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Stimuli- responsive Targeted Drug Delivery Strategies for Inflammatory Bowel Disease

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Abstract. Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, is a chronic and relapsing inflammatory condition of the gastrointestinal tract with increasing global prevalence. Conventional therapies—including aminosalicylates, corticosteroids, and biologics—often suffer from systemic side effects and limited localization to inflamed tissues, prompting the development of targeted drug delivery systems (DDS). Among these, stimuli-responsive DDS have attracted growing interest for their ability to selectively release therapeutic agents in response to pathological triggers such as colonic pH changes, bacterial enzyme activity, and elevated reactive oxygen species (ROS). This review summarizes the principles, materials, and examples of three major categories: pH-sensitive, microbiota-sensitive, and ROS-sensitive delivery systems. Preclinical studies demonstrate that such systems can improve drug accumulation at inflamed sites, enhance therapeutic efficacy, and reduce systemic exposure. However, challenges such as physiological variability, premature drug release, complex synthesis, and limited scalability remain obstacles to clinical application. Future innovations are expected to focus on multi-responsive platforms and biologically derived carriers to overcome current limitations. Overall, stimuli-responsive DDS represent a promising strategy for precise and efficient treatment of IBD and related inflammatory disorders.

Keywords: Inflammatory bowel disease (IBD), Targeted drug delivery, Stimuli-responsive nanoparticles, Microbiota-sensitive systems, ROS-triggered release

1. Introduction

1.1. Inflammatory bowel disease (IBD)

1.1.1. What is IBD

Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory disorder-encompassing both Crohn's disease (CD) and ulcerative colitis (UC) that can involve any part of the gastrointestinal tract [1]. Though both fall under the IBD spectrum, they differ significantly in clinical and pathological presentation. CD features segmental, transmural inflammation and may involve the entire gastrointestinal (GI) tract, while UC is confined to the colon with continuous inflammation limited to mucosal layer, often beginning in the rectum [2]. Its global prevalence is increasing, and

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patients with IBD face a heightened risk of developing colorectal cancer. From 2005 to 2019, hospitalization rates for both UC and CD rose steadily, with a notably sharper increase in Crohn's disease during the later years of this period (Figure 1, [3]).

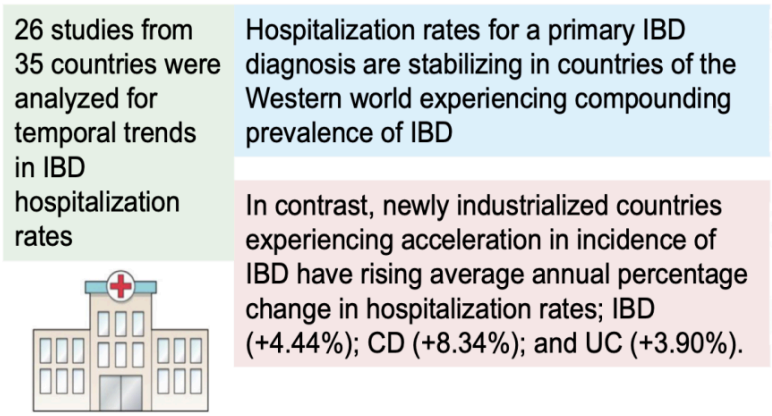


Figure 1. Global trends in IBD hospitalization rates: a contrast between western and newly industrialized countries [3]

Both conditions involve impaired mucosal barriers and abnormal immune responses to intestinal microbes. In CD, reduced defensin expression, particularly in the ileum, permits deeper bacterial invasion. In contrast, in UC, a thinned mucus layer leads to closer microbial contact with the epithelial surface. These barrier defects, rather than classical autoimmunity, are now considered central to IBD pathogenesis (Figure 2, [4]).

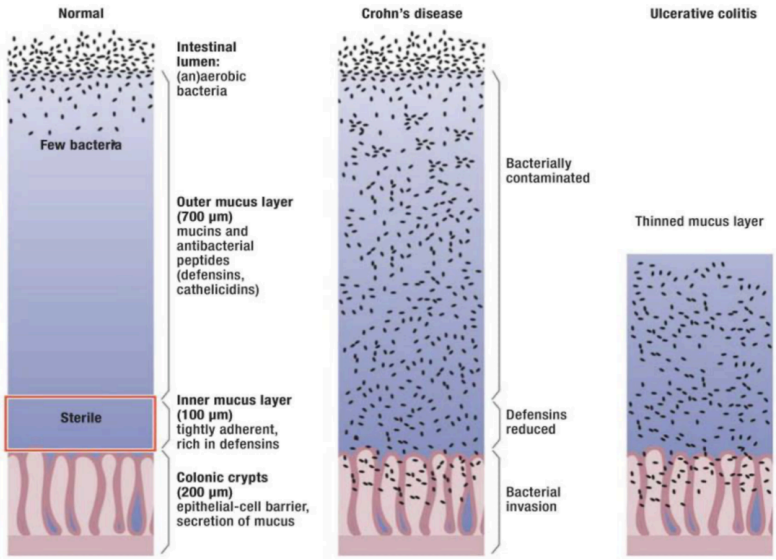


Figure 2. Impaired mucosal barrier function in IBD subtypes [4]

1.1.2. Why is IBD increasingly common world wide

In newly industrialized regions such as Asia, Latin America, and the Middle East, IBD incidence and hospitalization reached 8.43% for Crohn's disease and 3.90% for ulcerative colitis, marking a transition into epidemiologic stage 2 [5]. IBD is rising globally because developing regions now adopt Westernized diets, sanitation practices, and antibiotic overuse, which collectively disrupt the

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gut microbiota and trigger disease in genetically susceptible individuals [6]. As urbanization and industrialization progress, people are exposed to more processed foods, environmental pollution, and secondary lifestyles. These environmental changes not only affect human behavior and metabolism, but also profoundly change the composition and function of the gut microbiota, leading to microbial imbalance [7]. Microbial imbalance in IBD is commonly characterized by an increased abundance of Proteobacteria and Bacteroides species, accompanied by a loss of beneficial Firmicutes, resulting in reduced microbial diversity and a pro-inflammatory gut environment [8]. In addition to microbial balance, immune dysregulation-such as inappropriate activation of the mucosal immune system-also contributes to disease onset (Figure 3, [9]). Increasing cases among younger people heighten long-term risks like colorectal cancer [10]. At the same time, expensive biologic therapies remain out of reach for many healthcare systems in developing countries, widening treatment gaps [11]. These environmental pressures, including pollution, dietary shifts, and ecological change, interact with host genetic predisposition, forming a high-risk background for the development and persistence of chronic intestinal inflammation [12].

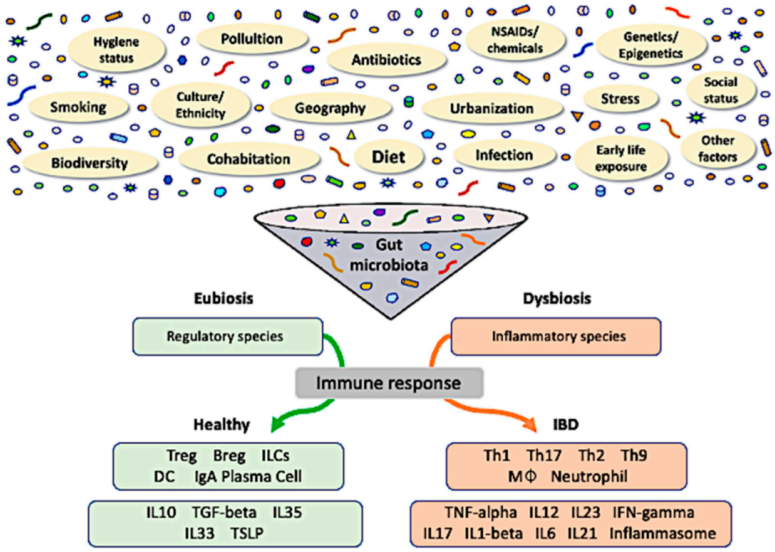


Figure 3. Main contributing factors to the global rise in IBD [9]

1.1.3. Available the rapies for treating IBD

Currently, treatment options for inflammatory bowel disease (IBD) mainly include amino salicylates, corticosteroids, and immunosuppressants, which help control inflammation but often cause systemic side effects and lack issue specificity (Figure 4, [13]). Biologic agents such as anti-TNF-α antibodies, which target tumor necrosis factor-alpha, a key pro-inflammatory cytokine involved in gut mucosal damage-have shown significant outcomes [14]. However, they require injection and are associated with the risk of systemic infections [15]. Taken together, these conventional therapies are often limited by their poor localization to the inflamed intestinal tissue, leading to reduced efficacy and unwanted off-target effects [16]. To enhance drug localization and reduce toxicity, drug delivery systems (DDS)-formulations or carriers that protect and release medication in response to colonic cues-have been developed [17]. For instance, pH-sensitive dexamethasone microcrystals layered with chitosan/alginate and Eudragit S release drug only at colonic pH, reducing off-target exposure [18], while polysaccharide-based DDS degrade via microbial enzymes to deliver anti-inflammatory agents precisely to inflamed tissue [19]. These

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approaches exploit the unique physiological conditions of the colon-such as its higher pH and dense microbial population-to ensure that therapeutic agents are activated only when and where they are needed, thereby enhancing treatment efficiency while avoiding unnecessary drug exposure on healthy tissues [20].

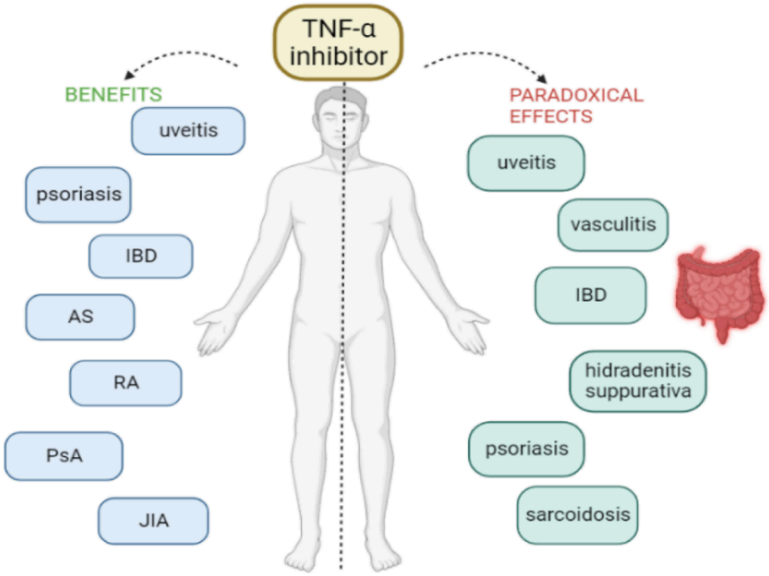


Figure 4. Overview of conventional IBD treatments and their systemic side effects [13]

1.2. Targeted drug delivery system

1.2.1. What are targeted drug delivery systems

Conventional therapies for IBD, including corticosteroids, immunosuppressants, and biologics, often suffer from poor site selectivity, systemic side effects, and limited patient compliance [21]. These challenges highlight the need for a more refined treatment approach that enhances therapeutic precision while minimizing collateral toxicity. Targeted drug delivery systems (DDS) are specifically designed to transport therapeutic agents directly to diseased tissues, thereby reducing systemic exposure, improving local efficacy (Figure 5, [22]).

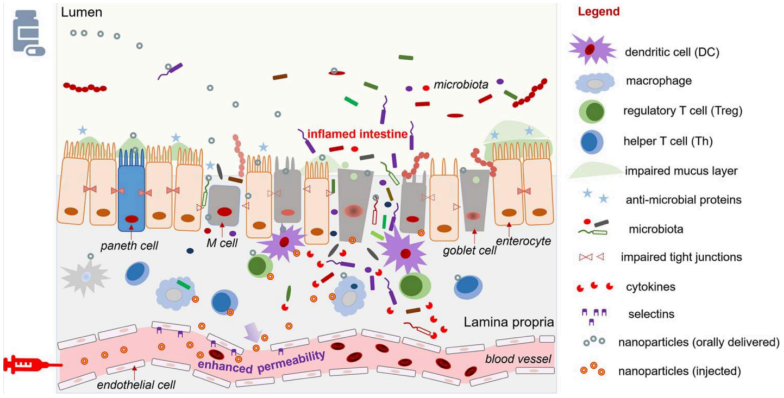


Figure 5. Schematic illustration of nanoparticle-mediated drug delivery targeting inflamed intestinal tissues in inflammatory bowel disease (IBD) [22]

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1.2.2. Classification of targeted drug delivery systems for IBD

• Stimuli-responsive: systems enable precise drug release at inflamed sites by responding to local cues. pH-sensitive dissolve at colonic pH; microbiota-sensitive carriers degrade via bacterial enzymes, ROS-sensitive systems respond to oxidative stress [23].

• Ligand-targeted systems: systems that leverage specific receptors overexpressed on inflamed cells, such as ICAM-1, VCAM-1, and folate receptors- can achieve active targeting and enable precise drug delivery in IBD therapy. These receptors are upregulated during inflammation to promote immune cell adhesion, providing selective binding sites for ligand-modified carriers [24].

• Time-dependent and other physical systems: systems rely on preset release timing, such as using coated capsules that release drug after passing through the upper GI tract, ensuring colonic delivery based on transmit time [25]. Unlike stimuli-response systems, which react to local triggers like pH or enzymes, these systems operate independently of the disease microenvironment.

This article primarily discusses the application of stimuli-responsive drug delivery systems (DDS) in the treatment of inflammatory bowel disease (IBD). By responding to pathological triggers such as pH changes, bacterial enzyme activity, and oxidative stress, these systems enable precise and localized drug release at inflamed sites, improving therapeutic efficacy while minimizing systemic side effects.

1.3. Current advancements in targeted therapies for IBD

• Commonly Used Targeted Therapies in IBD: Enteric-coated 5-ASA (mesalamine) remains the frontline approach for mild-to-moderate ulcerative colitis due to its ability to reach the colon intact and exert topical anti-inflammatory effects [26]. These formulations resist degradation in the stomach and small intestine, thus improving mucosal healing and patient compliance while minimizing systemic exposure [27].

• Emerging Combination Strategies and Smart Platforms: Recent preclinical studies have focused on advanced nanoparticle carriers-including polymeric, liposomal, and inorganic platforms-that preferentially accumulate in inflamed colonic regions via mechanisms such as increased vascular permeability, reactive oxygen species, and receptor-mediated endocytosis. These systems demonstrate enhanced localized drug release and reduced off-target toxicity in animal models [28, 29].

2. Main

2.1. Ph-sensitive drug delivery system in IBD

2.1.1. What is pH sensitivity, and which materials are used

pH sensitivity refers to the ability of drug carriers or coatings to respond to the changes in pH along the gastrointestinal (GI) tract, allowing targeted drug release at specific sites. In IBD, especially ulcerative colitis, pH-sensitive formulations are designed to remain intact in the acidic environment of the stomach and upper small intestine but dissolve and release the drug in the slightly alkaline pH of the colon ($pH \geq 7.0$) [30].

Common materials used for pH-sensitive drug delivery include synthetic polymers such as Eudragit S100 and Eudragit L100, which dissolve at pH 6.8-7.0 [31], and natural alginate, chitosan,

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and pectin [32]. These materials help protect drugs like corticosteroids or anti-inflammatory agents until they reach the inflamed colon [33].

2.1.2. Example 1: enteric-coated mesalamine (5-ASA) for ulcerative colitis

Mesalamine (5-ASA) is a cornerstone drug in the management of mild-to-moderate ulcerative colitis (UC), due to its topical anti-inflammatory effects on the colonic mucosa, achieved primarily through inhibition of cyclooxygenase and lipoxygenase pathways [34]. However, uncoated 5-ASA may be absorbed or degraded in the upper gastrointestinal (GI) tract before reaching the inflamed colon, thereby limiting its therapeutic effectiveness.

To overcome this limitation, pH-sensitive enteric-coated formulations have been developed using polymers such as Eudragit S100 and Eudragit L100, which dissolve at intestinal pH values (≥6.8-7.0), ensuring targeted drug release in the distal ileum and colon (Table 1, [35]). This coating strategy prevents premature drug release in the stomach and proximal small intestine, thereby enhancing its colonic availability.

Table 1. Summary of anatomical and physiological features of small intestine and colon [35]

Region of Gastrointestinal tract		Length (cm)	pH	Internal diameter
Stomach		…….	1.5-3 (fasted) 2-5 (fed)	……..
Small Intestine	Duodenum	20-30	6.1 (fasted), 5.4 (fed)	
	Jejunum	150-200	5.4	
	Ileum	200-350	7-8	
Large Intestine	Cecum	6-7	5.5-7	6
	Ascending colon	20		
	Transverse colon	45		
	Descending colon	30		
	Sigmoid colon	40	7-8	
	Rectum	12		
	Anal canal	3		

Studies have shown that such formulations significantly increase local mesalamine concentrations in the colon while minimizing systemic absorption and associated side effects like nephrotoxicity. This localized delivery is particularly beneficial for maintaining mucosal healing and achieving clinical remission in UC patients, especially during long-term maintenance therapy [36]. Furthermore, modified-release systems combining time-dependent and pH-sensitive mechanisms are under development to further synchronize drug release with colonic transit time and inflammation site [37].

2.1.3. Example 2: dexamethasone microcrystals with multilayer pH-sensitive coatings

Dexamethasone microcrystals (DXMCs) loaded into colon-targeted delivery systems have shown enhanced therapeutic performance in IBD models. An effective strategy involves coating the DXMC core with several layers of chitosan and alginate, forming a protective and mucoadhesive inner shell. A terminal layer of pH-sensitive polymer (e.g. Eudragit S100) is then applied to prevent drug release

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in acidic environments, while enabling dissolution at colonic pH (≥7.0), thereby ensuring precise drug release at inflammatory sites and reducing gastric and systemic exposure [38].

In vitro assays confirm that these Layer-By-Layer (LBL) coated DXMCs avoid premature "burst release" under gastric (pH 1.2) and early intestinal (pH 6.8) conditions, and instead exhibit controlled dexamethasone release at colonic pH over extended durations. In parallel, Dexamethasone-loaded chitosan-alginate beads, reported by Khan et al., exhibited similar pH-triggered release patterns, reinforcing the validity of using biopolymer multilayer coatings to regulate drug delivery (Figure 6, [39]).

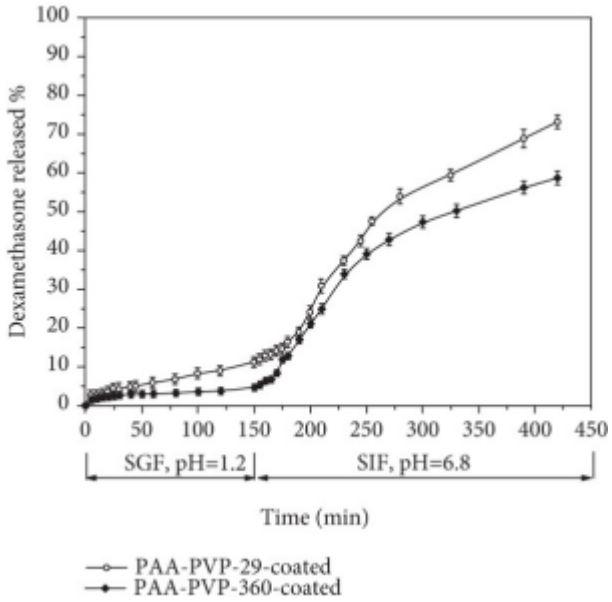


Figure 6. Dexamethasone-loaded chitosan–alginate beads exhibit minimal release at pH 1.2–6.8 and significant release at colonic pH (~7.4), underscoring the efficacy of multilayer, pHresponsive coatings [39]

2.1.4. Example 3: budesonide-loaded pH-sensitive nanoparticles

Budesonide is a glucocorticoid commonly employed in the management of IBD, but its therapeutic effectiveness is limited by extensive first-pass metabolism, which significantly reduces its systemic bioavailability. To address this challenge, researchers have developed pH-responsive nanoparticle carriers-often composed of PLGA or lipids-coated with enteric polymers such as Eudragit S100 (Figure 7, [40]). These coatings are designed to resist acidic gastric environments and only dissolve when the pH reaches approximately 6.5 or above, thus triggering drug release specifically at the colon site [40].

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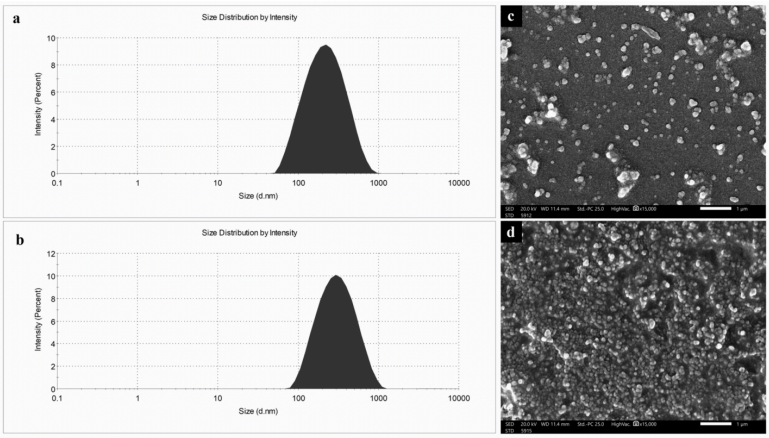


Figure 7. Particle size distribution and SEM images of uncoated and HA-coated budesonide nanoparticles. The particles appear spherical and uniformly dispersed under ×15,000 magnification [40]

This targeted delivery system offers distinct advantages: it shields budesonide from premature degradation in the stomach and small intestine, facilitates prolonged retention at inflamed colonic tissues, and reduces systemic exposure, thereby minimizing side effects. In murine colitis models (e.g., DSS or acetic acid-induced), these formulations have demonstrated superior outcomes in terms of lower histological inflammation scores, reduced pro-inflammatory cytokines, and accelerated mucosal restoration compared to conventional budesonide formulations(Figure 8, [41]). Thus, pH-sensitive budesonide nanoparticles represent a promising strategy for achieving localized and effective steroid therapy in colonic inflammation.

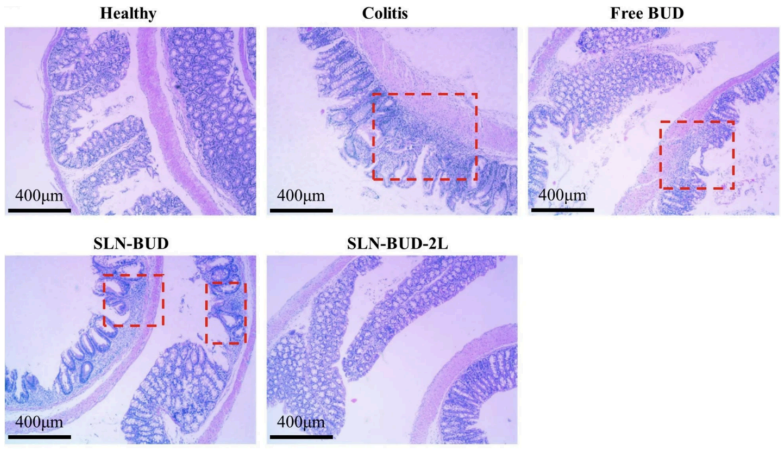


Figure 8. SLN-BUD-2L treatment greatly improved colon tissue structure in colitis mice, while free BUD and SLN-BUD showed only partial recovery [41]

2.2. Microbiota-sensitive drug delivery system in IBD

2.2.1. What is microbiota sensitivity, and which materials are used

Microbiota-sensitive drug delivery systems utilize the presence and enzymatic activity of colonic bacteria to trigger drug release. These systems take advantage of the fact that certain enzymes-such as azoreductase, glycosidase, and nitroreductase-are abundant in the colon but absent in the upper GI

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tract (Figure 9, [42]). The carriers remain intact during stomach and small intestine transit and release the drug upon microbial degradation in the colon. Common materials used in these systems include azo bonds, polysaccharides like pectin, guar gum, chitosan, and dextran, which are specifically degraded by colonic bacteria.

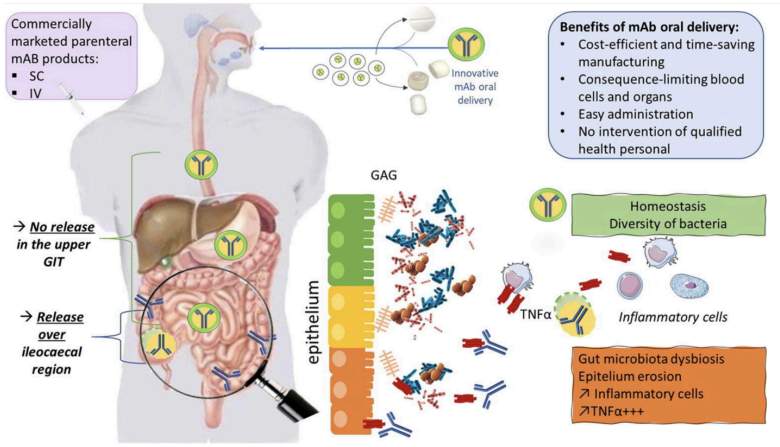


Figure 9. Microbiota-sensitive carriers stay intact in the upper GI tract and release drugs in the colon via bacterial enzyme-triggered degradation [42]

2.2.2. Examples 1: sulfasalazine and azo-bonded prodrugs

Azo-bonded prodrugs represent a foundational strategy in microbiota-sensitive drug delivery, enabling targeted release in the colon. The most classical example is sulfasalazine, developed for the treatment of inflammatory bowel disease (IBD), especially ulcerative colitis. Sulfasalazine chemically links 5-aminosalicylic acid (5-ASA), the active therapeutic compound, with sulfapyridine, an inert carrier, via an azo bond (-N=N-).

This azo bond is highly stable in the acidic and enzymatic conditions of the stomach and small intestine, allowing the prodrug to remain intact throughout upper gastrointestinal transit. Once sulfasalazine reaches the colon, it encounters anaerobic bacteria that produce azoreductases, enzymes capable of cleaving azo bonds under reductive conditions. The enzymatic cleavage releases active 5-ASA at the site of colonic inflammation, while sulfapyridine is absorbed systemically and subsequently excreted [43].

The chemical structures of these prodrugs are presented in Figure 10 of Teruel et al., 2020 [44], highlighting the chemical differences between sulfasalazine, olsalazine, and balsalazide. However, it should be noted that this figure only provides chemical structures without explicitly indicating the azo bond or the enzymatic cleavage site, which are essential to their mechanism of activation. Therefore, the illustration supports a structural comparison but does not depict the microbiota-triggered activation process in full detail.

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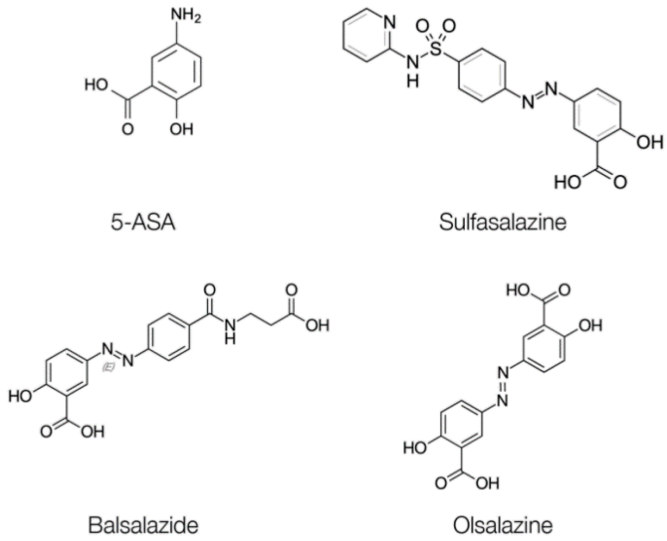


Figure 10. Chemical structures of 4 azo-bonded prodrugs

2.2.3. Examples 2: polysaccharide-based colon-targeted formulations

Polysaccharides such as chitosan, pectin, and alginate have emerged as promising materials for colon-targeted drug delivery systems due to their natural biodegradability and selective degradation by colonic microbiota. These carriers effectively protect therapeutic agents such as budesonide or mesalamine from premature release in the upper gastrointestinal tract and ensure controlled drug release within inflamed colonic regions, thereby reducing systemic toxicity and enhancing treatment efficacy.

For example, budesonide-loaded chitosan nanoparticles (BCN) have demonstrated structural stability in acidic and neutral pH environments, with targeted release triggered under simulated colonic conditions. Transmission and scanning electron microscopy confirmed the spherical morphology and surface integrity of the nanoparticles (Figure 11, [45]). This formulation significantly alleviated inflammation in dextran sulfate sodium (DSS)-induced colitis models and maintained therapeutic levels over extended periods, as reflected in colonic tissue analysis and drug release curves (Figure 12, [45]).

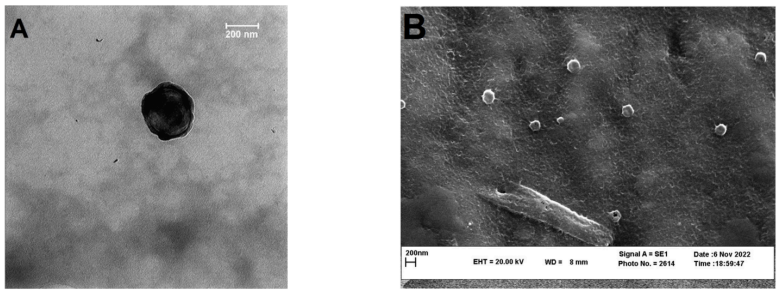


Figure 11. TEM image of BCN and SEM image of freeze-dried BCN [45]

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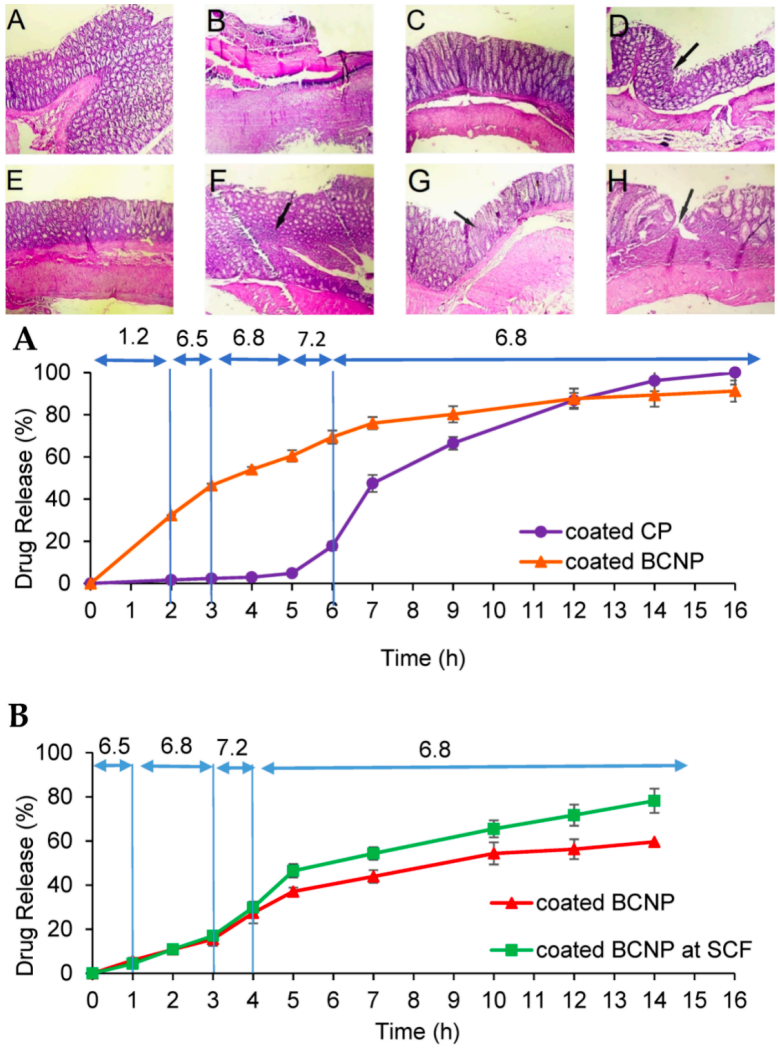


Figure 12. Comparison of colonic tissue recovery in DSS-induced colitis model and drug release [45]

Similarly, alginate–chitosan microcapsules developed for gastrointestinal delivery exhibited excellent mucoadhesion and multilayer architecture. Their morphology, as visualized through SEM, revealed uniform particle distribution and surface smoothness suitable for targeted intestinal transport [46].

Additionally, chitosan-coated alginate microspheres have shown enhanced protective capacity and site-specific delivery in various colonic conditions. Structural analysis via SEM confirmed the presence of layered coating (Figure 13, [47]). These delivery platforms collectively exemplify the potential of polysaccharide-based systems in achieving localized and sustained anti-inflammatory effects for IBD treatment.

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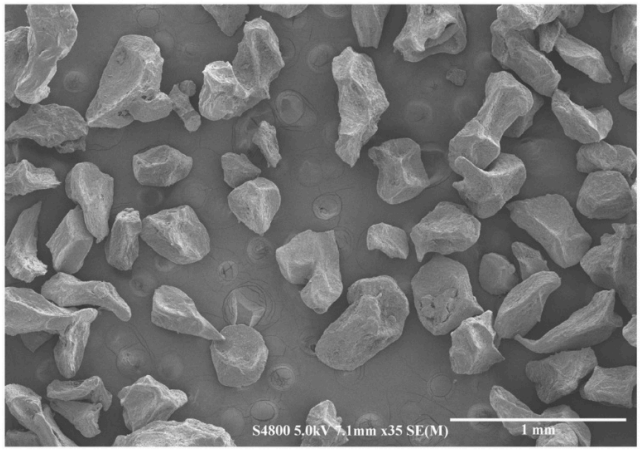


Figure 13. SEM image of chitosan-coated alginate microspheres [47]

2.3. Ros-sensitive drug delivery system in IBD

2.3.1. What is ROS sensitivity, and which materials are used

Reactive oxygen species (ROS), such as H_2O_2, O_2^-, and •OH, are naturally produced during metabolism and immune responses. In pathological conditions like atherosclerosis and inflammatory bowel disease (IBD), ROS levels become abnormally elected, leading to tissue damage and sustained inflammation. Interestingly, this oxidative microenvironment can be exploited to trigger drug release from specially designed carriers.

As shown in Figure 14 [48], common ROS-triggered mechanisms include solubility change, polymer cleavage, and prodrug activation. This strategy, referred to ROS sensitivity, enables nanocarriers to remain stable under normal conditions but degrade selectively in high-ROS environments. Materials frequently employed for this purpose include thioketal, boronic ester, and thioether linkers. Ji et al. reviewed various systems—such as micelles, nanoparticles, and hydrogels—successfully applied in vascular diseases for redox-triggered delivery [48].

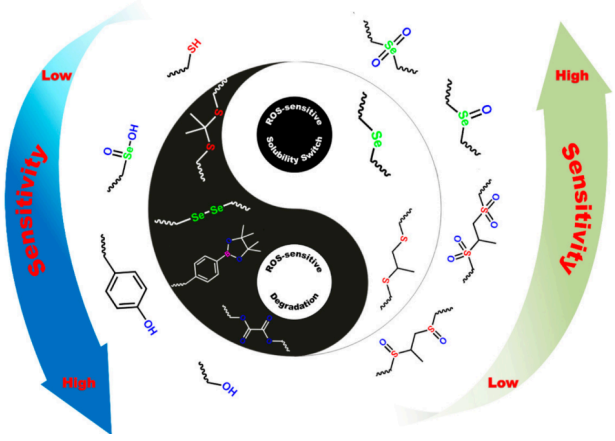


Figure 14. Schematic of ROS-triggered drug-release mechanisms: solubility switching, polymer backbone cleavage, and prodrug activation [48]

For example, Gardey et al. developed thioether-based micelles that specifically degraded in monocytes from IBD patients, without affecting healthy cells. Figure 2 [49] shows this ROS-

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dependent breakdown through reduced fluorescence in inflamed cells [49]. These findings support the potential of ROS-sensitive platforms for targeted anti-inflammatory therapy.

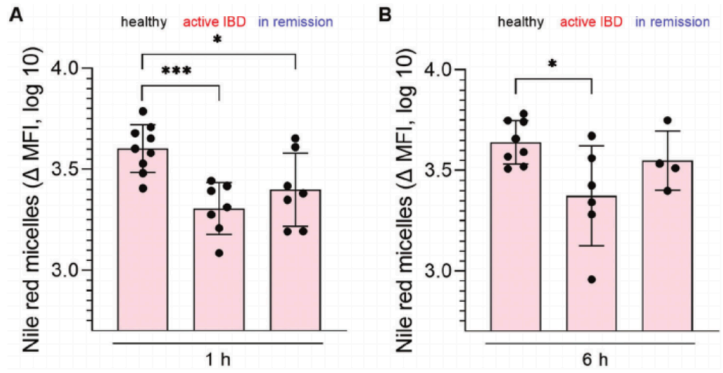


Figure 15. Nile red-labeled thioether micelles showing selective fluorescence loss in ROS-rich monocytes from IBD patients, confirming ROS-dependent degradation [49]

Moreover, ROS imbalance in the gut contributes to chronic immune activation. Aviello and Knaus emphasized that this redox disruption creates an ideal microenvironment for ROS-responsive treatments, particularly in gastrointestinal inflammation [50].

2.3.2. Example 1: oxidation-sensitive dextran nanoparticles (OxiDEX NP)

Phenylboronic ester-modified dextran nanoparticles (OxiDEX NP) are designed to respond to both acidic and ROS-rich microenvironments, making them highly suitable for targeted IBD therapy. According to Bertoni et al., OxiDEX NPs remain stable under physiological pH (7.4), but under acidic pH (~5.0) and elevated H_2O_2 levels, phenylboronic ester bonds are rapidly cleaved. This oxidative degradation releases encapsulated drugs in a controlled manner within inflamed colonic tissue (Figure 16, [51]).

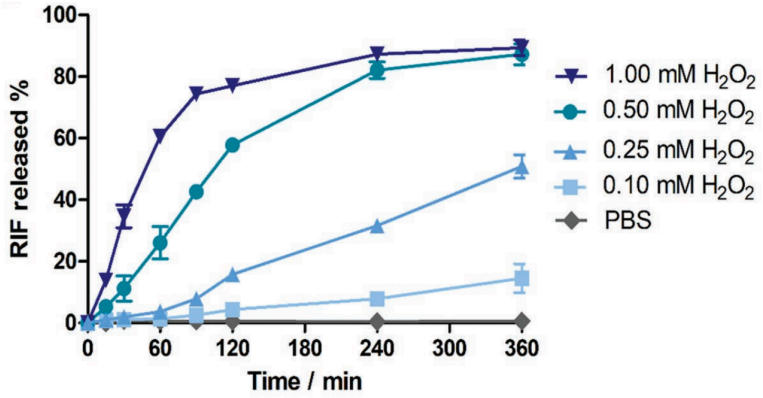


Figure 16. Drug release profile of OxiDEX NPs under various H_2O_2 concentrations. Higher levels of ROS lead to faster degradation and release

In vivo experiments in colitis models showed that orally administered OxiDEX NPs accumulated preferentially in inflamed regions, significantly alleviating disease symptoms with minimal systemic exposure [51].

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Complementary studies have demonstrated that dextran-coated cerium oxide nanoparticles (Dex-CeNP) not only target colitis tissue due to dextran affinity, but also act as ROS scavengers—reducing oxidative damage and improving imaging contrast in mouse models of IBD [52]. Furthermore, broader reviews on IBD nanomedicine highlight that OxiDEX-like dual pH/ROS-responsive systems offer precision-controlled release and enhanced mucosal accumulation, representing a promising therapeutic strategy [53].

2.3.3. Examples 2: ROS-responsive dual prodrug nanoparticles (thioketal-linked)

Thioketal (TK) bonds are uniquely suited for ROS-responsive dual prodrug nanoparticle systems: these linkages remain stable under normal physiological conditions but undergo rapid cleavage in ROS-rich environments, enabling targeted drug release. Rinaldi et al. reviewed multiple applications of TK linkers, detailing their use in smart nanomedicines—as drug conjugation linkers, prodrug formers, and core components in nanoparticles. They also included schematic illustrations that highlight how TK bonds trigger drug release and nanoparticle disassembly in oxidative environments (Figure 17, [54]). This comprehensive overview underscores the versatility of TK chemistry in designing inflammation-responsive DDS.

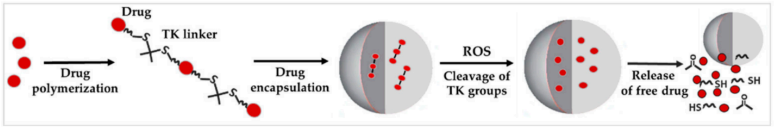


Figure 17. Schematic representation of TK-based ROS-responsive systems, showing druglinker and core-cleavage strategies [54]

In a recent study published in International Journal of Biological Macromolecules, researchers developed thioketal-linked alginate/chitosan dualprodrug nanoparticles. These carriers combine TK bonds with anti-inflammatory thiol drugs, forming a system that not only releases therapeutics in response to ROS but also scavenges ROS upon degradation. In vitro experiments showed significant prodrug release and ROS reduction at physiologically relevant ROS concentrations [55].

Together, these examples illustrate how integrating thioketal chemistry into dual prodrug nanoparticles offers a robust strategy for inflammation-specific, ROS-triggered drug delivery—especially promising for conditions like IBD and related diseases.

3. Discussion

3.1. Comparison and summary of current strategies

Stimuli-responsive drug delivery systems (DDS) represent a promising approach in the treatment of inflammatory bowel disease (IBD), as they enable precise and controlled drug release in response to pathological cues present in the gastrointestinal environment. These systems include pH-sensitive, microbiota-sensitive, and ROS-sensitive platforms, each designed to target specific features of the inflamed colon. pH-sensitive systems utilize enteric coatings that dissolve at higher pH levels found in the distal intestine, thereby minimizing premature release in the stomach. Microbiota-sensitive carriers rely on bacterial enzymes, such as glycosidases and azoreductases, to degrade specific linkages (e.g., polysaccharide or azo bonds), triggering site-specific drug release. ROS-sensitive systems are activated in environments with elevated oxidative stress, characteristic of inflamed tissues, where chemical bonds (e.g., thioketal) are cleaved to initiate release.

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These systems share a common advantage: localized release at disease sites, which improves drug concentration at inflamed areas while reducing systemic exposure. However, they differ in their triggering mechanisms and site of activation, providing diverse design options based on disease pathology. In summary, stimuli-responsive DDS allow for smart, non-passive delivery tailored to the inflammatory microenvironment, and represent the central focus of this study.

3.2. Limitations and challenges

Although stimuli-responsive drug delivery systems have demonstrated considerable potential in preclinical models of inflammatory bowel disease (IBD), several critical challenges must be addressed before clinical translation can be realized.

A major limitation of stimuli-responsive drug delivery systems lies in their dependence on patient-specific pathological variables. For example, the intraluminal pH in the colon may exhibit significant fluctuations across individuals and disease stages, which can adversely affect the release profile of pH-responsive formulations. Likewise, the functionality of microbiota-sensitive systems is contingent upon the enzymatic activity of colonic flora, which is frequently altered in IBD patients due to dysbiosis. ROS-responsive platforms, while attractive for targeting inflamed sites, may be triggered inconsistently due to the dynamic and spatially heterogeneous distribution of oxidative stress.

In addition, the physicochemical stability of these systems during gastrointestinal transit presents a notable obstacle. Before reaching the target site, carriers must endure exposure to acidic gastric environments and digestive enzymes. Premature degradation or unintended release in the upper gastrointestinal tract can severely compromise therapeutic efficiency and targeting accuracy.

Moreover, the complexity of material synthesis and scale-up feasibility remains a technical hurdle. The development of stimuli-responsive carriers often involves intricate chemical modifications and multistep fabrication processes, which pose challenges for reproducibility and industrial manufacturing. Furthermore, the long-term biosafety and regulatory approval of certain synthetic components require further investigation.

In conclusion, while stimuli-responsive drug delivery systems hold substantial promise for site-specific therapy in IBD, efforts must be directed toward enhancing their physiological robustness, formulation simplicity, and clinical translatability.

3.3. Future directions and innovations

3.3.1. Combination and multi-responsive systems

Recent nanoplatforms deploy dual or multi-stimuli responsiveness, integrating triggers such as pH and ROS, or ROS and enzymes, to improve specificity and release control. These systems are designed to remain inert during GI transit yet activate specifically within the inflamed colon. Importantly, recent reviews highlight 'layered programmable delivery', where multiple stimuli-responsive elements are combined in a single nanoparticle to synchronize release and minimize premature leakage [56].

3.3.2. Biologically derived and biometric delivery vehicles

Naturally derived carriers—such as plant-derived extracellular vehicles (EVs) or exosomes— have emerged as promising platforms for IBD therapy due to their inherent stability, biocompatibility, and

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ability to home to inflamed tissues. These biologically sourced vesicles are capable of carrying both drugs and therapeutic RNAs, displaying stimuli-responsiveness via natural cargo release within the inflammatory milieu [57]. This approach bridges synthetic stimuli-responsive materials with biomimetic targeting.

4. Conclusion

Stimuli-responsive drug delivery systems represent a promising and evolving approach for the treatment of inflammatory bowel disease (IBD), offering the potential for precise, localized, and sustained therapeutic effects. By leveraging pathological triggers such as pH shifts, microbiota activity, and reactive oxygen species (ROS) overexpression in the inflamed colon, these systems enable targeted release of anti-inflammatory agents while minimizing systemic side effects. Various platforms—including pH-sensitive coatings, enzyme-degradable carriers, and ROS-responsive nanoparticles—have demonstrated encouraging results in preclinical models, each with distinct mechanisms and material requirements.

However, despite these advances, significant challenges remain. Patient heterogeneity, gastrointestinal variability, and technical limitations in carrier design and scalability pose barriers to clinical translation. To overcome these, future efforts should focus on the development of multi-responsive and biologically derived systems, integration of smart materials with diagnostic tools, and personalization based on disease phenotype.

Overall, the refinement of stimuli-responsive DDS holds great potential not only to enhance therapeutic efficacy in IBD but also to set a foundation for next-generation targeted therapies in chronic inflammatory disorders.

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