Colon Targeting: A Novel Drug Delivery System

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Abstract

The oral route is considered to be the most preferred route for administration of drugs for systemic effect, but the oral route is not suitable to the administration of drug for lower gastrointestinal (GI) diseases, this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the accessibility of drugs at the lower GI tract. To overcome this difficulty, colon-specific drug delivery systems have been broadly analyzed during the last two decades. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, *etc*. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs, and anti-diabetic agents. This review article discusses, in brief, the introduction of the colon, factor affecting the colonic transition, colonic diseases and the novel and emerging technologies for colon targeting.

Keywords: Colon drug delivery, Crohn's disease, Inflammatory bowel disease, Lower GI tract, Ulcerative colitis, Amoebieasis

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Introduction

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs [1, 2]. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon [3]. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability [4]. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers [5]. Oral route is the most convenient and preferred route but other routes for CDDS may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal [6]. Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the

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depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity [7]. Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azoreduction and enzymatic cleavage i.e. glycosides [8]. These metabolic processes may be responsible for the metabolism of many drugs and may also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration. Target sites, colonic disease conditions and drugs used for treatment are shown in Table 1.

Table 1 Colon targeting diseases, drugs and sites

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

Limitations of colonic drug delivery

The development of a colon-specific drug delivery system is associated with specific limitations and challenges. A predominant and an obvious challenge is the fact that the colon is located in the distal part of the gastrointestinal tract (GIT). An orally administered dosage form has to traverse the entire alimentary canal in order to reach the target site. The GIT physiology is complex and has a wide range of pH values, fluid volumes, and transit times. Moreover, the presence of food and metabolic enzymes also increases the physiological complexity. These factors are an obstacle to the reliable and efficient delivery of drugs to the colon. Another factor is the drug solubility. Due to a low colonic luminal fluid volume, higher viscosity, and a neutral pH, the solubilization of the drug could be a rate-limiting factor for colonic absorption. Finally, maintaining the stability of the drug in the colon can be a matter of concern. The non-specific interactions of the drug with the colonic content *e.g.*, dietary residues, intestinal secretions, mucus, or faecal matter can have a negative influence on the stability of the drug [5]. In addition the colonic bacterial enzymes may also degrade the drug, rendering it ineffective.

Colon targeting diseases, drugs and sites

Inflammatory bowel disease (IBD) results from the interaction between genetic and environmental factors which influence the immune responses. Inflammatory bowel diseases are mainly divided into ulcerative colitis (UC) and Crohn's disease (CD). Crohn's disease is similar to UC, both of which have been classified as chronic IBD and which cause digestive disorders and inflammation in the gastrointestinal tract. Some of the symptoms of CD and UC include diarrhea, abdominal pain, rectal bleeding, and weight loss. They are mainly characterized by inflammation. Both the diseases may occur in adolescents and adults and affect men and women equally. Despite the similarity between the symptoms of these two diseases, there are some differences between the symptoms of CD and UC. Crohn's disease is one of the IBDs that occur in patients between ages 15-35 years. Unlike other inflammatory diseases, IBDs could not be suppressed easily. Consequently, the immune system is stimulated, and part of the intestine is destroyed. It causes pain, diarrhea, fever, and other symptoms. In addition to the serious effect on the lower part of the small intestine, CD can also occur in parts of the digestive tract including the large intestine, stomach, esophagus, or even mouth. Crohn's disease affects the mouth, anus, and the entire layers of the intestine. Ulcerative colitis affects the mucosal layer of the colon. The lesions occur in the rectum and the intestine. The symptoms are mild to severe

and may threaten life [1]. The symptoms of CD and UC are very similar. Malnutrition is very common in CD because the small intestine is responsible for the absorption of nutrients, and CD damages the small intestine [3]. Ulcerative colitis is associated with blood in stool, severe pain, and diarrhea, while in CD there is also a risk of bleeding in severe cases. Rectal bleeding is less common in CD, while UC is commonly associated with rectal bleeding. More than 50% of people with CD suffer from folate and vitamin D deficiency, while more than 50% of people with UC suffer from iron deficiency [4]. The affected areas of the digestive tract vary in these diseases. For example, CD often affects the ileum and a part of the large intestine. It may affect any part of the gastrointestinal tract (GI) including mouth, esophagus, stomach, small intestine, rectum, and anus. In CD, the small intestine often becomes inflamed, while UC is limited to the colon and is found mostly in some parts of the large intestine including colon and rectum. In UC, the large intestine becomes inflamed and the small intestine works naturally. Ulcerative colitis only affects the innermost part of the colon, while CD occurs in all layers of the bowel wall. By understanding the fact that CD and UC are both major categories of IBD, it could be pointed out that CD can cause serious problems particularly for skin and biliary stones, and UC will be associated with osteoporosis and possibly colon cancer if it lasts over 8–10 years. Crohn's disease is mostly associated with abdominal pain and problems such as fistula and rectal lesions. In contrast, people with UC usually suffer from intermittent pain consistent with bowel movements [6]. It affects both children and adults. It is estimated that UC affects 2.6 million in Europe and 1.2 million people in North America. Approximately 25% of these patients are diagnosed before the age of 18 years. The disease often begins in adolescence and approximately 25% of patients with IBD are younger than 20 years. Accordingly, clinical, endoscopic, histologic, and radiological tests are used to diagnose UC. About 7-10% of IBDs are unclear. According to literature, UC disease is a mucosal inflammation that is restricted to the colon and frequently expressed precisely by dysentery, abdominal pain, and tenesmus. Inflammatory bowel disease is one of the more frequent forms of dysbiosis diseases. The initial subtype of IBD that was known as a specialized distinct entity was UC; the term IBD includes the characteristics of both CD and UC. It has long been difficult to distinguish between these two diseases, but now there is a clinical definition for both. Both diseases can affect specific parts of the lives of patients, such as school, job, social life, and family life [11]. Therefore, this review paper aims to investigate the prevalence, causes, diagnosis, and treatment strategies for patients with IBD.

Introduction and research basis

The most common cases of IBD are reported at the age of 15-35 years. According to reports, 25-30% of patients younger than 20 years have been diagnosed with CD, while 20% of patients have been diagnosed with UC [12]. Javier and Pudolovsky reported an increased prevalence of IBD, especially CD, in countries with lower prevalence of the disease. They stated that environmental factors play a key role in the development of this disease. Despite the similarity of the clinical symptoms of the disease in children and adults, problems such as delayed growth have also been reported. Gribovski conducted studies of the possibility of developing an IBD at an early age, pointing out that it is possible to diagnose this disease during adolescence. However, he provided comprehensive reports on cases of CD and UC during infancy. In a comprehensive study of the CD in Sweden, Askling et al. reported that the disease increased from 2.4-5.4% in every 100 children in 1992–1990. In contrast, there was no increase in the prevalence of UC. Kugathasan et al. reported that out of every 100.000 children in the state of Wisconsin, 2.56% and 2.14% have been diagnosed with CD and UC, respectively. Similar studies in Iran (1969-2002) showed that the prevalence of IBD has been rising. Mikaeili et al. studied a total of 140 patients in Tehran over a period of 11 years. They reported that most patients with IBD suffered from UC and only a few patients with CD were reported. A comprehensive investigation into the prevalence of IBD in Iran (1973-1982; 1992-2002) reported an increase in the prevalence of UC. It should be pointed out that few people with CD were reported in Iran, emphasizing

the lower prevalence of CD. According to Malekzadeh et al., the increased IBD incidende in Iran raised awarness concerning this disease considering changes in lifestyle, diet, increased migration to cities, increased urban population, healthcare improvement and vaccinations. Accordingly, change in diet and health may increase the prevalence of IBD. According to the Cold Chain Theory, this change occurred in Iran later than it occurred in developed countries.

Causes of disease

Although the main cause of the IBD has not yet been fully understood, the comprehensive studies carried out in this regard highlight the role of genetic and environmental factors. Heymen et al. suggested two approaches for the main causes of IBD:

1. Disruption of the mucous system increases the immunological response rate in the human microbiota.
2. Any change in the content of the gut flora or the disruption of the epithelium function stimulates the pathologic response in the normal mucous system. On the other hand, Podolsky pointed out that pathogenicity in inflammatory bowel disease depends on factors such as the patient's susceptibility, mucosal immunity, and microflora of the intestine.

Several researchers have attempted to understand the microorganisms affecting the development of IBD, but no result has been obtained. Meanwhile, microbial flora varies in patients and healthy people. In his microbial culture experiment, Polovsky showed that the levels of Bacteroidetes in patients with CD increased in comparison with healthy people, while lactobacillus and bifidobacterium decreased. According to reports, the levels of enterobacteria increased significantly in patients with CD. On the other hand, patients with CD had higher antibody titers compared to *E. Coli* in healthy people. In a similar study carried out by Dickinson et al., on patients with UC, the side effects of IQA with high aggression and high adhesion were reported in stool specimens. In a comprehensive study, Marteau et al. showed that the levels of *E. Coli* and Bacteroidetes in the normal gut flora were higher in people with IBD. However, some microorganisms such as lactobacillus and bifidobacterium were introduced as useful bacteria which prevent the IBD. Some reports suggest that the prevalence of IBD does not follow the Mendel's genetic model. However, various pieces of evidence suggest that the role of genetic factors in the development of these diseases should not be underestimated. For example, various studies have highlighted the role of ethnic-racial differences in IBD, kinship, the prevalence of this disease in twins, chromosomal relationships, hereditary and genetic factors, as well as genetic syndromes. Heymen et al. investigated the effect of genetic factors on the prevalence of IBD. They reported that the risk of these diseases in the first-degree relatives of the patient was 7%, and these individuals are more prone to such diseases. On the other hand, Dickinson et al. reported that in families with a history of IBD, the prevalence of this disease is higher in young people. Similarly, Hayman et al. investigated the effect of genetic relationships between twins on the prevalence of this disease, showing that the effect of genetic relationships among twins was greater in CD than UC. Hample et al. reported that proper nutrition and breast milk can reduce the prevalence of CD and UC because breast milk protects the baby from gastrointestinal infections by helping the development and growth of the gastrointestinal mucosal system. Corra et al. reported that exposure to maternal infections in the fetal or early infancy, as well as newborn babies' exposure to infections could increase the risk of IBD. They also showed that infectious diarrhea during infancy could increase the prevalence of CD and UC. Koletzko et al. and Montgomery et al. investigated the role of viral infections in the prevalence of IBD. They stated that the measles infection can result in CD. Similarly, Walkkfield et al. carried out a comprehensive study of patients with viral infection in Sweden. They reported that measles increased the prevalence of CD. In contrast, they did not report any increase in the prevalence of UC. However, Ecbum et al by working on perinatal measles infection and subsequent CD, reported that there is no prevalence of measles and CD in England. Several studies were carried out on the role of measles vaccination and its effect on the prevalence of IBD, none of which reported

a significant relationship between the two.

Nutrition and inflammatory bowel disease

Given the fact that food first enters the digestive system, it can be said that diet can affect the prevalence of IBD to some extent. Several studies were carried out on the effect of different foods on the prevalence of IBD. For example, Davis et al. investigated the effect of sugar consumption on CD. Some others examined the effect of edible vegetable oils on UC. An investigation into the effects of fatty acid compounds showed that these substances greatly increase the prevalence of IBD. It should be noted that fatty acid compounds consist of acetic acid, tartaric acid, citric acid, and lactic acid. On the other hand, Belluzziet al. studied the effect of fish oil on IBD. They reported that fish oil consumption could be associated with a significant decrease in the clinical signs of IBD because fish oil affects the water-soluble protein molecules (cytokines and leukotrienes). Smoking can increase the amount of CD4+ T cells which are a type of white blood cell. They can release the inflammatory protein called interferon gamma, which is activated by smoking in the lungs. They move to the intestine and cause inflammation. Smokers are twice as likely to be affected by IBD, compared to other people. Additionally, it could be said that while smoking seems to have harmful effects in CD, but from the epidemiological view it has been overpoweringly proved that smoking protects against UC. However, Corrao et al.reported that smoking possibly has a significantly negative effect on developing UC disease, rather than on CD. On the other hand, studies on the effect of consumption of oral contraceptives have shown that contraceptives increase the prevalence of IBD. The appendix produces antigens that can help increase the immunity of the body against diseases. Appendicitis occurs due to the absorption of gut bacteria in the outer appendix, which increases the infections and appendicitis. Lashner et al. showed that removing the appendix could reduce the risk of UC, particularly after microbial infections. Forbes and Kalantzis investigated the effect of frozen foods in the United States and Europe. They showed that the prevalence of CD in the early twentieth century increased dramatically due to the increased prevalence of refrigerators. Anderson et al. and Forbes et al. showed that the enzymatic activity of psychotropics in refrigerators can contribute to IBD. One of the main causes of food corruption is microorganisms. Enzymes produced in these microorganisms decompose the proteins, fats, and sugars and lead to food corruption. The most dangerous microorganisms are those that are able to survive at the refrigerator temperature.

Signs and diagnosis of the inflammatory bowel disease (IBD)

In a comprehensive study, Hugot et al. investigated the clinical signs and diagnosis of IBD. In order to diagnose IBD, the clinical symptoms of the disease need to be examined. Some of the clinical symptoms of this disease are pediatric growth disorders, anemia, abdominal pain, bloody diarrhea, and arthritis. On the other hand, precise tests are needed to diagnose CD and UC. Common pathogenic bacteria causing IBD are *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Aeromonas*, *Clostridium Difficile*, *E. coli*, and tuberculosis. Several general assumptions reported by Garcia Rodriguez et al. have recommended that IBD disease develops by way of symbiosis between protective and harmful bacteria. Patients who suffer from an acute gastroenteritis have been presented with a raised risk of growing IBD. Gradel et al, by working on IBD and disclosing about pathogenic bacteria that can cause gastroenteritis disease such as *Campylobacter* and *Salmonella*, possibly play an essential role in the IBD etiology. In the case of initial rectal bleeding in children, who may occur due to hemorrhoids, polyps, or diverticulum, the possibility of IBD should be reported. CD is far more dangerous than UC; with more than half of the patients with CD suffering from severe infections in both colon and ileum. The most common clinical symptoms of CD include weakness, fatigue, long-term diarrhea with abdominal pain, weight variations, and rectal bleeding. These symptoms should be taken into account. Among people with inflammatory bowel disease, only a few were found to have viral infections in the mouth, stomach, or gastrointestinal tract. Accordingly, the highest number of infections was rectal infections. Burgmann et al. also conducted similar studies

to investigate the clinical signs of IBD [4]. The report revealed ulcers in the mouth and gums, chronic infections of the esophagus with pain, and severe swallowing disorders. Few patients had painful stomach ulcers and severe digestive disorders. In order to accurately diagnose CD and UC, modern medical equipment such as upper gastrointestinal radiography, endoscopy, colonoscopy, and gastrointestinal tract sampling are employed. The above mentioned equipment will help differentiate between these two diseases. However, it is very difficult to diagnose these two diseases in severe cases and in severe infection of the colon. Ulcerative colitis can emerge in various forms, such as inflammation of the rectal lining (proctitis) and panniculitis which occur in 40% and 20% of cases, respectively. In this disease, the results of the colonoscopy test indicate a progressive inflammation that affects the entire region of the rectum and colon. Moreover, some of the obvious clinical symptoms of this condition show that the colonic mucus is red with severe inflammation and small ulcers can be found around the colon. Once UC gets worse, benign tumors (polyps) may develop in the bowel wall. One of the most prominent symptoms of UC severe inflammation of the colonic mucus layers as well as severe inflammation of the rectum, which may extend to the deeper areas of the intestine. It can also affect the colon muscle layer. As a result, the number of intestinal movements decreases. This is known astoxic megacolon which is characterized by a much dilated colon, accompanied by abdominal distension and sometimes fever, abdominal pain, or shock [4, 5].

Some of the main symptoms of CD are mucosal constriction and fistula. Crohn's disease can cause intestinal mechanical obstructions due to scarring and swelling. Ulcers in the intestinal tract may develop into tracts of their own, known as fistulas. Crohn's disease can also increase the risk forcolon cancer, which is why people living with the condition must have regular colonoscopies. In order to introduce the best treatment for CD, areas of the body affected by the disease should be identified. For this purpose, radiographic methods can be used to diagnose more precisely the areas of the body affected by CD. Accordingly, CD is different from UC in terms of both medication and surgical treatment. However, in some cases, it is impossible to distinguish between patients with CD and UC. New studies have introduced capsule endoscopy as an important method for diagnosis of CD. Although there is no specific test for the diagnosis of CD or UC, some physical examinations, laboratory examinations, and endoscopy are needed for diagnosis. In some cases, inflammatory bowel disease can be diagnosed by accurate medical examinations such as stool testing, complete blood count (CBC), Barium X-ray imaging, radiological tests, sigmoidoscopy, colonoscopy, upper endoscopy, capsule endoscopy, and some other blood tests. Duigenan and Gee, by working on imaging of pediatric patients with inflammatory bowel disease, stated that CT enterography technique has become the initial imaging technique for appraising IBD and its difficulties in the US recently, because of a combination of rapid scan time, high-resolution evaluation of intestinal and extra-intestinal disease manifestations and 24hours availability in most hospitals. Clinical eye examinations can also play a useful role in diagnosing these diseases. Accordingly, rectal examinations can be performed as well. Thus, in 20-80% of patients with CD, perianal skin tags, itchiness, or pain around the anus may be suggestive of inflammation, fistulization, or abscess around the anal area, which are quite common. In addition to helping diagnose IBD, medical tests help us diagnose which patient needs endoscopy. After observing initial symptoms of the disease, the endoscopic test should be immediately performed to confirm the final diagnosis. It is necessary to examine the fecalcalprotecin. Accordingly, an increase in the fecalcalprotecin up to 81-91% can be suggestive of developing of the disease. On the other hand, an increase in the fecalcalprotecin up to 89-98% can have serious implications. An increase in the lactoferrin up to 80% is alarming, suggesting the likelihood of IBD. In a comprehensive study of the clinical features of UC, Moo et al. reported that some local side effects and external anomalies may appear in the disease. They also reported that severe rectal bleeding, sudden and severe colitis, and colon cancer may emerge. On the other hand, another study showed that the risk of cancer is

higher in people with UC who have a history of cancer in their family.

The difference between crohn's diseases, ulcerative colitis

Although there are many differences between CD and UC, both of them are characterized by bowel symptoms which can be seen in 25-40% of patients with IBD. Although most organs are affected by the diseases, symptoms first emerge in the eyes, skin, liver, and joints. The emergence of a symptom outside the bowel increases the risk of development in other organs. Eiden et al. examined other side effects of IBD, pointing out that side effects of CD are more obvious than UC. Some of the side effects of CD are colon bleeding, acute bowel perforation, fistula, abscess, and toxic mega-colon. Nugent and Roy conducted a study on 90 patients with CD. In a comprehensive report, they divided the disease into four stages- mild to moderate, moderate to severe, and chronic severe stage. The patient recovers when the symptoms of the disease disappear as a result of medication or surgical treatments. If medication fails to relieve the clinical symptoms of the disease, the patient will be likely to be at the mild to moderate stage, in which he/she will be able to keep fluids in the intestine but will not suffer from abdominal pain and bowel obstruction. If the disease is not detected or well-treated in the mild to moderate stage, it will progress to another stage (moderate to severe). Those who are at moderate to severe stage may suffer from fever, severe weight loss, acute abdominal pain, intermittent nausea, painful diarrhea (with no symptoms of recovery for up to a week), and anemia. Crohn's disease has more severe symptoms at the chronic stage, some of which are fever, continuous vomiting, bowel obstruction, abscess, severe abdominal pain, painful diarrhea, and cachexia. Danovitch investigated 27 patients with ulcerative colitis and described the disease in three stages. The mild stage is associated with rectal bleeding, mild diarrhea less than four-times a day, and mild pain due to proctalgia fugax. If no medication is taken at this stage, the disease will progress to moderate stage. Accordingly, the patient will experience more severe symptoms such as frequent watery diarrhea, painful stool, anemia, mild abdominal pain, and fever. In chronic and severe stages, the patient may suffer from severe abdominal pain, frequent diarrhea up to ten-times a day with severe pain due to proctalgia fugax, increased body temperature (up to 40°C), severe weight loss, and severe anemia.

History of diseases treatment

Kamm believed that the main objective of the diagnosis and treatment of the disease is to reduce the symptoms and improve the patient's health, to completely eliminate the symptoms of the disease or keep the disease at a fixed stage and avoid the surgical treatment. He also stated that in order to treat IBD, it was necessary to determine the type of disease before initiating the treatment. By carefully examining the clinical symptoms of the patient and performing several tests, the severity of the disease, as well as the areas affected by the disease, can be determined. It is important to realize how the body responds to the type of treatment. Inflammatory bowel disease can be treated by a combination of self-care and medical treatments. According to the Food and Drug Administration (FDA), an improved UC is a condition in which all inflammatory symptoms of the bowel, such as bleeding and severe diarrhea, ulcers, proctitis, and colon mucus are improved. Wheeler et al. investigated the diagnosis and symptoms of CD and concluded that unlike improved UC, the only way to detect recovery in CD is to report on improving the patient's quality of life. They attributed this to the lack of correlation between clinical symptoms of the disease and endoscopic observations. Feldman et al. conducted research on how to treat CD. The fact that the major causes of CD have remained unknown has hindered the development of strategies and treatments for the disease. Multi-dimensionality of the disease and uncertainty of the severity of the disease have complicated the diagnosis and treatment. Therefore, the objectives of the medical treatment were described as follows:

- Clinical treatment and improvement of the individual's clinical condition,
- Reducing the clinical side effects of the patient,
- Improving the quality of life,
- Reducing the drug poisoning,
- Nutritional support for the patient, and

- Restricting the patient's need for admission or surgery

The first step in treating IBD is pharmaceutical treatments. Physicians usually prescribe medication stage by stage. Firstly, less harmful drugs are prescribed; if these drugs do not provide the desired relief, some other drugs will be prescribed. Accordingly, the corticosteroids, aminosalicylates, antibiotics, supportive medications and immunosuppressive drugs are used to treat IBD. According to the American Therapeutic Association, aminosalicylates can be used to treat improved UC. For mild to moderate disease, aminosalicylates are proper selective drugs that can be used in various forms. The efficacy of aminosalicylates depends on the dosage. Wheeler et al. suggested corticosteroids for moderate to severe chronic conditions in order to improve the symptoms of the disease. Some antibiotics such as amoxicillin, ciprofloxacin, metronidazole, and azithromycin can improve the symptoms of CD. According to Afaf et al., azithromycin and erythromycin ameliorate the extent of colonic damage induced by acetic acid in rats; treatment with azithromycin significantly reduced the seriousness of gross lesions in a dose-dependent manner. On the other hand, erythromycin in small doses had no significant effect while higher doses had a significant effect on intensity of the inflammatory response. The effect of azithromycin is nearly doubled when compared to the corresponding doses of erythromycin used in their study. Also, treated rats showed a faster weight recovery as compared to the acetic acid control group. However, they cited that patients with resistance to antibiotic treatment can take corticosteroid drugs and immune regulators. Hanauer and Stromberg reported that drugs used to treat oral lesions in CD include sucralfate, carboxymethylene glucose, or hydrocortisone. On the other hand, Masuri et al. emphasized the effect of using drug compounds containing living microorganisms (probiotics) on the reduction of bowel wall inflammation. Methotrexate can also be used in patients who cannot tolerate azathioprine and mercaptopurine. However, surgical treatment can be used in cases where drug treatments do not improve the symptoms of IBD. Masuri et al. introduced scientific methods of treatment for CD and UC in a schematic diagram and classified. Jorgensen et al. reported that drug treatment in CD depends on the location of inflammation, the severity of the disease, the side effects of the disease, and the patient's response to drug treatment. Over the past decades, various drug treatments have been developed for this disease. The type of these drugsvaries, and they perform differently in enhancing the patient's immune system. However, the drug treatments increase the likelihood of adverse effects in the patient. Therefore, the main approach for the treatment of CD is to prescribe weaker drugs. Then, stronger drugs can be prescribed for the patient. Sulfasalazine, which contains 5-ASA, was the first aminosalicylate used to treat CD. This drug could improve the clinical symptoms of patients with mild to moderate Crohn's disease. Unfortunately, this drug was associated with side effects. However, patients who suffered from inflammation of the small intestine or underwent surgery were less likely to benefit from these drugs. Mesalamine as a nonsteroidal anti-inflammatory drug with drug class of 5-aminosalicyclic-acid derivative has been used for a long time and has a powerful effect in the remedy of IBD. As showed recently, this drug is really useful, well-tolerated and a safe drug for the remedy of ordinary ulcerative colitis that applied in most patients who suffer this disorder. One of the oldest remedies presently used in the management of IBD are aminosalicylates. Salazopyrin is the original drug in this category, but mesalazine (5-aminosalicylic acid [5-ASA]) is the active mediety drug of this category and is the principal aminosalicylate used in IBD remedy nowadays.

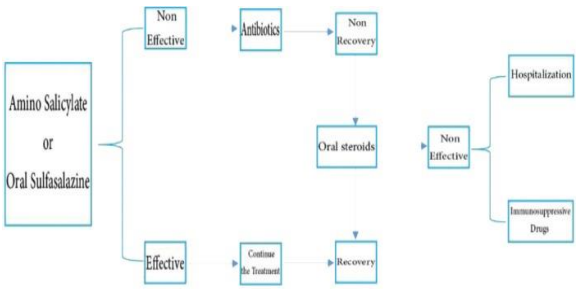

Figure 1 Treatment proposed by Mesuri et al. (1994) for Crohn's disease.

The initial stage of IBD remedy is by applying anti-inflammatory drugs. Frequent remedies in

this group include; Corticosteroids and Oral 5-aminosalicylates. Oral 5-aminosalicylates include sulfasalazine (Azulfidine), which contains sulfa, and mesalamine (Asacol HD, Delzicol, others). Oral 5-aminosalicylates have been widely used in the past but now are generally considered of limited benefit. On the other hand, corticosteroids such as prednisone and budesonide (Entocort EC) can help reduce inflammation in your body, but they don't work for everyone with CD. Doctors generally use them only if you don't respond to other treatments. These drugs work through direct contact with the inflammatory tissue. The possible side effects of anti-inflammatory drugs include nausea, vomiting, heartburn, diarrhea, and headache. Omega-3 fatty acids are also anti-inflammatory agents that can contribute to the treatment of IBD. Pentasa and Asacol are also used in the treatment of patients with CD and ileus colitis. Accordingly, Rowasa plays an important role in the treatment of patients with prostate cancer. Physicians usually start with Pentasa or Asacol for ileum colitis. If Pentasa or Asacol is fruitful, physicians may prescribe antibiotics such as Cipro or Flagyl for long periods (often several months). However, evidence suggests that antibiotics do not perform well in the treatment of CD. Siegel suggested that each patient should be treated separately because the type of disease and the clinical symptoms may vary from patient to patient. On the other hand, each patient with CD is familiar with symptoms, risk taking in treatment, fear of disease, morale, and treatment based on his/her personal experience. The general drugs for the treatment of CD are aminosalicylate, antibiotics, boneside, systemic corticosteroids, tyopurines, methotrexate, and TFT. These drugs can be used alone or in combination to optimize the treatment. Tanida et al. studied drug treatments for UC. They reported that the conventional treatments for UC include amniosalysilic-5, corticosteroids, and purine analogues (azathioprine and morapopurine- 6). They introduced anti-inflammatory cytokines such as TNF-α (tumor necrosis factor-α), interleukin 2, and integrin α4β7 as the main treatment for this disease. However, patients who cannot respond to conventional treatments are treated with other drugs such as calicineurin inhibitors, tacrolimus, TNF-α inhibitors, and a neutral antibody (vedolizumab). Tanida et al. pointed out that the treatments proposed for ulcerative colitis may be useful, but they are generally not effective. These treatments, while improving the early symptoms of the disease, may worsen the symptoms in the long run. Therefore, Tanida et al. suggested A2 (ANX) as a new molecular treatment strategy for the prevention of TNF-α destruction that could control ulcerative colitis. Metronidazole is one of the antibiotic drugs used in IBD, usually after surgical treatment or in cases where the side effects of inflammation appear in the body. Cyclosporine is the most commonly used drug in the treatment of ulcerative colitis. It should be pointed out that this drug can be toxic for patients with CD due to the need for higher doses. One of the most effective medications used in the treatment of UC is corticosteroid. However, body resistance to these drugs makes it difficult to take these drugs. Van Assche, Vermeire, and Rutgeerts reported that if UC does not respond to corticosteroid injections, it will be necessary to use cyclosporine, complete colectomy, or infliximab based on the patient's clinical condition and radiographic and laboratory findings. Similarly, Cima and Pemberton reported that sometimes patients with coronary fistula, CD, and UC do not respond to conventional treatments. In such cases, infliximab is used to treat the diseases. It is said that special treatment course can improve the symptoms of IBD in the short term. However, this method cannot improve and reduce the symptoms of the disease in long-term treatment. Corticosteroids can contribute to the treatment of CD. Accordingly, Zachos et al. reported that low-fat diets did not improve or reduce the symptoms of CDCD. Middleton et al. reported that minerals, proteins, liquids, vitamins, and sugar-free substances could relieve the side effects of IBD. On the other hand, it is stated that fruits, liquids, and fibers can reduce the risk of constipation in patients with UC.

Treatment and drug therapy

Ulcerative colitis treatment usually involves either drug therapy or surgery.

Several categories of drugs may be effective in treating ulcerative colitis. The type you take

will depend on the severity of your condition. The drugs that work well for some people may not work for others, so it may take time to find a medication that helps you.
In addition, because some drugs have serious side effects, you'll need to weigh the benefits and risks of any treatment.

Anti-inflammatory drugs

Anti-inflammatory drugs are often the first step in the treatment of ulcerative colitis and are appropriate for the majority of people with this condition. These drugs include: 5-aminosalicylates. Examples of this type of medication include sulfasalazine (Azulfidine), mesalamine (Asacol HD, Delzicol, others), balsalazide (Colazal) and olsalazine (Dipentum). Which one you take, and whether it is taken by mouth or as an enema or suppository, depends on the area of your colon that's affected. Corticosteroids, These drugs, which include prednisone and budesonide, are generally reserved for moderate to severe ulcerative colitis that doesn't respond to other treatments. Due to the side effects, they are not usually given long term.

Immune system suppressors

These drugs also reduce inflammation, but they do so by suppressing the immune system response that starts the process of inflammation. For some people, a combination of these drugs works better than one drug alone.

Immunosuppressant drugs include

Azathioprine (Azasan, Imuran) and mercaptopurine (Purinethol, Purixan). These are the most widely used immunosuppressants for the treatment of inflammatory bowel disease. Taking them requires that you follow up closely with your doctor and have your blood checked regularly to look for side effects, including effects on the liver and pancreas.
Cyclosporine (Gengraf, Neoral, Sandimmune). This drug is normally reserved for people who haven't responded well to other medications. Cyclosporine has the potential for serious side effects and is not for long-term use. Tofacitinib (Xeljanz). This is called a "small molecule" and works by stopping the process of inflammation. Tofacitinib is effective when other therapies don't work. Main side effects include the increased risk of shingles infection and blood clots. The U.S. Food and Drug Administration (FDA) recently issued a warning about to facitinib, stating that preliminary studies show an increased risk of serious heart-related problems and cancer from taking this drug. If you're taking to facitinib for ulcerative colitis, don't stop taking the medication without first talking with your doctor.

Biologics

This class of therapies targets proteins made by the immune system. Types of biologics used to treat ulcerative colitis include: Infliximab (Remicade), adalimumab (Humira) and golimumab (Simponi). These drugs, called tumor necrosis factor (TNF) inhibitors, or biologics, work by neutralizing a protein produced by your immune system. They are for people with severe ulcerative colitis who don't respond to or can't tolerate other treatments.

Vedolizumab (Entyvio). This medication is approved for treatment of ulcerative colitis for people who don't respond to or can't tolerate other treatments. It works by blocking inflammatory cells from getting to the site of inflammation. Ustekinumab (Stelara). This medication is approved for treatment of ulcerative colitis for people who don't respond to or can't tolerate other treatments. It works by blocking a different protein that causes inflammation.

Other medications

You may need additional medications to manage specific symptoms of ulcerative colitis. Always talk with your doctor before using over-the-counter medications. He or she may recommend one or more of the following. Anti-diarrheal medications, for severe diarrhea, loperamide (Imodium A-D) may be effective. Use anti-diarrheal medications with great caution and after talking with your doctor, because they may increase the risk of an enlarged colon (toxic megacolon). Pain relievers, for mild pain, your doctor may recommend acetaminophen (Tylenol, others) but not ibuprofen (Advil, Motrin IB, others), naproxen sodium (Aleve) and diclofenac sodium, which can worsen symptoms and

increase the severity of disease. Antispasmodics, Sometimes doctors will prescribe antispasmodic therapies to help with cramps. Iron supplements, if you have chronic intestinal bleeding, you may develop iron deficiency anemia and be given iron supplements.

Surgery

Surgery can eliminate ulcerative colitis and involves removing your entire colon and rectum (proctocolectomy). In most cases, this involves a procedure called ileoanal anastomosis (J-pouch) surgery. This procedure eliminates the need to wear a bag to collect stool. Your surgeon constructs a pouch from the end of your small intestine. The pouch is then attached directly to your anus, allowing you to expel waste relatively normally. In some cases a pouch is not possible. Instead, surgeons create a permanent opening in your abdomen (ileal stoma) through which stool is passed for collection in an attached bag.

Cancer surveillance

You will need more-frequent screening for colon cancer because of your increased risk. The recommended schedule will depend on the location of your disease and how long you have had it. People with proctitis are not at increased risk of colon cancer. If your disease involves more than your rectum, you will require a surveillance colonoscopy every one to two years, beginning as soon as eight years after diagnosis if the majority of your colon is involved, or 15 years if only the left side of your colon is involved.

Advantages of CDDS over conventional drug delivery

- Ideal site for the delivery of active agents to cure the colon diseases (ulcerative colitis, Chron's diseases, amoebiasis, *etc*.).
- Smaller drug quantities should be required for local treatment.
- Less side effects and drug interactions occurs.
- Dosage frequency is less so, cost effective.
- The long retention time of colon, improved bioavailability of poorly absorbed drug molecules (up to 5 days).
- Reduce gastric irritation caused by many drugs by preventing their absorption in upper GIT (*e.g*., NSAIDS).
- Bypass initial first pass metabolism.
- Extended daytime or night time activity.
- Limitation and challenges.
- Hard accessibility of the colon because of its location at the distal part of the alimentary canal.
- The drug may bind non-specifically to intestinal contents (dietary residues, intestinal secretions, fecal matter) cause reduce drugs bioavailability.
- Metabolic degradation of the drug by resident microflora could also affect colonic performance.
- Restrict drug transport across the mucosa and into the systemic circulation due to lower surface area and relative tight junctions in the colon.
- Lack of an appropriate dissolution testing method to evaluate the dosage form *in-vitro*.
- The drug in solution form required for successful colon delivery or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs.
- Factors to be considered in the design of colon-specific drug delivery system.
- Anatomy and physiology of colon.

Factors influencing colon-specific drug delivery and colonic bioavability

Several factors may influence the formulation/ development of a colon-specific drug delivery system (CDDS) and the colonic bioavailability of the drugs. Some of these factors are briefly discussed below.

Anatomical/physiological factors

The human large intestine is approximately 1.5-m long and forms the colon (ascending, transverse, and descending), with a small distal part forming the rectum. The colon is 2–3 in. in diameter, and its lumen is lined with mucus. The physiology of the colon differs significantly from other segments of the gastrointestinal tract (GIT) (Table 2). Moreover, the physiology and the physical properties of the colonic contents also differ between the ascending, transverse, descending, and sigmoidal colon. In addition, there exists variability in movement of food and dosage forms across the colon, which may present a challenge in the development of colonic drug delivery systems [7]. Another

physiological factor that affects colonic drug delivery and bioavailability is the variation in pH of the GIT. Significant intra- and inter-subject variability in the pH of the GIT have been observed between disease states, fasted/fed states, sexes, and ages in humans [8-10]. Factors such as the viscosity and volume of colonic fluids, the presence of microbial enzymes, and the resulting colonic metabolism are other important factors influencing CDDS performance which is discussed further.

Table 2 Variations in the physiology of human gastrointestinal tract [2, 7, 8]

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, intestinal juice which is mostly water, motilin, cholecystokinin, brush border enzymes (maltase, sucrose, lactase, enterokinase and carboxypeptidase) Bile (which contains electrolytes, fatty substances, 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 plays an important role in the performance of CDDS and the colonic bioavailability of drugs. The transit times are also influenced by colonic disease states such as UC and CD. Patients with UC are known to have shorter colonic times (~24 h) compared to healthy subjects (~52 h). Similarly, Rana *et al*. showed that in patients with IBD, the orocecal transit time was delayed. The transit of dosage forms generally depends on the time of administration, presence/ absence of food, and the type of dosage form. Stubbs *et al*. studied the effect of dawn and dusk on the motility of dosage forms in the colon. The results showed that colonic transit was delayed during sleep, and larger dosage forms, *e.g*., capsules transited faster compared to smaller dosage forms, *e.g*., dispersed particles.

Colonic fluid volume

The average human food intake is approximately 1.5 kg/day and mainly consists of undigested proteins, carbohydrates, and fats. These food components may serve as substrates for the microbial enzymes in the colon. The colon has a high water-absorbing capacity and can absorb ~90% of the water entering the colon. The colonic fluid volume is calculated to be in the range of 1–44 ml with an average volume of approximately 13 ml. Due to this low volume of colonic fluids, the dissolution of drugs from the dosage forms becomes challenging and may affect the local drug bioavailability.

Viscosity of colonic luminal contents

Due to a higher water-absorbing capacity, the viscosity of the colonic luminal contents is higher than upper GIT contents and presents a challenge for the dissolution of CDDS. Moreover, the viscosity of the contents progressively increases as it transits from the ascending colon towards the descending colon, resulting in a reduced drug dissolution and mucosal absorption. Viscosity also influences the penetration of the drug into the disease-causing bacteria in the colon. The mobility of bacteria in the colon has been shown to be dependent on the viscosity of colonic contents.

Colonic HP

The pH varies significantly between different regions of the GIT. For example, the pH of gastrointestinal contents can be as low as 1 to 2 in the stomach and rise to 7.5 in the distal small intestine. The pH then declines from the end of the small intestine to the colon and gradually increases once again in the colon. The pH of the colon may be influenced by a carbohydrate rich diet. This is due to the fermentation of polysaccharides by colonic bacteria and subsequent formation of short chain fatty acids. Similarly, polysaccharide-based drugs may also alter colonic pH. Laxative drugs like lactulose are known to be fermented by colonic bacteria to produce lactic acid and reduce colonic pH. Gastrointestinal disease states such as UC have also been found to influence the colonic pH. The pH of the colon affects the pharmacokinetic and pharmacodynamic behavior of a CDDS by influencing the solubility of drugs in the colonic fluid. Moreover, if one or more components of the dosage form are pH-sensitive, for example, a pH-sensitive coating membrane, the effect of colonic pH is even more pronounced on the drug release.

Colonic enzymes and metabolism

The colon is known to consist of over 400 different species of aerobic and anaerobic microorganisms like *Escherichia coli* and *Clostridium* species, respectively. These bacteria contain several hydrolytic and reductive metabolizing enzymes. The colonic enzymes catalyze a range of reactions, including the metabolism of xenobiotics (*e.g*., drugs) and

other biomolecules (*e.g.*, bile acid), deactivation of harmful metabolites as well as carbohydrate and protein fermentation. Polysaccharides such as chitosan, guar gum, pectin, *etc.*, are commonly employed as release rate-controlling components in colon-targeted dosage forms. These polysaccharides are known to be resistant to gastric and intestinal enzymes, but are metabolized by anaerobic bacteria in the colon. Drugs are also known to be susceptible to biotransformation by colonic enzymes. The metabolism of drugs by the colonic enzymes may result in the formation of metabolites that are pharmacologically active, inactive, or sometimes even harmful. Formation of a pharmacologically active metabolite by the colonic metabolism of drugs is a commonly used "prodrug" approach for the colon-specific drug delivery systems.

Formulation factors

The formulation factors that influence colonic drug delivery and bioavailability includes physicochemical properties of the drugs, the dose, and the dosage form factors. Due to the lower amount (1–44 ml) of colonic fluid available for dissolution, the solubility and the dose of a drug become important factors for its colonic bioavailability. Although the highly potent drug budesonide (dose, 9 mg) has a lower aqueous solubility, it is absorbed well in the colon and is used successfully in the treatment of UC. Mesalamine has a significantly higher solubility (3.64 mg/ml) compared to budesonide (0.24 mg/ml); however, it also has a significantly higher dose (4.8 g daily) which becomes a rate-limiting factor for its colonic absorption . Finally, the technology used in the dosage form development can also influence the colonic bioavailability of drugs. Useris® and Entocort EC® are currently approved budesonide products for the treatment of UC and CD, respectively .Useris® is a multi-matrix (MMX)-based delayed-release tablets, which ensures the drug release in the colon, while Entocort EC® is a capsule which releases the drug in the ileum to treat CD.

Criteria for selection of drugs for CDDS

Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule [17]. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems [13].

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

Anatomy of GIT

The GIT (alimentary canal) is a muscular, digestive tube that extends from mouth to anus, having functions to digest dietary food, to absorb nutrients, electrolytes, and fluids, and to prevent the absorption of potentially harmful substances as shown in Figure 2.

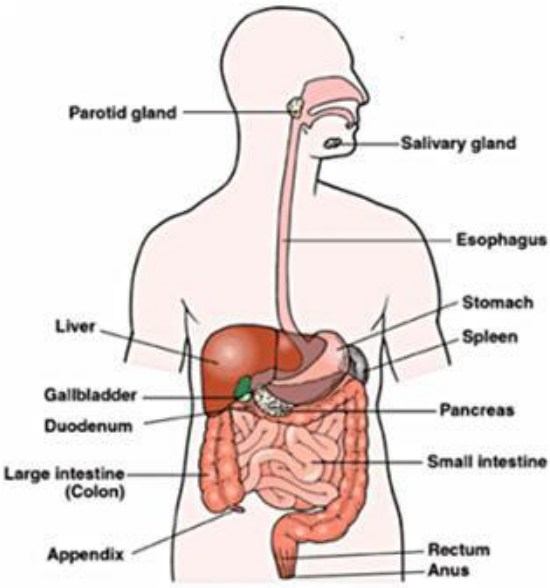

Figure 2 Anatomy of GIT

The GI tract is divided into stomach, small intestine, and large intestine. The longest part of the GIT is small intestine where most enzymatic digestion and absorption occur. The large intestine is the last major portion of the GIT (starts from the distal end of the ileum to the anus) and is about about 1.5 m long 10.

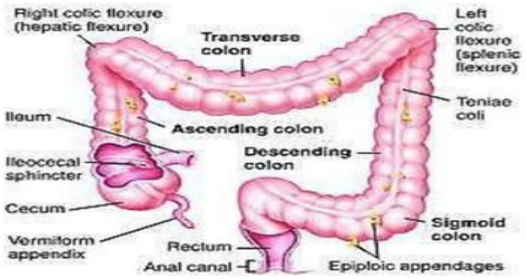

Figure 3 Structure of colon

Colon is upper five feet of the large intestine and mainly situated in the abdomen. Colon is a cylindrical tube that is lined by a moist, soft pink lining called mucosa as shown in Figure 3. The cecum is the first part of the colon and leads to the right colon or the ascending colon followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal. The right colon is made up of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon and left colon is made up of the left half of the transverse colon, splenic flexure, descending colon, and sigmoid. The colon does not have villi unlike small intestine, but due to the presence of plicaese-milunares (crescentic folds) the intestinal surface of the colon is increased to approximately 1300 cm2 [4,9,11]. The colon is made up of different layers and different parts as given in Table 4

Table 4 Different layers and parts of colon

Layers of colon	Description
Serosa	Exterior coat of the large intestine
Muscular External	Major muscular coat of the large intestine which composed of an inner circular layer of fibers surrounding the bowel and an outer longitudinal layer
Submucosa	A layer of connective tissue lies immediately beneath mucosa lining the lumen of the colon
Mucosa	The mucosa has three parts: epithelium, lamina propria, and muscular mucosa
Parts of colon	**Description**
Ascending colon	20–25cm long located behind the peritoneum hepatic flexure lies under right lobe of the liver
Cecum (Proximal right colon)	6 × 9 cm pouch covered with peritoneum appendix a vermiform (worm-like) diverticulum's located in the lower cecum
Cecum (Proximal right colon)	6 × 9 cm pouch covered with peritoneum appendix a vermiform (worm-like) diverticulum's located in the lower cecum
Transverse colon	Lies anterior in the abdomen, attached to gastrocolic ligament splenic flexure near tail of pancreas and spleen
Descending colon	10–15cm long located behind the peritoneum. After it enters the true pelvis it is known as the sigmoid colon
Sigmoid colon	This part describes an S-shaped curve in the pelvis that continues downwards to become the rectum
Rectum	This is a slightly dilated section of the colon about 13cm long. It leads from the sigmoid colon and terminates in the anal canal
Anal canal	This is the short passage about 3.8cm long and leads from the rectum to the exterior

Function of colon

- The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and storage of feces until excreted from the body.
- To provide a favorable environment for the growth of colonic microorganisms.
- Absorption of H2O and Na+ from the lumen, and secretion of K+ and HCO3

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

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

1) Primary approaches for CDDS

pH sensitive polymer coated drug delivery to the colon

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating [18]. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine [19]. From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers [20]. The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises [21]. Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor [22]. The decline in pH from the end of the small intestine to the

colon can also result in problems, lengthy lag times at the ileo-cecaljunctionor rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations.

Delayed (time controlled release system) release drug delivery to colon

Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability [23]. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h. However, the disadvantages of this system are:

Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug [24]. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea, and the ulcerative colitis [25, 26]. Therefore, time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hr [27]. The time-release function (or timer function) should work more efficiently in the small intestine as compared the stomach. In the small intestine drug carrier will be delivered to the target side, and drug release will begin at a predetermined time point after gastric emptying. On the other hand, in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time. Enteric coated time-release press coated (ETP) tablets, are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function) [28]. The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. The duration of lag phase is controlled either by the weight or composition of the polymer (HPC) layer.

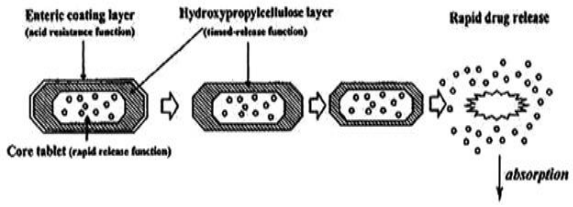

Figure 4 Design of enteric coated timed-release press coated tablet (ETP Tablet)

Microbial triggered drug delivery to colon

The microflora of the colon is in the range of 1011 -1012 CFU/mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc. This vast microflora fulfills its energy needs byfermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc [29, 30]. For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase [31]. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches. These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or

degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength [32-36]. They are then unable to hold the drug entity any longer [37].

Prodrug approach for drug delivery to colon

Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in vivo to release the active drug. For colonic delivery, the prodrug is designed to undergo minimal hydrolysis in the upper tracts of GIT, and undergo enzymatic hydrolysis in the colon there by releasing the active drug moiety from the drug carrier. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes [38]. A number of other linkages susceptible to bacterial hydrolysis especially in the colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, glactose, cellulose etc. Limitations of the prodrug approach are that it is not a very versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities, and need a lot of evaluation before being used as carriers [39]. A number of prodrug has been outlined in Table 5.

Table 5 Prodrugs evaluated for colon specific drug delivery with there in vitro/in vivo performance

Carrier	Drug investigated	Linkage hydrolyzed	In vitro/in vivo model used	Performance of the Prodrug/conjugates
Azo conjugates Suphapyridine (SP)	5-ASA	Azo linkage	Human	Site specific with a lot of side effects[59] associated with SP
5-ASA	5-ASA	Azo linkage	Human	Delivers 2 molecules of 5-ASA as compared to suphasalazine[60]
Amino acid conjugates glycine	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized by microflora of large intestine[61]
Tyrosine/methionine	Salicylic acid	Amide linkage	Rabbit	Absorbed from upper GIT, though metabolized by microflora of large intestine[62]
L – Alanin/D-Alanine	Salicylic acid	Amid linkage	In vitro	Salicylic acid-l-alanine was hydrolysed to salicylic acid by intestinal microorganism but salicylic acid-D-alanine showed negligible hydrolysis thereby showing enantiospecific hydrolysis[63]
Glycine	5-ASA	Amid linkage	In vitro	Prodrug was stable in upper GIT and was hydrolysed by cecal content to release 5-ASA[64]
Saccharide carriers	Dexamethasone/ prednisolone	Glycosidic linkage	Rat	Dexamethasone prodrug was site specific and 60% of oral dose reached the cecum. Only 15% of prednisolone prodrug reached the cecum[17]
Giucose/galactose/ cellobioside	Dexamethasone; prednisolone hydrocortisone, fludrocortisone	Glycosidic linkage	In vitro	Less hydrolysis of the prodrug was seen in contents of stomach and proximal small intestine (PSI).hydrolysis increased in contents of distal small intestine (DSI) and was maximum in cecal content homogenates. galactosides hydrolyzed faster than glucosides which hydrolyzed faster than the corresponding cellobioside[41]
Glucuronide conjugates glucuronic acid	Naloxone/nalmefene	Glucuronide linkage	Rat	When given to morphine dependent rats, these reversed the GIT side effects caused by morphine without causing CNS withdrawal symptom because of activation in large intestine followed by a resultant diarrheas which excreted the prodrug 7 drug[65]
	Budesonide	Glucuronide linkage	Rat	Was found to be superior than budesonide itself for treatment of colitis[66]

(ii) Azo-polymeric prodrugs

Newer approaches are aimed at the use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers have been used for this purpose. Sub synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety. These have been evaluated for CDDS. Various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreducatase in the large bowel. Coating of peptide capsules with polymers cross linked with azoaromatic group has been found to protect the drug from digestion in the stomach and small intestine. In the colon, the azo bondsare reduced, and the drug is released [28]. A number of azo-polymeric prodrugs are outlined in Table 6.

Table 6 Some azo polymer-based drug delivery systems evaluated for colon-specific drug delivery with summary of results obtained

Azo polymer	Dosage from prepared	Drug investigated	In-vitro/ in- vivo model used	Summary of the results obtained
Copolymers of styrene with 2-hydroxyethyl mrthacrylate	Coating over capsules	Vasopressin insulin	Rats dogs	These capsules showed biological respones characteristics of these peptide hormones in dog though it varied quantitatively[67-69]
Hydrogels prepared by copolymerization of 2-hydroxyethyl methacrylate with 4-methacryloyloxy) azobenzene	Hydrogen	5-fluorouracil	In vitro	Drug release was faster and greater in human fecal media compared to simulated gastric and intestinal fluids[70]
Segmented polynurethanes	Coating over pellets	Budesonide	Rat	These azopolymer-coated pellets were useful for colon-specific delivery of budesonide to bring healing in induced colites[71]
Aromatic azo bond containing urethane analogues	Degradable films	5-ASA	In vitro degradation of films in presence of lactobacillus	These films were degraded by azoreductase. The permeability of 5-ASA from lactobacillus treated films was significantly higher than that of control[72]

(iii) Polysaccharide based delivery systems

The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharides are found in abundance, have wide availability are inexpensive and are available in a verity of a structures with varied properties. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccrides can be broken down by the colonic microflora to simple saccharides [21]. Therefore, they fall into the category of "generally regarded as safe" (GRAS). A number of polysaccharide-based delivery systems have been outlined in Table 7.

Table 7 Polysaccrides investigated for colon specific drug delivery with their dosages forms and summary of results obtained

Polysaccharide investigated	Drug moiety used	Dosage form prepared	In vitro/ In vivo model used	Performance of the system
Chitosan	5-(6) carboxy fluorescein (CF)	Enteric-coated chitosan capsules	In-vitro	Little release of CF in upper GIT conditions and 100% drug release in 33% cecal contents within 4 h of dissolution[73]
Derivatives Chitson succinate Chitosan phthalate.	Sodium diclofenace	As matrices	In vitro	Reduced drug release was seen in acidic conditions and improved dissolutions under basic conditions[74]
Pectin (used as calcium salt)	Idomethacin	Matrices	In vitro	In the presence of rat cecal content drug release was 60.8±15.7% as compared to 4.9±1.1% in control[75]
Amidated pectin	Paracetamol	Matrix tablets	In vitro	These matrices were not suitable for drug delivery colon[76]
Amidated pectin / calcium pectinate	Ropivacaine	matrix tablet with ethyl cellulose as drug matrix additive	In vitro	Amidated pectin were more susceptible to pectinolytic enzymes as compare to calcium pectinate. Addition of ethyle cellulose increased the tablets strength and dissolution rate coating this formulation with Eudragit L100 reduced drug release in upper GIT conditions without effecting enzyme degradability[77]
Chondroitin sulphate, Cross linked chondroitin	Indomethacin	Matrix tablet	In vitro	Drug release increases in presence of rat cecal content. Also it was observed that as crosslinking increased, drug release decreased[78]
Alginates As calcium salt	5-ASA	Double coated swellable beads	In vitro	In basic media enteric coating dissolves and beads swell to exceed the strength of aquacoat film, which then burst releasing the drug[79]

2. Newly developed approaches for CDDS

Pressure controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules prepared using ethylcellulose, which is insoluble in water [62]. In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation [63, 64]. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drugdelivery systems. In pressure controlled ethylcellulose single unit capsules the drug is in a liquid [65]. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

Novel colon targeted delivery system (CODESTM)

CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems [66, 67]. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon, (Fig. 5). The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine [68]. Once the tablet arrives in the colon, the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to effect the dissolution of the acid soluble coating and subsequent drug release [69].

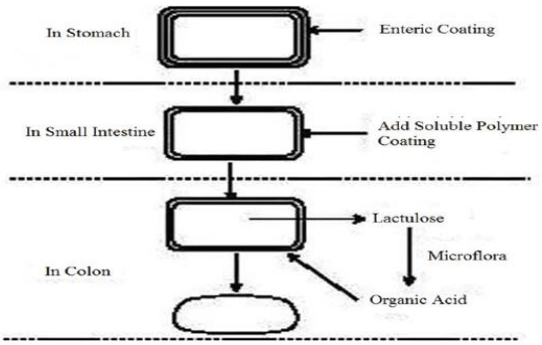

Figure 5 Schematics of the conceptual design of CODES™

Osmotic controlled drug delivery (ORDS-CT)

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable [70]. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, (Figure 6). Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves.

Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon [71-75]. Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

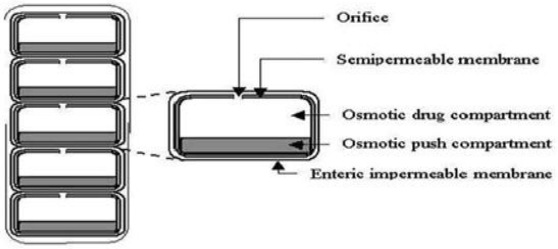

Figure 6 Cross-Section of the OROS-CT colon targeted drug delivery system

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

Invitro models used for CDDS

In vitro dissolution test

Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot fully mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon-specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract have been studied [76]. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileum segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4 [77].

In vitro enzymatic tests

Incubate carrier drug system in fermenter containing suitable medium for bacteria (strectococcusfaccium and B. Ovatus). The amount of drug released at different time intervals are determined. Drug release study is done in buffer medium containing enzymes (ezypectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

In vivo evolution

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human [78]. For rapid evaluation of CDDS, a novel model has been proposed. In this model, the human fetal bowel is transplanted into a subcutaneous tullel on the back of

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

Conclusion

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

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