



# Polysaccharide and Chitosan-Based Colon Drug Delivery System: An Advanced Approach for IBD Therapy

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## KEYWORDS

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## ABSTRACT:

Inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, is a chronic inflammatory disease of the gastrointestinal system that continues to affect millions of people every day all over the globe. Current therapies (amino salicylates, corticosteroids, immunosuppressing agents, and biologic medications) can provide symptomatic relief; however, they also have systemic side effects and poor bioavailability and are limited in the targeting of the inflamed tissue. Colon-targeted drug delivery systems (CDDS) were created to address these issues with newer drug delivery approaches that deliver the drug directly to the disease site of IBD—this designed targeting mechanism explains better therapeutic outcomes and fewer adverse effects. Chitosan and natural polysaccharides are among some of the most suitable drug carriers for CDDS systems because of a variety of reasons, such as biocompatibility, biodegradability, and their ability to respond to colonic biosystem parameters (pH, microbial enzymes, and oxidative stress). Polysaccharides such as pectin, dextran, alginate, inulin, and guar gum provide selective microbial degradation and therefore release the active pharmaceutical ingredients for controlled drug delivery. Since chitosan derivatives provide improved mucoadhesion and epithelial permeability. The more advanced formulations deliver nanoparticles, hydrogels, microspheres, and prodrug systems. This review summarizes the latest developments in CDDS based on polysaccharides and chitosan, as well as more recent methods such as pH-sensitive, time-controlled, and providing the capacity for colonic time-molecularly controlled drug absorption.

## 1. Introduction

In the twenty-first century, the incidence of inflammatory bowel disease (IBD), a condition that is common throughout the world, is still increasing. It is now a global public health concern. IBD is a systemic disease that affects several organs and systems in addition to the gastrointestinal tract. Clinically, it is categorized as one of the prevalent, multifactorial, and presently incurable diseases of the digestive system, marked by mucosal destruction and severe intestinal inflammation.<sup>[1]</sup> IBD, which includes Crohn's disease and ulcerative colitis, is a chronic, recurrent inflammatory gastrointestinal (GI) disorder that significantly reduces patient quality of life and places a heavy burden on healthcare systems around the world.<sup>[2]</sup> IBD's etiology is still complex, involving interactions between immune dysregulation, environmental triggers,

intestinal microbiota imbalance, and genetic predisposition.<sup>[3]</sup> Over 10 million people worldwide suffer from IBD as of 2023, a startling increase in prevalence, especially in developed countries where dietary and lifestyle changes contribute to gut inflammation.<sup>[4]</sup> Patients frequently exhibit symptoms including abdominal pain, rectal bleeding, diarrhoea, weight loss, and fatigue. Standard pharmacological interventions comprise amino salicylates, corticosteroids, immunosuppressants (e.g., azathioprine), and biologics such as anti-TNF agents.<sup>[5]</sup> Conventional treatment approaches that use systemic drug delivery have several disadvantages, including decreased bioavailability, non-specific drug release, and systemic side effects.<sup>[6]</sup> CDDS, or colon-targeted drug delivery systems, are designed to minimize off-target side effects, improve therapeutic efficacy, and localize the drug's action. This approach can also



reduce the required dosages and increase patient compliance.<sup>[7]</sup> To release its payload selectively, a well-designed CDDS must be able to pass through the acidic gastric environment, be broken down by enzymes in the small intestine, and arrive in the colon unharmed.<sup>[8]</sup> A neutral to slightly alkaline pH (6.5–7.5), a long transit time (up to 48 hours), and a high density of anaerobic microflora are some of the physiological characteristics of the colon that make it ideal for targeted delivery.<sup>[9]</sup> By enabling localized treatment and reducing systemic exposure, colon-targeted drug delivery systems (CDDS), especially those based on polysaccharides and chitosan, present promising alternatives. These biopolymers respond to colonic triggers like pH, microbial enzymes, and reactive oxygen species (ROS) and are biodegradable and biocompatible. Researchers have looked to natural polymers, especially polysaccharides and chitosan, as adaptable carriers for CDDS in order to take advantage of the colon's special environment.<sup>[10]</sup>

As polysaccharides like pectin, dextran, guar gum, konjac glucomannan, alginate, and inulin are susceptible to microbial degradation in the large intestine, they have been extensively investigated for colon-targeted delivery.<sup>[11]</sup> Formulations based on dextran and pectin exhibit good mucoadhesive qualities and have been used to encapsulate anti-inflammatory drugs for colonic delivery. Their potential as co-therapeutic agents as well as inert carriers is increased by these extra advantages.<sup>[12]</sup>

A partially deacetylated form of chitin, chitosan is a polycationic polymer that is mucoadhesive and capable of opening tight junctions in epithelial membranes.<sup>[13]</sup> Chitosan is frequently chemically modified to enhance its abilities in the colonic environment because of its poor solubility at neutral and alkaline pH. Trimethyl chitosan (TMC), carboxymethyl chitosan (CMCS), and thiolated chitosan are derivatives that have been effectively formulated into hydrogels, beads, microspheres, and nanoparticles.<sup>[14]</sup> Chitosan-based microparticles loaded with 5-ASA or budesonide showed notable anti-inflammatory effects and a prolonged colonic residence in DSS-induced colitis models. Due to its immune-modulatory properties and biocompatibility, chitosan is an excellent option for IBD.<sup>[15]</sup>

## 2. Ulcerative Colitis and Crohn's Disease:

One of the two primary types of inflammatory bowel disease (IBD), ulcerative colitis (UC) is a chronic illness with a complex etiology that is characterized by mucosal inflammation that stretches from the rectum to the proximal sections of the colon.<sup>[16]</sup> The aetiology of ulcerative colitis (UC), a chronic inflammatory bowel disease that affects the colon and rectum, is unknown. It has been proposed that UC pathogenesis is influenced by a number of factors, including genetic background, environmental and luminal factors, and mucosal immune dysregulation. New treatments have emerged as a result of a better understanding of the mechanisms underlying UC. The specific cause of IBD has not been established, and currently it is thought to be due to several factors involved in the pathogenesis; some of these factors include molecular and cellular mechanisms, microbial entities, microbiome interactions, genetic anomalies, and immune system dysfunction.<sup>[17]</sup> Since ulcerative colitis is a chronic condition with unpredictable time and intensity cycles of activity and remission, cumulative genomic changes take place during active disease and mucosal healing, creating a unique set of circumstances distinct from those linked to sporadic colorectal cancer.<sup>[18]</sup>

## 3. Pathophysiology And Therapeutic Perspectives of Inflammatory Bowel Disease (IBD):

IBD, which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, recurrent illness marked by aberrant immune responses in the gastrointestinal (GI) tract. IBD is known to result from intricate interactions between immune dysregulation, environmental triggers, gut microbiota dysbiosis, and genetic predisposition, even though the precise etiology is still unknown (Figure 1).<sup>[19]</sup>

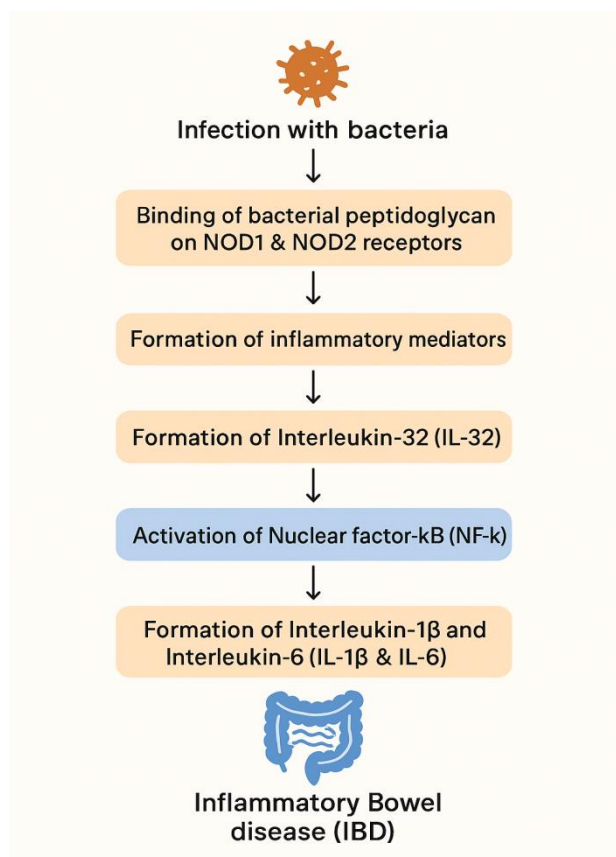


Figure 1: Pathophysiology of Inflammatory Bowel Disease

#### 4. IBD Treatments –

Drug selection for inflammatory bowel disease (IBD) is influenced by the severity and phenotype of the disease, with the majority of treatment plans aiming to induce symptom remission. The recommended initial treatment for patients with mild to moderate IBD is 5 amino salicylic acid (5 ASA), sometimes referred to as mesalazine or mesalamine.<sup>[20]</sup> However, traditional fast-release oral formulations release 5 ASA in the upper small intestine, where it undergoes extensive metabolization and systemic absorption, leading to less-than-ideal delivery to inflammatory colonic tissue.<sup>[21]</sup> Prodrugs like sulfasalazine, olsalazine, and balsalazide have been crucial because 5 ASA has a local therapeutic effect in the colon and elevated plasma levels provide little benefit. These formulations are designed to release the active 5 ASA moiety at the disease site by selectively activating in the colon, usually by bacterial azoreductase enzymes, while resisting release in the stomach and small intestine.<sup>[22]</sup> Approximately 90% of

sulfasalazine taken orally, for instance, does not break down until it enters the colon, where anaerobic bacteria break the azo bond and release 5 ASA.<sup>[23]</sup>

#### 4.1 Mechanism of Chitosan-Based Colon Drug Delivery System:

Many studies have been conducted on chitosan-based colon drug delivery systems because of its special qualities, which include mucoadhesiveness, pH sensitivity, biodegradability, and biocompatibility. The Mechanism of Chitosan-Based Colon Targeting Drug release shown in (Figure 2).

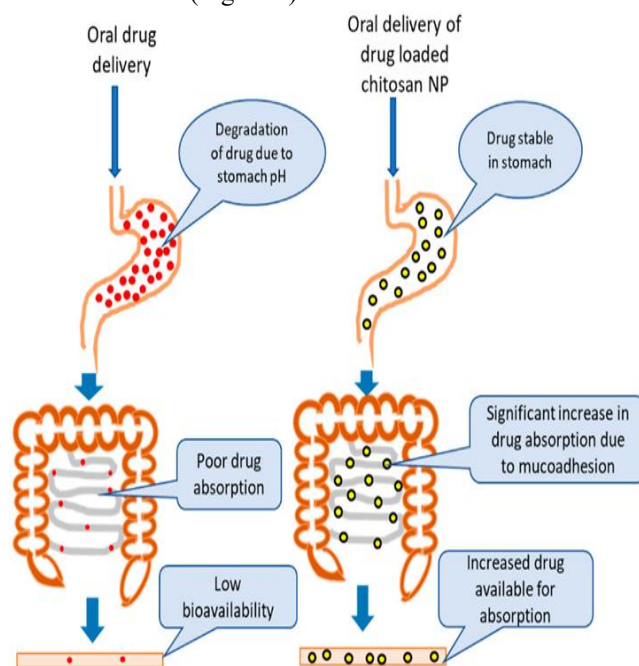


Figure 2: Mechanism of Chitosan – Based colon targeting delivery system

#### 4.2 CDDS Drug Selection Criteria-

Drugs that have restricted absorption in the upper gastrointestinal (GI) tract, such as peptides and protein-based agents, benefit greatly from colon-targeted drug delivery systems (CDDS).<sup>[24]</sup> Therapeutics aimed at inflammatory bowel disease (IBD), ulcerative colitis, diarrhoea, and colorectal cancer are best suited for colon-specific delivery due to the localized nature of these conditions.

The choice of a suitable drug carrier significantly affects the efficacy of Controlled Drug Delivery Systems (CDDS). The selection is influenced by the physicochemical properties of the drug and the



particular pathological condition being treated<sup>61</sup>. Factors such as drug solubility, stability, chemical nature, and partition coefficient, in addition to the use of absorption enhancers, are essential for optimizing delivery. The presence of functional groups, such as aniline or nitro moieties, on the drug molecule promotes chemical conjugation to aromatic carriers via azo bonds, thus allowing for site-specific release.<sup>125</sup>

## 5. Strategies For Colon-Specific Drug Delivery (CDDS)

There are a number of approaches to accomplish site-specific delivery. The following are the main approaches of CDDS.

### 1) Primary Approaches for CDDS –

#### A. Ph-Sensitive Polymer Coating Drug Delivery to the Colon:

A specific point in the gastrointestinal tract can be targeted by utilizing the pH gradient for drug release at specific sites. The stomach's pH during fasting is notably acidic, approximately ranging from 1 to 2, subsequently rising to approximately 6.5 within the proximal small intestine and further increasing to around 7.5 in the terminal ileum and As demonstrated by the concentrations decreasing in the colon (~6.4 in the cecum and as low as ~5.7 in the ascending colon), then rising again in the transverse and descending colon.<sup>126</sup> While pH-sensitive polymers are insoluble in acidic environments, they gradually dissolve at higher pH values to provide enteric protection in the stomach and upper small intestine. Despite these limitations, enteric coatings remain among the most widely used strategies for colon-specific delivery owing to their cost-effectiveness and ease of manufacture.<sup>127</sup> Methacrylic acid–methyl methacrylate copolymers (e.g., Eudragit® S, L, FS, P4135F, L30D-55) and cellulose-based enteric polymers such as Hypromellose acetate succinate (HPMCAS-LF) and Hypromellose phthalate (HP50, HP55) are applied to tablets, capsules, multi-particulates, and matrix systems.<sup>128</sup>

#### B. Drug Delivery Via Delayed (Time Controlled Release System) Release to Colon-

A promising approach for regulated drug delivery to the colon is Time-Controlled Release Systems (TCRS),

which include sustained or delayed-release dosage forms.<sup>129</sup> Individual differences in gastric emptying time, however, often lead to decreased colonic bioavailability, making it challenging to predict colonic arrival accurately.<sup>130</sup> Colon targeting can be tested in these systems by increasing the lag time to approximately five to six hours after administration.<sup>131</sup>

#### C. Ph- And Time-Triggered Combination Systems-

Transit through the small intestine is generally fairly consistent within and between individuals, as was previously mentioned. It is possible to achieve targeted delivery to the terminal ileum and colon by combining a time-dependent release element with an enteric coating to prevent premature drug dissolution in the stomach.<sup>132</sup> Multilayer coatings, which combine an inner time-controlled barrier (e.g., Eudragit® RS, ethyl cellulose, or HPMC) with an outer pH-sensitive polymer (e.g., Eudragit® S or L), are one successful tactic.<sup>133</sup> Such a system permits delayed dissolution after gastric emptying for several hours and inhibits early release in low pH environments. It illustrates a typical multilayer bead formulation for delivery that is controlled by pH and time.<sup>134</sup>

#### D. Microbially Triggered Drug Delivery to Colon-

Bacteroides, Bifidobacterium, Eubacterium, Clostridium, Enterococcus, Enterobacteriaceae, and Ruminococcus spp are among the anaerobic bacterial species that make up the majority of the human colon's dense and extensive microflora, which is between  $10^{11}$  and  $10^{12}$  CFU/mL, according to estimates.<sup>135</sup> Fermentation of undigested dietary residues from the small intestine, such as di- and trisaccharides and different polysaccharides, provides the main energy source for this intricate microbial ecosystem.<sup>136,37</sup>

#### I) Prodrug Approach for Drug Delivery to Colon-

A prodrug is a pharmacologically inactive derivative of a parent compound that, when converted spontaneously or by enzymes, releases the active drug in vivo. Because the prodrug is designed to withstand hydrolysis in the upper gastrointestinal tract and instead undergo selective enzymatic cleavage in the colon, the therapeutic agent is released precisely where it is intended in colon-targeted systems. The most studied are azo prodrugs, which are broken down by intestinal bacteria.<sup>138</sup> However, there are drawbacks to the prodrug approach. Its viability depends on the drug



molecule having the right functional groups for conjugation, which limits its adaptability.<sup>[39]</sup>

## II) Azo-Polymeric Prodrugs-

Using polymers as carriers to enable site-specific release in the large intestine has been the focus of recent approaches for colon-targeted drug delivery. Both artificial and natural polymers have been used; some artificial versions are made to create polymeric prodrugs by forming an azo bond between the active pharmaceutical ingredient and the polymer backbone. The colonic microbiota's azoreductase enzymes have been shown to cleave these systems, which have been thoroughly tested for colon-specific drug delivery systems (CDDS).<sup>[40]</sup>

## III) Polysaccharide Based Delivery Systems-

The use of natural polysaccharides for colon-targeted drug delivery is growing in popularity due to their abundance of physicochemical properties, variety, and affordability. These include high biocompatibility, hydrophilicity, safety, biodegradability, gel-forming qualities, and chemical and biochemical modifiability. The polymers, which originate from plants (guar gum, inulin), animals (chitosan, chondroitin sulfate), algae (alginates), and microbes (dextran), are selectively broken down by colonic microflora, making them GRAS (Generally Recognized as Safe) substances.<sup>[41]</sup> Biodegradable matrices, fermentable coatings, and prodrug conjugates are examples of polysaccharide-based systems that have been widely used to achieve site-specific drug release in the colon.<sup>[42]</sup>

## 5.1 Newly Developed Approaches For CDDS-

### 5.1.1 PRESSURE-CONTROLLED SYSTEMS DRUG-DELIVERY:

With regard to its stronger peristalsis, the colon has higher intraluminal pressures than the small intestine. Making use of this characteristic, Takaya and associates created pressure-controlled colon-delivery capsules made of water-insoluble ethylcellulose, in which the rupture of the capsule wall under colonic pressure triggers the release of the drug shown in (Figure 3). Capsule disintegration is significantly influenced by the ethylcellulose membrane's thickness, density, and size.<sup>[43]</sup> Clinical studies conducted on humans showed that there was a lag time of approximately three to five

hours between the administration of capsules and the absorption of the drug.<sup>[44]</sup>

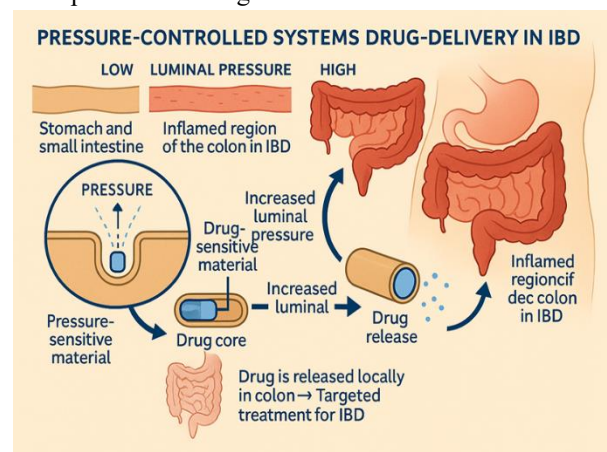


Figure 3: Systemic Design of Pressure-Controlled Systems Drug-Delivery

### 5.1.2 Newly Developed Colon Targeted Delivery System (CODESTM):

In order to overcome the limitations of traditional pH- and time-dependent targeting techniques, a novel technique known as CODESTM (Colon Drug Delivery System) was developed. This system combines pH-sensitive enteric protection with microbial activation to provide precise colonic drug release through a dual-trigger mechanism. In order to protect the lactulose-containing tablet core from small-intestinal transit, the formulation first coats it with an enteric polymer (Eudragit L) to withstand stomach acidity.<sup>[45]</sup> It was created using a mechanism where lactose triggers the release of drugs at specific sites in the colon (Figure 4).

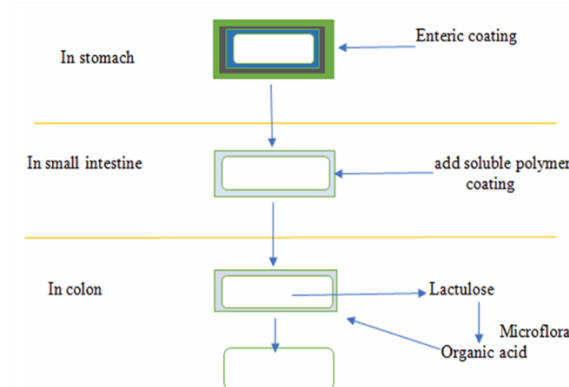


Figure 4: Systemic Design of CODESTM



### 5.1.3 Osmotically Controlled System (OROS-CT) Delivery:

The most common oral drug carriers are thought to be osmotic drug-delivery systems. The system was primarily developed based on the difference in osmotic pressure produced between the colon lumen and the system. A semipermeable membrane covering an osmotic drug compartment and an osmotic push compartment with a tiny hole drilled through the drug compartment makes up the main unit of osmotic-based drug delivery carriers. An enteric impermeable membrane encloses the entire unit (Figure 5). First, the gelatine capsule dissolves as soon as the system is swallowed, which could be the cascade mechanism of drug release from osmotic-based systems.<sup>[46]</sup> Due to the stomach's acidic pH, the entire system is protected by an impermeable membrane that prevents drug release. When the semipermeable membrane starts to dissolve and water enters the central, the osmotic push compartment swells and forms a flowable gel in the drug unit due to the intestine's higher pH ( $\text{pH} > 7$ ). The osmotic push unit, upon swelling, ultimately expels the drug gel from the orifice, thereby facilitating a regulated and accurate discharge of the medication.<sup>[47]</sup>

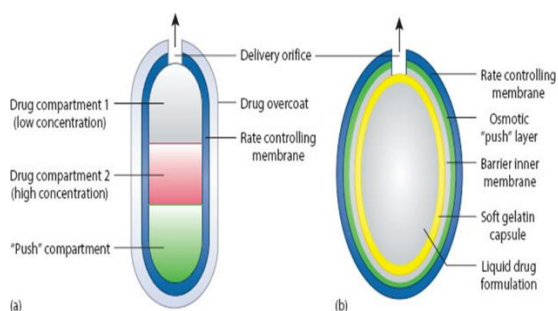


Figure 5: Schematic diagram of OROS-CT drug delivery system

### 5.1.4. Pulsatile Drug Delivery System (PULSINCAP®):

The PulsinCap® is the most popular time-dependent system. The technology is based on an insoluble half capsule design with an active ingredient, and the open end of the capsule is closed by an exact volume of a hydrogel plug; this plug coated with water soluble cap, and finally, the whole capsule coated with an enteric polymer film (Figure 6).<sup>[48]</sup> The capsule is resistant to various degradation processes in the stomach and the

polymeric coat starts to dissolve at higher pH of the small intestine.<sup>[49]</sup>

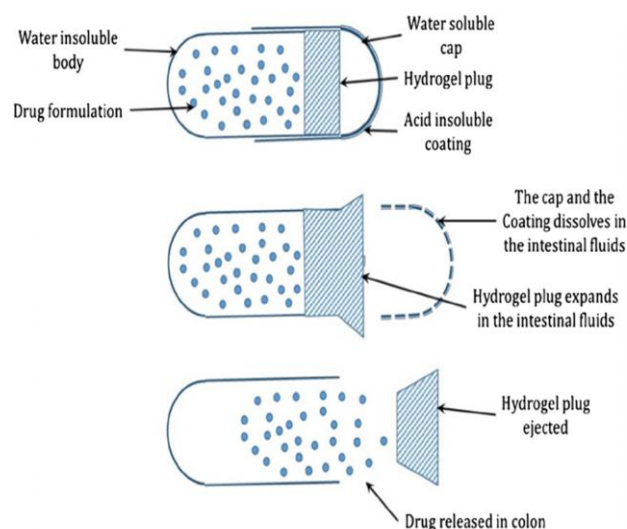


Figure 6: Schematic diagram of PulsinCap technology.

### 5.1.5. Other Novel Drug Delivery Systems:

To improve colon-specific drug targeting, a variety of recently developed colon drug delivery systems have been assessed during the past ten years. Redox-based systems, COLAL® tableting technology, MMX® technology, PHLORAL® technology, and bioadhesive-based systems utilizing a variety of polymers, such as polycarboxylates and polyurethanes, are a few examples.<sup>[50]</sup>

## 6. Conclusion:

CDDS (colon-targeted delivery systems) are an innovative option for treating inflammatory bowel disease (IBD). Unlike rather systemic delivery options, CDDS provides local therapy to the diseased segment of the colon while maintaining a greater level of patient compliance. Furthermore, CDDS can provide increased therapeutic options to limit or eliminate certain systemic side effects. As drug delivery vehicles for colon-specific targeting, polysaccharides have shown a lot of promise. Similarly, there has also been great promise with chitosan polymer as a carrier for colon-specific delivery due to its natural abundance, safety, and biodegradability, along with responsiveness to colon-specific conditions arising from pH, microbial activity, or oxidative stress. Polysaccharide carriers allow for controlled and site-specific release; whereas chitosan



and its derivatives have the added benefits of mucoadhesion and improved permeability. Recent advancements in formulation technologies have included nanoparticles, hydrogels, microspheres, and prodrug systems, and there has been some success with using these biopolymers in colon-specific applications. In parallel, other delivery platforms with differentiating properties such as pH-sensitive, time-controlled, microbially activated, and pressure-dependent systems are being developed which ultimately will improve reliability and specificity of targeting drugs to the colon. In general, polysaccharides and chitosan CDDS have a great potential towards enhancing IBD treatments in the future. The future of IBD therapies lies in continued investigation of these existing systems, optimizing them to drugs that are ultimately safer, more effective, and easier for patients to take, ultimately improving or changing the way we manage IBD.

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