

Colon targeted drug delivery systems: Based on Polymers

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Abstract

Research on colon-targeted polymers delivery systems is ongoing for conditions such ulcerative colitis, Crohn's disease, colon cancer, as well as the delivery of peptide or protein medications and vaccines. For colon-specific disorders in particular, focused nano-drug delivery to the colon is helpful because nanoparticles can build up in sick areas, improve therapeutic efficacies, and allow localized therapies, which lower systemic toxicity. The efficient delivery of NDDS to the colon, however, may be hampered by a number of obstacles, including burst drug release, enzyme and acidic degradation of drug and carrier in the stomach, pH fluctuations, mucus trapping, and systemic uptake in the upper small intestine. These obstacles might be surmounted with improvements in NDDS, resulting in effective drug delivery for colon-specific illnesses. This review provides an updated summary of recent advances in the development of orally administered NDDS for colon targeting and the future advancements in this research. It also discusses some potential colon-specific drug delivery areas, challenges faced by colon-targeted oral delivery systems, and potential drug delivery areas.

INTRODUCTION

Numerous studies have focused on colon-targeted drug delivery in recent years because of its potential to enhance the management of local disorders affecting the colon while reducing systemic side effects. Irritable bowel syndrome (IBS), Crohn's disease (CD), and ulcerative colitis are a few examples of diseases that affect the colon [1]. Sulfasalazine, dexamethasone, hydrocortisone, metronidazole, prednisolone, and other medications are routinely used to treat these conditions [2]. Because these medications are delivered directly to the colon rather than first being digested in the upper gastrointestinal (GI) tract, a larger concentration of the medication can reach the colon with less systemic absorption [3]. The colonic mucosa is known to aid in the absorption of various medications, and the colonic contents have a longer retention duration (up to 5 days), making this organ a suitable site for drug delivery [3,4]. An oral or rectal route might be used to deliver a medication to the colon. Due to their simplicity, oral dose forms are the most often used delivery method for colon-specific administration [4]. Additionally, oral dosage forms offer more manufacturing and design flexibility, better patient adherence, relatively safe administration, and do not need sterile preparation [2]. In order to target a medicine to specific colonic regions, direct rectal drug delivery is difficult [2,4]. Additionally, according to their spreading ability and retention period, different rectal dose forms have varying degrees of drug distribution. The effectiveness of a colon-specific drug delivery system (CDDS) depends on the physical and chemical characteristics of the medication, the kind of delivery device, all other variables that may affect GI transit time, and the level of drug-GI tract interaction [1]. To prevent the medication from being released in the stomach and small intestine, oral CDDS is crucial [4]. As a result, some procedures used in the development of a CDDS have shown to be more effective than others in postponing the drug release until the system reaches the colon. A number of commercial formulas claim to combine the traditional and more modern methods mentioned above (Table I).

TABLE:1 Currently marketed formulation

Colon disease/ disorder	Drugs	Delivery system
Inflammatory bowel disease	Mesalazine	
Ulcerative colitis	- Asacol -Pentasa Sulfasalazine -Azulfidine EN-tabs	DR tablets TR tabltles DR tablets
Crohn's disease	Prednisone -Rayos Budesonide -MMX -Uceris -clipper Prednisolone (colon-pred) Metronidazole (Flagyl ER) Azathioprine (Azasan) Mercaptopurine (Purinethol) Cyclosporine (Gengraf)	DR tablets Multi-matrix tablets ER tablets Gastro-resistant prolonged-release tab Oral colon-targeted pellets ER tablets IR tablets IR tablets IR tablets, oral solution
Diverticulosis and diverticulitis	Methylcellulose (Citrucel) Psyllium (Metamucil) Mesalazine (Asacol) Rifaximin (Xifaxan)	Oral powder, IR tablet Oral powder, IR capsule DR tablets IR tablets
Colonic amoebiasis	Doxycycline (Doryx) Metronidazole (Flagyl ER)	DR tablets ER tablets
Irritable bowel syndrome	Methylcellulose (Citrucel) Psyllium (Metamucil) Loperamide (Imodium) Dicyclomine (Bentyl) Hyoscyamine (Levbid) Lubiprostone (Amitiza) Linaclotide (Linzess) Rifaximin (Xifaxan) Amitriptyline (Elavil)	Oral powder, IR tablets Oral powder, IP capsule IR capsule IR capsule, IR tablets ER tablets Soft gelatin, IR capsule IR capsules IR tablets IR tablets

The oral route of administration is thought to be the most convenient for patients. Normally dissolves as intestinal fluid in the stomach and is absorbed from these GIT regions. In situations where localized drug delivery into the colon is required, this is a major drawback because drugs must be protected from the hostile upper GIT environment. Local treatment of colonic pathologies, systemic delivery of protein and peptide drugs, and local treatment of a variety of bowel diseases like ulcerative colitis, cirrhosis, amoebiasis, and colonic cancer all benefit greatly from targeted drug delivery into the colon. The colon-specific drug delivery system (CDDS) ought to be able to safeguard the drug on its way to the colon—that is, drug release and absorption ought not to occur in the stomach as well as the small intestine, and neither the bioactive agent nor the dissolution sites ought to be degraded. Instead, the drug ought to be released and absorbed only once the system reaches the colon. [24]. Because of its abundance of lymphoid tissue, the colon not only serves as a shield for these labile molecules but also serves as an ideal location for the oral administration of vaccines. Uncertain side effects can be reduced using a targeted colonic approach[25]. It is necessary for a triggering mechanism to release the drug upon reaching the colon for colon-specific delivery systems to prevent drug release in the upper GIT. Additionally, a formulation tailored to the colon could be utilized to extend drug delivery. It should be thought of as helpful for treating colon diseases. Drugs can be delivered locally or systemically through the colon . Irritable bowel diseases like Crohn's and ulcerative colitis can be treated topically. Glucocorticoids and sulphasalazine are typically used to treat inflammatory conditions like these. Drugs aimed at the colon might also be able to treat more effectively a number of other serious colon diseases, such as colorectal cancer. Drugs that are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, which is heavily influenced by hepatic metabolism, such as therapeutic proteins and peptides, can also be delivered using formulas for colonic delivery.

FACTORS INFLUENCING COLON-SPECIFIC DRUG DELIVERY AND COLONIC BIOAVAILABILITY

The formulation and development of a colon-specific drug delivery system (CDDS) as well as the drugs' bioavailability in the colon may be influenced by a number of factors [2,5].

Some of these factors are briefly discussed below:

Anatomical/Physiological Factors

The rectum, or ascending, transverse, and descending colon, is a small portion of the human large intestine's distal end that is approximately 1.5 meters long. The lumen of the colon is lined with mucus and has a diameter of two to three inches. Table II shows that the physiology of the colon is very different from that of the other parts of the gastrointestinal tract (GIT). The contents of the ascending, transverse, descending, and sigmoidal colons all have unique physiological and physical characteristics. Additionally, the variability in the movement of food and dose forms throughout the colon may make it challenging to develop colonic drug delivery systems [6]. Another physiological factor that influences the administration and absorption of colonic medication is the GIT's fluctuating pH. There are significant differences in the pH of the GIT in humans based on illness, fasting/eating, gender, age, and other factors [7-9]. The viscosity and volume of colonic fluids, the presence of microbial enzymes, and the subsequent colonic metabolism are additional significant factors that influence CDDS efficacy.

TABLE :2 Variations In The Physiology Of Human Gastro- Intestinal Tract

Organ	Contents	pH
Stomach	Thin soluble mucus, HCL, intrinsic factor, pepsin, lipases, gastrin, histamine, serotonin, somatostatin	1-1.5
Small intestine	Chyme (from stomach), alkaline mucus, intestine juice which is mostly water, motilin, cholecystokinin, brush border enzymes (maltase, sucrose, lactose, enterokinase and carboxypeptidase) Bile (which contain electrolytes, fatty substance, bile salts and pigments) pancreatic juice (a bicarbonate-rich fluid containing enzymes)	5-7.5
Cecum	Mucus, enteric bacteria , vitamins, food residue, gases such as carbon dioxide and methane	5.5-7
Ascending colon	Mucus, enteric bacteria , vitamins, food residue, gases such as carbon dioxide and methane	5,7-6.9
Transverse colon	Mucus, enteric bacteria , vitamins, food residue, gases such as carbon dioxide and methane	5.8-7.4
Descending colon	Mucus, enteric bacteria , vitamins, food residue, gases such as carbon dioxide and methane	6.3-7.7
Rectum	Undigested food residues, mucus, epithelial cells from the intestinal lining, numerous bacteria(millions). Some remaining water	-7

Intestinal-Colonic Transit Time:

The intestinal-colonic transit time has a significant impact on both the efficacy of CDDS and the bioavailability of medications in the colon. Transit times are also affected by states of colitis like UC and CD. It is known that UC patients have shorter colonic times (24 h) than healthy people (52 h) [13]. In a similar vein, Rana et al. demonstrated that IBD patients had a longer orocecal transit time [14]. The type of dosage form, the duration of administration, and whether or not food is present all influence the transit time of dosage forms. Stubbs and co. Investigated how the ability of the colon to move medication changed at dawn and dusk. The findings indicated that larger dosage forms, such as capsules, transited the colon more quickly than smaller dosage forms, such as scattered particles, and that sleep delayed colonic transit [15].

Colonic Fluid Volume:

People typically consume 1.5 kilograms of food each day, the majority of which is unabsorbed proteins, carbohydrates, and fats. The microbial enzymes in the colon may use these food components as substrates [16]. The colon is very good at taking in water; it can absorb about 90% of the water that enters it [17]. The estimated volume of the colonic fluid ranges from 1 to 44 milliliters, with an average of about 13 milliliters [18]. It is challenging to dissolve medications from dosage forms due to the low volume of colonic fluids, which may have an effect on local drug bioavailability.

Colonic pH

The pH of the various GIT areas varies significantly. For instance, the pH of substances in the digestive tract may range from one to two in the stomach to seven and a half in the distal small intestine [13,14]. After dropping at the end of the small intestine, the pH slowly rises again in the colon [13,14]. The pH of the colon may be affected by a diet high in carbohydrates. This is because the bacteria in the colon ferment polysaccharides and then make short-chain fatty acids [15]. Polysaccharide-based medications have the potential to alter the colon's pH. It is well known that laxatives like lactulose can lower the pH of the colon by causing the bacteria in the colon to produce lactic acid [16]. In addition, it has been discovered that gastrointestinal diseases such as UC alter the pH of the colon [17]. The pharmacokinetic and pharmacodynamic behavior of a CDDS is influenced by the colonic pH's effect on the solubility of medications in colonic fluid. Additionally, if one or more dosage form components, such as a pH-sensitive coated membrane, are pH-sensitive, the impact of colonic pH on drug release is increased.

Criteria For Selection Of Drug For Colonic Drug Delivery

Drug candidate The most suitable drugs for CDDS are those with poor stomach and intestinal absorption, such as peptides. Local colon delivery is an excellent option for the medication that is used to treat IBD, ulcerative colitis, diarrhea, and colon cancer [20]. **Drug carrier** The disease for which the system will be used and the physiochemical nature of the drug itself influence the choice of a carrier for a particular drug candidate. The choice of a carrier is influenced by the drug's chemical nature, stability, and partition coefficient, as well as the type of absorption enhancers chosen. Additionally, the drug molecule's functional groups influence the choice of drug carrier [21]. The systems' release properties and efficacy may be affected by the carriers that contain additives like polymers (which can be used as matrices and hydro gels as coating agents) [22].

Structure And Function Of Colon

The colon is the lowest part of the digestive system, running from the ileocecal junction to the anus (Fig.1). The big intestine's lower six inches are called the rectum, and the upper five feet are called the colon. The rectum is mostly a part of the pelvis, while the colon is mostly in the belly. The lumen, or passageway, of the colon is a cylindrical tube with a diameter of 2 to 3 inches and is lined with the mucosa, a pink, moist lining. The small intestine (ileum) and colon meet in the lower right abdomen. The spherical first part of the colon is known as the cecum. The appendix is suspended by the cecum. In the order in which the contents flow, the next section of the colon is the ascending (proximal) colon. It is situated close to the rib cage, just below the liver, at an angle or bend known as the hepatic flexure. After that, the colon changes to the transverse colon, which is a long horizontal tract. Behind the left rib cage at the splenic flexure, the colon descends to become the distal (descending) colon. This is due to the sigmoid colon, which curves in an S shape from the hip to the midline in the left bottom of the abdomen. The rectum and colon receive blood through an anatomical route. Along these arteries of blood, lymph nodes can be seen. In the circulatory lymphatic system of the body, lymph nodes are organs that produce and store cells that fight cancer, inflammation, infection, and foreign proteins. The colon's primary function is to store feces until it is excreted by converting the contents of the intestines into feces through the absorption of electrolytes and water. More than 90% of the fluid that enters the colon through the ileocecal valve is absorbed by the intestines. This indicates a very high capacity for absorption. In a healthy human

colon, the sodium and chloride ions are typically secreted³. The average colon is thought to only have 220 grams of wet material and 35 grams of dry material. The majority of this dry material is made up of bacteria. The colon's activity consists of segmenting and propulsive movements. Segmenting movements, most of which are made by circular muscle and give the appearance of haustra, mix the luminal contents. Significant propulsive action occurs three to four times per day on average and is associated with feces and influenced by longitudinal muscle. [10,11]

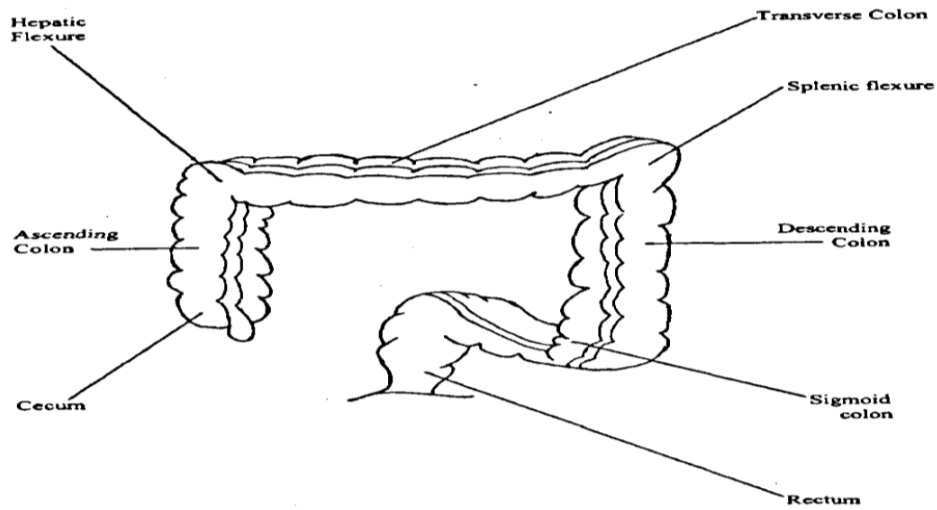


Fig. 1 : Schematic Diagram of Colon

Methods for Targeting Drugs into the Colon (figure 2).

When a therapeutic delay in systemic absorption is desired, colonic targeting is useful for treating disorders of the colon, oral protein and peptide delivery, arthritis, and nocturnal asthma.

Utilisation of bacterial enzyme

When the enzymes of the colonic bacterium are active, it is used to create prodrugs and dosage forms from which a medicine is released. The enzymes that colonic bacteria produce are capable of catalyzing a variety of metabolic processes, some of which include reduction (of double bonds, nitro groups, azo groups, aldehydes, sulphoxides, ketones, alcohols, N oxides, and arsonic acid), hydrolysis (of glycosides, sulphates, amides, esters, nitrates, and sulphonates), deamination, decarboxylation [12].

Polymers used In colon targeted delivery system :-

Polymers have made a significant contribution to the development of drug delivery technology by enabling cyclic dosage, tunable release of hydrophilic and hydrophobic drugs, and controlled release of therapeutic agents in constant doses over extended periods of time. targeted drug delivery due to the fact that it typically dissolves in stomach acid but swells in intestinal acid.

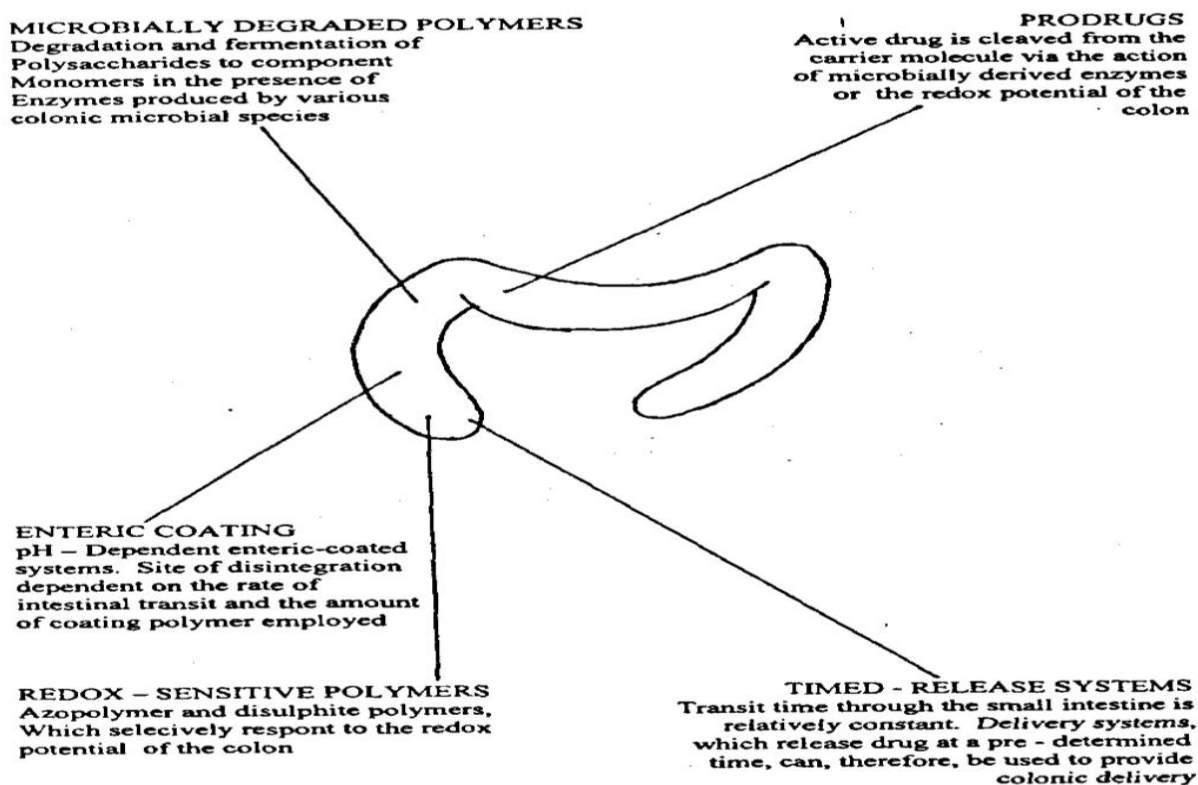


Fig. 2 : Colon Targeting Mechanisms

Azo- polymers

Divinylazobenzene has been used to cross-link polystyrene and hydroxyethyl-methacrylate for colon delivery [13]. To make hydrophilic azo polymers, various ratios of methyl-methacrylate to hydroxyethyl-methacrylate (HEMA) have been used; The most susceptible individuals to colonic breakdown were those with high HEMA concentrations [14,15]. Polyamides and azo-containing polyurethane have produced comparable outcomes [16].

Hydrogels have been created by cross-linking acrylic acid, N, N-dimethylacrylamide, and N-terbutylacrylamide with azo aromatic compounds [17]. In order to accommodate bacterial azoreductase enzymes, the polymer expands in the colon at a pH-dependent rate.

TABLE:3 Technique And Polymer(S) Used

Technique employed	Polymer(s) used	Drug used
pH dependent	Eudragit L100 and S100	Mesalazine
	Eudragit L100 and S100	NS
	Eudragit L100 and S100	Diclofenac sodium and 5-ASA
	Eudragit S, Eudragit FS, Eudragit P4135 F	Prednisolone
	Eudragit L 30 D-55 and Eudragit FS 30 D	Paracetamol
Time dependent	Hydroxy propyl methyl cellulose	Pseudo ephedrine HCL
	Hydroxyethyl cellulose, ethyl cellulose,	Theophylline
	microcrystalline cellulose lactose/ behinic	

	acid	Indomethacin
	Hydroxy propyl methyl cellulose	NS
	Hydroxy propyl methyl cellulose acetate succinate	Diltiazem HCL
Bacteria dependent/ polysaccharide based	Chitosan	Diclofenac sodium
	Pectin	Indomethacin
	Guar gum	Dexamethasone
	Chondroitin sulphate	Indomethacin
	Amylose	5-Acetyl salicylic acid
	Alginates	5- Acetyl salicylic acid
Mucilaginous	Cellulose acetate phthalates (CAP)	
	Hydroxypropyl methyl-cellulose phthalate (HPMCP) 50 and 55,	
Biodegradable	Guar Gum	
	Pectin	
	Chitosan	
	Dextran	
	Cyclodextrin	
	Inulin	
	Amylose	
	Aliphatic polyesters	Poly Glycolic Acid
		Poly Lactic Acid
		Poly Lactic Acid
		Poly Caprolactone
		Polydioxanone

OTHS POLYMERS AND EXAMPLES:

BIODEGRADABLE POLYMERS:

Natural polysaccharides are frequently used to create solid oral dosage forms for drug delivery through the colon[32]. Various bacteria in the colon secrete numerous enzymes that can cause hydrolytic cleavage of glycosidic bonds, such as -D-galactosidase, amylase, pectinase, -D-glucosidase, dextranase, and -D-xylosidase. Biodegradable polymers are generally hydrophilic in nature and have limited swelling characteristic of acidic pH[33]. These polymers are affordable and come in a variety of shapes. While linear polysaccharides remain intact in the stomach and small intestine, they are degraded by the bacteria of the human colon, making them potentially useful in targeted drug delivery systems for the colon[34].

Bio adhesive water soluble polymers for colon-specific drug delivery:

Azoreductases, which can cleave aromatic azobonds on water-soluble polymers, are primarily found in the colons of various species of bacteria [35]. Additionally, it is known that some bacteria, such as *Shigella flexneri*, bind to the colonic mucosa of

guinea pigs in a way that is specific for glucose and fructose [36]. This is why we are looking into a new oral drug delivery concept that combines colon-specific drug delivery with the bioadhesive properties of water-soluble polymeric carriers [37]. Saminosalicylic acid (5-ASA) is contained in HPMA copolymers made of N- (2-hydroxypropyl) methacrylamide; a drug used to treat ulcerative colitis) were made that were bound by aromatic azobonds and bioadhesive moieties (monosaccharides) [38-40]. Using rat cecal cell-free extracts [38] and *Streptococcus faecium*, a common colonic bacteria [39], The release of 5-ASA from HPMA copolymers in vitro was examined. These polymers' bio adhesive properties and synthesis have recently been the focus of our research.

Need for colon targeting drug delivery

- Targeted drug delivery to the colon to ensure that treatment is delivered directly to the disease site (local delivery), at lower doses, and with fewer systemic side effects [28].
- Peptide and protein drugs could be administered orally through a site-specific or targeted drug delivery system; colon-specific formulation could also be used to extend drug delivery [29].
- A drug delivery system designed specifically for the colon is thought to be helpful in the treatment of colon diseases [29].
- Topical treatment of inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, can be accomplished at the colon, where both local and systemic drug delivery can be achieved. Glucocorticoids and sulphasalazine are typically used to treat inflammatory conditions like these [30].
- Drugs aimed at the colon might also be able to treat more effectively a number of other serious colon diseases, such as colorectal cancer [31].
- Drugs that are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, which is heavily influenced by hepatic metabolism, such as therapeutic proteins and peptides, can also be delivered using formulas for colonic delivery [31].

Advantages of colon targeting drug delivery system: [23, 24, 25]

The colon is an excellent location for the delivery of agents that can treat colon-specific diseases. The advantage of local treatment is that it requires less medication. reduces the frequency of doses. Consequently, less expensive drugs. Possibly resulting in a lower incidence of drug interactions and side effects. The colon is a desirable location for drug molecules that are poorly absorbed because it may enhance bioavailability. Reduce drug-induced gastric irritation (e.g., NSAIDS). Bypass the initial metabolic step. An extended activity during the day or at night. Improve compliance with patents. System for the targeted drug delivery, It appears to be highly responsive to agents that enhance the absorption of poorly absorbed drugs and has a longer retention time. Peptides, oral vaccines, insulin, and growth hormones can be administered this way because it has less peptidase activity and a less hostile environment [28].

Limitations of colon targeting drug delivery system:

- Multiple manufacturing steps
- The resident microflora may also affect colonic performance through metabolic degradation of the drug.
- Drug bioavailability may be low due to drug binding in a nonspecific manner to dietary residues, intestinal secretions, mucus, or faecal matter.
- For poorly soluble drugs, the drug should be in solution prior to absorption and serve as a rate-limiting step.
- The absence of a suitable dissolution testing method for in-vitro dosage form evaluation.[29]

Conclusion:

In recent years, formulation scientists have shown an increasing interest in the creation of oral drug delivery systems with a focus on the colon. As was previously said, colon-specific drug delivery systems provide patients tremendous therapeutic advantages in terms of safety, efficacy, and patient compliance. The successful formulation of a colon-specific drug delivery system is influenced by and may be complicated by factors such as the physicochemical properties of the medication, formulation and process variables, and GI physiological parameters. Because they are secure, non-toxic, affordable, and chemically compatible with the other excipients in the formulation, biodegradable polymers are gaining popularity daily.

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