Review
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From Prodrug to Multimatrix: Recent Advancement of Colon Specific Drug Delivery System

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Abstract: Prevalence of colonic diseases such as inflammatory bowel disease, colorectal cancer, angiodysplasia, salmonellosis, etc, are increasing daily and are reducing the quality of life of the patients. These diseases can be difficult to treat due to their ability to alter the normal environment of the colon such as the pH, microbiota, enzymes, and more. Anatomy and physiology of the colon also pose difficulty in case of targeted drug administration. Additionally, there are variations in how each colonic disease influences the colon, making it essential to design a Colon-Specific-Drug-Delivery System (CSDDS) that would ensure proper targeting and delivery of the drugs. To reduce systemic side effects and achieve desired therapeutic effects, the dosage form should be designed in such a way that allows for direct and precise targeting of drugs into the colon, while also preventing premature gastrointestinal drug release. In this review, we discuss the conventional (for example, prodrug, CODES, pulsatile drug delivery) and novel (OPTICORE, Phloral, MMX technology, 3D bicompartmental device) approaches aimed at ensuring drug release and absorption within the colon, as well as examine the factors that affect drug delivery targeted at the colon. Despite considerable progress, significant challenges and gaps remain, including the need for a deeper understanding of colonic environmental variability, the development of advanced biocompatible materials, and the implementation of personalized treatment strategies are highly required.

Introduction

There are numerous therapeutic opportunities and possibilities that the colon provides. Although the colon has a low surface area and viscous luminal fluid which provides considerable challenges in drug delivery, the colon's enriched microbiota, variable pH, and enzymes present can be utilized to aid the delivery and maximize the bioavailability of drugs. The presence of efflux transporters and metabolic enzymes such as cytochrome P450 are often lower in the colon. Cytochrome P450 enzymes can metabolize drug molecules, which consequently lowers the bioavailability of drugs. Thus, CSDDS improves the bioavailability of drugs by reducing drug metabolism (1). Because the intended site of action is not reached by the drugs in the right concentrations, the majority of the current drug delivery systems for treating colonic ailments are not a substantial success (2). Colon targeting offers several clinical advantages for drugs that are destroyed by stomach acid or metabolized by pancreatic enzymes. It enhances patient compliance by reducing dose and frequency and allows more effective localized treatment for conditions like colorectal cancer, ulcerative colitis, and Crohn's disease. However, pH-dependent systems, which can protect formulations in the upper GI tract, may release drugs prematurely in the lower intestine due to pH changes, particularly in diseases like inflammatory bowel disease where colon pH decreases. Additionally, the colon's lower fluid content compared to the small intestine can hinder the dissolution of poorly water-soluble drugs, necessitating their use in presolubilized

forms and targeting the more fluid-rich proximal colon (3, 4, 5).

In order to provide safe and effective therapy for some colonic diseases, CSDDS can be utilized to target the colon (2). CSDDS protects the drug entering into the colon i.e. inhibits premature drug release into the GIT. In this drug delivery system, absorption does not occur in any part of the gut other than the colon. Thereby, the degradation of bioactive agents does not occur in either the stomach or the small intestine; instead, the drug is released and absorbed only when the system reaches the colon (6). Technologies such as CODESTM, Pulsincap® system, prodrug approach, nanoparticle drug delivery systems, etc, provide such protection and site-specific drug release. Although the intrarectal route is one of the possible routes for CSDDS, the oral route is the most practical and recommended one (7). Hirchsprung's disease, angiodysplasia, salmonellosis, ulcerative colitis, and other inflammatory bowel disorders can all benefit from CSDDS. For example, Budesonide, a drug used for the treatment of CD, is coated with azo-polymer to transform it into a prodrug (7, 8). Phloral™ technology offers an advanced drug delivery method, particularly beneficial for the treatment of inflammatory bowel disease (IBD) and similar conditions (9). This review is focused on the anatomy, physiology, diseases of the colon, and also the factors that affect drug delivery in the colon. Most importantly, it discusses various old and novel colon-specific drug delivery approaches, while encouraging further exploration. Reviewing the topic of colon-specific drug delivery systems (CSDDS) is crucial due to ongoing advancements in drug delivery technologies and the increasing prevalence of colonic diseases like Crohn's disease, ulcerative colitis, and colorectal cancer. Previous reviews may not encompass the latest innovations such as 3D printed drug devices, and advanced coating technologies like OPTICORE and Phloral™. This review is urgent because it highlights cutting-edge approaches that significantly improve drug bioavailability, reduce systemic side effects, and offer more precise targeting of colonic regions, providing new insights into overcoming existing delivery challenges and optimizing therapeutic outcomes.

Need for CSDDS

An orally administered dosage form must traverse the entirety of the digestive system to reach the colon, facing several obstacles. These obstacles impede the development of an optimal colon-specific drug delivery system (CSDDS). The gastrointestinal tract (GIT) has a complex physiology with varying fluid quantities, differing transit times, multiple metabolic enzymes, and other factors that hinder effective and consistent drug delivery to the colon (3). Developing a suitable in vitro dissolution method that accurately predicts in vivo performance remains a significant challenge (10). Additionally, the colon's intestinal fluid volume is low, the fluid is highly viscous, and the pH is neutral around 7, all of which can limit drug solubilization and absorption rates (3). The colon has a smaller surface area compared to the small intestine which results in BCS class III and IV drugs to have limited colonic permeabilities and low bioavailability of less than 50%. A double layer of mucus, that acts as a physical barrier between the microbiota and the colonic epithelium, covers the whole colonic epithelium. This layer also facilitates the transit of chyme into the lumen. The mucosal layer can hinder the crossing of drugs across the epithelium and absorption, posing a serious obstacle to systemic bioavailability (11).

There are several reasons why colon-specific drug delivery systems (CSDDS) are necessary: they ensure smaller dosages, reduced frequency of dosing, reduced systemic side effects, and precise treatment at the disease site through local delivery (3, 12). They improve the bioavailability of orally administered proteins and peptide drugs, which are not readily absorbed into the bloodstream from the gastrointestinal tract due to the colon's long transit and residence time, and its natural absorptive characteristics (13). CSDDSs are effective in treating colon diseases and inflammatory bowel diseases (IBD) like Crohn's disease (CD) and ulcerative colitis (UC) (14, 15). Moreover, they can minimize first-pass metabolism, making them suitable for drugs that are polar, prone to breakdown by enzymes, or affected by the acidic environment in the upper GI tract, as well as those significantly impacted by hepatic metabolism (15).

Anatomical Features and Physiology of Colon

The large intestine, which is a cylindrical closed receptacle, comprises the caecum, colon, and anus. The colon, which is approximately 1.5 meters in length, can be divided into two main parts: the proximal and distal colon. The proximal colon consists of the caecum, ascending colon, and transverse colon. The distal colon, on the other hand, is further divided into four parts: the descending colon, sigmoid colon, rectum, and anus (11). An important feature of the colon is the hepatic flexure, a 90° bend that connects the ascending colon to the transverse colon. Conversely, the descending colon and transverse colon are linked by the splenic flexure. The colon is lined with a soft, pink mucosa (11, 16). The diameter of the colon measures approximately 2-3 inches (3), with some variations observed between genders (11). These variations pertain to both the length and diameter of different colonic regions. The summarized measurements are presented in Table 1 (16).

Table 1. Length and diameter of different colonic regions.

Segment	Length (cm)	Diameter (cm)
Caecum	6-9	8
Ascending colon	20-25	6
Descending colon	10-15	5
Transverse colon	40-45	5
Sigmoid colon	35-40	5
Rectum	12	4

The blood supply around the absorptive section of the epithelium is essential for the absorption of drugs from the colon. Arterial blood is supplied through the mesenteric and inferior mesenteric artery to the proximal and distal colon respectively. Blood flow is higher in the proximal portion of the colon compared to the distal portion. The colon has an intestinal surface area of 1300 cm^2 and is capable of absorbing large volumes of water, electrolytes, and also short-chain fatty acids. The key roles of the colon are storage and removal of fecal content and absorption of sodium and water thus concentrating fecal content (17).

Colon Diseases and Their Impact on Colon Characteristics Changes

Different colonic diseases include IBD (UC, Crohn's disease), Hirchsprung's disease, salmonellosis, angiodysplasia, colorectal cancer, amebiasis, diarrhea, and colorectal polyps, etc. The following table summarizes different colonic diseases, changes of colon characteristics and drugs in the treatment.

Table 2. Different colonic diseases, characteristics and drugs used in the treatment of colonic disorders.

Disease Name	Affected Region	Characteristic changes	Drug Used
Ulcerative Colitis	Inflammation starts in the lower portion of the colon and the rectum, although it can affect the whole colon (18).	Ulcerative colitis is a form of IBD (19). Inflammation and damage to the mucosal surface of large intestine occur, leading to issues with motility and secretion (18, 20).	Prednisolone, 6-mercaptopurine, Sulfasalazine, Balsalazide, Golimumab (13)
Crohn's disease	The entire gastrointestinal tract is affected along with all layers of the gut wall (19),	Crohn's disease is a form of IBD (19). Condition causes patients to have a tender mass in the right lower quadrant, thickened bowel loops, thickened mesentery, or an abscess. Chronic localized, transmural, discontinuous, patchy, and inflamatory perianal fistulas or abscesses may also be present (21).	Prednisolone, Mesalazine, Sulfasalazine, Methotrexate, Infliximab, Budesonide, Methotrexate (8, 22)
Amebiasis	Inflammation of large intestine occurs (23, 24).	Amoebic invasion occurs through the mucosa, penetrating into the submucosal tissues. The distinctive flask-shaped ulcer which is characteristic of amoebiasis is caused by lateral extension through submucosal tissues (25).	Metronidazole, Tinidazole, Nitazoxanide, Paromomycin, Iodoquinol (26)
Colorectal cancer	22% of all colorectal cancers occur in the distal colon, 28% involve the rectum and approximately 41% occur in the proximal colon (27).	Colorectal cancer development is attributed to mutated genes that regulate tumor growth (tumor suppressor genes) and genes that promote tumor formation (oncogenes) (28). Most colorectal cancers arise from adenomas. Frequently, one or more synchronous adenomas are found in operative specimens of colon cancer (29). Presence of palpable mass is common in right colon cancer. The most common association between malignant blockage of the large bowel and sigmoid carcinoma is this (30).	Bevacizumab, Oxaliplatin, Aflibercept, Regorafenib, Tucatinib, Capecitabine (31)
Hirschsprung disease	The rectosigmoid portion of the colon and the entirety of the colon is affected (32).	Functional colonic obstruction is caused due to various lengths of distal colon not being able to relax and distension of proximal segments (megacolon) (33). Hirschsprung disease results from absence of ganglion cells in the distal hindgut(32, 34). Larger neural trunks take the place of ganglion cells (34).	Metronidazole, Ampicillin, Gentamicin (35)

Salmonellosis	Distal ileum and proximal colon are affected (36).	Salmonellosis is caused as a result of ingestion of food contaminated with Salmonella (a gram-positive bacteria). (36). Salmonella releases high level of inflammatory cytokines, enhances proliferation activity, and promotes tumorigenesis. Salmonella infection can also induce colitis that is similar to UC. It causes serious colitis with severe emaciation and diarrhea, erosion of the colonic epithelium, and increases inflammation substantially increased (37)	Ciprofloxacin, Ceftriaxone, Ampicillin, Cefixime, Chloramphenicol, Dexamethasone, Amoxicillin (38)
Diarrhea	Colon, small intestine (39)	Pathogenic microorganisms cause epithelial damage thus, reducing the absorptive area and function; leading to unabsorbed solutes drawing water into the intestinal lumen. Enterotoxins from bacteria stimulate cAMP or cGMP, leading to significant water secretion and dehydration (40).	Bismuth subsalicylate, Loperamide, Fluoroquinolone, Azythromycin, Ciprofloxacin, Rifaximin (41)
Angiodysplasia	Affects upper gastrointestinal tract, small intestine, colon (42).	Angiodysplasias of the colon refers to the presence of abnormally enlarged and delicate blood vessels within the colon, which can occasionally lead to bleeding in the lower portion of the gastrointestinal tract (43). Angiodysplasia can be characterized as the observation of abnormal, dilated, ectatic, tortuous and mostly tiny (less than 10 mm) blood vessels that can be seen in the mucosal and submucosal layers of the GIT. Diseased blood vessels are lined solely by the endothelium and barely have any smooth muscle (42).	Thalidomide, Somatostatin analogs (44)
Colorectal Polyps	Occurs usually in the colon.	It is characterized by extension of mass/growth from the mucous membrane into the lumen (45)	Sulindac (46)

Factors Affecting Colon Targeted Drug Delivery

Gastric Transit Time

Upon oral administration, the primary factors influencing drug distribution to the colon are gastric emptying and bowel transit time. The dosage form, the peristaltic phase, and the presence or absence of food are factors that affect this time (3, 11).

Gastric emptying time is observed to be longer in the fasted state and is significantly delayed by the intake of high-fat food. Females of reproductive age exhibit a notably longer gastric emptying time compared to males and post-menopausal females (11). Diseased states such as UC and Crohn's disease also change gastric transit time (3). Patients suffering from diarrhea have shorter transit times than those suffering from constipation (47). Patients having type 2 diabetes mellitus are reported to have a gastric transit time of up to 300% times longer than healthy individuals (11).

Large variability of gastric emptying time is observed between and within individuals. Under typical circumstances, the colon transit time ranges from 5 to 7 h. However, this transit time changes according to the gastrointestinal tract's fed and fasting states. In the fasted condition, transit time ranges from 3 to 5 h and in the fed condition, it varies between 6 to 10 h. The Table 3 summarizes the transit time of different segments of GIT (48)

Table 3. Lists the transit times of various segments of the GIT.

Segment of GIT	Transit time
Stomach	Fasted condition: 10 min – 2 h Fed condition: >2 h
Small intestine	3-4 h
Colon	20-35 h

pH of Colon

Variation of pH is observed between individuals. Consumption of food, diseased state, etc, can affect the pH levels of the GIT (47). The pH of luminal fluid does not remain the same along the GI tract. While the pH of gastric fluid varies with fed and fasted state and gender, the ascending colon typically has a lower pH than the ileocaecal area. The pH of the ascending colon is about 6.4±0.6 while the pH of the traverse colon ranges around 6.6±0.8 (49). This is caused by the colonic bacteria producing lactate and short-chain fatty acids (SCFAs). Meanwhile, pH of distal colon is comparatively higher, around 7.0±0.7 (11, 49). The pH of the sigmoid colon is also comparatively higher at about 7.4 ± 0.6 (11). Colonic pH may be altered by polysaccharide-based drugs and laxative drugs, e.g. lactulose. Diseased states such as ulcerative colitis (UC) also affect pH of the colon. In UC patients, the pH of proximal regions of the colon ranges from 2.3-4.7

(49). Pharmacokinetics and pharmacodynamics of CSDDS are affected by colonic pH, as the solubility of drugs is being influenced (3).

Colonic Microbiota and Enzymes

Enzymes in the gastrointestinal tract, including bacterial enzymes like azoreductase, nitrate reductase, nitroreductase, and sulfatase abundant in the colon, significantly influence drug bioavailability and digestion efficiency. These enzymes play pivotal roles in drug metabolism and the breakdown of mucosal glycans, impacting the absorption of orally administered protein drugs and other pharmaceuticals within the gastrointestinal environment (50). Over 400 distinct bacterial species inhabit the colon, such as Escherichia coli and Clostridium, which produce enzymes that can increase the rate of metabolism of drugs and other biological molecules (3, 50, 51). Some bacterial enzymes include azoreductase, involved in the metabolism of azo dyes, nitro-aromatic, and azoic drugs, resulting in the formation of amine (52, 53); nitrate reductase, which biotransforms nitrate to nitrite (52); nitroreductase, facilitating the conversion of nitroaromatic compounds into aromatic amines, changing nitro groups into hydroxylamine or amino groups in the presence of nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP) (54); and sulfatase, which plays a role in breaking down mucosal glycans, including those found in colonic mucins (52). Other than bacteria, the colon also consist of fungi, viruses, archaea, free DNA, metabolites, etc (11). According to histochemical staining reports in a study, in general, high expression of CYP P450 enzymes was observed in UC and CD patients compared to normal (55). In a study done by Carrette et al, it was observed that the activity of β-D-Galactosidase and Azoreductase was significantly low in patients with CD compared to normal (56).

Volume and Viscosity of Colonic Fluid

The composition of the colonic fluid varies depending on factors like the amount of food and/or water consumed. Usually, colonic fluids are constituted of water, chyme, microbiota, electrolytes, proteins, bile acids, short-chain fatty acids (SCFAs), and other different metabolites (11). The colon has a propensity to absorb higher amounts of water, thus it is capable of absorbing 90% of the water that enters it. However, colonic fluid volume is quite low, ranging from 1 - 44 mL, which can make the dissolution of drugs difficult (3). The colon's strong propensity to absorb water results in its viscous contents, thereby resulting in reduced availability for absorption of most drugs through the colon’s membrane (16). After a meal, the colonic fluid increases due to the intake of liquid and food. As it travels along the colon, the fluid volume gradually decreases due to the colonic absorption of water (11).

Pharmaceutical Factors

Several factors influence the development of colon-specific drug delivery systems and the bioavailability of drugs in the colon. These factors, both intrinsic and extrinsic, play vital roles in formulation considerations. Intrinsic factors such as intestinal colonic transit time, fluid volume, pH levels, colonic microflora, enzymatic metabolism, drug absorption, and colonic luminal content viscosity, significantly impact drug delivery efficacy. For instance, the transit time of dosage forms in the colon varies based on factors like diet, mobility, and colonic disease, affecting drug retention and release. Meanwhile, extrinsic factors like the nature of the drug candidate and the choice of polymeric drug carriers are equally important. The selection of drugs depends on their chemical properties, solubility, and intended therapeutic targets, with drugs treating conditions like inflammatory bowel disease and colon cancer being particularly suitable for localized colon delivery. Polymeric carriers, whether synthetic or natural, offer versatile options for formulation development, providing favorable physicochemical properties for drug release and targeting. These factors collectively underscore the complexity and importance of optimizing colon-specific drug delivery systems for enhanced therapeutic outcomes (57).

Conventional Approaches for Colon Targeted Drug Delivery System

Prodrug

Prodrug is an inactive compound that encloses the original drug. It undergoes enzymatic and biotransformation in the body to enable drug release at its designated site. This design is intended to improve pharmacological and physicochemical drug properties while reducing toxicity (58). Azo-polymers have been used to coat drugs like 5-amino salicylic acid (5-ASA), Budesonide, etc, to evaluate their potential as CSDDS. Azo-polymers can undergo degradation by azoreductase which is found in the large intestine. Therefore, the drug product will neither be broken down in the stomach nor the small intestine; resulting in colon-specific delivery (7). Glycosidic prodrugs can be used as a strategy for colon targeting since they are minimally absorbed from the stomach and small intestine but are cleaved by bacterial glycosidase which is present in the large intestine (59). In an experiment by Yang et al, metoclopramide (MCP) was azo-linked with 5-ASA and tested on a rat model. The result of the experiment showed that a significant amount of both MCP and 5-ASA reached the large intestine (60). The therapeutic availability of a colon-specific prodrug and a parent drug is dependent on its availability at the target site. If the parent drug is

metabolically stable, its level primarily depends on the prodrug's conversion rate. On the other hand, if the parent drug is not stable, its level is determined by the difference between the prodrug conversion rate and the parent drug metabolism rate in the target organ. It can be challenging to modify drugs into such a suitable prodrug. Moreover, a suitable functional group is required for conjugation to occur with a colon-specific promoiety. The covalent bond should only cleave in the large intestine. Additionally, polymeric prodrugs cannot be formulated using hydrophobic or low efficacy drugs (61).

Coating with pH-Sensitive Polymers

The colonic pH is high, therefore, a CSDDS can be devised where the release of drugs from the drug product occurs at a high pH (50, 62). The formulation can be coated with polymers that are pH sensitive such as cellulose, acrylic acid derivatives, and Eudragit®; or be incorporated into pH-sensitive materials. The polymer used must disintegrate at a pH that is present in the colon and should have a narrow pH release range so that premature release does not occur. Mesalazine formulations, such as Salofalk® and Claversal®, depend on pH and are coated with Eudragit-L. They disintegrate when the pH is greater than or equal to 6, leading to the drug release in the middle to the distal portion of the ileum as well as the colon. If Eudragit-S is used as a coating, as in Asacol®, the drug product disintegrates at a pH less than or equal to 7, which causes drug release in the terminal portion of the ileum and colon (51).

pH-sensitive hydrogels are 3-dimensional structures made up of a polymer framework, water, and crosslinking agents. They can expand significantly in water without dissolving. They shrink in acidic environments and swell in alkaline environments. When the drug product comes in contact with the high pH of the colon, it swells and bursts, releasing the drug. Colonic disorders like UC and CD can be treated locally with it (62). However, only small amount of drug can be incorporated in matrices and hydrogels, so it cannot be used when a greater amount of drug is needed. Drug loading is also a problem of using hydrogels. A high drug yield can be achieved by loading the hydrogel during polymerization, though this risks intolerable levels of residual monomers or initiators, whereas loading drugs after hydrogel formation results in a lower drug level. Moreover, intestinal pH varies with numerous factors such as food, diseased states, etc. Therefore, it is extremely difficult to predict the pH of the colon when formulating a dosage form (63).

Time-Based Formulations

In time-based formulations, once a predetermined amount of time has passed, the drug is liberated. Therefore, it can be used to target particular regions of the body. An example of such a formulation is Pentasa®, an ethylcellulose-coated mesalazine tablet that gradually releases the drug from the duodenum to the rectum. Mechanisms of some time-dependent formulations include swelling and/or osmosis (41). The Time Clock® system is a type of reservoir device characterized by a tablet core encased within a layer of natural waxes and surfactants. It is then coated with an enteric film. In the small intestine, dissolution of the film would occur which would then initiate the dissolution of the inner layer; resulting in the release of the active pharmaceutical ingredient (API) into the colon (64). Although time-dependent releases do not depend on pH, it is affected by variations in gastric emptying time, gastric transit time, presence of food, and many other factors (7). Moreover, gradual release throughout the GIT can result in higher systemic side effects (51). The gastric retention time has significant variability which makes it challenging to predict the exact drug release location using this method. Limitations of time-dependent formulations include limited in-vivo evaluation and its usefulness only in diseases which particularly depend on circadian rhythm (62).

Pressure-Dependent Systems

Due to strong peristalsis, the colonic content faces greater luminal pressure compared to the small intestine (7, 59). The viscosity of the contents in the colonic lumen is high due to water reabsorption and feces formation (59). Based on the high pressure in the colon which can reach as high as 110 mmHg for 14 s, Takaya et al. developed a capsule formulation that is pressure-controlled and disintegrates in the colon (7, 51, 62). The capsule shells are made using a hydrophobic polymer called ethyl-cellulose (65). Due to the pressure inside the colon, the capsule bursts and the drug is released. The thickness of the shell can be modified to withstand different levels of pressure while the size of the capsule and its density can also affect the system (7). Very limited data can be obtained regarding how the luminal pressure varies across different regions of the GIT, and how food affects luminal pressure is also yet to be documented. It is also unclear if pressure in the lumen varies across subjects (62).

CODES Technology

CODES is a distinctive and special CSDDS. It uses a combination of colonic microflora and pH-sensitive polymer for drug release. Generally in tablets manufactured by the CODES configuration, three layers of polymer coat the main tablet. The simple tablet core contains the active ingredient mixed with excipients such as lactulose (7). The three layers of the coating are: the first layer, encompassing the core, is a polymer that is acid-soluble combined with a

degradable polysaccharide (lactulose), the second is a layer of enteric polymer, such as Eudragit E and the third is a layer composed of Eudragit L (66, 67). The idea behind this technology is that the tablet in the stomach is protected by an enteric coating Eudragit L, and it dissolves soon after gastric emptying. After gastric emptying, the tablet travels to the small intestine where the Eudragit L layer undergoes dissolution due to the high pH environment (pH 6) (65, 67). Thus, the Eudragit E coating is revealed and the small intestine does not break down this layer. Rather, this coat allows the lactulose to be released close to the tablet (67). Upon reaching the colon, polysaccharide (lactulose) is broken down into organic acid by the colonic microflora (59). Thus, pH is lowered, which facilitates the breakdown of the acid-soluble coating and ensue the release of the drug (67). The release of drugs via this approach may be influenced by inter and intra-subject variability. Moreover, the drug release can also be impacted by pH similarity between the colon and the small intestine. In diseased conditions, there might be changes in the gut microbiota which can also contribute to variation in drug release (62).

Nanoparticle Drug Delivery System

The nano drug delivery system contains several variations including size-dependent delivery, charge-mediated delivery, redox-responsive delivery, and ligand receptor-mediated delivery.

Size-Dependent Nanodelivery System

In this formulation, the size of the drug particles is reduced to nanoscales (51). Penetration of nanosized particles is increased in inflamed regions due to enhanced permeability and retention (EPR) (68). Boloqui et al discussed in a study, conducted on mice that had been induced with colitis, that elimination of Budesonide-loaded nanostructured lipid carriers is slow even in the case of diarrhea which frequently occurs in IBD (69). Reduced particle size not only allows for increased residence time but also enhances preferential absorption of the drug by immune cells which are abundant in areas of inflammation (70). The smaller the particle, the more likely it is to be absorbed systemically which can result in systemic side effects (68).

Charge-Mediated Nano Drug Delivery

It is possible to regulate how the nanoparticles interact with the mucosa of the colon by modifying their surface charge. The colonic mucosa contains carbohydrates, sialic acid, sulfates, and colonic mucin which are negatively charged (68). Therefore, positively charged nanoparticles attracted to these molecules can be used for targeted delivery (51). Niebel et al conducted an experiment where nanoparticles loaded with clodronate were modified by positively charged polymethacrylate and tested on mice with induced Crohn's disease and UC (71). Mucoadhesion could be a promising approach towards targeting Crohn's disease due to higher levels of mucus production associated with this disease (51).

Redox-Responsive Nano Drug Delivery System

Overproduction of reactive oxygen species (ROS) is evident in inflammatory diseases like UC and CD. Therefore, a delivery system that is redox-dependent might be a promising approach for IBD treatment. Nano-drug formulations that are broken down by ROS could be used to target the colon (72). Vong and his team developed a novel redox nanoparticle that consists of a center containing nitroxide radicals, which work as ROS scavengers in the treatment of colon cancer (73). Redox-mediated drug delivery systems face challenges due to their susceptibility to volatility in acidic environments, exposure to high enzyme concentrations, and rapid release of drug (68).

Ligand Receptor Mediating Nano Drug Delivery

Expression of some receptors and ligands increases during inflammation. These can be target sites for the attachment of nanodrug particles (74). In an experiment, mannosylated bioreducible nanoparticles were created which targeted mannose receptors that are overexpressed on macrophages (75). A liposome-based nano-particles targeted at 7 integrin (7 I-tsNPs) and loaded with siRNAs was developed by Peer et al. It was intended to silence Cyclin D1 (CyD1) in the treatment of Dextran sulfate sodium (DSS)-induced murine colitis. Expression of CyD1 increases in IBD, therefore, the delivery of CyD1-siRNA using 7 I-tsNPs resulted in a significant decrease in intestinal tissue damage and a reduction in infiltration of leukocytes into the colon. Exosomes can also be used to target inflammatory sites since they have certain proteins on their membrane that are highly selective and thus, allow them to target specific sites (74). This approach shows potential as CSDDS, but there are concerns involving the instability of ligands in the GIT (68).

Bacterial Degradable Polymer Coatings

The colon is home to an extensive range of bacteria, most of which are anaerobes, such as Bacteriocides, Enterobacteria, Bifidobacteria, Eubacteria, etc. The bacterial population in the colon ranges between 10^{11}-10^{12} CFU/mL. The majority of the microflora obtain energy by fermenting certain substrates like di-saccharides, and polysaccharides, using enzymes such as xylosidase, arabinosidase, galactosidase, azoreductase, urea de-hydroxylase, glucuronidase, nitroreductase and deaminase (7, 59). Using this mechanism, natural polymers, e.g. inulin, guar gum, amylose, etc, can be used to coat the drug. These compounds are able to resist degradation in the upper GIT but can act as substrates for the colon's anaerobic

bacteria, causing delivery that is site-specific. However, these polymers have poor film-forming properties and can produce toxic by-products (76). Qiyan Chen et al. devised a drug delivery system for UC that consisted of hyaluronic acid, polyethyleneimine, yeast cell wall microparticles (HA/PEI-RH NYPs), and modified rhein. The yeast cell wall provided protection to the drug from the gastric environment, but it could be broken down by β-glucanase that is formed by the bacteria present in the colon. The results from the in vivo studies suggested that this could be a great oral drug delivery system for colon-targeted drug delivery (50). The bacterial enzyme-mediated conversion rate of colon-specific prodrug to its active parent drug primarily depends on the susceptibility of the linkage between the drug and its promoiety to colonic metabolic processes. The degree of susceptibility may vary based on nature of the promoieties and the drug, even when the linkage is of the same type. This can prove to be a challenge when designing a drug with bancterial degradable polymer (61).

Chitosan-Based Drug Delivery Systems

Chitosan (CS) is an alkaline polysaccharide that can be derived from chitin which is a naturally occurring compound found in the exoskeleton of crustaceans (77, 78). It exhibits a wide array of pharmacological as well as biological functions such as antioxidant, anticoagulant, anti-tumor, anti-diabetic, etc. Moreover, due to its non)-toxic, stable, antibacterial, and biocompatible nature, it is a valuable and high-demand resource (78).

Alhakamy et al conducted a study where simvastatin (SMV), which has shown anticancer properties, was formulated in chitosan and then coated with Eudragit S100 (ES100). The formulation showed significant release in the colonic pH and adhesion to the colonic tissues (77). In another study by Zhou et al, Escherichia coli Nissle 1917 (ECN), which is a probiotic that is administered orally, was genetically modified with the intention of treating IBD. The active material was coated with a biofilm of sodium alginate and chitosan using the Layer-by-Layer Self Assembly technique. This formulation exhibited better protection of the drug compared to regular enteric coating (79). However, chitosan has weak mechanical characteristics and is susceptible to degradation. It is also thermally unstable, highly hydrophilic, swellable and poorly water-soluble. To prevent rapid degradation of Chitosan, it is usually cross-linked with other polymers. It is also necessary to improve solubility of Chitosan (80).

Pulsatile Drug Delivery System (PDDS)

Pulsatile drug release systems show sustained release as the drug is released within a therapeutic window for an extended duration. These systems have advantages such as reduced dose size, dosing frequency, side effects, and adaptation of drugs to the circadian rhythm of body functions and diseases (81). Pulsatile drug delivery systems are primarily controlled by time with a lag phase. The pH, motility, and enzymes in the GIT does not influence drug delivery in this approach. It has the capability to deliver drugs in cases where dosage is required during sleep. It can also be used in the case of drugs that are extensively metabolized in the liver and have site-specific absorption. However, this approach does not show consistent reproducible results in terms of therapeutic efficacy and manufacturing. Moreover, it is expensive to manufacture since it requires advanced technology and expert personnel. Additionally, large amounts of drugs cannot be loaded in this formulation, and in vivo-in vitro correlation is also not predictable (82).

Pulsincap® System

Variations in gastric emptying time and gastrointestinal transit caused by peristalsis or disorders of the gastrointestinal tract often make time-dependent systems unideal for drug delivery in the colon (18). This is where a Pulsincap system comes into work. Pulsincap system is a formulation that combines the advantages of both the timed-release systems and the pH-dependent systems (83). Most of these systems are created as capsules, consisting of a water-soluble cap and a water-insoluble body treated with formaldehyde. Within the body of the capsule, a mixture of drug, osmogen, and swelling agent is inserted (81, 83). At the open end of the water-insoluble body a hydrogel plug is placed which is then covered by the water-soluble cap (84). The capsule is enteric coated with an acid-insoluble film. Thus, preventing drug release in the stomach and preventing variable gastric emptying. After the dissolution of the enteric coating, the hydrogel plug swells when the capsule comes in contact with the dissolving fluid, and the drug is released as the plug pushes itself out. The drug releases with a lag time caused by the plug swelling, and the release relies on the length of the plug and how deeply it is inserted (3, 81, 83).

Osmotic Controlled-Release Oral Delivery System

An Osmotic Controlled-Release Oral Delivery System (OROS-CT) is a system regulated by osmotic pressure (3). It was adopted for drugs with low water solubility (81). The formulation consists of 5-6 push-pull units, each having a diameter of 4mm, contained within a hard gelatin capsule. A drug-impermeable enteric coating surrounds each unit within which there is a semipermeable coating that surrounds an osmotic push layer and a drug layer (3, 7). The drug layer is composed of poorly soluble drugs, osmotic agents, and suspending agents (84). The enteric coating protects the drug in the acidic pH of the stomach and dissolves

in the high pH state (pH>7) of the small intestine, causing water to enter the unit. When water permeates the unit, the osmotic push compartment undergoes swelling, leading to the formation of a gel that is flowable (3, 7). The gel is pushed through the membrane adjacent to the drug compartment through an aperture. The rate at which water enters the units determines the drug's flow rate (3). Each push-pull unit is made with a 3-4 h post-gastric delay to prevent drug distribution in the small intestine during the treatment of UC. The drug is released when the unit reaches the colon. Drugs can be released using OROS-CT units at a consistent pace for up to 24 h or over a brief period of 4 h (7).

Novel Approaches

OPTICORE

The OPTICORE (OPTImised COlonic RElease) is a novel drug coating technology that was devised for rapid drug delivery in the ileocolonic area (11). It consists of a drug core which is enclosed by an inner alkaline layer. The outer layer of OPTICORE™ makes use of a dual trigger mechanism (enzyme and pH) and is made from a combination of Eudragit® S and resistant starch (85). Resistant starch undergoes enzymatic degradation by bacteria in the colon while Eudragit® S is affected by the pH of the colon. The inner layer is meant to accelerate the drug release rate. It was found in a study that in OPTICORE™, drug release starts just 1 h after reaching the colon (86). A 1600 mg 5-ASA drug product that has been formulated using OPTICORE has received market approval and is currently used for the treatment of UC (85).

Phloral Technology

Accurately targeting the colon plays a significant role in treating inflammatory bowel diseases. The recent approaches of stimulating drug release target three variations in gastrointestinal physiology- transit time, pH, and rise in the concentration of bacteria in the distal gut. An earlier approach makes the use of a polymer coating that is pH-responsive, such as Eudragit® S. This coating dissolves at an intestinal pH of around 7.0 and triggers drug release. Although this approach yielded positive results in the treatment of UC, infrequently, whole undissolved tablets were found in the patient's feces. This infrequent occurrence may be attributed to exposure to insufficient volumes of fluid in a neutral or alkaline environment for the required time period and scarcity of fluids in the distal small intestine and large intestine. As the colonic pH of UC patients is reportedly lower than healthy individuals, exposure of the drug to fluid of pH 7 is hindered. The amount of fluid in the intestinal region is generally lower and the presence of fluid in pockets contributes to this issue more. Thus to facilitate fail-safe drug release, Ibekwe et al suggested combining both pH and enzymatic triggers into a single coating system, referred to as Phloral™. The pH trigger is made up of a polymer coating (Eudragit® S) and the enzymatic trigger is a resistant starch polysaccharide. The enzymatic trigger aids drug release in cases where the environment is not alkaline enough for the required time period to dissolve the enteric polymer. Resistant starch can be classified into four types and the type RS2 is used in Phloral coating technology. The RS2-resistant starch consists of a high amount of amylose which causes the RS2 to gelatinize at a higher temperature compared to the other starches and often not gelatinize at all; thus making it less digestible and more suitable to be used in drug delivery systems that specifically target the ileo-colonic region. The microbial population gradually increases along the small intestine, but increases by several folds beyond the ileo-colonic region.The prime source of fermentable carbohydrates for the bacterial population in this area is undigested polysaccharides, and they also play a key role in metabolism of oral drug. Thus, this two-trigger mechanism provides a timely and thorough drug release (9).

3D Printed Bicompartmental Devices

3D printing of pharmaceutical products is rising due to the convenience it provides and how it allows us to easily modify or control drug release kinetics, dose, appearance, and texture (87). There is a shift towards utilizing materials that allow the development of composite-based products, especially in technologies that depend upon Fused Deposition Modeling (FDM) (88). FDM is a method of thermal extrusion where molten thermoplastic filaments are deposited layer by layer onto a surface in order to create 3D solid structures based on a computer-aided design (CAD) model. In a recent experiment, a drug product was developed using polyvinyl alcohol and hydroxypropyl methylcellulose acetate succinate as the polymers to build the matrix. The latter dissolves at the colonic pH, making it suitable for targeting the colon. The outer compartment was cylindrical while the inside consisted of a spiral compartment with an opening on top that allows it to communicate with the surrounding media. The special shape of this device allows the release of large doses of drugs in a controlled manner. The drug used was 5-ASA, which is an anti-inflammatory drug used for IBD and CRC (89).

MMX Technology

The Multimatrix (MMX) is a drug formulation that facilitates the release of high-concentration active drugs into the colon. This formulation ensures uniform distribution of drugs into the colon, especially the distal colon. In this formulation, a hydrophilic structure disperses the lipophilic matrix. The drug and excipients are trapped in the matrix in a net of hydrophilic and amphipathic polymeric material (90). This matrix is coated with a pH-resistant enteric coating. The

hydrophilic excipients in the matrix swell as they come into contact with the gastric fluid due to the disintegration of the enteric coating (91). The drug becomes more soluble in the amphipathic polymeric matrix, which also relaxes the hydrophilic material and makes it swell. As a result, the drug is distributed uniformly throughout the colon (92). The swelling of the tablet forms a viscous gel mass, which causes slow diffusion of the drug into the colonic lumen from the tablet core. The gel mass that surrounds the tablet core gradually breaks off as it moves through the colon. Lipophilic excipients limit the rate at which drugs dissolve by preventing digestive fluids from penetrating the tablet core. This prolongs drug release (91). This formulation provides effective delivery of active molecules to the site of action due to low systemic absorption and reduced adverse events. MMX® mesalamine and budesonide have gained worldwide registration for treating ulcerative colitis (90).

Authors Perspective

The unique colonic environments can act as a base for developing different CSDDS. It is important to develop a drug delivery system that maximizes the release and activity of drugs in the colon while minimizing side effects. Most conventional approaches rely on a single trigger system while most novel approaches are based on multiple trigger systems such as OPTICORE and Phloral™. The prevalence of colonic diseases is increasing daily. We've noticed that although there are quite a few CSDDS, there is a gap in the personalized treatment of colon diseases. Characteristics of different colonic diseases and the environment of the colon can vary amongst individuals. Therefore, in order to provide a treatment tailored to individual patients, it is crucial that more studies regarding the correlation amongst each colonic diseases, CSDDS and other factors (food, gender, body weight, history of other diseases, etc) are conducted. We believe 3D printing technology could aid in the advancement of personalized treatment and allow vast customization. Moreover, the integration of nano-drug particles in 3D printing technology could also be used to develop newer CSDDS. Although CSDDS is used in an array of colonic diseases, in case of a few diseases, there are not enough drug treatments available and hence no delivery system can treat the disease. For example, no effective preventive treatment currently exists for gastrointestinal angiodysplasia (GIADs). Studies on pharmacological agents like lanreotide have shown promising results in a significant number of patients, but these studies involved small, non-comparative samples. Octreotide and lanreotide have been more effective than endoscopic therapy in reducing recurrent bleeding and have fewer adverse effects. Reduced bleeding episodes were also observed in studies with thalidomide, but significant side effects were observed. While somatostatin analogs and thalidomide show potential, more prospective, controlled, and randomized studies, as well as cost-benefit analyses, are needed.

Conclusion

Studying colon-specific drug delivery systems (CSDDS) is a vital area in pharmaceutical research since it offers many potential treatments for various diseases that affect the colon, which is a crucial part of the digestive system. The pH environment, fluid content, microbiota, enzymes present, pressure, etc, varies across different regions of the colon. This unique feature of the colon imposes challenges in drug delivery. Although it is a challenge, these characteristics of the colon can be utilized using CSDDS to precisely target the drug in different areas of the colon while enhancing drug bioavailability, reducing systemic side effects, and thereby optimizing therapeutic outcomes.Conventional approaches such as prodrugs, pH-sensitive coatings, and time-based formulations have led to innovative technologies like 3D-printed devices, OPTICORE, Phloral™, MMX technology; offering promising solutions to the advancement of colon-specific drug delivery. The novel systems have many advantages over the previous approaches, including drug release site specificity, varied release kinetics and more. Many conventional approaches act as bases for some novel approaches. The novel approaches could be combined (such as, 3D printing of an oral dosage form using nanoparticles and coating with pH sensitive, biodegradable polymers) to design an even better CSDDS that is safe, highly accurate, specific with minimal side effects. However, there are more areas to explore regarding the variabilities in the colonic environment and more research to be done on some of the novel approaches, so that they do not remain just as treatment possibilities and can become viable treatment options.

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