Review Article

THE DESIGN OF COLON-SPECIFIC DRUG DELIVERY SYSTEM AND DIFFERENT APPROACHES TO TREAT COLON DISEASE

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ABSTRACT

Oral administration of different dosage forms is the most commonly used method due to flexibility in design of dosage form and high patient acceptance, but the gastrointestinal tract presents several formidable barriers to drug delivery. In oral colon-specific drug delivery system, colon has a large amount of lymphoma tissue (facilitates direct absorption in to the blood), negligible brush boarder membrane activity, and much less pancreatic enzymatic activity as compared with the small intestine. Colon-specific drug delivery has gained increased importance not just for the delivery of the drugs for treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. Different approaches are 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, microspheres, liposomes for colon targeting. The delivery of drugs to the colon has a number of therapeutic implications in the field of drug delivery. In the recent times, the colon specific delivery systems are also gaining importance not only for local drug delivery of drugs but also for the systemic delivery of protein and peptide drugs. This review updated the research on different approaches for formulation and evaluation of colon-specific drug delivery systems (CDDS). Reduce the dosage size and frequency, enhance drugs solubility, permeability and bioavailability, accumulation of the particulate carrier system in the desired site may be get by CDDS.

Keywords: Polysaccharide, Gastrointestinal tract, Colon specific drug delivery system, Microbial degradation.

INTRODUCTION

Now a day, various routes of administration have been explored for the effective delivery of the drug. The oral route is considered to be most convenient for the administration of drugs to patients. On oral administration of conventional dosage forms drug normally dissolves in the gastro-intestinal fluids and is absorbed from these regions of the gastro-intestinal tract, which depends upon the physicochemical properties of the drug. It has a serious drawback in conditions where localized delivery of the drug in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs in the colon rather than upper GIT has number of advantages. Oral delivery of drugs in the colon is valuable in the treatment of diseases of colon (colon cancer, ulcerative colitis, crohn's disease and inflammatory bowel disease) whereby high local concentration can be achieved while minimizing side effects. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a long retention time and appears highly responsible to agents that enhance the absorption of poorly absorbed drugs. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coating or extremely slow releasing matrices. Further, drug targeting to colon would prove useful where intestinal delayed drug absorption is desired from therapeutic point of view in the treatment of diseases that have peak symptoms in the early morning such as nocturnal asthma, angina or arthritis. Although, this region has such drawbacks as impaction of faeces (which might act to entrap drug) and the presence of bacterial enzymes and toxins but these concerns are easier to deal with than the exhaustive destruction drug experiences in the stomach and small intestine.

FACTOR TO BE CONSIDERED IN THE DESIGN OF COLON-SPECIFIC DRUG DELIVERY SYSTEM

Anatomy of Colon: Colon is divided in to the caecum, ascending colon, transverse colon, rectum and anal canal (figure 1). The caecum has a dilated portion, which is blinded interiorly and is continuous with the ascending colon superiorly. Ascending colon passes upwards from the caecum to the level of the liver where it bends acutely to the left at the right colic flexure to become transverse colon. The transverse colon, that extends across the abdominal cavity, in front of the duodenum and the stomach to the area of the spleen. The descending colon passes down the left side of the abdominal cavity then bends towards the midline. Pelvic colon describes an S-shaped curve in the pelvic, then continuous downwards to become the rectum.[1]

Colon consists of layer of tissues, i.e. the longitudinal muscle fiber, submucous layer, mucous membrane lining. Arterial Blood supply in the colon is mainly by superior

and inferior mesenteric arteries and venous drainage is mainly by the superior and mesenteric vein.

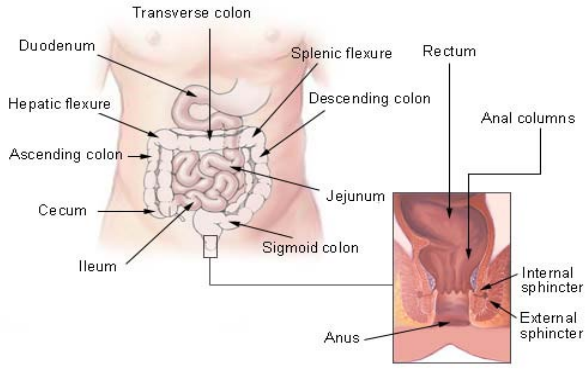

Figure 1: Small and Large Intestine

Factors affecting colon absorption [2, 3]

- Physical properties of drug such as pKa and degree of ionization.
- Colonic residence time as commanded by GIT motility.
- Degradation by bacterial enzymes and metabolic products.
- Local physiological action of drug.
- Selective and non-selective binding to mucus.
- Disease state.

Transit through GIT:[4] The drug delivery systems first enter into stomach and small intestine via mouth and then reach colon. The nature and pH of gastric secretion and gastric mucus influence the drug release and absorption. In order to successfully reach colon in an intact form, the drug delivery systems should surpass the barriers in the stomach and small intestine. Gastrointestinal transit varies from 1 hr to 3 hrs depending upon the condition (fasting or non-fasting). Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hrs to reach the ileocecal junction and the time period is consistent. During this period the dosage form is exposed to enzymes present in small intestine. Compared to the other region of GIT, movement of material through the colon is slow. Total time for transit tends to be highly variable and influenced by number of factors such as diet particularly dietary fiber content, mobility, stress, disease condition and drugs. The colonic transit time of a capsule in adult is 20-35 hrs. Improved residence time with subsequent longer transit time and the contact of dosage form with micro flora in colon govern the release and absorption of drug from dosage form.

Colonic Microflora:[5] The human alimentary canal is highly populated with bacteria and other microflora at both ends, the oral cavity and the colon/rectum. In between these two sites, the GIT is very sparsely populated with microorganisms. Microorganisms of the oral cavity do not normally affect oral drug delivery systems and as such will not be considered here further. However, gut microflora of the colon have a number of implications in health and the treatment of disease such as IBD. This section presents some background information on gut micro flora as it relates to colonic-based delivery system. Concentration of gut microflora rises considerably in the terminal ileum to reach extraordinarily high levels in the colon. The gut bacteria are capable of catalyzing a wide range of metabolic events as shown in table 1. Many colon-specific drug delivery systems rely on enzymes unique to gut micro flora to release active agents in the colon. However, only two or three enzyme systems have been exploited in this area: azoreductases and glycosidases (including glucuronidase). A large number of polysaccharides are actively hydrolyzed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. In addition, ethereal sulfate prodrugs or carboxylated prodrugs may be metabolized in the colon to the parent drug leading to local delivery in the colon. There is certainly room for innovative approaches to carry and release drugs in the colon based on the metabolic capabilities of the colon microflora. Azoreductases produced by colon play a central role in a number of delivery systems, most notably in catalyzing the release of 5-ASA from a variety of prodrugs. The second class of enzymes used to trigger the release of drugs in the colon is glycosidases (including glucuronidases). The main bacterial groups responsible for β-glycosidases activity are lactobacilli, bacteroides and bifidobacteria. As with azo-reductase activity, the level of bacterial glycosidase activity in the gastrointestinal tract is associated with the concentration of bacteria in a given region.

Stomach and Intestinal pH: Generally, the release and absorption of orally administered drugs are influenced by the GI pH. The gradient in the GIT is not in an increasing order. In stomach the pH is 1.5-2 and 2-6 in fasted and fed conditions respectively.[6] The acidic pH is responsible for the degradation of various pH sensitive drugs and enteric coating may prevent it. In small intestine, the pH increases slightly from 6.6-7.5 and decreases to 6.4 in colon.

Radio-telemetry shows the highest pH level (7.5±0.5) in the terminal ileum. On entry into the colon, the pH drop to 6.4+0.6. The pH in the mid colon is 6.6+0.8 and in the left colon 7.0+0.7.[7] Since there is minimal variation in the pH from ileum to colon, apparently pH dependent polymer drug delivery may not be much selective. However, possible exploitation of pH variation in GIT leads to successful development of various colon-specific drug delivery systems.

Drug candidates for colon delivery:[8] Theoretically, any drug can be a candidate for colon targeted drug delivery. However only those drugs, which show poor bioavailability from the stomach or intestine and peptide drugs, are the most suitable for colonic targeting. The ideal drug candidates for colonic drug delivery include agents that are useful for disorders such as IBD, ulcerative colitis, amoebiasis and colon cancer.

Table 1: Various non-peptide and peptide drug candidates for colonic delivery system

Criteria	Pharmacological Class	Drug Candidate	
		Non-Peptide Drugs	Peptide Drugs
Drug used for local effects in colon against GIT diseases	Anti-inflammatory drug	Oxyprenolol, Metoprolol, Nifedipine, Diclofenac sodium	Amylin, Antisense oligo-nucleotide, Calcitonin
Drug poorly absorbed from upper GIT	Antihypertensive and antianginal drugs	Ibuprofen, Isosorbides, Theophylline	Cyclosporine A, Desmopressin
Drug for colon cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon
Drug that degrade in stomach and small intestine	Peptides and proteins	Bromophenaramine, 5-Flurouracil, Doxorubicin	Gonadoreline, Insulin, Interferons
Drugs that undergo extensive firstpass metabolism	Nitroglycerin and corticosteroids.	Nimustine, Bleomycin, Nicotine, Dexamethasone	Molgramoatim, Protirelin, Sermorelin, Saloatonin
Drugs for targeting	Antiarthritic and antiasthmatic drugs	Prednisolone, Hydrocortisone, 5-Amino-salicyclic acid (5-ASA)	Somatropin, Urotoilitin, Vasopressin

Table 2: GIT diseases, which affect the performance of colon-specific drug delivery systems[10]

Disease	Effects on colonic absorption of drugs
Colon cancer, Inflammatory Bowel Diseases (crohn's disease and ulcerative colitis)	Diarrhoea, fever, anaemia, obstruction of lymphatic drainage and hyperplasia of lymphoid tissue, which are observed in this condition may affect the drug release and absorption. The inflammatory response extends from mucosa to serosa through intestinal wall. Impairment of lymphatic drainage causes malabsorption of fats and highly lipophilic drugs. Thickening of mucosa and submucosa may reduce surface area and obstruct diffusion.
Diarrhea	Hypermotility and frequent passage of hypertonic liquid faeces significantly affect drug absorption and release.
Antibiotic associated	Overgrowth of Clostridium difficile and its toxin production, which alters mucosal surface area, may reduce drug absorption.
Constipation	Decreased peristaltic movement of bowel decreases diffusion and availability of drug at absorption sites. Severe constipation reduces bowel movement once or twice a week and interferes with the movement of formulations.
Gastroenteritis	Diarrhoea due to increased mucosal secretion may affect the performance of formulations.
GIT infections	Diarrhoea due to colonic protozoal and bacterial infections causes extremely low transit time and increased mucus production, interferes with localization of drug and absorption. Toxins produced may obstruct diffusion process.

Table 3: Approaches for the development of colon targeted drug delivery [11, 12]

Approach	Basic feature
I. Chemical Approaches	
1. Azo conjugates	The drug is conjugated via an azo bond
2. Cyclodextrin conjugates	The drug is conjugated with cyclodextrin
3. Glycosidic conjugates	The drug is conjugated with glycoside
4. Glucuronide conjugate	The drug is conjugated with glucuronate
5. Dextran conjugates	The drug is conjugated with dextran
6. Polypeptide conjugates	The drug is conjugated with polypeptide
7. Polymeric prodrugs	The drug is conjugated with polymer
II. Pharmaceutical Approaches	
1. Coating with polymer	
i. Coating with pH-sensitive polymer	Formulation coated with enteric polymers release drug when pH moves towards alkaline range
ii. Coating with biodegradable polymer	Drug is released following degradation of the polymer due to the action of colonic bacteria
2. Embedding in matrices	
i. Embedding in biodegradable polysaccharides	The embedded drug in polysaccharide matrices is released by swelling and biodegradable action of polysaccharides.
ii. Embedding in pH sensitive matrices	Degradation of pH sensitive polymer in the GIT releases the embedded drug
3. Timed released systems	
4. Redox-sensitive polymers	
5. Bioadhesive system	Drug coated with bioadhesive polymer that selectively provides adhesion to colonic mucosa.
6. Coating of miroparticles	Drug is released through semipermeable membrane
7. Osmotic controlled delivery	Osmotic pressure

Gastrointestinal Disease State:[9] General intestinal diseases (table 2) such as IBD (inflammatory bowel disease), crohn's disease, constipation, diarrhoea and gastroenteritis may affect the release and absorption properties of colon-specific drug delivery system. Various approaches are available to target the colon (table 3).

Pharmaceutical approaches

➢ **Coating with polymers**

The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers which degrade only in colon.

➢ **Coating with pH-sensitive polymers**

The pH dependent systems exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion) small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum.[13] The coating of pH sensitive polymers to the tablets, capsules or pellets provides delayed release and protects the active drug from gastric fluid.[14] The threshold pH of commonly employed pH-sensitive polymers is depicted in table 4.

Table 4: Threshold pH of commonly used polymers for coating [15]

Polymer	Threshold pH
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit L 30 D	5.6
Eudragit FS 30 D	6.8
Eudragit L 100-55	5.5
Polyvinyl acetate phthalate	4.5-4.8
Hydroxypropyl ethylcellulose phthalate	5.2
Hydroxypropyl ethylcellulose phthalate 50	5.2
Hydroxypropyl ethylcellulose phthalate 55	5.4
Cellulose acetate trimelliate	4.8
Cellulose acetate phthalate	5.0

➢ **Embedding in the matrices**

The drug molecules are embedded in the polymer matrix. The polymers used for this technique should exhibit degradability in the colon for liberation of entrapped drug.

➢ **Embedding in biodegradable polysaccharides**

Polysaccharides retain their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine, but once they reach in the colon, they are acted upon by the bacterial polysaccharidases and result in the degradation of the matrices.[16, 17] The family of natural polymers has an appeal to the area of drug delivery as it is comprised of polymers with a large number of derivatizable groups a wide range of molecular weights, varying chemical compositions and for the most part, a low toxicity and biodegradability, yet a high stability. The most favourable property of these materials is that they are already approved as pharmaceutical excipients.[18] Problems encountered with the use of polysaccharides is their high water solubility. An ideal approach is to modify the solubility while still retaining their biodegradability. large number of polysaccharides have already been tried for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondrotin sulphate, cyclodextrins, dextrose, guar gum, inulin, pectin, locust been gum and amylase .[19]

- **Pectin**

Pectins are non starch, linear polysaccharides extracted from the plant cell walls. They are predominantly linear polymer of mainly α-(1, 4)-linked D-galacto uronic acid residues. pectin has a few hundred to about one thousand building blocks per molecular weight of about 50000 to about 180000. These polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon. Being soluble in water, pectin is not able to shield its drug load effectively during its passage through the stomach and small intestine. It was found that a coat of considerable thickness was required to protect the drug core in simulated in vivo conditions. So the focus shifted to the development of such derivatives of pectin, which were less water soluble but were degradable by the colonic microflora. Calcium salts of pectin reduced their solubility by forming an egg – box configuration. Amount of calcium in the formulation should be carefully controlled to ensure optimum drug delivery. Matrix tablets of indomethacin were prepared with calcium pectinate and also with pectin.[7] For calcium pectinate-indomethacin tablets release was only 16.2±0.2% within 72 hr in absence of enzymes. In presence of pectinolytic enzymes the total amount of drug was released within 6 hr. Compression coating technique is also useful to deliver water insoluble drugs. Methoxylated pectin system where the acid group had been 70% methoxylated, applied as a compression coat was found to be protective to the core tablet invitro condition mimicking mouth to colon transit.[20] In the colon coating was susceptible to enzymatic attack. Low methoxylated pectin was more susceptible to degradation and it was assumed that the presence of calcium increased the susceptibility to enzymatic attack. Another derivative of pectin, amidated pectin was considered for colonic delivery because of its biodegradability, higher tolerance to pH variations and fluctuations in calcium levels. They were susceptible to enzymatic break down. Pectin 920 and 4200 having different degree of absorption were evaluated. In another attempt to overcome the drawback of high solubility of pectin, mixed films of pectin with ethyl cellulose were investigated as coating material for colon specific drug

delivery system. Working on similar grounds, the leaching of pectin from mixed films prepared with aqua coat ECD 30, Eudragit RS 30D or Eudragit NE 30 D was studied in the presence and absence of pectinolytic enzymes. Pectin was quickly released from all the films except mixed films of pectin –Eudragit RS.[21] Ionic complex of high methoxylated polycationic pectin with polycationic Eudragit RS incorporated in swellable polymer. Eudragit NE 30 D is also useful for colon targeting. An interpolymer complex of pectin with chitosan was also found to be promising for colon delivery of poorly soluble and soluble drugs. Combinations of pectin, chitosan and HPMC films have also been studied for colon specific drug delivery system.

- **Chitosan**

Chitosan is a high molecular weight cationic polysaccharide derived from naturally occurring chitin crab and shrimp shells by deacetylation[22] have used Chitosan in the form of small capsules (length 3.5 mm) to deliver insulin to Othe colon for systemic absorption in rats. They also studied the effect of protease inhibitors and absorption enhancers on the bioavailability of insulin. The findings of the study suggested that Chitosan capsules might be useful carriers for the specific delivery of peptides including insulin.

- **Guar gum**[23, 24, 25, 26, 27]

Guar gum is a natural polysaccharide derived from the seeds of *Cyamopsis tetragonblobis* (Family Leguminosae). A novel tablet formulation for oral administration using guar gum as the carrier and indomethacin as a model drug has been investigated for colon specific drug delivery using *in vitro* methods . *In vivo* gamma scintigraphic studies were carried out on the guar gum matrix tablets, using technetium-99m-DTPA (^{m}Tc-DTPA) as a tracer, in healthy subjects to evaluate their *in vivo* performance.

Absorption of Drug from Colon The primary routes by which drugs are absorbed from the gastrointestinal tract are illustrated in fig. 2 below.

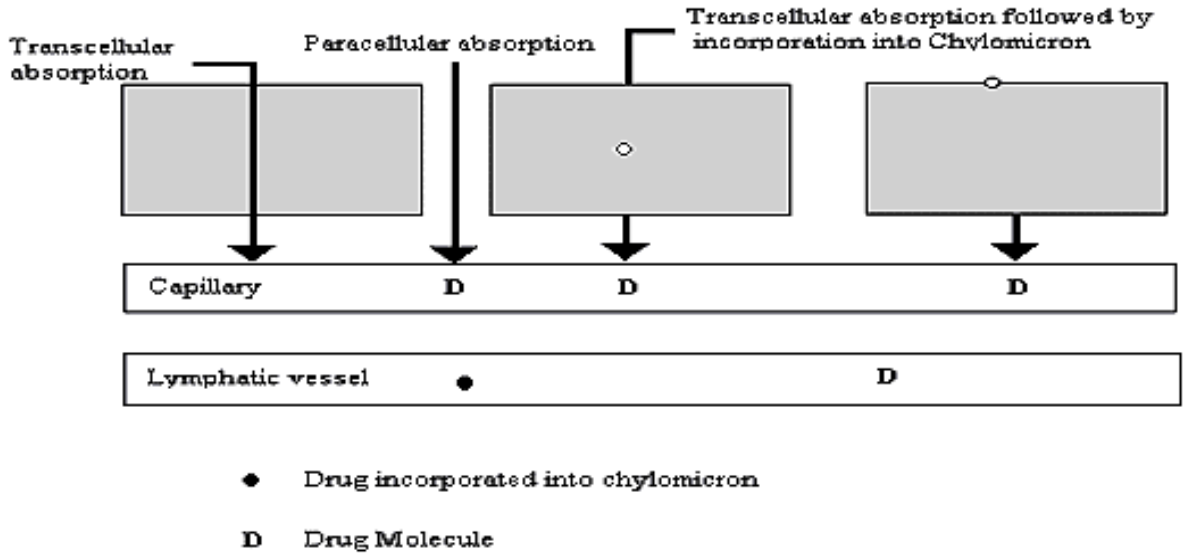

Figure 2: The primary routes by which drugs are absorbed from the gastrointestinal tract

DIFFERENT APPROACHES TO TREAT COLON DISEASE

Prodrug Approach

A prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous enzymatic transformation in vivo to release the active drug .[28, 29] In this method the prodrugs are designed to undergo minimum absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the carrier. Different types of conjugates were used to prepare 5-ASA prodrugs, which are succeed in releasing the 5-ASA in colonic region. They are biodegradable poly (ether-ester) azo polymers[30], azo-linked polymeric prodrugs[31], acrylic type polymeric prodrugs[32] and cyclodextrin prodrugs. Glucuronide prodrugs were developed for corticosteriod to deliver the drug to the large intestine of colitic rats .[33] Azo-containing urethane analogues synthesized for colon drug delivery. A urethane-based analogue containing an azo aromatic linkage in the backbone was synthesized by reacting touline-2, 6-diisocyanate with a mixture of an aromatic azodiol.[34] Cyclodextrin prodrugs were prepared by conjugating 5-ASA on to the hydroxyl groups of α-, β-, γ-cyclodextris through an ester linkage and investigated the release in cecum and colon. After oral administration in rats the conjugate passed through stomach and small intestine without degradation or absorption and in the cecum and/or colon site-specific degradation of conjugate released 5-ASA.[35] An azo prodrug of 5-ASA with histidine was synthesized for targeted drug delivery to the inflammated gut tissue in inflammatory bowel disease. The synthesized prodrug was found to be equally effective in mitigating the colitis in rats, as that of sulfasalazine without the ulcerogenicity of 5-ASA and

adverse effective of sulfasalazine.[36] In a recent study by[37], explained the potential of 5- amino salicyliltaurine as a colon specific prodrug of 5ASA by in vivo evaluation to treat experimental colitis. The prodrug was prepared by conjugating 5ASA with taurine and tested in 2,4,6, trinitrobenzene sulfonicacid (TNBS) induced colitis rats. Taurine conjugation of 5-ASA greatly reduced absorption of 5-ASA from the intestine. Oral administration of the conjugate not only increased the colonic delivery efficiency of 5-ASA but also decreased the systemic absorption of free 5-ASA as compared to other conjugates prepared with glycine and asparticacid. Taurine conjugate of 5-ASA is slightly more effective than sulfasalazine in alleviating the colonic inflammatory induced by TNBS. N-Nicotinoylglycyl-2-(5-fluorouracil-1-yl)-D, L-glycine was synthesized as a prodrug of 5 fluorouracil colon specific drugdelivery.[38]

PH-Dependent System

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 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 give the desirable release rates. A novel colon-specific drug delivery system was developed with methacrylate derivatives of 5-ASA using pH sensitive swelling and drug release properties.[39] Composite film coated tablets of 5-ASA were prepared for colon specific delivery. In this method 5-ASA core tablets were prepared and coated with dispersion contained Eudragit RS and dessterrifed pectin, polygalacturonic acid, or its potassium and sodium salts. Negligible drug release occurred during first five hours where the coated tablets were in the stomach and small intestine. After that the release of 5-ASA from coated tablets occurred linearly as a function of time due to the action of pectinolytic enzymes.[40] A comparison study of the usual enteric-coated polymers viz. Eudragit, Cellulose acetate phthalate with Shellac and Ethyl cellulose as carriers for colon specific drug delivery was conducted to select a suitable carrier. In this study lactose based indomethacin tablets were prepared and coated with one of the above coating polymers to a varying coating thickness. From the dissolution data at a coat concentration of 3% shellac provided the most appropriate polymer coat for colon-specific drug delivery. Variation in the shellac coat thickness can facilitate drug delivery to terminal ileum, distal or proximal colon.[41] EUDRACOLTM is a novel pH and time controlled multiple unit colon drug delivery systems in which the pellets coated with Eudragit RL /RS and Eudragit FS 30D. Caffeine is used as marker drug for pharmacokinetic studies using the multi particle principle and delayed release in the colon; reduction of dosing frequency may be achieved. Due to its specific coating structure, the Eudracol system offers a new dimension for colon drug targeting via the oral route.[42] 5-ASA pellets were coated with the enteric coating solution containing different ratios at Eudragit L-100 and Eudragit S-100 for colon drug delivery. The release of 5-ASA is depending on the thickness of the layer and the ratio of Eudragit copolymers.[43] PH-sensitive hydrogels were prepared for colonic delivery of therapeutic peptides, proteins. New pH-sensitive glycopolymers were developed by free radical polymerization of methacrylic acid and 6-hexandiol diacrylate and 6-hexandiol propoxylate diacrylate.[44]

Time-Dependent System

The basic principle involved in the system is the release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at right time and in the right amount.[45] Colon targeting could be achieved by incorporating a lag time into formulation equivalent to the mouth to colon transit time. A nominal lag time of five hours is usually considered sufficient to achieve colon targeting. In this method the solid dosage form coated with different sets of polymers and the thickness of the outer layer determines the time required disperse in aqueous environment. Colon drug delivery system of diclofencac sodium (DS) was developed using time dependent approach. In this, diclofencac sodium tables were coated with ethylcelluese 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 ethycellulose coating layer. By increasing the thickness of the coating layer, longer the lag time of DS release.[43] Formulation of fast release enteric coated tablets for colon drug delivery using two different approaches .The first one is using super disintegrate and the second one is based on osmogen. In the first approach core tablets (celicoxib as a model drug) were prepared using different concentrations of super disintegrates like cross-linked PVP. In second approach concentrations tablets were prepared using potassium chloride, sodium chloride as osmogen. Then they are coated with Eudragit L-100: Eudragit S-100 in the ratio of 1:5 to achieve a desired thickness. The tablets with super disintegrates are fast released where the tablets with osmogen are sustain released. The coat weight determines the lag phase that required eliminating the release in stomach and small intestine.[46] Hydroxy Propyl Methyl Cellulose (HPMC) compression coated tablets of 5-fluorouracil were studied for colon drug delivery that based on time-dependent approach. In this, the core tablet was prepared by wet granulation method and then

coated with 50% of HPMC/lactose coat powder by compression-coating method. Drug release characteristics were evaluated in distilled water by using a Chinese pharmacopoeia rotatable basket method.[47]

Micro flora Activated System

The basic principle involved in this method is degradation of polymers coated on the drug delivery system by microflora present in colon and there by 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.[41] In this method drugs and/or dosage forms are coated with the biodegradable polymers i.e., the polymers degrade due to influence of colonic microorganisms. When the dosage form passes through the GIT, it remain intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating.

Combination of Different Approaches of CDDS

An oral colonic drug delivery system of 5-ASA 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 three to four hours in pH 6.8 phosphate buffer.[48] 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 gelation 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.[49]Pectin based CDDS of 5-fluorouracil was developed using calcium pectinate gel. Calciumpectinate gel beads were prepared by ionotropic gelation method followed by enteric coating with Eudragit S-100 and evaluated using USP paddle type dissolution apparatus in different simulated mediums.[50]A new microbial-triggered colon targated osmotic pump (MTCT-OP) was developed for CDDS based on chitosan for a model drug, budesonide. The combination of osmotic technology and microbial-triggered mechanism had a high potential to deliver to drug load in colonic region. In this method the core tablet of budesonide was prepared with chitosan, which is used to produce osmotic pressure, and to form the insitu delivery pores for colon-specific drug release. Cellulose acetate in acetone along with chitosan (as pore forming agent) was coated on tablet as a semipermiable membrane and finally coated with Eudragit L-100-55 in ethanol as an enteric coating layer that could prevent cellulose acetate membrane from forming pore or rupture before reaching colon region. Budesonide release from developed system was inversely proportional to the osmotic pressure to the release medium.[51]

Hydrogel based CDDS

Amydated pectin hydrogel beads prepared for colon specific delivery of indomethacin and sulfamethoxazole.[52] Glutaraldehyde cross-linked dextran capsules were prepared for colon targeting. 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 specific delivery.[53] 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 corss-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.[54] Methacrylated inulin hydrogels designed for colon targeting the proteins like Bovine serum albumin or Lysozyme.[55] Organic redox-initiated polymerization technique was used to fabricate pH responsive hydrogels for colon specific delivery.[56] Glutaraldehyde corss-linked guar gum hydrogel discs were prepared as vehicles for colon specific drug delivery of ibuprofen. Percent drug release increased with glutaraldehyde concentration. Cross-linking decreased the swelling of guar gum. The fabricated hydrogels discs may prove to be beneficial as colon-specific drug delivery vehicles for poorly water-soluble drugs like ibuprofen.[57] Novel complex hydrogel beads were prepared using pectin and zein for colon-specific drug delivery. Pectin/Zein complex hydrogel beads showed the capability to protect incorporated drugs from premature release into stomach and small intestine. The inclusion of a small portion of zein (a protein from corn) in to the pectin efficiently suppressed the swelling behavior of pectin, thus stabilizing the structural property of the pectin networks. Likewise the pectin networks protected the bound zein from protease digestion. These properties made pectin/zein complex beads a promising system for colon specific drug delivery.[58] Cross-linked HPMC hydrogels were synthesized and used to develop 5-ASA colon drug delivery system.[59]

NOVEL DRUG DELIVERY SYSTEMS FOR CDDS

Now a days the basic CDDS approaches are applied to formulate novel drug delivery systems like Multiparticulate systems, Microspheres, Liposomes, Microencapsulated particles etc.

- **Multiparticulate systems**

Multiparticulates (pellets, non-peariles etc.) are used as drug carriers in pH-sensitive, time dependent and microbially control systems for colon targeting. Multiparticulate systems have several advantages in comparison to the conventional single unit for controlled release technology, such as more predictable gastric emptying and fewer localized adverse effect than those of single unit tablets or capsules.[60] A multiparticulate dosage form was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug release properties. This system was constituted by drug loaded cellulose acetate butyrate (CAB). Microspheres loaded by an enteric polymer (Eudragit S). Here the enteric coating layer prevents the drug release below pH 7. After that CAB microspheres efficiently controlled the release of budesonide, which is depended on the polymer concentration in the preparation.[61] Azo polymer coated pellets were used for colon-specific drug delivery to enhance the absorption of insulin and (Asu1,7) Eel calcitonin.[62] A multiparticulate chitosan dispersed system (CDS) was prepared for colon drug delivery and it was composed of the drug reservoir and the drug release-regulating layer, which was composed of water insoluble polymer and chitosan powder. The drug reservoir was prepared by drug containing multiparticulates like Non peariles in the study. In this study the multiparticulate CDS was adopted not only for colon specific drug delivery but also for sustained drug delivery.[63] A multiparticulate system combining pH sensitive property and specific biodegradability was prepared for colon targated delivery of metronidazole. The multiparticulate system was prepared by coating cross-linked chitosan microspheres explorting Eudragit L-100 and S-100 as pH sensitive polymers. The in-vitro drug release studies shows that no release of drug at acidic pH and higher drug release was found in presence of rat caecal contents indicating susceptibility of chitosan matrix to colonic enzymes released from rat caecal contents.[11] High-Amylose cornstarch and Pectin blend microparticles of diclofencac sodium for colon-targeted delivery were prepared by spray drying technique. The blending of high-amylose cornstarch with pectin improved the encapsulation efficiency and decreased the drug dissolution in the gastric condition from pectinbased microparticles. The drug released in colonic region by the action of pectinase from microparticles [64].[65] investigated the effect of sodium glycocholate as an absorption promoter on orally administrated insulin absorption utilizing a colon-targeted delivery system. A novel insulin colon-targeted delivery system (Insulin- CODES) contains insulin, lactulose as a trigger for colon-specific release, citricacid as a solubilizer of insulin, meglumine as a pH adjusting agent and sodium glycocholate as an absorption promoter.

- **Microspherical Delivery System**

Microspherical are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature.[2,3]

Advantages of microspheres

- Provide selective passive targetting to tumour tissues.
- Flexibility to couple with site-specific ligands to achieve active targetting.
- Increased efficacy and therapeutic index.
- Increased stability via encapsulation.
- Reduction in toxicity of the encapsulated agent.
- Improved pharmacokinetic effects.

Other novel drug delivery systems

A new microparticulate system containing budesonide was prepared by microencopsulition for colon specific delivery.[66] In the study by[67] a novel formulation for bee venom peptide was developed using coated calcium alginate gel beads-entrapped liposome and investigated for colon specific drug delivery in vitro. The release rate of bee venom from formulation was dependent on the concentration of calcium and sodium alginates and the amount of bee venom in the liposome, as well as coating. A human γ-scintigraphy technique was used for in vivo studies and the results showed that this formulation had great potential for colon-specific drug delivery. A novel colon specific drug delivery system containing flubiprofen microsponges was designed. Microsponges containing flubiprofen and Eudragit RS100 were prepared by quasi-emulsion solvent diffusion method and/or flubiprofen was entrapped in to a commercial microsponge-5640 system using entrapment method. Using these flubiprofen microsponges the colon specific tablets were prepared using triggering mechanism. The particulate form (microsponges) has been used to provide more uniform distribution linked guar gum microspheres delivered most of the drug load (79%) to the colon, where as plain drug suspensions could deliver only 23% of there total dose to the target tissue.[68] Colon specific microspheres of 5-fluorouracil were prepared and evaluated for the treatment of colon cancer. In this method core microspheres of alginate were prepared by modified emulsification method in liquid paraffin and by cross-linking with calcium chloride. The core microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach and small intestine. The results showed that this method had great potential in delivery of 5-fluorouracil to the colon region.[69]

CONCLUSION

From past two decades, considerable amount of research work has been carried out in the area of colon targeting. By considering the advantages of CDDS like providing friendlier environment for protein and peptide drugs that reducing the adverse effects in the treatment of colonic diseases, site specific release to treat colonic cancer, amoebiasis, and helminthiasis etc, minimizing the extensive first pass metabolism of steroids and produces delay in absorption of drugs to treat rheumatoid arthritis, angina and nocturnal asthma etc., different approaches are designed to develop colonic drug delivery system. The release of drug load in colon region is depended on pH of GIT, gastro intestinal transit time and microbial flora and their enzymes to degrade coated polymers and breaking bonds between carrier molecule and drug molecule. The preferred CDDS is that should release maximum drug load in colon region. Among different approaches the pH dependent system is less suitable than others due to the large inter and intra subject variation in the gastro intestinal pH, but gives better results with combination of time-dependent system, microbially activated system and others. Different polymers are used to prepare CDDS by various approaches and are evaluated for their efficiency and safety. Colon targeted drug delivery systems are exploited to selectively target the drug release to the colon. Several approaches have been investigated to achieve site specificity to colon. The selection of suitable polysaccharide is a critical parameter in the fabrication of colon specific drug delivery.

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