# Various Pharmaceutical Approaches: A Comprehensive Review on Colon Specific Drug Delivery System

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## *ABSTRACT*

*Considerable attention has been given to the development of colon-specific drug delivery systems in recent years. The goal is to create drug delivery systems that can release drugs specifically in the colon in a predictable and reproducible manner. The colon is a site where drugs can be delivered locally or systemically. In order to achieve successful colon targeted drug delivery, it is necessary to protect the drug from degradation, release, and absorption in the upper portion of the gastrointestinal tract (GIT). Additionally, the drug must be released abruptly or in a controlled manner in the proximal colon. This review focuses on understanding the latest approaches for dosage forms that target the colon, including pH-sensitive systems, microbially triggered systems such as prodrugs and polysaccharide-based systems, timed release systems, osmotically controlled drug systems, and pressure-dependent release systems.*

## Introduction

The prevalence rate of inflammatory bowel disease (IBD) is estimated to be 6.8 million, with a high prevalence rate of ulcerative colitis (UC) [1]. This high rate is particularly observed in industrial areas [2]. Various treatments have been attempted for UC, but their success has been limited. Therefore, the need for effective therapy for UC has become increasingly important. The treatment options for UC can be divided into two categories: those that target the presumed cause of UC and those that manage its severity and symptoms. Many patients experience relapses and disease progression during their clinical course. The therapy for UC is divided into maintenance therapy, induction therapy, treatment for refractory disease, and surgery. Among these, effective acute therapy and safe maintenance therapy play crucial roles in the treatment of UC. There are three main classes of agents used for UC treatment: corticosteroids, immunomodulators, and mesalamine (also known as 5-aminosalicylic acid or 5-ASA). Additionally, antidiarrheal and antispasmodic preparations have been reported to help control the severity and symptoms of UC. Other preparations such as antipsychotics, antidepressants, and sedatives are not recommended for daily use, but low doses may be recommended to alleviate symptoms in UC patients [3, 4].

Until now, MES has been the primary medication for UC. Various drug delivery systems targeted specifically for the colon have been previously documented for MES.

These include mini tablets coated with guar gum and Eudragit S100, press-coated tablets based on hydroxy propyl methyl cellulose E-15 and Eudragit S100, mesalamine microspheres based on chitosan/Eudragit S100, and microspheres based on guar gum/xanthan gum. However, these formulations have been found to have certain limitations. For instance, pH-dependent delivery systems experience premature drug release during disease states when the pH of the gastrointestinal tract changes. Similarly, polysaccharide-based delivery systems suffer from incomplete drug release due to the loss of gut microflora. In recent years, there have been several attempts to develop oral formulations of MES in combination with other drugs, probiotics, or prebiotics to achieve successful treatment. This approach has been considered because an imbalance in the colonic microflora is one of the major causes of the disease [5].

Over the past few years, researchers have investigated the potential of silver nanoparticles (AgNPs) and modified apple polysaccharide (MAP) in the treatment of UC, thanks to their anti-inflammatory properties. Inflammation during UC is triggered by the release of prostaglandin and chemotactic substances such as interleukin-1 (IL-1), complement factors, TNF-α, and tumor growth factor-β (TGF-β). AgNPs have shown the ability to inhibit the activity of these inflammatory markers [6].

MAP has recently been found to be effective in producing gold nanoparticles through the reduction of aurochloric acid. In fact, insulin was successfully delivered orally by loading it with MAP capped gold nanoparticles. Building on this discovery, AgNPs were created using MAP as a reducing agent to reduce silver nitrate. The resulting MAP capped AgNPs were then loaded with MES (AgNPs-MES) and tested for their potential to treat ulcerative colitis in a rat model induced by acetic acid. Both MES and AgNPs are expected to provide anti-ulcer and anti-inflammatory effects, while MAP is expected to provide dual benefits by delaying the complete release of the drug in the upper gastrointestinal tract and providing anti-inflammatory effects against UC. This combination is expected to achieve multiple benefits, including better absorption and therapeutic efficacy of MES at much lower doses due to its loading with AgNPs to treat UC [7].

**Signs and symptoms of ulcerative colitis**

The initial symptoms of ulcerative colitis include severe abdominal pain, tenesmus, loss of appetite, and bloody or mucous diarrhea. In contrast, Crohn's disease does not typically present with bloody diarrhea. Additional severe symptoms of ulcerative colitis include weight loss, rapid heartbeat, anemia, rectal bleeding, and bowel distension. The severity of the disease determines its classification into various categories such as extensive, distal, proctosigmoiditis, and ulcerative proctitis [8].

Geographic, environmental, and socio-economic factors contribute to the varying global estimates of UC, which continue to rise. The majority of cases occur in individuals aged 10-40 years, with an estimated 240,000 affected in the UK, 1.4 million in the United States, and 2.2 million in Europe. Unfortunately, there is no permanent cure for inflammatory bowel disease, which can affect individuals of any age and persist throughout their lifetime. As a result, lifelong drug administration is necessary to maintain health-related quality of life. Over time, inflammation in UC can extend to more proximal regions of the colon, with the rectum typically involved. In contrast, CD typically involves inflammation in the distal ileum provides a comparison of Crohn's disease and ulcerative colitis [9].

**Epidemiology of ulcerative colitis**

In western Europe, Asia, and North America, the annual incidence of UC is approximately 24.3 per 100,000 population per year, 6.3 per 100,000 population per year, and 19.2 per 100,000 population per year, respectively. On the other hand, Crohn's disease has a lower incidence compared to UC, with approximately 12.7 per 100,000 population per year in Europe, 5.0 per 100,000 population per year in Asia, and 20.2 per 100,000 population in North America. The increasing incidences and prevalences of IBD worldwide are making it a global disease over time. However, Asia, Africa, and South America have significantly lower incidences of IBD. In the United States, it is estimated that over 1 million individuals, including 100,000 children, are suffering from IBD. Among gastrointestinal diseases, IBD ranks 5th in terms of prevalence [10].

Ulcerative colitis (UC) is a chronic and recurring inflammatory disorder of the colon. It primarily affects the distal bowel, specifically the distal colitis and proctitis, in approximately 60% of cases. The development of UC can be attributed to various factors, including both primary immunological dysfunction and an inappropriate immunological response to the surrounding environment, such as commensal intestinal microorganisms. The dysregulation of the immune system is the primary cause, leading to an excessive immune response against normal microflora. Additionally, abnormalities in epithelial cells and alterations in the composition of gut microflora contribute to an abnormal mucosal immune response. Another factor is the impaired gene expression, particularly the mutation of the CARD15/NOD2 gene located on Chromosome 16, as well as other genes like OCTN 1 and 2 on Chromosome 5, which are associated with Crohn's disease [11].

Gastroenterologists and immunologists are still puzzled by the origins of idiopathic inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Ulcerative colitis is a localized inflammatory disorder of the bowel, characterized by continuous inflammation of the mucosal lining from the rectum to the cecum. It is often associated with excessive production of IL-13. On the other hand, Crohn's disease is a recurring inflammatory disorder that can affect any part of the gastrointestinal tract, but is most commonly found in the terminal ileum and colon. It is characterized by discontinuous ulceration and inflammation, often involving granulomas, and is associated with excess production of IL-12/IL-23 and IFN-c/IL-17, ulcerative colitis focusing on the activation of T-lymphocytes. Previous studies have suggested that alterations in intestinal barrier function may play a significant role in the development of ulcerative colitis. Some authors have proposed that abnormally increased intestinal permeability is the underlying cause of the disease and contributes to its persistence. Consequently, the disrupted barrier function of the epithelial wall leads to increased permeability of the mucosa to luminal antigens, bacteria/microorganisms, and the loss of water and electrolytes, thereby triggering the inflammatory process. This disruption of the barrier also results in the loss of various electrolytes and water from the body through the epithelium. Furthermore, the damaged intestinal epithelial cells lose their polarity, leading to the apical expression of the transferring receptor protein. Normally, this protein is expressed on both the apical and basolateral regions of enterocytes in the inflammatory mucosa of patients with inflammatory bowel disease [12-14].

**Major challenges in the treatment of ulcerative colitis**

The primary obstacle in managing ulcerative colitis is the need to minimize the side effects of medication through targeted drug delivery to the colon. Additionally, long-term medication use often leads to numerous side effects that significantly impact the quality of life for patients with ulcerative colitis. Developing a delivery system that effectively delivers the maximum amount of medication to the specific site in the body at the appropriate time poses a significant challenge. Numerous drugs used to treat inflammatory bowel diseases have been associated with adverse effects such as peptic ulcers, diarrhea, nephro and hepatotoxicity, glaucoma, vomiting, Cushing's syndrome, etc. [15]

During the last 20 years, scientists have been faced with the primary obstacle of directing drugs specifically to the colonic area of the gastrointestinal tract (GIT). Another hurdle for children suffering from inflammatory bowel disease (IBD), particularly Crohn's disease, is the negative impact on skeletal and growth development caused by inadequate nutrition. Moreover, inflammatory mediators like cytokines can lead to mutations in hormonal axes, directly affecting growth. To address these challenges, the most effective approach involves implementing a suitable anti-inflammatory therapy alongside proper nutrition [16-18].

**Various drugs used for the treatment of ulcerative colitis**

The treatment of UC depends on the severity of the disease, its subtype, and any pre-existing conditions. The primary drugs used for treatment are anti-inflammatory agents, specifically 5-amino salicylates such as olsalazine, mesalazine, and balsalazide. These medications are primarily used for mild to moderate attacks and to maintain remission in UC. Immunosuppressive agents, including azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus calcineurin inhibitors, are also commonly used. Another class of drugs that can be utilized are corticosteroids like prednisolone, as well as anti-TNF-a-antibodies for moderate to severe cases of Ulcerative Colitis. In situations where the disease is refractory or in a fulminate stage, surgery may be considered as a better option for IBD patients [19].

**Conventional/unconventional drug therapy for UC**

**Conventional drug therapy**

**Amino salicylates.** Sulfasalazine is a first-class antibiotic drug that contains 5-aminosalicylic acid (5-ASA) and sulphapyridine. While 5-ASA has anti-inflammatory effects, sulphapyridine has anti-bacterial properties. The exclusive mechanism of action of 5-aminosalicylates involves the stimulation of nuclear receptors that regulate inflammation and cell proliferation. It helps to reduce the production of chemoattractant leukotrienes and inhibits the cellular release of interleukin-1 [21].

It additionally hinders the transcriptional activity of nuclear-factor jB, which controls the genes responsible for immunity and inflammation. Due to extensive metabolism in the liver, its systemic bioavailability is poor. This class of drugs induces remission in 40-80% of patients. It is administered orally in the form of sustained-release tablets or granules, and locally applied as suppositories or enemas. However, its usage is limited due to intolerance related to sulphapyridine. Numerous studies have reported that ciprofloxacin is the commonly prescribed antibiotic for moderate to severe ulcerative colitis. Approximately 80% of remission can be achieved within the first 2-4 weeks of initiating first-line therapy [22].

**Corticosteroids**

Corticosteroids have the ability to initiate remission during UC flares, although they are unable to sustain remission. The precise mechanism by which they operate remains uncertain, but it is believed to involve the suppression of cytokine release through the inactivation of NFK. Consequently, this results in a decrease in lymphocyte recruitment, a reduction in vascular permeability, and the inhibition of cytokine-induced tissue necrosis. Various forms of corticosteroids, including oral, topical, and intravenous, can be employed for treatment [23].

There is no disparity in the rates of remission induction when using oral or parenteral steroids. Parenteral steroids, such as methyl-prednisone, prednisolone, or hydrocortisone, are administered in severe cases or when patients are unable to take medication orally. These steroids can be given as a bolus or through continuous infusion. A recent study on patients with severe UC found that continuous infusion of methylprednisolone was equally effective and safe as bolus administration [24]. Oral prednisone, at doses of 30-60 mg daily, can also be used to induce remission. Higher doses do not provide additional benefits and may lead to side effects, especially at doses exceeding 40 mg daily. Steroids induce remission in approximately 50% of patients and elicit a response in 80% of patients. If steroids are used for more than 2 weeks, the dosage should be gradually tapered to prevent hypoadrenalism. Long-term use of steroids can result in adverse effects such as hypertension, diabetes, weight gain, psychiatric disorders, and infections. The prevalence of osteoporosis in patients with inflammatory bowel disease (IBD) varies between 12% and 42% depending on the population studied [25]. Steroids can also contribute to osteoporosis, putting these patients at an increased risk of vertebral fractures. Patients on steroids should be supplemented with calcium (1200 mg/day) and vitamin D (800 IU/day) [26].

**Azathioprine/6-mercaptopurine**

Azathioprine (AZA) is a prodrug that undergoes a nonenzymatic reaction in red blood cells and other tissues to convert into 6-mercaptopurine (6-MP). The main mechanism of action of AZA/6MP is the inhibition of purine synthesis, which ultimately affects DNA and RNA synthesis. Additionally, they also inhibit the proliferation of T- and B-lymphocytes. However, the exact mechanism of action in ulcerative colitis (UC) is still unknown. Both AZA and 6-MP can be used to induce and maintain remission in UC, with efficacy rates ranging from 60% to 70%. They can also be utilized to reduce the dosage or completely discontinue the use of steroids in patients who have shown improvement with steroids and in those with chronic active disease that is not fully controlled with steroids. The metabolism of 6-MP involves three enzymes: Thiopurine-S-methyltransferase (TPMT) methylates it to 6-methylmercaptopurine (6-MMP), Hypoxanthine-guanine-phosphoribosyl transferase transforms it into 6-thioguanine (6-TG), which is the active metabolite, and Xanthine oxidase catalyzes its conversion to inactive thiourate. The absorption of AZA in healthy individuals ranges from 16% to 50%, but it may be lower in UC patients due to increased intestinal motility during acute UC exacerbations [27-30].

Measurement of TPMT genotypes prior to initiating AZA or 6-MP treatment can aid in preventing toxicity by identifying individuals with low or absent TPMT enzyme activity. Patients with a normal phenotype can receive a standard weight-based dose.

Heterozygous individuals, who have half the enzyme levels, would require reduced initial doses of the medication. Homozygous deficient patients, with very low enzyme levels, should avoid the drug altogether. The usual weight-based maximum dose for AZA is 2.5 mg/kg, while for 6-MP it is 1.0-1.5 mg/kg. There is a dosage conversion factor of 50% between AZA and 6MP. Serious adverse events are rare at doses below 2.5 mg/kg/day for AZA and 1.5 mg/kg/day for 6MP. Concurrent use of mesalamine, which reduces TPMT activity, can cause an increase in 6-TG levels. Allopurinol, which blocks the enzyme xanthine oxidase, can also elevate 6TG levels. In patients taking allopurinol, these medications should be initiated at half the usual dose. Once AZA/6-MP treatment is well tolerated and remission is achieved, it should be continued indefinitely. There is no compelling evidence to support dose reduction for the prevention of long-term side effects. Moreover, reducing the dose may increase the risk of relapse for the patient [31, 32].

**Cyclosporine**

Patients who have severe or fulminant colitis and do not show improvement with steroids may be considered for cyclosporine therapy. Cyclosporine can be particularly beneficial for individuals with new-onset ulcerative colitis who have severe or fulminant colitis and are not mentally prepared for a colectomy. In a controlled trial involving 11 patients who received cyclosporine, 9 individuals responded positively within an average of 7 days, whereas none of the 9 patients in the placebo group showed improvement. Another study examining the long-term effects of cyclosporine found that 62% of the 42 patients were able to avoid colectomy after 5.5 years [33].

Cyclosporine, an 11-amino acid lipophilic peptide, has the ability to bind to a group of cytoplasmic proteins called cyclophilins. When combined with cyclophilins, cyclosporine inhibits calcineurin, resulting in reduced transcription of cytokine genes like interleukin (IL)-2 and tumor necrosis factor (TNF) alpha [34].

In a few research studies, the prescribed dosage of cyclosporine for patients with ulcerative colitis experiencing an acute flare-up was 4 mg/kg/day. This dosage maintained a stable trough level between 300 and 400 ng/ml, as mentioned in a study by Kornbluth et al. in 1997. However, two other studies conducted by Rayner et al. in 2003 and Van Assche et al. in 2003 have demonstrated that a lower dosage of 2 mg/kg/day, with a trough level ranging between 150 and 250 ng/ml, can yield similar effectiveness while potentially causing fewer side effects. It is crucial to monitor the blood trough levels of cyclosporine throughout the therapy. At our institution, we utilize the monoclonal assay provided by Abbott. Nevertheless, other institutions may have access to alternative assays such as the polyclonal assay or high-pressure liquid chromatography (HPLC) assay. Additionally, it is advisable to assess cholesterol levels before initiating the therapy, as low cholesterol levels can increase the risk of seizures [35].

**Anti-tumor necrosis factor therapy**

Infliximab (Remicade) is a chimeric monoclonal antibody that specifically targets tumor necrosis factor-alpha (TNF-alpha). It is indicated for inducing remission in patients with moderate-to-severe ulcerative colitis (UC) who have not responded to or cannot tolerate mesalazine (5-ASA) medications and immunomodulators.

Additionally, it can be used to maintain remission in UC patients who have failed treatment with mesalamine and immunomodulators. The effectiveness of infliximab in UC patients who are dependent on steroids is uncertain. However, it can be considered for use in acute cases of steroid-resistant UC in patients who are hesitant to undergo surgery [36].

The two primary clinical trials conducted to evaluate the efficacy of infliximab are known as ACT 1 and ACT 2. Both trials included a total of 364 patients with ulcerative colitis (UC). In ACT 1, the patients had active UC and were treated with either steroids, 6-MP, or AZA. On the other hand, ACT 2 involved UC patients who were unresponsive to at least one standard therapy, including 5-ASA, corticosteroids, or immunosuppressants [37].

In ACT 1, the clinical response was greater in both treatment groups compared to the placebo group after 8 weeks. However, in ACT 2, the clinical response was similar between the drug and placebo groups. By week 30, both studies demonstrated an enhanced clinical response in the infliximab group. Furthermore, the infliximab group exhibited higher clinical remission rates at all time points in both studies. It is worth noting that case reports have indicated limited efficacy of infliximab in chronic pouchitis [38].

**Antibiotics**

Luminal bacteria are believed to play a significant role in the development of inflammatory bowel disease (IBD). The efficacy of antibiotic therapy in ulcerative colitis (UC) is attributed to various mechanisms, such as reducing the concentration of luminal bacteria, modifying the composition of gut microflora, minimizing bacterial invasion into tissues, and preventing bacterial translocation and systemic dissemination. While numerous clinical studies have investigated the use of antibiotics in IBD, most of them have focused on patients with Crohn's disease (CD). In contrast, studies involving UC patients have not consistently demonstrated therapeutic benefits. However, a randomized placebo-controlled study involving 83 patients revealed that the addition of ciprofloxacin improved the outcomes of conventional therapy. Antibiotics may be indicated in cases of fulminant colitis in order to prevent life-threatening infections [39,40].

**Methotrexate**

The efficacy of methotrexate in the management of ulcerative colitis remains uncertain. While some uncontrolled studies have indicated potential benefits of low-dose methotrexate [41], a single controlled trial involving UC patients did not demonstrate any advantages [42].

**Alternative therapies**

**Probiotics**

Probiotics play a crucial role in regulating the immune system within the gastrointestinal tract by promoting the production of protective cytokines while inhibiting the release of proinflammatory cytokines. Clinical trials have demonstrated the efficacy of probiotics in preventing relapse in individuals with ulcerative colitis (UC). In one study, E. coli 1917 Nissle was found to be equally effective as 5-ASA in preventing relapse. Another study conducted by Tursi et al. in 2004 revealed that a combination of eight bacterial species known as VSL#3,

when used alongside balsalazide, exhibited slightly superior efficacy compared to balsalazide or mesalamine alone in individuals with mild-to-moderate UC demonstrated that Lactobacillus GG was more effective than mesalamine in prolonging the duration of relapse-free periods in individuals with UC [43].

**Fish oil**

Patients who have active ulcerative colitis exhibit elevated levels of leukotriene B4 in their rectal mucosa. The activity of leukotrienes can be inhibited by eicosapentaenoic acid (EPA) derived from fish oil. A study conducted by Aslan and Triadafilopoulos in 1992 demonstrated that dietary supplementation with fish oil leads to clinical improvement in patients with mild-to-moderate active ulcerative colitis. However, this supplementation does not result in a significant reduction in mucosal leukotriene B4 production when compared to placebo therapy [44].

**Nicotine**

Epidemiological investigations have indicated that UC primarily affects individuals who do not smoke. A couple of clinical trials have demonstrated the positive effects of transdermal nicotine in treating mild active UC. Conversely, another trial has revealed that transdermal nicotine is not effective in sustaining remission [45].

**Colona targeting Drug Delivery system**

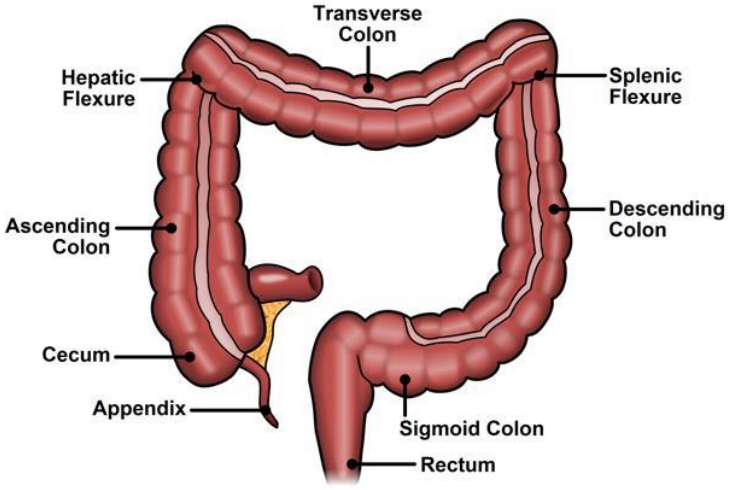
The colon contains a significant amount of lymphoid tissue. For example, when antigens are taken up by mast cells in the colonic mucosa, it leads to the rapid production of antibodies in the local area. This process plays a crucial role in efficient vaccine delivery. Compared to the stomach and small intestine, the colon is recognized as having a less hostile environment with lower diversity and intensity of activity [46].

**Advantages of CDDS over conventional drug delivery**

Glucocorticoids and other anti-inflammatory agents are currently used to treat chronic colitis, specifically ulcerative colitis and Crohn's disease. However, the administration of glucocorticoids like dexamethasone and methyl prednisolone through oral and intravenous routes can lead to systemic side effects such as adenosuppression, immunosuppression, cushinoid symptoms, and bone resorption. Therefore, it is important to find a way to selectively deliver drugs to the colon in order to reduce the required dosage and minimize the systemic side effects associated with high doses [47].

## FACTORS AFFECTED IN THE DESIGN OF COLON SPECIFIC DRUG DELIVERY SYSTEM

The GIT is comprised of the stomach, small intestine, and large intestine. The large intestine, which extends from the ileocecal junction to the anus, is further divided into three main parts. These parts include the colon, the rectum, and the anal canal. The colon, measuring approximately 5 feet (150 cm) in length, is divided into five major segments. The right colon consists of the cecum, ascending colon, hepatic flexure, and the right half of the transverse colon, as indicated in Table 2. On the other hand, the left colon encompasses the left half of the transverse colon, descending colon, splenic flexure, and sigmoid. Finally, the rectum serves as the last anatomical segment before reaching the anus [48]




**Colon pH**

The pH levels in the gastrointestinal tract (GIT) can vary both between individuals and within the same individual. Factors such as diet, disease, and food intake can influence the pH of the gastrointestinal fluid. These variations in pH have been utilized for targeted drug delivery to the colon. According to radio telemetry data, the highest pH (7.5 ± 0.5) is observed in the terminal ileum. As the fluid enters the colon, the pH decreases to 6.4 ± 0.6. In the mid colon, the pH is around 6.6 ± 0.8, while in the left colon, it is approximately 7.0 ± 0.7. The drop in pH upon entering the colon is attributed to the presence of short-chain fatty acids produced by bacterial fermentation of polysaccharides. For instance, colonic bacteria ferment lactose, resulting in the production of lactic acid and a subsequent decrease in pH to around 5.0 [49].

**Colonic microflora and enzymes**

A significant quantity of anaerobic and aerobic bacteria can be found throughout the entire length of the human gastrointestinal tract (GIT). Intestinal enzymes play a crucial role in triggering the release of drugs in different parts of the GIT. Typically, these enzymes are derived from the abundant gut microflora residing in the colon. They are responsible for breaking down coatings or matrices and separating an inert carrier from an active agent, resulting in the release of a drug from a prodrug. Researchers have identified over 400 distinct bacterial species, with 20-30% belonging to the bacteroides genus. The concentration of bacteria in the human colon is approximately 1000 CFU/mL. Among the anaerobic bacteria, bacteroides, bifidobacterium, eubacterium, peptococcus, peptostreptococcus, ruminococcus, and clostridium are considered the most significant [50].

**Transit of material in the colon**

In contrast to other parts of the digestive system, the colon exhibits a sluggish movement of materials. The duration of transit can vary greatly and is affected by various factors including diet, specifically the amount of dietary fiber, physical activity, stress, illnesses, and medications. The time it takes for materials to pass through the colon can range from 50 to 70 hours. The weight of stool significantly increases when there is active disease, likely due to exudates from inflamed epithelium, heightened mucus secretion, and a decrease in the reabsorption of fluid and electrolytes [51].

**Drug absorption in the colon**

Drugs can be absorbed in two different ways: passively through either the paracellular or transcellular route. Transcellular absorption occurs when drugs pass through cells, and this is the preferred route for lipophilic drugs, which are soluble in lipids. On the other hand, paracellular absorption involves the transport of drugs through the tight junction between cells, and this is the preferred route for hydrophilic drugs, which are soluble in water [52].

**Criteria for selection of drug for CDDS**

The drugs that are most suitable for colon-specific drug delivery systems (CDDS) are those that have low absorption rates from the stomach or intestine, including peptides. These drugs are commonly used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhea, and colon cancer. The selection of drugs for CDDS is based on specific criteria, which are summarized in Table 3. Another important factor in CDDS is the choice of drug carrier. The selection of a carrier depends on the physiochemical properties of the drug and the targeted disease. Factors such as the chemical nature, stability, partition coefficient of the drug, and the type of absorption enhancer chosen all influence the carrier selection. Additionally, the functional groups present in the drug molecule play a role in determining the appropriate drug carrier. For instance, drugs with aniline or nitro groups can be linked to another benzene group through an azo bond. Carriers that contain additives like polymers (which can be used as matrices, hydrogels, or coating agents) can also affect the release properties and effectiveness of the drug delivery systems [53].

## APPROACHES FOR CDDS

**pH sensitive system**

The drug release mechanism in this approach relies on the pH levels. By taking advantage of the pH difference between the upper and lower parts of the gastrointestinal tract (GIT), drugs can be efficiently delivered to the colon. It is important to consider that the pH in the intestine and colon can be influenced by various factors, including diet, food consumption, intestinal movement, and disease conditions.

The complexity of the task faced by experts in this field is increased due to the need to create a delivery system that can effectively endure the fluctuations in gastric pH as it transitions from the stomach to the small intestine. To address this challenge, researchers have utilized their understanding of polymers and their solubility in various pH environments to develop delivery systems that can accurately target the desired site for drug release. Copolymers consisting of methacrylic acid and methyl methacrylate have been extensively studied for their potential use in drug delivery systems for the colon [54].

**Time controlled or Time dependent system**

Time-controlled systems have proven to be valuable in synchronizing drug administration with specific patient needs or targeted sites within the gastrointestinal tract (GIT). These systems are particularly beneficial in treating diseases that are influenced by circadian rhythms. Additionally, time-controlled formulations designed for colonic delivery are considered delayed-release formulations, where the timing of drug release is based on a predetermined time delay. Developing such formulations to achieve precise drug release in the colon poses a challenge, as the release site is determined by the transit time of the formulation in the GIT.

Ideally, these formulations should be unaffected by individual variations in gastric emptying time, stomach and small intestine pH levels, or the presence of anaerobic bacteria in the colon. On average, it takes approximately 3 hours for an orally administered dosage form to traverse the length of the small intestine and reach the beginning of the colon. In comparison to gastric emptying, the transit time through the small intestine remains relatively consistent [55].

**Microbially triggered system**

These systems rely on the utilization of the specific enzymatic activity of the microflora (enterobacteria) found in the colon. The bacteria in the colon are mainly anaerobic and produce enzymes that can break down substrates like carbohydrates and proteins that were not digested in the upper gastrointestinal tract. The bacterial population in the colon is significantly higher, reaching around 1011-1012 CFU/mL, and consists of approximately 400 different species. Among these species, there are predominantly aerobic bacteria such as Bacteroides, Bifidobacterium, and Eubacterium, among others [56].

**Targeted prodrug Design**

Classical prodrug design often employs a general chemical approach to conceal undesirable drug properties, such as low bioavailability, lack of site specificity, and chemical instability. In contrast, targeted prodrug design introduces a novel strategy for precise and efficient drug delivery. Specifically, prodrugs that target a specific enzyme or membrane transporter, or both, hold great potential as drug delivery systems, particularly in cancer chemotherapy. The design approach focuses on targeting the specific enzyme or carrier substrate specificity to overcome various undesirable drug properties. This requires extensive knowledge of the molecular and functional characteristics of the enzyme or carrier system [57].

## CONCLUSIONS

The gastrointestinal tract (GIT) has seen an increase in the importance of the colonic region as a site for drug delivery and absorption. Targeting drugs to the diseased colon offers several advantages, including reducing systemic side effects, minimizing drug dosage, delivering the drug only when needed, and maintaining the drug's integrity close to the target site. Various approaches to colon drug delivery exist, providing treatment options for local colon diseases or facilitating the absorption of poorly absorbable drugs into the systemic circulation. However, the presence of a wide range of pH values and different enzymes throughout the gastrointestinal tract poses challenges in terms of reliability, formulation delivery efficiency, and successful targeting to the colon.

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