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Review Article

# ADVANCING COLON-TARGETED BUDESONIDE DELIVERY: A REVIEW OF THE LATEST DEVELOPMENTS AND FUTURE PERSPECTIVES

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**ABSTRACT**

Colon-specific drug delivery is advantageous for treating various local diseases, including inflammatory bowel disease, ulcerative colitis, Crohn's disease, chronic pancreatitis, and colonic cancer. Corticosteroids are considered the first-line drug therapy for the treatment of colon-specific diseases but also cause adverse side effects. Budesonide, a second-generation corticosteroid characterized by a relatively low side effect profile and low bioavailability resulting from extensive first-pass liver metabolism, has received approval from the Food and Drug Administration for the treatment of colon-specific diseases. Various methods have been employed for colon-targeted drug delivery. Key approaches include pH-sensitive drug delivery, time-controlled delayed release, and microbially triggered drug delivery, along with additional strategies such as prodrug delivery and pressure-controlled drug delivery. Budesonide can be given in many different formulations such as coated tablets, multi-matrix tablets, pellets-based formulations, capsules, 3D-printing, and nanoparticles-based formulation techniques. This detailed analysis of budesonide can help to improve the development of new techniques and treatments for colon-specific drug delivery.

**Keywords:** Budesonide, Corticosteroids, Inflammatory bowel disease, Colon-specific delivery, Targeting approaches.

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## INTRODUCTION

Millions of people worldwide suffer from colon-related diseases such as inflammatory bowel disease (IBD), and the condition's prevalence is rising. Because its etiology and pathogenesis are poorly understood, it is regarded as an incurable disease. IBD symptoms can interfere with day-to-day functioning and range from ulceration and total blockage of the gastrointestinal (GI) tract to bloody diarrhea and weight loss [1]. In recent years, significant focus on colon-targeted drug delivery was seen because of its potential to enhance the treatment of localized colon diseases while reducing systemic side effects [2]. The colon serves as a location for both localized and systemic drug delivery [3]. Locally, it facilitates the treatment of IBDs. The targeted delivery of drugs to the colon has been shown to offer several therapeutic advantages [4]. Medications that are inactivated through pancreatic enzymes or stomach acid ingestion experience minimal changes in the colon, leading to a steady release of these drugs over time [5]. Some common diseases that affect the colon include Crohn's disease (CD), ulcerative colitis (UC), irritable bowel syndrome, amebiasis, chronic pancreatitis, and colonic cancer as shown in Fig. 1 [6]. The colon serves as a site of systemic absorption for various medications intended to treat conditions other than colonic disease. If given to the colon, intact medications such as proteins and peptides which get degraded at extremely high pH can be absorbed systemically by the colonic mucosa [7]. The colon-specific drug delivery system (CDDS) ought to be able to safeguard the drug's path to the colon; that is, the drug must not be released or absorbed in the stomach or small intestine, and the bioactive ingredient should not be broken down in either of the dissolution sites; instead, it should only be released and absorbed once the drug reached the colon [8]. CDDS effectiveness is contingent upon the physio-chemical characteristics of the drug, the kind of delivery mechanism used, any additional variables that might affect the GI transit time, and the extent of the drug's interaction with the GI tract. Because of their convenience, increased manufacturing flexibility, better patient adherence, relative safety, and lack of sterile preparation requirements, oral dosage forms are the most popular delivery method for colon-specific delivery [9].

Numerous approaches have been explored for colon-targeted drug delivery, including pH-sensitive polymer-coated drug delivery, time-release drug delivery, drugs released by bacteria, and many new developments such as pressure-control drug delivery or innovative colon-targeted delivery systems [10,11]. Numerous studies have focused on developing drug delivery systems for specific medications used in the colon, including metronidazole, tinidazole, ornidazole, prednisolone, budesonide, naproxen, mesalazine, and others, utilizing different types of polymers such as pectin, guar gum, chitosan, Eudragit L100, Eudragit S100, and others [12]. This article gives a brief understanding on different targeting approaches for treating colon-related diseases.

### Role of Glucocorticoids (GCs) in IBD

GCs are naturally occurring hormones (cortisol, cortisone, and corticosterone) which are also produced in laboratories and are commonly used for treating various illnesses. The release of GCs is mainly controlled by the hypothalamic–pituitary–adrenal (HPA) axis, influenced by the body's daily cycle, stress, and inflammation. For instance, when certain proteins such as cytokines, interleukin-1, tumor necrosis factor, and interleukin-6, are released, they can cause severe damage to tissues by triggering uncontrolled inflammation. This, in turn, stimulates the HPA axis to produce and release GCs. The HPA axis manages inflammation by affecting both genetic and non-genetic processes, which in turn, inhibits the growth, movement, and multiplication of immune cells from both the innate and adaptive immune systems [13]. The Glucocorticoid receptor (GR), which are mostly located in the cytoplasm of cells and are linked to a complex consisting of many proteins such as heat-shock proteins, immunophilins, kinases, and phospholipases, are the key factor influencing their behavior. Following the interaction between GC/GR and the resulting changes in shape, the GR separates from the receptosome and moves into the nucleus [14]. Two zinc finger motifs in a particular DNA sequence cause the GR to become active in the genome. To control the expression of several genes, including those involved in inflammation and gene transcription [such as activator protein-1 and nuclear factor-kappa B

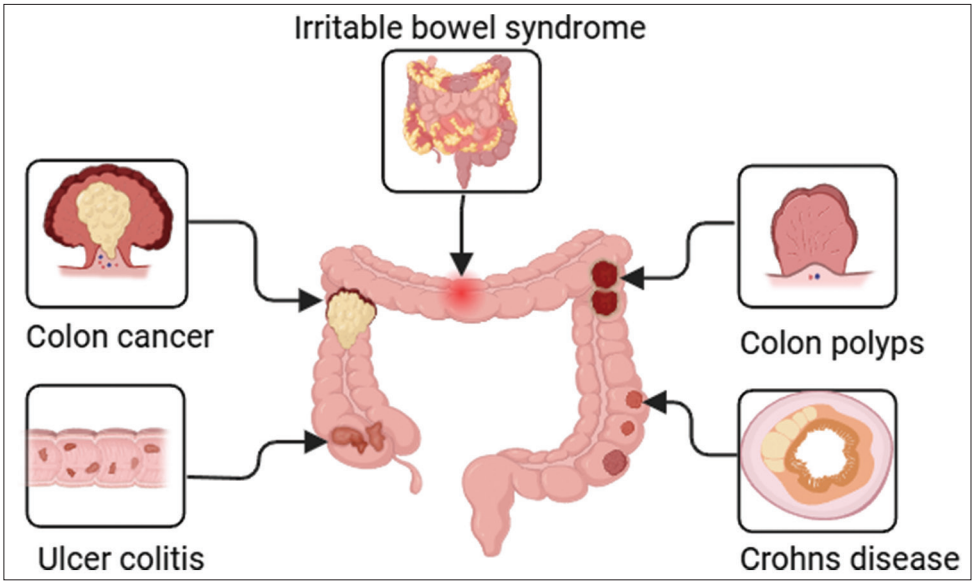


**Fig. 1: Common diseases affecting the colon**

(NF-κB)], this sequence points the GR toward particular glucocorticoid-responsive elements (GRE) [15,16]. Glucocorticoid-induced leucine zipper is a key target of GC/GR transcriptional activity. It inhibits the expression of the NF-kB gene and the mitogen-activated protein kinase pathway, which regulates immunological and inflammatory responses [17-19]. However, the presence of GRE alone does not fully explain how the GR controls its gene expression. The specific functions of GCs vary by cell type and are influenced by additional factors, such as the accessibility of the target genes' DNA, which affects the availability of DNA sequences [20,21]. Furthermore, non-genomic effects add to the intricacy of GC/GR signaling. These effects often lead to a brief delay in response and involve the production of intracellular second messengers and various signaling pathways, including phospholipase activation, changes in cyclic adenosine monophosphate levels, alterations in protein kinase pathways, and mobilization of calcium ions [22,23].

GCs play a crucial role in regulating the breakdown of carbohydrates, fats, proteins, water, calcium, and other minerals, as well as ensuring the proper functioning of the endocrine, skeletal, cardiovascular, nervous, and immune systems [24,25]. Long-term use of GCs intensifies the natural effects of these hormones, which frequently result in negative outcomes such as high blood pressure, elevated blood sugar levels, weakened bones, Cushing's disease, and changes in mood [26,27]. Thus, while GCs may have significant anti-inflammatory and immunosuppressive properties, these benefits are short-lived. The impact of GCs on the intricate regulation of how cells react to stress and in managing inflammation is closely related to the negative side effects that come with their long-term use, necessitating the cessation of treatment [28,29].

GCs are classified as follows (Fig. 2):

**First generation GCs**

The main goal of using GCs is to achieve clinical remission. A structured treatment plan ensures a decrease in symptoms and adverse reactions from these medications. Every GC is a suitable choice for managing IBD. The most frequently employed GCs include prednisone, methylprednisolone, and hydrocortisone. These medications can be administered individually or together with mesalamine for the purpose of achieving and sustaining clinical remission in individuals with chronic IBD [30-33].

The optimal amount of prednisone for treatment is typically between 1 mg/kg and 40–60 mg daily, with higher doses not showing any

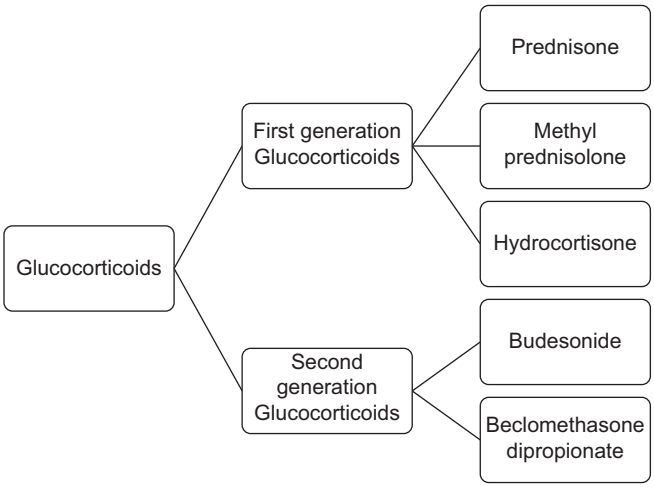


**Fig. 2: Types of glucocorticoids**

additional benefits in treatment effectiveness [34,35]. The initial dosage is usually between 40 and 60 mg daily, but it is necessary to lower the dose slowly to stop treatment while still keeping IBD symptoms under control. Research has also found that treating every other day can help lessen and prevent side effects on the brain. Using prednisone together with other medications (like azathioprine) allows for reducing or stopping the use of GCs while continuing treatment [36]. It is crucial to recognize that prednisone can be life-saving in severe conditions, particularly in chronic UC treatments ranging from 6 to 3 months. However, the benefits are short-lived, with patients often losing the advantages after 9 months of treatment [37]. Research has demonstrated that the use of first-generation GCs, like methylprednisolone (ranging from 12 to 48 mg daily), in conjunction with other medications, such as sulfasalazine (3 g daily), plays a crucial role in enhancing symptom relief. It has been observed that these benefits manifest more rapidly when compared to treatment with sulfasalazine by itself [38].

The selection of treatment and its dosage also depends on the method of administration, which varies based on the location of the disease. For individuals with UC, applying the medication directly to the affected area is possible if there is proctitis, or it can be both topical and systemic for UC on the left side. Conversely, in CD, the decision to use GCs is primarily based on the severity of the disease, as patients may not respond well

**Table 1: Different formulation strategies for colon targeting using budesonide**

| Formulation | API | Excipients | Disease | Key finding | References |
|---|---|---|---|---|---|
| 1. Fast dissolving tablet | Budesonide | Guar Gum, HPMC, HEC, CAP, CSS, Eudragit- s100 | Colon targeting | In the treatment of nocturnal asthma and irritable bowel syndrome, budesonide tablets are helpful. | [52] |
| 2. Sustained release tablet | Budesonide | Lactose, Eudragit RL100, Eudragit- L100 | Inflammatory bowel disease | Budesonide compression-coated tablets are potentially beneficial for treating irritable bowel syndrome, with Batch F4 showing the best results. | |
| 3. Compression coated tablet | Budesonide | Eudragit-S100, Eudragi-L100, CAB, Pectin, guar gum. | Inflammatory bowel disease. | Budesonide compression-coated with 75% pectin shows potential benefits for treating inflammatory bowel disease | [67] |
| 4. Pellet-based tablet | Budesonide | Xanthan gum, Eudragit NE30D, Eudragit L30D55, Eudragit FS30 | Ulcerative colitis, Inflammatory bowel diseases | The colon-targeting pellets adequately shield the small intestine and stomach simulation environments. | [68] |
| 5. Colon targeted tablet using SNEDDS | Budesonide | Capmul MCM C8, Tween 80, polyethylene glycol 400 | Colon targeting | Developed colon-targeted drug for budesonide using solid SNEDDS, with potential applications for other poorly water-soluble drugs. | [69] |
| 6. Zero-order release of Budesonide tablet | Budesonide | Eudragit S100, HPMC, SSF, PEG 6000, Croscarmellose sodium, MCC, etc. | Ileocolonic inflammatory bowel disease | The goal of the *In vitro* research was to create zero-order sustained-release tablet that targeted the ileo-colonic and contained either 3 mg or 9 mg of budesonide. | [70] |
| 7. Pectin Film Coated Pellets for Colon-targeted Delivery of Budesonide | Budesonide | Eudragit RS30D, Eudragit NE30D, Pectin | Ulcerative colitis | Pectin/Sure lease-coated pellets (1:3 ratio, 35% coating) significantly increased budesonide release in the presence of rat cecal content. | [71] |
| 8. 3D printing colonic targeting tablet of Budesonide | Budesonide | | Inflammatory bowel disease (IBD) | The study offers fundamental proof of concept for using 3D printing technology to target oral medications in the GI tract in a controlled manner. | [72] |

to treatment and could require surgery if the disease is severe [39]. It is important to mention that the lack of response to GCs is similar in both CD and UC. While first-generation GCs are effective, they are linked to a number of severe adverse effects, such as osteoporosis, high blood sugar, high blood pressure, changes in mood, stomach ulcers, and a higher risk of infections [26,38]. This aspect restricts their use over an extended period. Therefore, it is not advised to continue treatment with GCs on a systemic level.

**Second-generation GCs**

New medications such as budesonide and beclomethasone dipropionate (BDP) have been developed to retain their anti-inflammatory qualities while reducing their absorption and, consequently, their systemic adverse effects, in response to the limitations of long-term use of first-generation GCs [40]. Budesonide is broken down by the liver before it enters the bloodstream, which helps to lower the risk of side effects related to corticosteroids. Numerous studies have been done to prove how well oral budesonide works. A random study was assigned where budesonide was found to be equally effective as prednisone in reaching remission in randomly assigned individuals with mild, active CD where either budesonide (9 mg daily for 2 months) or prednisone (40 mg daily for the first 2 weeks, then 30 mg daily for the 3rd month) was given [41]. Budesonide also had fewer side effects (33% compared to 55% with traditional GCs). There have been no reports of budesonide directly causing changes in bone density or adrenal function, but it is important to note that some people may be more sensitive to it, leading to these issues. Therefore, there is no direct link between budesonide use and the development of osteoporosis symptoms or adrenal insufficiency. Several reviews have shown that budesonide is effective in inducing remission and it is equally effective to take it once daily as it is to take it three times. For more severe conditions, budesonide is not as effective as prednisolone in achieving remission [42,43].

BDP, a newer type of GC, is a modified version of cortisone. It shows effects on the skin and does not show any significant systemic activity. It is given as a prodrug and is partly broken down in the lower part of the digestive system. At low doses, BDP has been found to cause fewer side effects than traditional GCs that are taken systemically [44]. The effectiveness of BDP in treating CD has been thoroughly studied, with eight double-blind randomized trials published. BDP has been approved for use in treating UC in several countries. In one study, BDP was given as a daily dose of 5 mg for 4 weeks, followed by a week off, then another 4 weeks of the same dose. The results were similar to those seen with prednisolone, and there was no difference in the number of side effects. However, as a second-generation GC with low systemic absorption, BDP leads to fewer side effects than first-generation GCs [45-47].

## MECHANISM OF COLON TARGET DRUG DELIVERY

Various advanced pharmaceutical techniques and mechanisms have been developed to achieve effective colon-targeted drug delivery. Different formulation strategies for colon targeting using different drugs have already achieved like Budesonide which is listed in Table 1. These include the use of pH-sensitive polymer coatings that dissolve at specific pH levels encountered in the colon, time-dependent drug-

release systems that delay drug release until the formulation reaches the colon and enzyme-dependent release mechanisms that leverage the action of colonic microbial enzymes to trigger drug release. These strategies are designed to enhance drug bioavailability, improve therapeutic outcomes, and minimize side effect.

**pH-dependent system**

The pH-dependent system generally exploits the idea that the pH of human GI tract increases progressively from the stomach (pH 1.2–3), small intestine (pH 6.5–7.0) to the colon (pH 7.0–8.0) [48]. These variations in pH are the foundations for the use of pH-dependent polymers. The polymers described as pH dependent in colon-specific drug delivery are insoluble at low pH levels but become more soluble as pH rises [49]. The pH variations that occur during GI tract passage are the basis for most commercialized system for local drug administration to the colon. The usefulness of pH-dependent systems as a single colonic delivery mechanism in various physiological or pathological circumstances in the GI tract has been questioned, notwithstanding their simplicity. The pH-dependent release of these formulations means that there is no effective rate-controlling mechanism to ensure extended release of the drug along the entire length of the colon [50]. The dosage form containing the active medication in a core is coated with pH-dependent material that dissolves at the colon's pH to take advantage of the colon's highest pH value.

**Time-dependent system**

Time-dependent delivery has been proposed as a means of targeting the colon. These systems deliver their medication after a delay that is set before use. To ensure the medication reaches the colon, the delay should match the time it takes for the system to travel there. Predicting this time in advance is challenging, but a delay of 5 h is often thought to be enough, especially since the time it takes for the small intestine to move contents is generally consistent, ranging from 3 to 4 h [51]. However, the drawback of the time-dependent release system is its inability to sense any variation in the upper GI tract transit time [52]. GI movement, especially peristalsis or contraction in the stomach, would result in change in GI transit of the drug [53]. Besides, any variation in gastric emptying time may lead to drug release in the small intestine before arrival to the colon [52].

**Microbial triggered system**

Humans normally carry between 103 and 104 bacteria/milliliter (CFU/mL) in their stomach and small intestine. However, when we proceed from the ileum to the ascending colon, the number of bacteria increases substantially, reaching 1,011–1,012 CFU/mL. These bacteria are primarily anaerobic, including ruminococcus, bifidobacteria, eubacteria, clostridium, enterococci, and bacteroides [54]. These bacteria are able to survive and flourish by breaking down a variety of substances, such as complex sugars (such as oligosaccharides, polysaccharides, and mucopolysaccharides), which are not fully digested in the small intestine. Therefore, a system that is controlled by enzymes is seen as an effective method for delivering drugs specifically to the colon, where the drug can only be released once the system reaches the colon [55].

Utilizing biodegradable polymers for medication administration to the colon seems to be a more targeted approach than others because biodegradable enzymes are mostly located in the colon. These polymers effectively convey the medication to the colon while shielding it from the severe environment of the stomach and small intestine [56]. When they get there, they are either broken down by enzymes, ingested by microbes, or the structure of the polymer degrades, which lowers their molecular weight and compromises their structural integrity. As a result, the medication can no longer be retained by the polymer [57].

**Others targeting approaches**

*Prodrug approach for colon delivery*

Prodrug is chemically an inactive version of main drug that needs to be naturally or with the help of enzymes converted into its active form inside the body to become effective. When it comes to deliver drugs through the colon, prodrugs are created to have the least amount of absorption and breakdown in the upper part of GI tract and then are broken down by enzymes in the colon, allowing the active drug component to be released from the carrier [58]. The metabolism of azo compounds by the intestinal bacteria is one of the most extensively studied bacterial metabolism processes. Both intracellular and extracellular reduction has been observed. In many cases, bacterial hydrolysis specially for colon specific have been prepare by attaching the drug with hydrophilic moieties such as amino acid, glucuronic acid, glucose, galactose, and cellulose. Limitations of the prodrug approach is 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 [59].

*Azo polymeric prodrug/azo polymeric coating*

New strategies are being developed to use polymer as drug carriers for drug delivery to the colon. Certain synthetic polymers have been reported to form polymeric prodrug through azo-linkage between the polymer and drug component [60]. These have been evaluated for colon targeted drug delivery. One such prodrug consisting of a non-absorbable sulfanilamide ethylene polymer linked to 5-ASA was found to be more effective than sulfasalazine in reducing inflammation in guinea pig [61]. Different azo polymers have also been evaluated as coating materials over drug cores. These have been found to be equally vulnerable to being broken down by the azo-reductase in the large intestine. Coatings of peptide capsules with polymers cross-linked with azo-aromatic group have been found to protect drug from digestion in the stomach and small intestine. In the colon, the azo bonds weakens and the drug gets released [62].

*Polysaccharide-based delivery system*

Polysaccharides are commonly utilized in drug delivery to the colon due to their availability, affordability, ease of chemical or biological modification, stability, safety, non-toxicity, and biodegradability. They encompass naturally present polysaccharides derived from plants (such as guar gum and inulin), animals (such as chitosan and chondroitin sulfate), algae (including alginates), or microorganisms (such as dextran). The colonic bacteria then break these polysaccharides into simple sugars. Polysaccharide-based delivery systems shield the medication from the harsh conditions in the upper GI tract [63]. Upon reaching the colon, the glycosidic bonds within the polysaccharides are broken down, releasing the active drug component. The primary bacteria species involved in this process are Bacteroides and Bifidobacterium [64].

Chitosan, also referred to as poly(N-glucosamine), is a high-molecular-weight cationic polysaccharide that is produced by deacetylating the chitin found in crab and shrimp shells. The abundant intestinal bacteria break it down. Chitosan was primarily developed as a capsule-forming substance for colon-specific medication administration. It has been discovered that enteric-coating capsules are highly site specific [65]. Another linear polysaccharide that is not starch is pectin, which mostly consists of $\alpha$-(1-4)linked d-galacturonic acid residues broken up by 1,2-linked L-rhamnose residues. It primarily affects the small intestine and stomach physiological states and is broken down by bacteria, particularly bacteroides, which inhibit the human colon [66].

**New therapeutic GC-based delivery approaches in chronic IBD**

Numerous research efforts have focused on creating innovative ways to administer current medications to enhance treatment effectiveness by minimizing the adverse reactions tied to certain drugs or the development of drug resistance. The intricacy of biological pathways and the networks that control life processes has emerged as a key concern in biological science. Consequently, "molecular stratification" represents a fresh strategy that considers individual patient needs, their vulnerability to illness, and the diversity of their genetic makeup. Investigations concentrate on particular components of various biological pathways. The aim of these drug-delivery systems is to boost

the therapeutic benefits of medications. They are crucial for managing properties such as solubility, aggregation of drugs, low bioavailability, poor distribution throughout the body, and reducing unwanted side effects [73,74].

Red blood cells (RBCs) constitute the largest group of blood cells, primarily responsible for transporting oxygen throughout the body's tissues. To serve as carriers for active substances, RBCs need to develop temporary openings in their membranes, allowing the substance to pass through. This process is triggered by external factors such as ultrasound. In addition, substances can be taken up by the cell through a process called endocytosis when specific chemicals, like hydrocortisone, are present. Substances of various sizes can be incorporated into the cell or attach to its surface [75,76]. The typical lifespan of RBCs ensures that the therapeutic effect lasts for about 120 days, which is why inactive substances like dexamethasone-21-phosphate are utilized. Over the past decade, there has been a focus on refining drug selection and understanding how certain drugs interact with RBCs to minimize potential drawbacks. The development of prodrugs, such as corticosteroid prodrugs and nucleotide prodrugs, has enhanced the effectiveness of RBCs as carriers. Should the delivered substance be inactive, RBCs have the ability to convert it into its active form [77].

Budesonide is delivered throughout the entire colon in a controlled manner using a colonic delivery device called the Multi-Matrix System (MMX®). According to research using MMX, headaches, nausea, and urinary tract infections were the most commonly reported adverse effects [78,79]. The HPA axis is less active and natural cortisol production is reduced when active GCs, such budesonide MMX, are administered. The effectiveness of 5-aminosalicylic acid (5-ASA), the first line of treatment for mild-to-moderate active UC, is comparable to that of 9 mg of oral budesonide MMX daily, which is significantly more effective than a placebo and can induce remission in mild-to-moderate UC [80]. The effects of GCs are seen more quickly compared to 5-ASA, which typically takes about 2 weeks to take effect, making it unsuitable for moderate disease as the only treatment [81]. A different approach to delivering drugs involves the use of nanoparticles (NPs), which can be either organic, inorganic, or made of polymers, and range in size from 1 to 100 nm. In the field of pharmaceuticals, several synthetic polymers are utilized, including poly-L-lactic acid, polyvinyl alcohol, poly (lactic-co-glycolic acid), and polyethylene glycol (PEG) [82]. The effectiveness of NPs largely depends on their ability to quickly and selectively enter the intestine, leading to reduced drug excretion following diarrhea, a common symptom of IBD. The process by which NPs enter cells involves either paracellular transport or endocytosis into the cells' surface [83]. Research has demonstrated that NPs with a diameter of 200 nm, when coated with cetyltrimethylammonium bromide and maintained at a neutral charge, were able to bind to both healthy and inflamed tissue in the colon, as well as in a model of colitis induced by 2,4,6-trinitrobenzene sulfonic acid, and in a model of colitis induced by oxazolone [84]. It is important to investigate other factors that can affect uptake, in addition to particle size. Studies in both animal and laboratory settings have indicated that the charge of the NPs can influence their targeting in the colon. Cationic NPs stick to the intestinal lining due to the attraction between the positively charged NPs and the negatively charged intestinal mucosa. Anionic NPs, on the other hand, tend to bind more strongly to specific sites due to their electrostatic interaction with the higher concentration of positively charged proteins. Research is also underway to develop NPs that are hydrophilic and uncharged [85,86]. It has been demonstrated that using PEG-coated NPs improves their passage through the mucous layer and extends their half-life. The use of polymeric micelles, in which PEG is integrated to increase circulation time and decrease drug release, is another technique for nanoformulation for GI delivery. According to a nano formulation employing resin microcapsules composed of Eudragit S100 and 717 anion exchange resin can precisely target dexamethasone to the colon, enhance the treatment of UC, and lessen the harmful side effects that are linked to it [87].

## CLINICAL APPLICATION AND EFFICACY

### Clinical studies: Key clinical trials and studies that have evaluated colon-targeted budesonide formulation

1. Preliminary efficacy and safety study of a new budesonide-MMX® 9 mg extended-release tablets in patients with an active left sided – A total of 56 patients underwent screening, with 36 eventually participating in the study and being randomly assigned to one of the two treatment groups. However, the study was prematurely halted before it could reach its intended target of 40 participants. The groups receiving budesonide-MMX® 9 mg and placebo were evenly split, with 9 out of 9 patients in the budesonide group and 12 out of 6 in the placebo group being male, and the same ratio held for females. The average age of the participants was 44.5±12.6 years, with an average body weight of 72.7±15 kg and an average height of 171.7±9.5 cm. The average time from the onset of UC to the start of the study ranged from 0 to 35 years, with a median duration of 9 years in the budesonide group and 10 years in the placebo group. After 4 weeks in the test group, 8 participants (47.06%) met the main goal by showing a CAI decrease of at least 50%, indicating a symptomatic improvement (all CAI values were ≤4). The remaining 8 participants (47.06%) experienced a less significant CAI reduction, while one individual (5.88%) did not see any improvement (p-value for CAI vs. initial values was 0.0001). In the control group, 5 participants (33.33%) met the main goal, with an additional 5 (33.33%) experiencing a CAI reduction and 5 (33.33%) maintaining their clinical condition or experiencing a deterioration (p-value for CAI vs. initial values was 0.0923). The difference in outcomes between the two groups was 13.73, which did not achieve statistical significance (p-value from $\chi^2$ test was 0.1393). The lack of statistical significance could be attributed to the relatively small sample size of 32 participants, which was intended to be 40. Taking the PK data from healthy participants and the clinical trial experience with Entocort CIR®, this small-scale research aimed at evaluating the clinical, endoscopic, and histological outcomes of budesonide-MMX® 9 mg tablets in patients with moderately active UC on consistent treatment with 5-ASA or similar drugs or azathioprine. The efficacy findings suggest that budesonide-MMX® 9 mg tablets can lead to a swift clinical improvement or remission in patients with active moderate UC when taken at a daily dose of 9 mg for a minimum of 4 weeks [88].
2. GI transit, release, and plasma pharmacokinetics of a new oral budesonide formulation – Two separate, phase I research projects were conducted on distinct groups of participants. The first involved a single-dose pharmacological scintigraphy trial, while the second was a randomized, open-label, multi-dose pharmacokinetic study. Both were approved by the local ethics committees and conducted in accordance with the Good Clinical Practice Guidelines of the European Commission and the Declaration of Helsinki. Twelve Caucasian male volunteers participated in each investigation. The participants in the first trial were 32 years old on average, 178 cm tall, 81.1 kg in weight, and had a body mass index (BMI) of 25.5 kg $m^{-2}$. Participants in the second research were marginally younger, averaging 22 years old, 177 cm in height, 74.1 kg on average weight, and 23.5 kg $m^{-2}$ BMI on average.

Subjects were randomized into two groups of six for single-dose PK. A high-fat, high-calorie breakfast was given to one group, and a pill was given 30 min after breakfast. One budesonide tablet was given to another group following an overnight fast of 10 h. In multiple dose PK, the 12 participants in the single dose trial get a budesonide pill once daily in the morning following a 12-h overnight fast for a consecutive set of days following a 7-day washout period. At predose, blood samples were drawn from the vein in the arm on days 2, 4, 6, and 7. Between 4- and 24-h following treatment, MMX®-budesonide tablets were found in the ascending colon using scintigraphy imaging. Twelve to 24 h after injection, the drug left the descending colon. The ratio of the AUC target to AUC24 was computed using the plasma AUC values during the period when radioactivity was present in the target area

(mean±standard deviation AUC target: 15,114±14,402 pg $h^{-1}$ $mL^{-1}$; mean AUC24: 15,607±14,549 pg $h^{-1}$ $mL^{-1}$) to ascertain the percentage of budesonide that was absorbed from the intended area (i.e., the space between the ascending and descending–sigmoid colon). During the course of the study, budesonide absorption occurred across the whole colon, including the sigmoid colon, as indicated by the average percentage of absorption of 95.9±4.2% [89].

**Comparative effectiveness**

Since corticosteroids have strong anti-inflammatory effects, they have traditionally been the mainstay of treatment for active CD. Their systemic nature, however, frequently results in a variety of adverse effects. Despite its effectiveness, glucocorticoids therapy is a less desirable option because up to 80% of patients have short-term adverse effects such acne and moon face in addition to long-term dangers like osteoporosis [90].

Budesonide, a second-generation GC, offers a promising alternative by minimizing these adverse effects. This topical steroid has a strong affinity for the GC receptor and undergoes rapid first-pass metabolism in the liver, reducing its systemic bioavailability to just 10%. Consequently, budesonide provides the therapeutic benefits of traditional GCS while significantly lowering the risk of common steroid-related complications. Its localized action in the intestine makes it particularly effective for IBDs like CD, offering a safer therapeutic approach with fewer long-term consequences [91,92]. This shift to budesonide represents an important step forward in the search for safer, yet effective treatments for CD, addressing both patient and clinician concerns regarding steroid therapy [92].

## CONCLUSION

Budesonide, a medication specifically designed for the colon, represents a major breakthrough in treating CD by delivering potent anti-inflammatory benefits with fewer negative effects on the body compared to conventional corticosteroids. Its strong effectiveness at the site of action, along with a significant amount of it being metabolized before it reaches the bloodstream, leads to a lower amount reaching the rest of the body, thereby reducing the typical side effects linked to steroid use. This quality of budesonide makes it a promising choice for ongoing treatment, enhancing the safety aspect of steroid therapy and improving the results in treating IBDs. The direct delivery to the colon further boosts its effectiveness, offering a safer, more localized method for treating CD and other similar conditions.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## CONTRIBUTION OF AUTHORS

All authors equally contributed to conceptualization, literature search, compilation, and writing different parts of review article.

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