic effect. When the system design is concerned & prototype formulation with acceptable *in-vitro* characteristics is obtained, *in-vivo* studies are usually conducted to evaluate the site specificity of drug release and to obtain relevant pharmacokinetic information of the delivery system.

Future Prospects

Earlier research indicates interest in colon site where poorly absorbed drug molecules may have improved bioavailability. The distal colon is considered to have less hostile environment as well as enzyme activity compared to stomach and small intestine. The development of a dosage form that improves the oral absorption of drugs with low bioavailability because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for oral delivery of drug in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for delivery of drugs like peptides, proteins, oligonucleotides and vaccines. Therefore, more research has been focused on the specificity of drug uptake at the colon site. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

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