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Polysaccharide-Based Colon-Targeted Drug Delivery System

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Abstract

Polysaccharide-based colon-targeted drug delivery systems (CDDS) have gained significant attention for the localised management of colonic disorders, including inflammatory bowel disease and colorectal cancer. Conventional oral delivery systems often lead to premature drug release and systemic exposure, thereby limiting therapeutic efficacy. In contrast, polysaccharides remain intact in the upper gastrointestinal tract and are selectively degraded by the colonic microbiota, thereby enabling site-specific drug release.

This review outlines the physiological and microbial basis of colon targeting and critically examines key polysaccharides and their derivatives used in CDDS. Major drug release mechanisms, including microbial, enzymatic, pH-dependent, and time-controlled systems, are discussed, with emphasis on multi-trigger strategies for improved targeting reliability.

Recent advances in nanocarrier systems and stimuli-responsive formulations highlight the evolving potential of these platforms. However, challenges such as microbiota variability, formulation reproducibility, and regulatory limitations continue to hinder clinical translation.

Overall, polysaccharide-based CDDS offer a rational and promising approach for precise colonic drug delivery, with future progress dependent on overcoming current translational barriers.

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1. INTRODUCTION

1.1 An Overview of Colon-Related Diseases

There are a lot of diseases that can affect the human colon that are important to doctors, such as inflammatory bowel disease (IBD), colorectal cancer (CRC), infectious colitis, irritable bowel syndrome, and diverticular disease. These diseases are putting a lot of strain on healthcare systems around the world. IBD, or inflammatory bowel disease, affects more than 6.8 million people around the world. It is a long-term inflammation of the gastrointestinal tract that keeps coming back. It includes Crohn's disease (CD) and ulcerative colitis (UC). The number of cases is rising, particularly in nations that are urbanising and rapidly assimilating Western dietary practices amid industrialisation [1]. A recent systematic review and meta-analysis of 215 population-based studies revealed a global prevalence of inflammatory bowel disease (IBD) at 229.7 per 100,000 individuals, with incidence rates of 9.7 per 100,000 person-years, and projected increases in Asia, South America, and Africa [2]. Colorectal cancer caused by IBD is responsible for 10–15% of deaths in this group of patients. People with chronic, severe ulcerative colitis are much more likely to get colonic neoplasia over time, and this risk gets worse as the condition lasts longer and the inflammation gets worse [3]. Colorectal cancer is the third most common cancer and the second most common cause of cancer-related deaths in the world. It causes about 1.9 million new cases and more than 935,000 deaths every year [4]. The pathogenesis of this condition involves a clearly delineated multi-step transition from normal epithelium to adenoma and finally to carcinoma, driven by genetic mutations, epigenetic dysregulation, chronic inflammatory signalling, and microbiome dysbiosis [5]. Pathogens such as Clostridioides difficile, enterohemorrhagic Escherichia coli, and Campylobacter species. can also lead to infectious colitis. It makes it much more likely that people will become sick, especially older people and people with weak immune systems, and it makes it harder to fight infections [6].

1.2 The necessity for colon-targeted drug delivery

The colon is the last part of the gastrointestinal tract, which is about 1.5 meters long and takes 20 to 72 hours to get through. The colon is useful for some medical reasons, but it also makes it hard to give drugs by mouth [7]. Aminosalicylates, corticosteroids, immunomodulators, and cytotoxic agents are examples of locally acting drugs that are used to treat colonic disorders. Their main goal is to get higher levels of the drug to the site of the disease while keeping it from being absorbed by the body. Systemic absorption decreases local bioavailability and generates adverse side effect profiles, complicating patient adherence to treatment and hindering long- term outcomes [8]. The colon serves as an effective site for administering systemic drugs that are prone to degradation in the upper gastrointestinal tract, including therapeutic proteins, peptides, nucleic acid-based medications, and vaccines. It's also a good place for therapy in the area. The small intestine has more enzymes than the colon. The mucosa also has a lot of lymphoid tissue and a fast immune response. This means that the colon can absorb macromolecular drugs and immunologically active agents well [9].

1.3 Drawbacks of Traditional Drug Delivery Systems

Traditional oral dosage forms that are made to release drugs in the stomach and small intestine include immediate-release tablets, capsules, and suspensions. These forms do not deliver the medication effectively to the colon. Drugs given in these forms break down a lot, dissolve, and are absorbed in the upper gastrointestinal tract, so only tiny amounts reach the colon that are useful for treatment [10]. Enteric-coated formulations, designed to endure gastric acid and disintegrate in the alkaline environment of the small intestine, fail to achieve colon specificity due to the variability in intestinal pH and the dissolution occurring significantly proximal to the colon [11]. Prodrug strategies face challenges due to limited chemical tractability, potential carrier toxicity, and the difficulty of maintaining consistent enzyme activity in pathological conditions [12]. Time-controlled release systems are vulnerable to individual differences in gastric emptying and small intestinal transit, particularly in patients with inflammatory bowel disease who demonstrate altered gastrointestinal motility [13].

Table 1: Comparison of Conventional and Colon-Targeted Drug Delivery Systems

Parameter	Conventional Oral Systems	Colon-Targeted Systems
Primary release site	Stomach / proximal small intestine	Ascending and transverse colon
Drug release trigger	Dissolution, disintegration	Microbial enzymes, pH, transit time
Colon drug concentration	Low (extensive proximal absorption)	High (site-specific release)
Systemic drug exposure	High	Reduced
Systemic toxicity risk	Significant	Substantially lower
Therapeutic applicability	Systemic conditions	Colonic diseases; macromolecule delivery
Formulation complexity	Low–moderate	Moderate–high
Mucoadhesive potential	Absent	Present (polysaccharide-based systems)
Regulatory excipient status	Well-established	Largely GRAS; established for natural polysaccharides
Representative examples	Immediate-release tablets, enteric-coated capsules	Chitosan nanoparticles, pectin beads, guar gum tablets

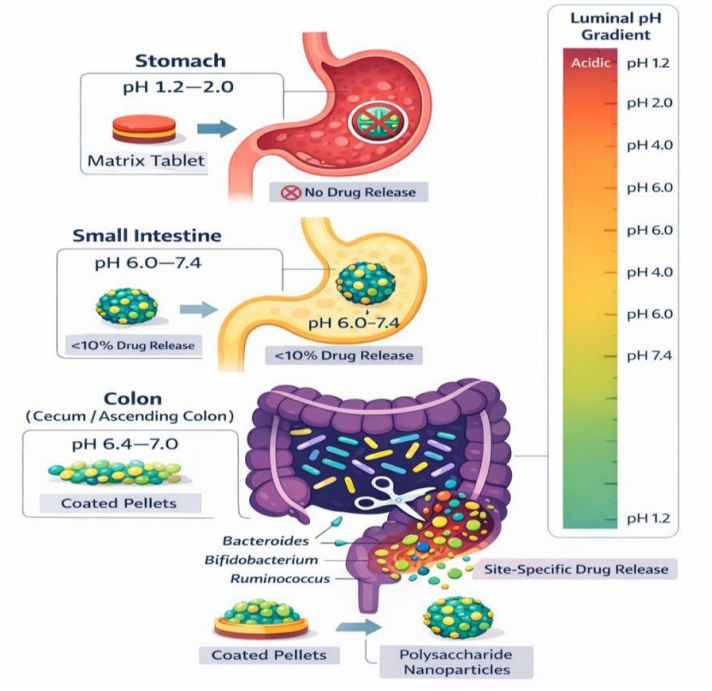
GRAS: Generally Recognised as Safe.

1.4 The Role of Polysaccharides in Colon- Targeted Delivery

High polysaccharides- molecular-weight carbohydrate polymers composed of monosaccharide units connected by glycosidic bonds- are currently under investigation as functional excipients for colon-targeted drug delivery.

The main reason to use them is that the stomach and small intestine's digestive enzymes can't break them down, but the many anaerobic bacteria in the colon that make polysaccharides can break them down [14]. Polysaccharides are not only a way to target things, but they are also a useful and abundant material platform. Their different structural architectures—linear, branched, and cross-linked shapes with different types of monosaccharides, molecular weights, and functional group densities—give them a wide range of physicochemical properties that make them suitable for drug loading, matrix formation, hydrogel crosslinking, nanoparticle self- assembly, and mucoadhesive interaction with the colonic epithelium [15]. Carboxymethylation, acetylation, quaternization, thiolation, or grafting with synthetic polymers can change how soluble polysaccharide backbones are, how much they swell, how much charge they have, and how responsive they are [16]. Regulators have either accepted or said that polysaccharides like chitosan, alginate, pectin, guar gum, hyaluronic acid, and inulin are safe to eat. This makes it much easier to put them in products [17].

Figure 1: Schematic representation of the gastrointestinal tract depicting site-specific drug release zones, luminal pH gradients (pH 1.2–2.0 in stomach; pH 6.0– 7.4 in small intestine; pH 6.4–7.0 in colon), and representative polysaccharide-based formulation types at each GI segment.



2. Rationale for Colon Targeting

2.1 Physiological Factors: pH and Travel Time

The pH gradient in the gut is very easy to see. This gradient is the basis for colon- targeted delivery systems that depend on pH. Your stomach's pH is between 1.0 and 3.0 when you haven't eaten anything. It goes up to between 3.0 and 5.0 after you eat. The pH in the jejunum and duodenum is always between 5.5 and 6.8. The pH of the terminal ileum is between 7.0 and 7.4, and the pH of the colonic lumen is between 6.4 and 7.0. Fermenting microbiota creates short-chain fatty acids (SCFAs), which make the cecum a little more acidic [18]. This pH structure gives a pharmacokinetic reason for using enteric polymers with dissolution thresholds at or above pH 6.8 as coatings for the colon. However, this method isn't as reliable on its own because the pH difference between the ileum and colon is so small [19]. The amount of time it takes for food to move through the digestive system is an important pharmacokinetic factor for getting drugs to the colon. In three to five hours, food moves through the small intestine. People don't have a lot of different times for this. Food takes a lot longer to move through the colon, though. It usually takes 20 to 72 hours, but it can take longer or shorter if someone is sick [20]. Timed-release systems use the small intestine's steady transit time by programming a 4–6-hour delay before the drug is released. Nonetheless, the significant variability in gastric emptying and small intestinal transit, both inter-individually and intra- individually—particularly in patients with inflammatory bowel disease (IBD)— considerably undermines the reliability of time-dependent methodologies that do not incorporate a secondary colon-specific trigger [21]. These physiological factors all show that polysaccharide systems triggered by microbiota are better because they don't depend on transit time or pH.

2.2 Function of Colonic Microbiota

The human colon has the most diverse and densely populated microbial ecosystem in the body, with an estimated 10^{11}–10^{12} colony-forming units per gram of colonic content, made up of more than 400 different types of bacteria, mostly from the phyla Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria [22]. Polysaccharides are the best way to get drugs out of the colon because they pass through the stomach and small intestine without changing and are only broken down by colonic microbiota to release the drug payload [23]. The connection between the structure of polysaccharides and the specificity of microbial degradation is very important for pharmacology. Mammalian enzymes find it very hard to break down polysaccharides that have β-glycosidic linkages and branched structures. Only Bacteroides and Bifidobacterium species from the colon are capable of fermenting them [24]. A significant issue is that individuals with active IBD may experience considerable dysbiosis, characterised by decreased levels of Bacteroidetes and Firmicutes and increased levels of Proteobacteria. This might make it harder for their bodies to break down polysaccharide matrices, which is what colon-targeted therapy needs the most [25].

2.3 The Colon's Enzymatic Environment

The microbiota needs a lot of different enzymes to do its job, and the colon has a lot of them. Colonic bacteria make important polysaccharidases, including β- glucuronidase, xylosidase, arabinosidase, galactosidase, pectinase, amylase, dextranase, inulinase, and chitosanase, to name a few [26]. Each of these enzymes works with a certain polysaccharide because it fits its shape. This means that you can use some

interactions between enzymes and substrates to make formulations that break down drugs and release them in a controlled way [27]. For example, Bacteroides species make pectinase enzymes that break down the galacturonic acid backbone of pectin. Inulinase is made by Bifidobacterium species. breaks down inulin. Specifically breaks down the β(2→1) fructosyl links in inulin [28]. The right polysaccharide substrate can help colonic bacterial enzymes work better. This means that the enzymes make more of themselves when the right substrate is there. The polysaccharide delivery vehicle makes the enzymes work harder to break it down and release the drug [29]. This starts a cycle of good feedback.

3. Polysaccharides for targeting the colon:

3.1 Natural Polysaccharides

Chitosan is a linear polysaccharide with a positive charge. To make it, chitin is partially deacetylated. It comes from the shells of crustaceans and the walls of fungal cells. It has β(1→4) glycosidic bonds that link units of glucosamine and N-acetylglucosamine. The pH, the amount of deacetylation, the molecular weight, and the pKa (about 6.5) all affect how well this substance dissolves in water. Chitosan can dissolve and become protonated when the pH is below 6.5. But it can't dissolve when the colon's pH is close to neutral. This stops the microbiota in the colon from breaking it down as it moves through the upper GI tract [30]. It can interact with the negatively charged mucin glycoproteins in the colonic mucosa because it has a positive charge density. This causes it to stick to mucus, which keeps the drug in the body longer and makes the epithelium more permeable. Chitosanase enzymes from Bacillus and Streptomyces species in the colon break down chitosan, which is another way to release enzymes [31]. Pectin is a linear, anionic, water-soluble polysaccharide made mostly of α(1→4)-linked galacturonic acid residues that have different levels of methyl esterification. High-methoxyl pectins, which have an esterification degree of more than 50%, gel by hydrophobic interactions. Low- methoxyl pectins, in contrast, ionotropically crosslink with divalent cations, particularly Ca^{2+}, to form robust hydrogel networks [32]. Mammals don't have pectinase, so the enzymes in the stomach and small intestine can't break down pectin. Bacteroides, Bifidobacterium, and Faecalibacterium prausnitzii are the only bacteria that can break it down in the colon. The degree of esterification significantly influences the rate at which enzymes degrade pectins. For instance, pectinase has a harder time breaking down pectins that have a lot of methoxyl groups than pectins that have a lot of low-methoxyl groups. This lets you change how quickly drugs are released [33]. Alginate is a type of polysaccharide that is made from brown seaweed. There is β-D-mannuronic acid.
(M) and α-L-guluronic acid (G) residues that are connected by (1→4) bonds. The G/M ratio is what makes alginate gels have their own special physical properties. G- rich alginates make hard gels because they connect with Ca^{2+} ions. Alginates with a lot of M make gels that are softer, stretchier, and stick to mucus. Alginate is affected by pH. At gastric pH, its carboxyl groups become protonated and collapse. They ionise and swell when the pH is neutral to alkaline. This property is used in colon delivery systems that are sensitive to pH [34]. Some bacteria in the colon, like Bacteroides ovatus, make enzymes called alginate lyases that help break down alginate in some places [35]. Galactomannan is a type of polysaccharide that doesn't have any ions. Guar gum is a kind of galactomannan. It comes from the endosperm of Cyamopsis tetragonolobus. There is twice as much mannose as galactose in the backbone and side chains. It doesn't dissolve well because it has a lot of hydrogen bonds and a high molecular weight, but it does get bigger. Guar gum doesn't break down in the small intestine, but it does break down in the colon by β- mannanase and galactosidase made by Bacteroides and Ruminococcus species. One big problem with native guar gum is that it absorbs water too quickly and expands too much, which can make drugs come out too soon. Changing the chemical structure or mixing it with other polymers usually fixes this [36, 37]. Inulin is a plant- based linear β(2→1)-linked fructan polysaccharide that is found in chicory, Jerusalem artichoke, and agave. There can be anywhere from 2 to 60 units of polymerisation. Inulin is not broken down by human digestive enzymes and reaches the colon unchanged. There, it is fermented by Bifidobacterium and Lactobacillus species, which have prebiotic effects and help drugs get released [38, 39]. Hyaluronic acid (HA) is a glycosaminoglycan that does not contain sulfur. It has a special biological role in going after the colon. This is because it only attaches to CD44 receptors that are too many on activated macrophages in inflamed colonic tissue and colorectal cancer cells. This enables active targeting of receptors instead of passive release induced by the microbiota [40]. Leuconostoc mesenteroides makes dextran, which is a branched α-glucan. Human α- amylase does not break it down, but dextranase-producing bacteria in the colon do. In dextran-drug conjugates [41], this is used to send prodrugs to the colon. Bacteroides species make colonic chondroitinase, which breaks down chondroitin sulfate, a type of sulfated glycosaminoglycan. It has strong anti- inflammatory effects and works well with anti-inflammatory drugs when used as a carrier [42].

3.2 Altered and Artificial Polysaccharides

Chemical modification of natural polysaccharides has emerged as a significant strategy to address the challenges associated with native polymers, including their pronounced hydrophilicity, uncontrolled swelling, and variable drug loading capacity, while preserving their biocompatibility and targeting characteristics. Adding carboxymethyl groups to the backbone of a polysaccharide is what carboxymethyl modification does. This makes the substance dissolve better in water and makes the anionic charge denser, which lets it swell based on the pH [43]. Thiolation of polysaccharides yields mucoadhesive compounds capable of forming disulfide bonds with cysteine-rich mucin glycoproteins in the colonic mucus layer, thereby significantly enhancing residence time [44, 45]. When chitosan is cationic quaternized, it makes N-trimethyl chitosan (TMC), which gets around the problem of solubility depending on pH by keeping a steady positive charge across the physiological pH range. This

makes mucoadhesion and tight junction regulation better [46]. Graft copolymerization makes it easier to create amphiphilic or stimuli- responsive structures that can hold drugs better and release them at different rates [47].

3.3 Biodegradability and Biocompatibility

From a regulatory and toxicological point of view, there is no doubt that the polysaccharides used in CDDS are biodegradable and biocompatible. Polysaccharides that are found in nature are broken down by the colon into oligosaccharides, monosaccharides, and short-chain fatty acids. The colonic epithelium can easily absorb or get rid of these metabolites. This stops polymers from building up and the health problems that come with it. Modified polysaccharides retain their intrinsic biodegradability, depending on the degree and type of chemical alterations that exclude non- biodegradable structural elements or cytotoxic substituents [48]. Researchers have carefully tested polysaccharide-based nanoparticles for biocompatibility in cell lines and rodents. They have consistently shown very low levels of cytotoxicity in Caco-2, HT-29, and HCT-116 colorectal cell lines at concentrations that are relevant for therapy.

Table 2: Natural Polysaccharides Used in Colon-Targeted Drug Delivery Systems

Polysaccharide	Source	Structure	Colonic Enzymes	Properties	Applications
Chitosan	Crustacean chitin	β (1→4) glucosamine/GlcNAc	Chitosanase (Bacillus, Streptomyces)	Cationic, mucoadhesive, pH-sensitive (pKa ~6.5)	IBD NPs, 5-FU matrices, gene delivery
Pectin	Citrus peel, apple pomace	α (1→4) galacturonic acid; variable methyl esterification	Pectinase, polygalacturonase (Bacteroides)	Anionic, ionotropic gelation (Ca^{2+}), mucoadhesive	Mesalamine beads, IBD hydrogels, CRC nanocarriers
Alginate	Brown seaweed	β-D-mannuronic / α-L-guluronic acid (1→4)	Alginate lyase (B. ovatus)	Anionic, pH- responsive swelling, ionotropic gelation	Microspheres, IBD hydrogels, and insulin delivery
Guar Gum	Cyamopsis tetragonolobus	β(1→4)-mannose; α (1→6)-galactose branches	β-mannanase, galactosidase (Bacteroides)	Non-ionic, high MW, viscosity-enhancing	Matrix tablets, coated granules, CRC delivery
Inulin	Chicory, Jerusalem artichoke	β (2→1)-fructose; terminal glucose	Inulinase (Bifidobacterium, Lactobacillus)	Prebiotic, GRAS, resistant to mammalian enzymes	IBD hydrogels, electrosprayed microparticles
Hyaluronic Acid	Bacterial fermentation	β(1→4)-GlcNAc–GlcA repeats	Hyaluronidase (Bacteroides)	CD44-targeting, mucoadhesive, anti-inflammatory	CRC active- targeted nanoparticles
Dextran	Leuconostoc mesenteroides	α(1→6) backbone; α(1→3) branches	Dextranase (colonic bacteria)	Biocompatible, derivatisable for prodrug conjugates	Prodrug conjugates, 5-ASA delivery
Chondroitin Sulfate	Bovine/shark cartilage	Alternating GlcA– GalNAc; sulfation C-4/C- 6	Chondroitinase (Bacteroides)	Anti-inflammatory, sulfated, CD44 affinity	IBD combination NPs, anti- inflammatory systems

GlcNAc: N-acetylglucosamine; GlcA: glucuronic acid; GalNAc: N-acetylgalactosamine; MW: molecular weight; IBD: inflammatory bowel disease; CRC: colorectal cancer; NPs: nanoparticles; 5-FU: 5-fluorouracil; 5-ASA: 5- aminosalicylic acid.

4. How Polysaccharide-Based Drugs Are Released

4.1 Microbial Breakdown:

The best way to get drugs to the colon that is both physiologically and pharmacologically sound is to let microbes break them down and release them. The polysaccharide, whether it is the core matrix, the coating shell, or a covalent prodrug linker, stays structurally intact as it moves through the stomach and small intestine like this. This stops the drug from being released too soon. When the thick anaerobic microbial community gets to the cecum and ascending colon, it comes into contact with the polysaccharide substrate. This lets polysaccharidases out, which break the glycosidic bonds. This slowly breaks down the polymer matrix and lets the drug out [49]. There are a lot of things that work together to speed up the breakdown of microbes. These factors include the molecular weight and degree of polymerisation of the polysaccharide, the extent and arrangement of chemical substitution, the crosslinking density of the formulation matrix, the composition and metabolic activity of the local microbial community, and the colonic luminal environment [50]. Recent reviews have identified a significant limitation: in patients with active inflammatory bowel disease (IBD), severe dysbiosis markedly diminishes colonic polysaccharidase activity, potentially hindering drug release. This creates a strange "dysbiosis-delivery failure" situation that needs to be looked into right away [25].

4.2 Release Triggered by Enzymes

Enzyme-triggered drug release includes not only broad-spectrum microbial degradation but also more specific enzymatic reactions that are built into CDDS designs. The most chemically specific way to do this is with prodrug methods. They connect the therapeutic molecule to a polysaccharide carrier with a linker that is sensitive to enzymes. Dextran-5-aminosalicylic acid conjugates linked by azo bonds, which are degraded by colonic azoreductases, exemplify this design [51]. Covalent prodrug conjugation is better than matrix entrapment because it almost completely stops drugs from being released too soon in the upper gastrointestinal tract. In nanoparticulate systems, enzyme-triggered release has been modified so that colonic enzymes break down the polysaccharide shell of a core-shell nanoparticle, revealing a drug-loaded inner core for rapid localised release [52, 53].

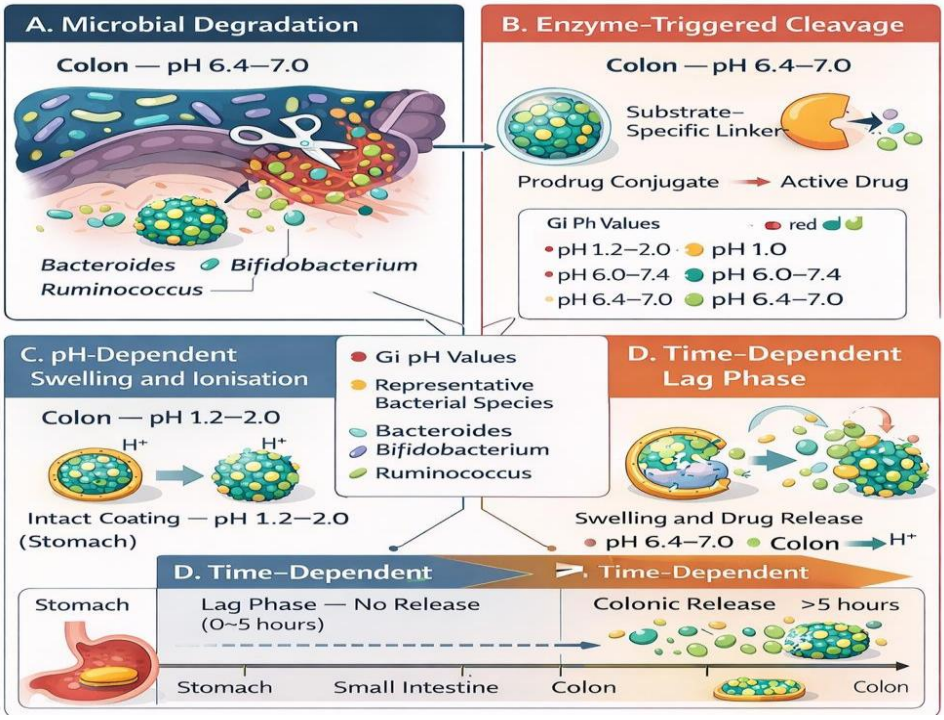
4.3 pH-Dependent Systems

Polysaccharides with carboxyl, amine, or sulfate functional groups that are sensitive to pH change shape, swell, or dissolve when the pH of the lumen changes. Anionic polysaccharides, such as alginate and carboxymethyl derivatives, undergo protonation and degradation in the acidic environment of the stomach. But at the colonic lumen's near-neutral pH, they ionise and swell a lot, which starts drug release through matrix expansion and diffusion [54]. Cationic chitosan dissolves in acidic pH but not in nearly neutral pH. This makes it very useful when mixed with anionic polysaccharides or synthetic pH- responsive polymers in multilayer or polyelectrolyte complex structures [55]. The practical limitation of exclusively pH- dependent systems is the narrow pH gradient between the terminal ileum (pH 7.0–7.4) and the colon (pH 6.4–7.0), further complicated by individual variability in colonic pH in inflammatory bowel disease (IBD) [56]. Hybrid pH/microbiota- triggered systems, distinguished by a pH-sensitive exterior and a polysaccharide interior, demonstrate superior strength compared to singular mechanisms [57].

4.4 Time-Dependent Systems

Time-dependent colon-targeted systems leverage the duration of food transit through the small intestine, which is 3 to 5 hours. They do this by making the drug stay in the body for a while before giving it. The primary practical application of this technology is to produce coatings from hydroxypropyl methylcellulose (HPMC) that possess a specific thickness and degrade or dissolve after a predetermined duration, irrespective of the lumen's pH [58]. When you mix polysaccharides with systems that change over time, like when you use HPMC with guar gum or amylose in combination coatings, you get a second release mechanism that is triggered by microbiota. This fixes the problem with the time-dependent trigger not working when transit is sped up or slowed down [59, 60]. This dual-trigger architecture—temporal in the small intestine and enzymatic in the colon—embodies a formulation design philosophy that has garnered considerable acceptance as a method for enhancing the reproducibility of colon targeting across various patient physiologies.

Figure 2: Combined schematic diagram illustrating the four mechanisms of polysaccharide-based colon-targeted drug release: (A) microbial degradation of polysaccharide matrix; (B) enzyme-triggered cleavage of prodrug conjugates; (C) pH-dependent swelling and ionisation; (D) time-dependent lag phase followed by colonic drug release. Includes GI pH values, representative bacterial species, and corresponding formulation types at each segment.



5. Formulation Strategies

5.1 Matrix Systems

Matrix-based formulations are the most common way to get polysaccharides to the colon. In this method, a network of polysaccharide polymers evenly spreads the drug. As enzymes get to the colon, they break down, swell, or wear away the polymers. Some of the first polysaccharide- based CDDS designs were single-matrix tablets that were made by mixing the drug with pectin or guar gum. In simulated gastric and small intestinal fluids, they markedly impeded drug release; conversely, in simulated colonic fluid with rat cecal contents, the drug was entirely released [61]. Combination matrix systems with two or three polysaccharides that work well together, like guar gum and pectin, are better for targeting and have bimodal release profiles that are good for treating IBD [62]. When you add synthetic polymers like Eudragit or HPMC to polysaccharide matrices, you can change the lag time and release rate separately.

5.2 Coated Systems

Coating strategies, which involve wrapping a drug-loaded core in a polysaccharide- based coat, have the benefit of keeping the drug reservoir and the targeting polymer separate from each other. This makes it easier to make the core hold more drugs and the coat release drugs faster on its own. Polysaccharides that have been compressed, like guar gum or pectin, make up the outer layer of compression-coated tablets. They can be made all the time, and preclinical studies have shown that they work well at targeting the colon [63]. Spraying on film-coated systems that use aqueous dispersions of polysaccharides gives you a more even coat and lets you choose how thick it is. Multi-trigger release architectures are the best way to keep drugs from being released too soon [64]. They are made by using multi-layer coating techniques, such as applying several layers of different polysaccharides or compolysaccharide layers with synthetic polymer layers that are sensitive to pH.

5.3 Hydrogels

Hydrogels are three-dimensional crosslinked polymer networks that can hold a lot of water without breaking down. They are now very helpful for getting drugs to the colon. A classic polysaccharide hydrogel system is calcium alginate hydrogels that are ionotropically crosslinked. They make round beads that can hold more than 80% of drugs that are hydrophilic [65]. The swelling of chitosan-alginate polyelectrolyte complex hydrogels changes with pH, and they stick to things better than the individual polymers. They let out less than 10% of the drug when it's in a simulated stomach or intestine and more than 85% when it's in a simulated colon [66]. Advanced injectable and self-healing hydrogels, made from chemically modified polysaccharides, have been designed for minimally invasive intracolonic delivery with in situ gelation. This means that drug concentrations stay high in one area for weeks after a single dose [67].

5.4 Nanoparticles and Microparticles

Polysaccharide-based nanoparticle (NP) and microparticle (MP) systems are the fastest-growing and most technologically advanced type of controlled drug delivery systems (CDDS). Chitosan nanoparticles, which are made by ionic gelation with tripolyphosphate, nanoprecipitation, or desolvation techniques and are between 100 and 400 nm in size, increase the permeability of drugs through mucous membranes by 2 to 5 times compared to drug solutions. This improvement is because chitosan has a positive charge, which makes it stick to mucus and temporarily opens tight junctions [68, 69]. Polyelectrolyte complexation forms pectin- chitosan nanoparticle systems that integrate the enzymatic degradation of pectin in the colon with the adhesive properties of chitosan, facilitating the transit of substances. A recent study demonstrated that nanoparticles featuring a BSA core, modified with chondroitin sulfate, and enveloped in a chitosan-pectin shell containing tofacitinib, diminished the disease activity index in DSS-induced colitis mice by 38.89% [70]. Alginate- based nanoparticles functionalized with folate, transferrin, or hyaluronic acid ligands enable an active targeting mechanism, allowing receptor-mediated internalisation by colorectal cancer cells [71]. Electro-spraying has been employed to fabricate inulin-lipid core-shell microcapsules aimed at targeting gut microbiota and enhancing pharmaceutical delivery. This can make treatments for digestive system diseases work better and help patients get better [72].

5.5 Tablets with Compression Coating

Compression coating technology is a scalable and GMP-compatible way to target polysaccharides in the colon. It works by using hydraulic pressure to squeeze a mixture of polysaccharide powders around.

6. Assessment and Characterisation

6.1 In vitro studies

The in vitro characterisation of polysaccharide-based CDDS includes a wide range of physicochemical, pharmaceutical, and biological tests that are meant to predict how the CDDS will work in real life. The standard dissolution test employs a multi-pH protocol comprising simulated gastric fluid (pH 1.2 for 2 hours), simulated small intestinal fluid (pH 6.8 for 3 hours), and simulated colonic fluid (pH 6.8 or 7.4) with colonic enzymes or rat cecal/human faecal content (6 hours) [74]. The most important thing is how much of the drug comes out in each phase. The gastric and intestinal phases should be less than 10%, and the colonic phase should be more than 80%. DLS, or dynamic light scattering, measures the size of particles and their zeta potential. Transmission electron microscopy (TEM) or scanning electron microscopy (SEM) shows how a pre-formed inner tablet has drugs in it. The outer polysaccharide layer makes it hard for drugs to leave the GI tract. But enzymes from microbes in the colon break down the coat in a controlled way so that the drugs can dissolve and the inner tablet can leave quickly. The weight of the coat, the size range of the polysaccharide powder particles, and the hardness of the tablet

all affect how quickly the coat breaks down and the drug is released [73]. Compression- coated systems are still very useful for high- dose drugs and active pharmaceutical ingredients that don't work well with the conditions needed for nanoparticle or film- coating processes. This is because they are a good alternative that keeps the drug stable and lets it out in a controlled way in the digestive system. particles are shaped. Fourier transform infrared spectroscopy (FTIR) checks how drugs are packaged and how they interact with polymers. Differential scanning calorimetry (DSC) checks the drug's thermal properties, while X-ray powder diffractometry (XRPD) checks its shape [75]. Mucoadhesion studies utilising mucin particle sedimentation assays or rotating cylinder methodologies assess the intensity and duration of polysaccharide–mucin interactions [76].

6.2 In vivo studies

The dextran sulfate sodium (DSS)-induced or trinitrobenzene sulfonic acid (TNBS)- induced colitis murine model is frequently employed for preclinical in vivo evaluation of polysaccharide-based controlled drug delivery systems (CDDS). The disease activity index (DAI), colon length, histopathological evaluation of mucosal inflammation, and the measurement of pro- inflammatory cytokines (TNF-α, IL-6, IL-1-1β, and IL-17) in colonic tissue homogenates and serum are all examples of efficacy endpoints [77]. Studies of pharmacokinetics in rodents after giving them polysaccharide-based controlled drug delivery systems (CDDS) and regular formulations by mouth—looking at plasma drug concentration-time profiles and colon tissue drug levels—provide quantitative proof of the colon-targeting advantage [78]. To test how well CRC-targeted formulations work, researchers use xenograft tumour models in mice with weak immune systems and subcutaneous or orthotopic colorectal tumour cell lines (HT-29, HCT-116, Caco-2, SW480) [79].

6.3. Investigation into Drug Release and Degradation

Mechanistic characterisation of polysaccharide degradation kinetics in simulated colonic media elucidates the pharmacological foundation for comprehending drug release profiles. Gravimetric degradation studies look at how much m00ass a formulation loses over time in media that have enzymes added to it. These studies find out how fast erosion happens and make it easier to figure out how long polysaccharides last [80]. Size exclusion chromatography (SEC) or gel permeation chromatography (GPC) shows how the molecular weights of polysaccharides change as enzymes break them down. This shows at the molecular level that glycosidic bonds have been broken. Rheological evaluations of polysaccharide hydrogels examine the mechanical stability of the delivery matrix under simulated physiological conditions [81]. Using Korsmeyer-Peppas, Higuchi, zero-order, and first-order kinetic models to mathematically model drug release data helps find the main release mechanism and supports regulatory submissions.

7. Recent Advances

7.1 Intelligent Delivery Systems

Scientists have made a new kind of "smart" controlled drug delivery system (CDDS) by combining polysaccharide chemistry with advanced materials science. This system can respond to more than one stimulus at once or in a certain order. This design idea is called multi-trigger or multi-stimuli-responsive delivery. These systems are affected by the colon's pH, microbial enzymes, reactive oxygen species (ROS), glutathione (GSH), and temperature. This means that drug release can happen when more than one disease-specific physiological signal comes together [82]. People with IBD have a lot of oxidative stress in their inflamed colonic mucosa. This is how ROS-responsive polysaccharide delivery systems work. In these individuals, the concentrations of hydrogen peroxide, superoxide, and hypochlorous acid are elevated by 10 to 100 times compared to healthy tissue. They do this by putting ROS-labile chemical bonds into the polysaccharide matrix [83]. In CRC xenograft models, nanoparticles made of hyaluronic acid with disulfide crosslinks that respond to GSH have shown that they can release drugs in a way that is specific to the tumour microenvironment. This is because tumour cells have 100 to 1000 times more GSH than normal cells [84].

7.2 Methods in Nanotechnology

Combining nanotechnology with polysaccharide-based colon-targeted drug delivery systems (CDDS) has greatly improved the effectiveness of disease treatments. Polysaccharide-coated lipid nanoparticles, liposomes, and solid lipid nanoparticles (SLN) combine the drug- encapsulating and biocompatible properties of lipid-based nanocarriers with the colonic targeting and mucoadhesive properties of polysaccharide shells. This makes it possible to encapsulate a lot of hydrophobic drugs like curcumin, paclitaxel, and doxorubicin [85]. Polysaccharide-inorganic nanocomposite systems containing metal oxide nanoparticles or mesoporous silica can employ magnetic guidance, photothermal therapy, or photodynamic activity as adjunctive treatment modalities alongside the administration of chemotherapy agents [86]. Polysaccharide- based controlled drug delivery systems (CDDS) have utilised three-dimensional printing (3DP) and bioprinting technologies to fabricate intricate shapes with programmable drug release profiles unattainable through conventional methods [87].

7.3 Stimuli-Responsive Systems

Systems responsive to stimuli, including single-stimulus-responsive polysaccharide systems targeting specific pathological signals in the colon, have been extensively studied alongside multi-stimuli-responsive systems. Researchers have looked into using cellulose-based temperature- responsive systems as thermogelling formulations for rectal use. These formulations have lower critical solution temperature (LCST) properties and keep the drug in contact with the mucosa for a longer period of time [88]. When exposed to an alternating magnetic field from the outside, magnetic-responsive chitosan nanoparticles with superparamagnetic iron oxide nanoparticles

(SPIONs) cause local hyperthermia, which speeds up the release of drugs and kills CRC cells at the same time [89]. Microbiome-modulating delivery systems, which use polysaccharide carriers that have prebiotic properties, help restore the microbiome and deliver drugs at the same time. This is a two-pronged approach that works well for managing IBD [90].

Table 3: Representative Recent Studies on Polysaccharide-Based Colon-Targeted Drug Delivery Systems (2020–2025)

Study (Year)	Polysaccharide(s)	Drug / Therapeutic	Form Evaluation Type	Key Finding	DOI
Liang et al., 2024	Chitosan, alginate, pectin	Various IBD drugs	Nanocarrier review	Superior mucosal accumulation and anti-inflammatory efficacy in IBD models; synergistic microbiome modulation highlighted	10.1016/j.ijbiomac.2024.136392
Shao et al., 2025	Chitosan, pectin, guar gum, alginate, HA, dextran	5-FU, curcumin, oxaliplatin	Comprehensive CDDS review (CRC)	Improved tumour apoptosis and reduced systemic toxicity vs conventional chemotherapy in CRC models	10.1016/j.ijbiomac.2024.139177
Chen et al., 2025	Chitosan, pectin, chondroitin sulfate	Tofacitinib	Core-shell NPs (Tof@BSA-Chs-CP)	38.89% reduction in DAI vs DSS group; pH- sensitive upper GI protection + pectinase-triggered colonic release	10.1038/s41598-024-84322-2
Moutaharrik et al., 2024	Guar gum	5-FU (model drug)	Oral colon delivery system	Microbially degradable coating reduced premature drug release; validated in vitro with rat cecal content	10.1007/s13346-023-01439-z
Udaipuria et al., 2024	Chitosan, pectin, guar gum, alginate, HA, dextran	Chemotherapeuti cs	Intelligent carbohydrate polymer CDDS	AI-guided stimuli-responsive systems demonstrated pH/redox/enzyme triple- trigger precision; 3DP integration reviewed	10.1002/bip. 23632
Manna et al., 2024	Guar gum derivatives	Various drugs	Matrix tablets, coated granules, NPs	Graft-copolymerised guar gum derivatives showed markedly reduced uncontrolled swelling; superior colon specificity	10.1016/j.carbpol.2024.122009
Ibrahim et al., 2023	Chitosan, pectin, alginate, inulin	Mesalamine, 5-ASA, curcumin	Oral CTDDS review	Systems restrict drug release to <10% in the first 5 hours; clinical translation gap and dysbiosis challenge identified	10.7759/cureus.336 36
Long et al., 2024	Multiple polysaccharides + synthetic polymers	Anti-inflammatory agents	Stimulus-responsive nanoplatforms (IBD)	ROS/pH/enzyme triple-responsive systems demonstrated lesion-Specific drug release; IBD and CRC dual-indication potential	10.1016/j.actbio.2024.09.007

5-FU: 5-ffuorouracil; 5-ASA: 5-aminosalicylic acid; IBD: inffammatory bowel disease; CRC: colorectal cancer; DAI: disease activity index; DSS: dextran sulfate sodium; HA: hyaluronic acid; NPs: nanoparticles; CDDS: colon- targeted drug delivery system; CTDDS: colon-targeted drug delivery system.

8. Clinical Applications

8.1 Inflammatory Bowel Disease

IBD is the most studied and clinically proven therapeutic target for polysaccharide-based CDDS because of the link between IBD's inflammatory effects on the colon and distal ileum and the ability of polysaccharide systems to deliver drugs directly to the site of action. Aminosalicylates, corticosteroids, immunomodulators, and biological agents are the most common drugs used to treat IBD. Targeted delivery to the colon would raise the levels of the drug in the local mucosa, lower the drug's effects on the whole body, and lower side effects [91]. In DSS-induced colitis rat models, chitosan- based multiunit delivery systems for mesalamine have shown much higher drug levels in colonic tissue and lower systemic plasma AUC than enteric-coated conventional mesalamine tablets [92]. Alginate-chitosan microspheres containing icariin exhibited over 85% drug retention in simulated gastric and intestinal environments, complete release in simulated colonic fluid with β-glucosidase, and a notable reduction in TNF-α and IL-6 levels in colitis rat colon tissue [93]. The recent use of polysaccharide-based systems to deliver nucleic acid therapeutics, such as siRNA that targets NF-κB or TNF-α mRNA, shows a big change from small molecules to nucleic acid therapeutics. Chitosan, known for its ability to bypass endosomes and condense nucleic acids,

is the most studied polysaccharide carrier for colonic gene therapy [94].

8.2 Colorectal Cancer

Polysaccharide-based controlled drug delivery systems (CDDS) can be used to treat colorectal cancer (CRC) by sending cytotoxic chemotherapeutics (5- fluorouracil, oxaliplatin, irinotecan, and curcumin) directly to the tumour site and actively targeting receptors on CRC cells with polysaccharides that have ligands for those receptors. 5-fluorouracil is a common drug used to test controlled drug delivery systems (CDDS) that are based on polysaccharides. Different formulations of chitosan, pectin, alginate, guar gum, and hyaluronic acid are more harmful to HT-29 and HCT-116 colorectal cancer cell lines in vitro than free 5-FU. This greater effectiveness is due to a higher accumulation of the drug inside cells through receptor-mediated endocytosis and a longer release of the drug inside cells [95]. Hyaluronic acid-based nanoparticles use the fact that colorectal cancer (CRC) cells have too many CD44 receptors to actively target tumours, as well as passive polysaccharide enzymatic degradation [96]. Alginate nanoparticles that target folate receptors have been shown to cause 3–5 times more drug accumulation in FR-positive CRC cells than in cells that don't have FR. This has led to increased pro- apoptotic and anti-proliferative activity [97].

8.3 Targeted Antimicrobial Therapy

Colonic infectious diseases, particularly Clostridioides difficile-associated colitis and Campylobacter enterocolitis, are increasingly prevalent justifications for colon-targeted antimicrobial delivery. This is especially true now that antibiotic resistance is rising and systemic antibiotics can kill the good bacteria that live in the gut. Chitosan nanoparticles combined with rifaximin showed better mucoadhesion to inflamed colonic mucosa. In ex vivo studies of porcine colonic tissue, they had eight times higher mucosal rifaximin concentrations than standard rifaximin capsules, while still being effective against C. difficile at concentrations below the minimum inhibitory concentration (MIC) because of long-term localised release [98, 99]. The strategic combination of polysaccharide-based antimicrobial delivery with prebiotic activity, like inulin or guar gum-based systems that deliver both the antimicrobial agent and promote the growth of beneficial bacteria that are resistant to the drug, is a new way to treat infections in the colon that keeps the microbiome healthy while getting rid of the pathogen.

9. Challenges and Limitations

9.1 Changes in Microbiota and Dysbiosis

The main and clinically important problem with polysaccharide-based controlled drug delivery systems (CDDS) is that they depend on the activity of colonic microbial enzymes, which can be different for each person, disease, age group, diet, and history of antibiotic use [100]. The gut microbiome composition exhibits significant variability among individuals. Research shows that less than 20% of bacterial strains are shared by people who are not related. This biological uniqueness is directly linked to differences in the functions and profiles of polysaccharidase enzymes. In individuals with active inflammatory bowel disease (IBD), pronounced microbiome dysbiosis creates an enzymatic environment that may be fundamentally inadequate for the degradation of polysaccharide matrices— the “dysbiosis-delivery failure” paradox—underscoring a significant translational gap that remains insufficiently investigated in the current literature [101]. There are many technical problems with formulation design, manufacturing, and quality control in the pharmaceutical development of polysaccharide-based CDDS. Suggested ways to lessen the effects include combining microbiota-induced release with backup triggers that are sensitive to pH or time, giving probiotic supplements at the same time, and making products that are activated by pathological signals that are made stronger rather than weaker in the diseased state [102].

9.2 Problems with Formulation

The inconsistent drug loading efficiency, release kinetics, and mechanical properties of naturally sourced polysaccharides are due to their uneven molecular weight distribution, different levels of polymerisation, and differences in physicochemical properties from batch to batch [103]. It is still very hard to move the making of polysaccharide nanoparticles from the lab to the pilot stage and then to full-scale production. This is because processes that are easy to do with milligrams to grams of material become very hard with kilograms of material because of problems with hydrodynamics, heat transfer, and mixing that change particle size distributions, encapsulation efficiencies, and stability profiles [104]. Nanoparticles made of polysaccharides are also not very stable when they are stored or moved through the GI tract. Most polysaccharides are very hydrophilic, which means they don't work well as carriers for drugs that don't dissolve well in water unless they are chemically changed or mixed with lipid-based components [105].

9.3 Problems with rules

It is hard to follow the rules for polysaccharide-based CDDS, especially nanoparticulate systems. The rules are not yet completely in line with the rules in all major areas of regulation. The FDA, EMA, and CDSCO classify polysaccharide-based nanoparticle drug delivery systems as either combination products or novel drug delivery systems, depending on how much they have been changed and what the therapeutic claim is. This classification may necessitate significantly elevated standards of evidence for safety and efficacy compared to standard drug applications [106]. Because modified polysaccharides are now considered new molecular entities, questions arise about how reliable the safety data for the parent polysaccharide is. There are no standardised in vitro dissolution methods for controlled drug delivery systems that use polysaccharides. This is especially true because there is no standardised enzyme composition in compendial simulated

colonic fluid. This makes it hard for regulators to see how in vitro and in vivo results are connected (IVIVC) [107].

10. Future Perspectives

In the next ten years, research on polysaccharide-based CDDS will go in a certain direction because of new findings in microbiome science, materials engineering, personalised medicine, and regulatory science. This will make it more likely that colon-targeted therapies will be more accurate, reliable, and useful in the clinic.

Using metagenomics and metabolomics to group patients—especially by finding microbiome signatures that predict polysaccharide enzymatic activity and drug release capacity—makes it possible to make CDDS that are just right for each person. This resolves the issue of individual variability that presently hinders clinical translation [108]. The integration of artificial intelligence and machine learning into the formulation of polysaccharide CDDS represents a groundbreaking methodological advancement: machine learning models, trained on extensive datasets of polysaccharide physicochemical properties and formulation variables, can predict optimal formulation compositions and process parameters, thereby significantly accelerating the development cycle [109]. Three-dimensional bioprinting of patient-specific polysaccharide hydrogel implants for intracolonic placement opens the door to truly personalised and long- lasting colonic drug depot systems [110]. One of the most interesting new areas of research is creating polysaccharide-based delivery systems that can be taken by mouth for nucleic acid therapies like CRISPR- Cas9 ribonucleoprotein complexes, antisense oligonucleotides, and siRNA. These systems look at genes that are linked to diseases in the colon's epithelial tissue or the area around tumours. Thiolated, quaternized, and lipid-conjugated chitosan derivatives are beginning to fix big issues with physical protection and escaping endosomes [111]. Lastly, it will be very important to make sure that the rules for talking about polysaccharide nanoparticles are the same everywhere. This means coming to an agreement on what important quality attributes mean, using validated colonic enzyme media for standardised in vitro dissolution methods, and giving advice on the minimum in vivo evidence packages needed for IND approval. This will help turn the many promising preclinical data in this field into therapies that are safe for use in humans [112].

11. CONCLUSION

Polysaccharide-based colon-targeted drug delivery systems are a scientifically advanced, mechanistically clear, and clinically promising way to treat colonic disorders with precision pharmacotherapy. Polysaccharides are the best materials for this use because they are biologically selective (the colonic microbiota can break down polysaccharides), their physicochemical properties can be changed, they are GRAS-approved, they are biocompatible, and they work with different formulation architectures [113]. The comprehensive preclinical literature examined indicates the consistent benefits of polysaccharide-based controlled drug delivery systems (CDDS) compared to traditional delivery methods, especially in colon-specific drug targeting, localised tissue drug concentration, diminished systemic exposure, and enhanced therapeutic efficacy in animal models of inflammatory bowel disease (IBD) and colorectal cancer (CRC) [114]. Even though there is a lot of research on polysaccharide-based controlled drug delivery systems (CDDS), they can't be used in clinical settings yet because of big problems with microbiome variability and dysbiosis-related drug release failures. There are also concerns about how well the formulations can be scaled up and how stable they are. There are no rules that are specific to this kind of complex drug product [115]. The introduction of multi-stimuli-responsive hybrid nanosystems, AI- driven formulation development, patient microbiome stratification strategies, and nucleic acid delivery applications marks a new era of innovation in the field [116]. By addressing the translational issues discussed in this review, we can improve the therapeutic potential of polysaccharide- based CDDS for millions of people around the world who suffer from IBD, CRC, and other colonic disorders.

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