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Targeting IBD treatment: smart drug delivery systems for oral administration

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ABSTRACT

Inflammatory bowel disease is a global widespread condition that significantly reduces patients' quality of life. Conventional oral therapies suffer from poor site-specific targeting, systemic absorption, and limited drug stability, leading to reduced efficacy and adverse effects. Smart drug delivery systems have emerged as a promising strategy to overcome these challenges by leveraging stimuli-responsive mechanisms, including internal triggers (pH, reactive oxygen species, enzymes, receptors and microbiota) and external stimuli (magnetic fields, light, ultrasound and temperature). These advanced platforms enable precise, localized drug release, enhancing therapeutic efficacy, minimizing systemic toxicity, and improving patient compliance. Preclinical studies highlight their potential in prolonging remission and promoting mucosal healing. As research progresses, further optimization of formulation design, clinical validation, and addressing interpatient variability will be essential for translating these innovative drug delivery systems into effective clinical applications for IBD management. Herein, we summarize and discuss the rational design of smart oral drug delivery systems for IBD treatment, highlighting their mechanisms, therapeutic advantages, and current challenges. The potential clinical applications, along with existing limitations and future directions for optimizing these advanced delivery platforms, are also clarified.

1. Introduction

Inflammatory Bowel Disease (IBD) is a chronic, relapse-prone, immune-mediated condition characterized by multifactorial pathogenesis, encompassing Crohn's Disease (CD) and Ulcerative Colitis (UC) [1,2]. IBD, with an increasing incidence, poses a significant health burden. An extensive study examining the global impact of IBD from 1990 to 2017 identified an increase in the age-specific prevalence of IBD throughout this period. This trend was markedly evident in developed countries. The prevalence of IBD exceeds 0.3 % in several countries across North America, Oceania, and Europe [2,3]. and is experiencing a rapid rise even in areas traditionally reporting lower prevalence rates, such as Southern and Eastern Europe, Asia, and many developing countries [4]. Over the last four decades, certain Asian nations have witnessed a surge in the incidence and prevalence of IBD, ranging from a 1.5-fold to an almost 20-fold increase [5]. In CD, intestinal resection is required in 40 %–70 % of patients within 10 years of diagnosis, with a high rate of postoperative recurrence [6,7]. In the case of UC, 25 % of individuals will experience acute severe episodes, and up to 50 % may undergo colectomy as a result [8,9]. The long-term complications of IBD, including strictures, fistulas, and an elevated risk of colorectal cancer, place a significant strain on healthcare systems, particularly in regions

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with higher disease prevalence, thus emphasizing the substantial global health burden of IBD.

IBD manifests with symptoms like fever, abdominal pain, diarrhea, rectal bleeding, and weight loss, all of which greatly impair patients' quality of life (Fig. 1) [10]. Additionally, IBD is characterized by persistent chronic ulceration of the colonic mucosa, which can result in abscess formation. It typically begins in the rectum but may extend proximally into the colon and, in rare cases, even involve the appendix [11]. IBD may involve deeper than superficial mucosal penetration; it may proceed to a level involving the submucosal part of the bowel wall. Extension into other body parts is likely to cause colorectal malfunction, including stricture, impaired colonic permeability, decreased drug efficacy, submucosal fibrosis, and other cardiovascular disease risks due to its chronicity, with potential impacts on the brain and cognitive functions. Patients with IBD whose risk of colorectal cancer is extremely high also come up as a result of chronic inflammation of the intestine and immune cell and cytokine irregularities, necessitating long-term pharmacological intervention. Despite considerable therapeutic progress, the attainment of sustained remission with minimal adverse effects remains a major challenge [12–14].

Oral administration is the most widely used route for IBD treatment due to its non-invasive nature, ease of use, and high patient compliance. Conventional drugs, including 5-aminosalicylic acid (5-ASA), corticosteroids, and immunosuppressants, play a crucial role in managing inflammation. However, these therapies lack site-specific targeting, resulting in systemic drug absorption, increased toxicity, and reduced therapeutic efficacy. Additionally, many active pharmaceutical ingredients (APIs) suffer from low stability and poor solubility in the harsh gastrointestinal tract (GI) environment, further limiting their effectiveness.

To address these challenges, sustained-release formulations have been developed to enhance drug retention and mitigate frequent dosing. By prolonging drug action and maintaining therapeutic concentrations, sustained-release systems reduce dosing frequency and improve patient adherence. Despite these benefits, traditional sustained-release formulations still exhibit limitations, such as incomplete drug release, unpredictable absorption profiles, and inadequate localization of inflamed intestinal sites. These drawbacks underscore the need for more advanced drug delivery strategies that can precisely control drug release while enhancing therapeutic outcomes.

Nanotechnology-based drug delivery systems (NDDSs) have emerged as a promising alternative to conventional formulations. Nanoparticles, including polymeric nanocarriers, liposomes, dendrimers, and mesoporous silica nanoparticles, enable improved drug encapsulation, stability, and controlled release. These carriers enhance intestinal permeability and drug retention, increasing the bioavailability of therapeutic agents. However, traditional NDDSs still face several limitations, such as nonspecific drug distribution, rapid clearance from the GI tract, and potential toxicity due to prolonged nanoparticle accumulation. Moreover, passive targeting approaches fail to precisely deliver drugs to inflamed tissues, reducing their overall therapeutic potential.

To overcome these limitations, stimulus-responsive nanoplatforms (SRNPs) have been developed to achieve site-specific and on-demand drug release. These platforms exploit distinct alterations in the IBD microenvironment, including pH fluctuations, elevated reactive oxygen species (ROS) levels, enzyme activity, and redox imbalances, to enable precise and controlled drug release at inflamed intestinal sites [15]. By responding dynamically to disease-specific microenvironments, SRNPs significantly enhance drug localization, minimize off-target toxicity, and improve treatment efficacy. These advancements underscore the clinical significance of targeted drug delivery, marking a shift toward precision medicine in IBD therapy. Different targeting strategies are summarized in Table 1.

Compared with previously published reviews, this work uniquely integrates disease molecular mechanisms (cytokine pathways and genetic susceptibility) with stimulus-responsive carrier design, presents a unified internal/external stimuli framework, and emphasizes translational and regulatory considerations that are critical for clinical translation.

Building upon SRNPs, Smart Drug Delivery Systems (SDDSs) represent the next generation of intelligent, adaptable drug carriers that integrate multi-stimuli responsiveness, real-time drug release control, and self-regulation mechanisms. These systems incorporate broad adaptability, allowing for sustained, targeted, or delayed drug release while maintaining therapeutic drug levels at inflamed sites. SDDSs can be classified into endogenous-responsive systems, such as pH-sensitive, enzyme-triggered, and ROS-responsive carriers, which exploit IBD-specific biochemical alterations; exogenous-responsive systems, such as magnetically controlled, ultrasound-triggered and near-infrared (NIR)-activated carriers, which allow precise spatiotemporal drug activation; and multi-responsive systems that integrate multiple stimuli for enhanced specificity and controlled drug release.

Given the growing demand for precision medicine in IBD treatment, this review aims to provide a comprehensive overview of smart drug delivery systems for oral administration. We will analyze their design principles, mechanisms of action, and clinical applications, highlighting their potential to overcome current therapeutic challenges and improve patient outcomes. By synthesizing recent advancements in

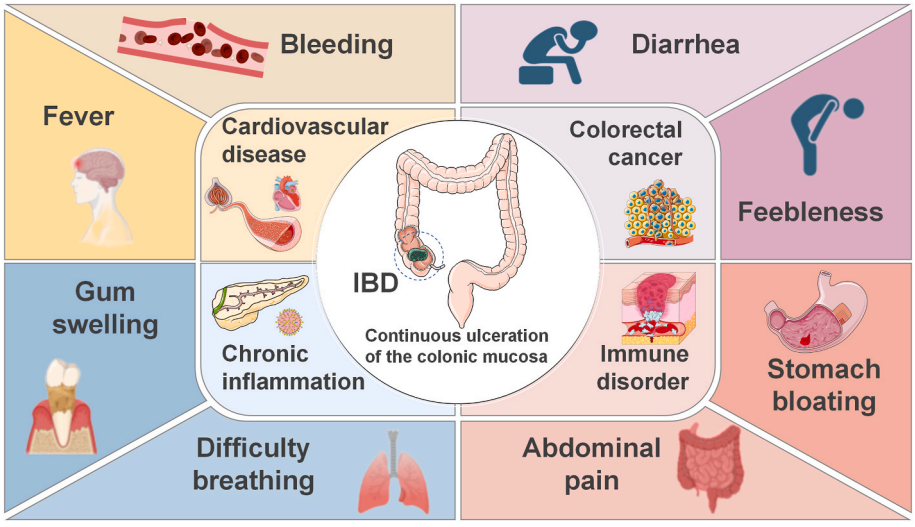


Fig. 1. Primary symptoms of Inflammatory Bowel Disease: fever, abdominal pain, diarrhea, rectal bleeding, weight loss, etc.

Table 1
Mechanisms of oral targeting strategies in IBD therapy.

Strategy type	Representative examples	Key advantages	Limitations	Ref.
Size-dependent	Polymeric NPs (5-ASA, HA-PLGA)	Preferential accumulation in inflamed tissues; immune cell uptake	Possible systemic absorption; variability in clearance	[16–19]
pH-responsive	Eudragit-coated NPs, MSZ@PRHS	Stable in stomach; release in colon; scalable polymers	Colonic pH variability may cause premature/ incomplete release	[20–24]
ROS-responsive	Thioketal NPs, TEMPOL carriers	Selective release in inflamed tissue; ROS scavenging	Heterogeneous ROS levels; risk of off-target effects	[25–27]
Enzyme-responsive	α-amylase- or MPO-sensitive NPs	High specificity; precise drug activation	Enzyme activity varies across patients; potential off-target release	[28–33]
Receptor-responsive	HA-CD44, mannose NPs, antibody-modified carriers	Receptor-mediated uptake; improved selectivity	Ligand instability; high cost; receptor heterogeneity	[34–37]
Microbiota-responsive	Probiotic-based systems (EcN/5-ASA@Alg, engineered Bifidobacterium)	Active microbiota modulation; dual therapeutic effect	Inter-individual microbiota differences; biosafety concerns	[38–43]

nanotechnology, stimulus-responsive platforms, and intelligent drug carriers, this review will offer valuable insights into the future of targeted and personalized IBD therapy, ultimately contributing to the development of safer and more effective treatment strategies.

2. Conventional therapies for IBD and the importance of smart drug delivery systems

Despite extensive research, the exact etiology of IBD remains unclear and no curative therapy exists. Current management therefore focuses on inducing and maintaining remission of inflammation [44,45]. Conventional pharmacological therapies include aminosalicylates, corticosteroids, immunosuppressants, biologics (anti-TNF, anti-IL-12/23, anti-integrin antibodies), and more recently, small-molecule inhibitors such as JAK inhibitors. Microbiota modulation strategies (antibiotics, probiotics, fecal microbiota transplantation) have also been explored [46–63]. As outlined in Table 1, these drugs remain the backbone of IBD management, but their limitations highlight the need for improved delivery strategies. This review therefore focuses on how smart stimuli-responsive systems are designed to directly overcome these conventional shortcomings.

Although conventional treatments have greatly expanded therapeutic options, their efficacy is often undermined by systemic side effects, incomplete response, secondary loss of response, and significant patient-to-patient variability [52,64,65]. Such limitations set the stage for more advanced strategies.

Oral administration remains the preferred route for IBD therapy, as it enables local action at the inflamed intestinal mucosa and improves patient compliance. However, unfavorable gastrointestinal conditions—including acidic gastric pH, digestive enzymes, and fluctuating microbiota—compromise drug stability and localization [66–68]. Conventional colon-targeting methods often fail to achieve precise release, leading to premature drug liberation along the GI tract and insufficient accumulation in the inflamed colon.

These drawbacks have driven the development of smart drug delivery systems (SDDSs), engineered to improve bioavailability and reduce side effects by enabling site-specific and controllable release. Their design primarily focuses on two aspects: enhancing targeting precision and regulating the release profile. Building on traditional carriers such as liposomes [69], micelles [70], mesoporous silica nanoparticles [71], dendrimers [72], gold nanoparticles [73], superparamagnetic iron oxide nanoparticles [74], carbon nanotubes [75], and quantum dots [76], SDDSs incorporate stimuli-responsive mechanisms that trigger structural or physicochemical changes, allowing spatiotemporally controlled drug release. This marks a shift from passive carriers to intelligent, precision-oriented platforms.

At the nanoscale, these systems can accumulate in diseased tissues through the enhanced permeability and retention (EPR) effect, leading to improved stability, prolonged circulation, and greater targeting capacity [77]. Yet, barriers such as limited tissue selectivity and inefficient intracellular release remain, and even actively targeted nanocarriers often fail to achieve sufficient site-specific payload liberation [78]. Stimuli-responsive designs offer a promising solution, releasing drugs in response to internal cues (e.g., pH, redox potential, enzymatic activity, temperature) or external triggers (e.g., electromagnetic fields, light, radiation, ultrasound) [79]. Internal stimuli are particularly attractive in diseases like IBD, where pathological features such as abnormal pH gradients, oxidative stress, and enzyme overexpression can be exploited for autonomous drug release. In contrast, external triggers, though requiring auxiliary devices and less convenient for patients, enable precise on-demand control and real-time adaptability, showing great potential for future applications[79–81].

Unlike conventional colon-targeting approaches that often suffer from premature release along the gastrointestinal tract, SDDSs are capable of responding to pathological cues, ensuring drug activation specifically at inflamed colonic sites. This strategy minimizes systemic toxicity and maximizes therapeutic efficacy, highlighting the need for advanced carriers to achieve precise colon-targeted delivery (Fig. 2).

Significant progress has been made in developing SDDS for oral IBD treatment, offering innovative solutions to the limitations of traditional approaches. These systems are uniquely designed to utilize internal and external stimuli, enabling precise, site-specific drug release tailored to the disease environment. Herein, we provide an overview of recent advancements in the design and development of SDDS for oral IBD therapy, highlighting responsive mechanisms and their effectiveness in preclinical and clinical evaluations over the years (Fig. 3). We also summarize current treatments for managing IBD (Table 2), explore their clinical applications, address existing challenges and limitations, and outline future directions for research and innovation.

3. IBD pathophysiology in targeting delivery

Understanding IBD pathophysiology is essential for smart DDS design, as disease-specific alterations provide natural ‘triggers’ for precise drug release. Active disease is characterized by several alterations highly relevant for drug delivery. Active IBD alters several local factors relevant for DDS: colonic pH is reduced [105,106]; ROS levels are elevated [107,108]; enzymes such as myeloperoxidase, esterases, and glycosidases are upregulated [109,110]; receptors like CD44 and mannose receptor are overexpressed [111]; and intestinal dysbiosis reshapes the microbial environment [112–114]. These changes provide diverse triggers for pH-, ROS-, enzyme-, receptor-, and microbiota-responsive systems (Fig. 4).

Beyond local triggers, cytokine pathways sustain inflammation and influence therapy: the IL-23/Th17 axis induces IL-17, TNF-α, and IL-6 secretion [115], while IL-6/JAK-STAT signaling amplifies inflammation and contributes to anti-TNF resistance [116]. Genetic variants such as NOD2, ATG16L1, and IL23R further increase susceptibility and modulate responsiveness to biologics [117]. These insights highlight the need to integrate molecular pathology into DDS design.

Formulations must remain stable in the acidic stomach and proteolytic small intestine, necessitating protective approaches such as

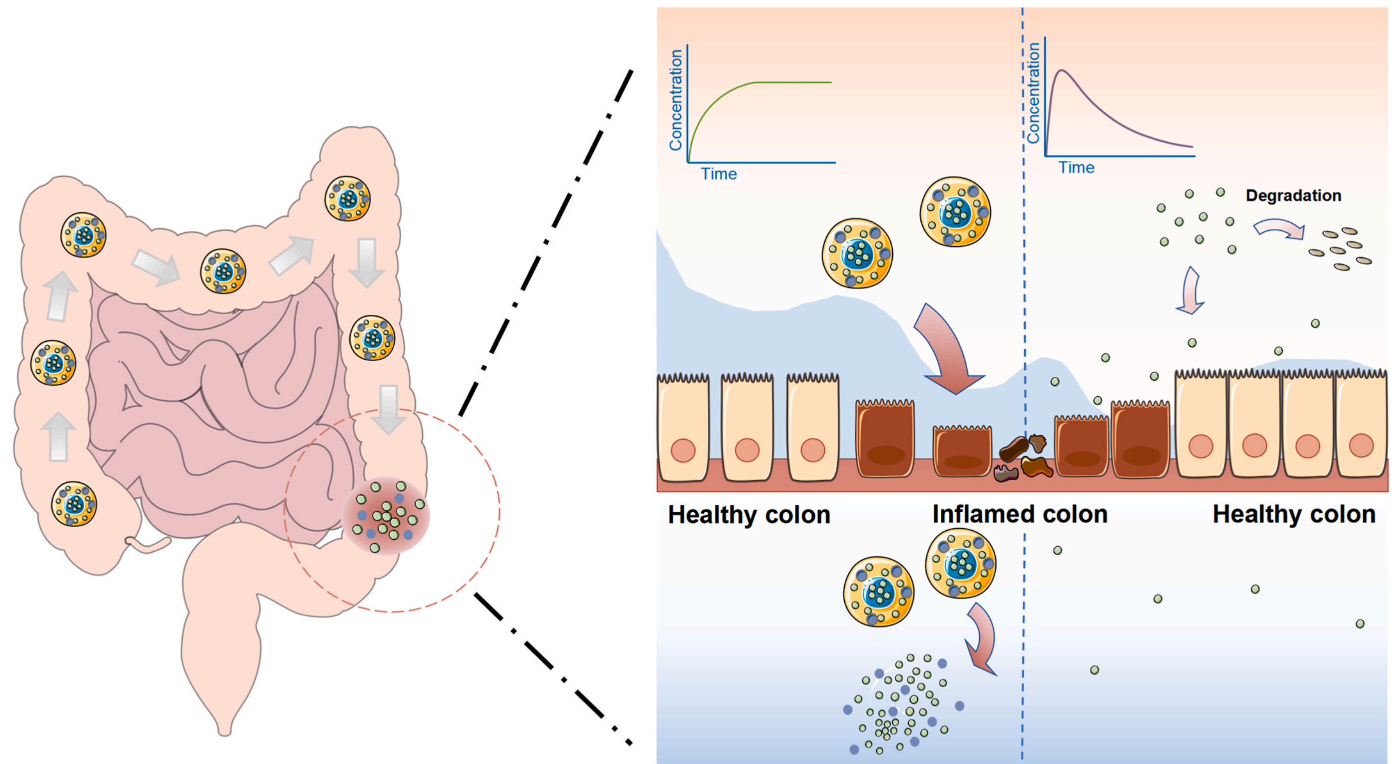


Fig. 2. Existing IBD drug delivery systems tailored to colonic environment characteristics: optimize drug release directly at the inflamed sites within the colon.

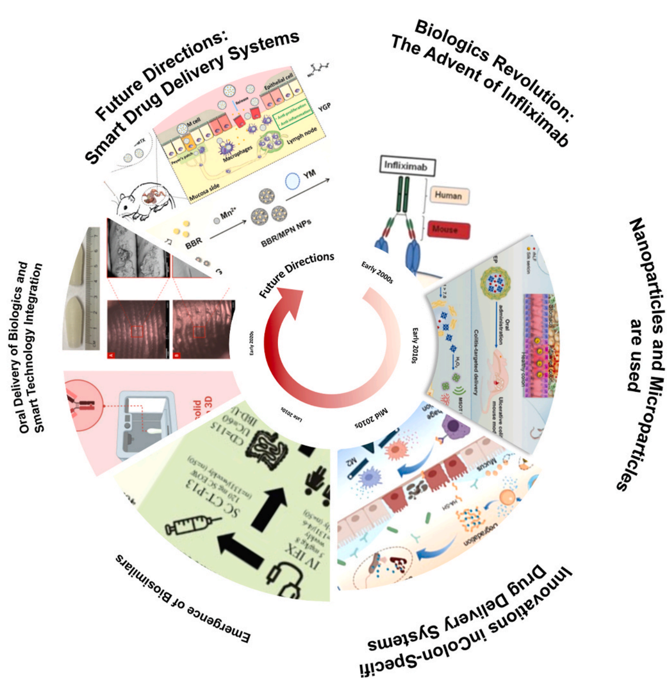


Fig. 3. The evolution and future directions of drug delivery systems for IBD. Image for early 2000s: reproduced with permission [82]. Copyright 2015, Crohn's & Colitis Foundation of America, Inc. Image for early 2010s: reproduced with permission [83,84]. Copyright 2022, Elsevier. Image for mid 2010s: reproduced with permission [85]. Copyright 2021,Wiley-VCH. Image for late 2010s: reproduced with permission [86]. Copyright 2022, Oxford University Press. Image for early 2020s: reproduced with permission [87]. Copyright 2023, Elsevier. Image for future directions: reproduced with permission [88]. Copyright 2020, Wiley-VCH.

encapsulation, pH-sensitive coatings, or bacteria-activated prodrugs [118]. In IBD, variable GI transit times and disrupted barrier function further emphasize the need for advanced DDS that can adapt to altered motility and local physiology [119–121].

As summarized in Fig. 5, rational DDS development must integrate these multifactorial changes: (1) colonic pH variation, (2) oxidative stress, (3) enzymatic changes, (4) receptor overexpression, (5) microbiota dysbiosis, (6) cytokine-driven inflammation, and (7) genetic susceptibility. Together, these pathophysiological changes highlight why stimuli-responsive platforms are especially suited for IBD therapy, directly linking disease biology with carrier.

Rather than serving as standalone background, these pathophysiological features are directly connected to delivery system design, illustrating how SDDS address the root mechanisms of IBD. Altogether, integrating physiological and pathophysiological insights provides the foundation for designing colon-targeted DDS that are both effective and safe, enabling precise therapy under both healthy and diseased GI conditions and advancing their translation in pharmaceutical sciences.

4. Smart drug delivery systems for IBD

SDDSs offer a promising solution to the limitations of conventional drug therapies for IBD, particularly by enabling targeted, site-specific release of therapeutics at the inflamed intestinal regions. These systems are designed to respond to specific internal or external stimuli, ensuring precise drug release and reducing systemic side effects.

Internal stimuli-responsive strategies, triggered by factors like pH, enzymes, or oxidative stress, exploit the unique biochemical conditions of the IBD microenvironment. In contrast, external stimuli-responsive strategies use triggers such as light, temperature, or magnetic fields, offering precise control over drug delivery through external means. The distinction between internal and external stimuli reflects the need for tailored approaches to optimize therapeutic outcomes, with each type responding to distinct treatment goals. The features, advantages, and disadvantages of different responsive strategies are summarized in

Table 2
Current treatments for managing inflammatory bowel disorder.

Therapy class	Representative drugs/agents	Mechanism of action	Advantages	Limitations	Ref.
Aminosalicylates	5-ASA, mesalamine	Anti-inflammatory at mucosal sites	Widely used, safe	Premature release; low colon availability → benefit from colon-targeted DDS	[16–19]
Corticosteroids	Prednisone, budesonide	Broad immunosuppression	Rapid induction of remission	Severe systemic side effects; relapse after withdrawal → need localized release	[46]
Immunosuppressants	Azathioprine, methotrexate	Inhibit T/B cell proliferation	Useful for maintenance	Slow onset; toxicity; monitoring required → limited compliance	[47]
Biologics	Anti-TNF (infliximab), anti-IL-12/23, anti-integrin	Neutralize cytokines or block adhesion	High efficacy in moderate–severe cases	Loss of response; infection risk; high cost → targeted carriers may reduce dose	[89–95]
Small-molecule inhibitors	JAK inhibitors (tofacitinib, filgotinib)	Block cytokine signaling	Oral option; effective in refractory cases	Safety issues (VTE, infections) → controlled release systems desirable	[21,39]
Microbiota modulation	Probiotics, FMT	Alter gut microbial composition	Potentially restores balance	Inconsistent efficacy; limited trials → engineered microbiota-responsive DDS	[96–102]
Traditional Chinese medicine	YNBY, TwHF	Multi-target immunomodulation	Ancillary role, patient acceptance	Limited clinical validation → requires standardized delivery systems	[103–105]

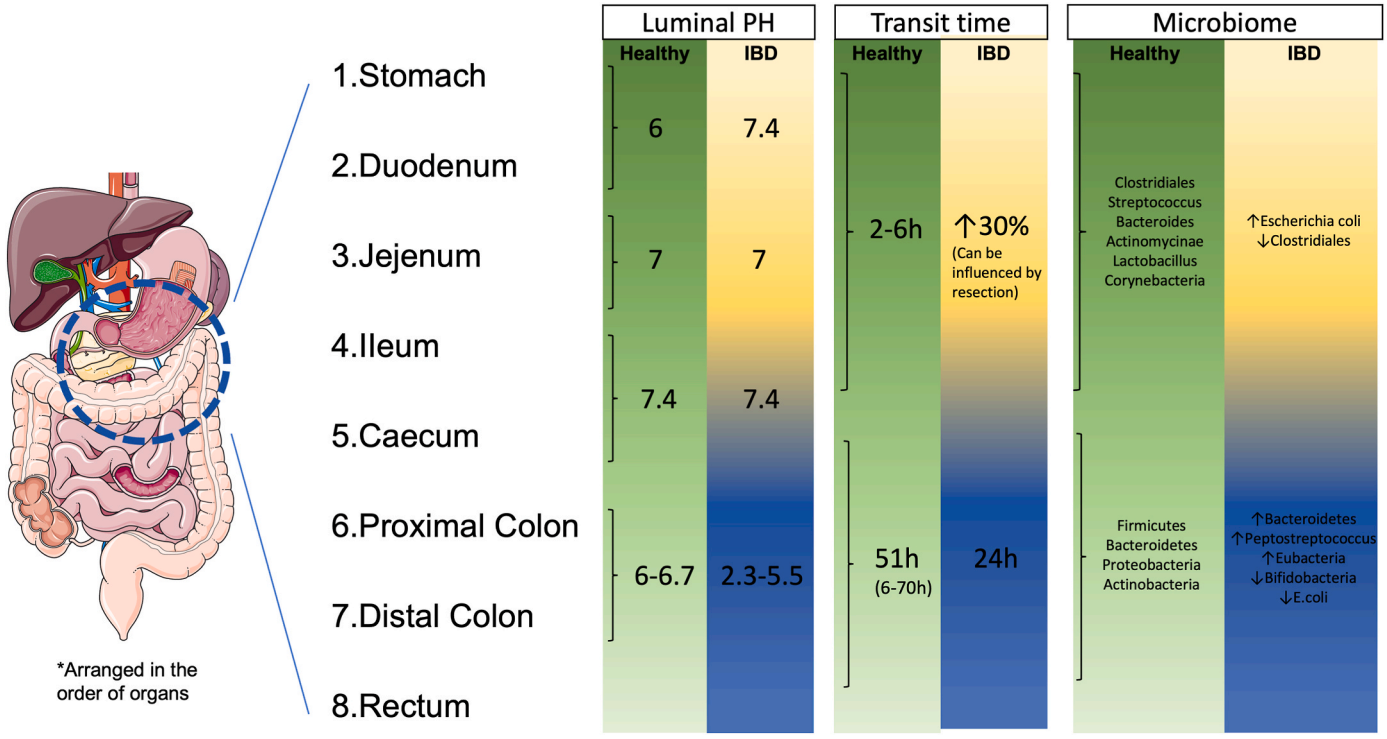


Fig. 4. Comparative analysis of gastrointestinal tract characteristics in healthy individuals and IBD patients.

Table 3.

Additionally, multiple stimuli-responsive systems, which integrate both internal and external triggers, are gaining attention for their potential to provide more versatile and effective treatments. This section will explore these strategies in detail, discussing their mechanisms and applications in IBD therapy.

4.1. *Internal stimuli-responsive strategies*

The development of nanocarriers responsive to internal stimuli has become a prevalent strategy for delivering a range of active agents, including pharmaceuticals, peptides, and genetic materials. These nanosystems are specifically designed to enhance solubility, improve bioavailability, and prolong circulation in the bloodstream, while also facilitating targeted drug release at precise action sites. By addressing physiological and pathological barriers through chemical modifications, they significantly enhance therapeutic outcomes. This section explores the functional groups that react to various internal triggers—such as pH changes, redox conditions, enzymatic activity, receptor interactions, and microbiota—providing an in-depth analysis of their design principles and medical applications.

4.1.1. *pH-responsive strategies*

The nano-delivery systems of pH-dependent concept drugs are state-of-the-art, tailor-made to exploit the variable pH environment along the gastrointestinal tract and, hence, target the release site of the intended drugs under conditions such as IBD and colorectal cancer. The hypothesis underlying this approach is that the gastrointestinal pH changes are broad, ranging from extremely acidic conditions in the stomach (pH 1.0–2.5) to conditions that can be considered quite basic in the colon (pH 5.0–7.0) [125–127]. Nanoparticles have been designed to take advantage of these pH variations. Such pH-responsive nanoparticles protect the encapsulated drug as they navigate the highly acidic environment of the stomach and upper intestine, subsequently releasing the active compound in the colon's comparatively alkaline conditions, where it exerts its therapeutic effects [128]. Acrylates, anionic polymers, and methacrylic acid copolymer materials (Eudragit) [179] are among those commonly used to design these pH-responsive systems, which

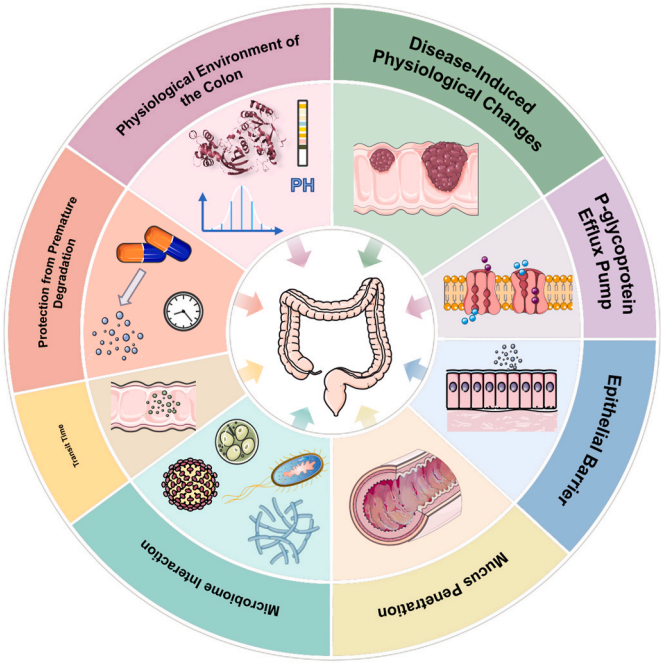


Fig. 5. Key considerations for optimizing colon-targeted drug delivery.

solubilize or swell above a given pH and hence provide drug targeting.

For pH-responsive polymers (e.g., methacrylic acid copolymers such as Eudragit), release is governed by polymer ionization and swelling. The degree of ionization α can be approximated by the Henderson–Hasselbalch relation: α = 1/(1 + 10^{pKa − pH}). When local pH exceeds the polymer pKa, ionization increases, swelling/solubilization occurs and payload release is enabled. Therefore, setting polymer composition to match the expected colon pH window (typically pH 6–7 for healthy colon, but lower in active IBD) is critical to avoid premature or incomplete release. Among the polymers, Eudragit polymers have found wide usage for oral drug delivery in the formulation of pH-dependent coatings. The pH at which the polymers dissolve can be regulated by changing their composition or modifying them, thereby affecting the change or adjustment of the release profile of encapsulated drugs. For example, in formulations containing Eudragit L100 and Eudragit S100 [129], dissolution may occur at pH values typical for the colon (6–7), making them suitable for colon drug delivery systems. This technology has widely been used for a series of drugs, including budesonide—a potent corticosteroid with very strong anti-inflammatory activity—and prednisolone, another steroid drug with immunosuppressive properties. In these cases, the nanoparticles are pH-sensitive and exhibit a strong pH-dependent release behavior, ensuring not only one effective therapeutic effect by releasing the drug specifically at the place of inflammation but alos at the same time reducing the systemic side effects [31,130]. For example, budesonide-loaded nanoparticles demonstrated better efficacy in treating colitis compared with conventional formulations used in animal models, due to their high adhesion to inflamed mucosal tissues and low systemic bioavailability [131].

This development marks notable progress, as such pH-sensitive drug carriers at the nanoscale offer a promising approach for treating site-specific pathological diseases within the GI tract. Researchers have further developed nanoparticles to react specifically to the pH environment of the colon, thereby enhancing site specificity. Zhao et al. [132] designed oral composite nanoparticles (MSZ@PRHS) incorporating mesalazine (MSZ) loaded into rough mesoporous silica (RHS), which was further encapsulated within a CAP polymer membrane, to target inflammation in colitis. These nanoparticles exhibited minimal MSZ release under the acidic conditions of the stomach and small intestine but achieved substantial release in the colon's higher pH environment. In a mouse model of acute colitis induced by dextran sulfate

Table 3
Comparison of different response strategy types.

Strategy type	Representative carriers/drugs	Key advantages	Limitations	Ref.
Internal stimuli-responsive strategies				
pH-responsive strategies	Eudragit-coated systems (e.g., MSZ@PRHS, budesonide formulations)	Protect drugs in stomach, release in colon; scalable polymers with clinical use	Interpatient variability in colonic pH may cause premature or incomplete release	[31,111–118, 122–124]
ROS-responsive strategies	Thioketal-based NPs, TEMPOL-loaded nanocarriers	Selective release in inflamed tissues with high ROS; reduce oxidative stress	ROS levels heterogeneous across patients and disease stages; risk of insufficient release	[120,121, 125–130]
Enzyme-responsive strategies	DHC NPs (α-amylase-triggered), HSA–5-ASA NPs (MPO-targeted)	Exploit overexpressed enzymes in inflamed colon for precise release	Enzyme activity varies; some enzymes present in non-inflamed tissue → risk of off-target release	[131–136]
Receptor-responsive strategies	HA-PLGA-Cur NPs (CD44 targeting), Mannose-PLGA-OVA NPs	High selectivity via receptor-mediated uptake; improved mucosal adhesion	Receptor heterogeneity; ligand instability; cost of antibody-based ligands	[38,137–149]
Microbiota-responsive strategies	EcN/5-ASA@Alg, engineered Bifidobacterium carriers	EcN/5-ASA@Alg, engineered Bifidobacterium carriers	Microbiome composition differs across individuals; biosafety and regulatory concerns	[150–155]
External stimuli-responsive strategies				
Magnetic-response strategies	SPION–mesalamine, magnetic nanogels	External magnetic fields enable colon targeting and sustained release	Limited penetration depth in humans; biosafety concerns with repeated exposure	[156,157]
Light-responsive strategies	Cur@AuNRs (NIR), Ce6-loaded micelles	Spatiotemporal precision; can combine photothermal/photodynamic therapy	Shallow tissue penetration; risk of phototoxicity; device dependency	[158–167]
Ultrasound-responsive strategies	Ultrasound-sensitive liposomes, microbubble-assisted dexamethasone	Non-invasive, deeper penetration than light; enhances mucosal uptake	Risk of cavitation-induced injury; requires ultrasound equipment	[168]
Temperature-responsive strategies	Thermosensitive hydrogels (PDLLA-PEG-PDLLA)	Gelation at body temperature; forms protective barrier with sustained release	Small physiological temperature gradient; external heating often required	[169–172]
Multi-stimuli	OPTICORE™ (pH + microbiota), dual pH/enzyme hydrogels, Mn_3O_4 nanozyme thermogels	Redundancy + synergy reduce patient variability; more robust precision therapy	Higher complexity in design, manufacturing, and regulatory approval	[173–178]

Overall remark: Single-trigger strategies provide proof-of-concept but face variability and clinical limitations. Multi-stimuli systems integrating pH, ROS, enzyme, or microbiota cues offer redundancy and synergy, representing the most promising path for robust and precise IBD therapy.

sodium (DSS), oral delivery of PRHS-loaded nanoparticles markedly improved IBD symptoms and demonstrated superior therapeutic outcomes compared to MSZ administered as a solution. The release of these nanoparticles is governed by a pH threshold, where the polymer membrane dissolves once the pH exceeds a specific value, typically occurring in the more alkaline environment of the colon. The solubility of the polymer increases at this threshold, triggering the release of the encapsulated drug, thus providing precise therapeutic effects. However, variability in patient-specific pH values, especially under inflammatory conditions, may lead to premature or incomplete drug release, highlighting a critical limitation of threshold-based systems. Understanding pH thresholds is therefore essential for optimizing drug release in such systems, as discussed in Ref. [180]. This not only explains the mechanism of threshold-based release but also underscores its clinical limitations. This design also highlights the potential of pH-driven interface conversion for site-specific drug delivery, as also underscored in the comprehensive study by Jiang et al. [133] which emphasizes the precision and scalability of pH-responsive nanoplatforms for IBD treatment.

Building on this concept, another study introduced the CuS/DSF/EL/PVP nanoplatform [133] as an innovative therapeutic approach for treating IBD, that not only effectively targeted the colon and mitigated acute colitis in mice, but also regulated immunity and restored gut microbiota diversity, offering broader therapeutic benefits. The nanoplatform notably modulated inflammation-related cytokines and promoted the repair of intestinal mucosa. Furthermore, its ability to enhance gut microbiota diversity, along with its cost-efficient and scalable manufacturing process, underscores its promise as an innovative and effective therapeutic solution for IBD. This approach offers promising opportunities for personalized medical interventions Fig. 6 demonstrates that pH-responsive mesalazine-loaded nanoparticles markedly alleviated colitis symptoms in DSS-induced mice, confirming their therapeutic advantage over free drug formulations. Although Fig. 6 shows improved DAI and colon length in acute DSS mice, these data derive from an acute model; translation to chronic/relapsing IBD and dose-dependent microbiota effects remain to be established.

Both studies highlight the promise of pH-sensitive nano-systems in improving therapeutic outcomes and providing scalable, clinically relevant strategies for IBD management. Nevertheless, current research is limited mainly to acute murine models, with insufficient exploration of chronic and relapsing disease contexts. Moreover, variability in intestinal pH across patients, incomplete mechanistic understanding, and lack of long-term biosafety evaluations remain major obstacles. While pH-responsive nano-delivery systems offer clear advantages in site-specific targeting and enhanced efficacy, challenges such as inter-patient variability in pH levels and the potential for inconsistent release timing remain significant obstacles. In summary, these systems represent a significant advance in the field of precision medicine, especially in improving the management of conditions like IBD and colorectal cancer. However, further validation in diverse models and clinical settings is essential before full translation into clinical practice can be realized, as emphasized in the study by Jiang [133].

4.1.2. ROS-responsive strategies

ROS-responsive nano-delivery systems have garnered significant attention for their potential in treating IBD, the production and accumulation of ROS play a key role in the inflammatory microenvironment of IBD [134,135,181]. The damaged intestinal mucosa at inflammatory sites activates a large number of immune cells, particularly neutrophils and macrophages, which generate a significant amount of ROS, creating a pathological microenvironment of oxidative stress. This abnormally high level of ROS not only exacerbates intestinal inflammation but also provides an ideal trigger for smart responsive nanodelivery systems. By leveraging the specific sensitivity of nanomaterials to ROS, drugs can be precisely delivered to the inflammatory lesions, thereby maximizing therapeutic efficacy and significantly reducing toxicity to healthy tissues.

In the development of ROS-responsive nano-platforms, researchers have adopted a variety of innovative strategies. Early studies primarily focused on designing basic ROS-degradable nanocarriers to achieve either targeted drug delivery or ROS scavenging. For instance, thioketal nanoparticles (TKNs), prepared from poly (1,4-phenyleneacetone dimethylene thioketal) (PPADT), were developed. Their unique thioketal bond structure enables them to selectively degrade in the presence of ROS, facilitating the targeted delivery of TNF-α siRNA to alleviate colonic inflammation [137]. Similarly, nitroxide radical–containing nanoparticles (RNPO) were utilized to specifically target the inflamed colon to deliver the ROS scavenger TEMPOL, directly counteracting oxidative stress [138]. To overcome potential limitations in the stability of these early systems, researchers integrated a cationic lipid (DOTAP) into TKNs, further enhancing the nanoparticles' stability, mucosal transport ability, and cellular uptake efficiency.

Recently, the field has evolved from simple delivery and scavenging to the development of more complex, multifunctional systems for comprehensive inflammation regulation. For example, Han et al. developed an innovative system that uses yeast particles to encapsulate curcumin-loaded supramolecular nanoparticles [139]. This approach not only addresses UC by reducing oxidative stress but also promotes macrophage reprogramming to resolve inflammation. Building on this concept, Prussian blue analogs (PBAs) were used to modify curcumin (CCM) [136]. This composite material leverages the varied valence states of cobalt (Co (III)) and iron (Fe (II)) to exhibit multi-enzyme-like activity, supporting both ROS clearance and macrophage phenotype regulation, which significantly mitigated UC symptoms and even arrested disease progression in mouse models. Fig. 7 depicts the therapeutic benefits of CCM-CoFe PBA, showing significant alleviation of colitis symptoms through ROS scavenging and macrophage regulation. These studies represent a clear evolution from single-function to multi-functional synergistic therapeutic strategies.

Despite their significant therapeutic promise, ROS-responsive systems still face considerable challenges in clinical application. The primary obstacle is that the dynamic nature of ROS levels at inflammatory sites can lead to unpredictable and uncontrolled drug release, thereby compromising therapeutic efficacy. Furthermore, upon oral administration, these nano-systems risk premature degradation or non-specific activation within the complex GI environment [140,141]. Another crucial challenge is that the specificity of these systems is often limited to a narrow spectrum of ROS types, potentially failing to fully respond to the complex oxidative stress signals present in the inflammatory milieu.

Therefore, future research should therefore prioritize the development of multifaceted delivery systems. These systems should incorporate various targeting mechanisms, including pH sensitivity and ligand-receptor dynamics, and respond to a wider array of ROS. Researchers are now actively striving to overcome these challenges. While significant difficulties exist, the field is showing immense promise. The latest research is focused on utilizing a novel diselenide-bond-modified nanocarrier that ensures drug stability within the GI tract. This system leverages its negative surface charge to precisely target and accumulate on the cell membranes of oxidatively stressed inflammatory cells, thereby significantly improving the drug's specificity [182]. It is anticipated that by developing multifunctional delivery systems capable of responding to a wider range of ROS and integrating with other targeting mechanisms, we can pave the way for more precise, effective, and reliable IBD treatments.

4.1.3. Enzyme-responsive strategies

Enzyme-responsive strategies in oral drug delivery systems represent a significant advancement in targeted therapy for IBD. These systems exploit the unique enzymatic environment of the inflamed gastrointestinal tract to facilitate precise drug release. Some studies utilize α-amylase, an enzyme with elevated levels in the inflamed colon, as a trigger. For example, Xu et al. [142] developed DHC nanoparticles that deliver dexamethasone and a ROS scavenger using hydroxyethyl starch

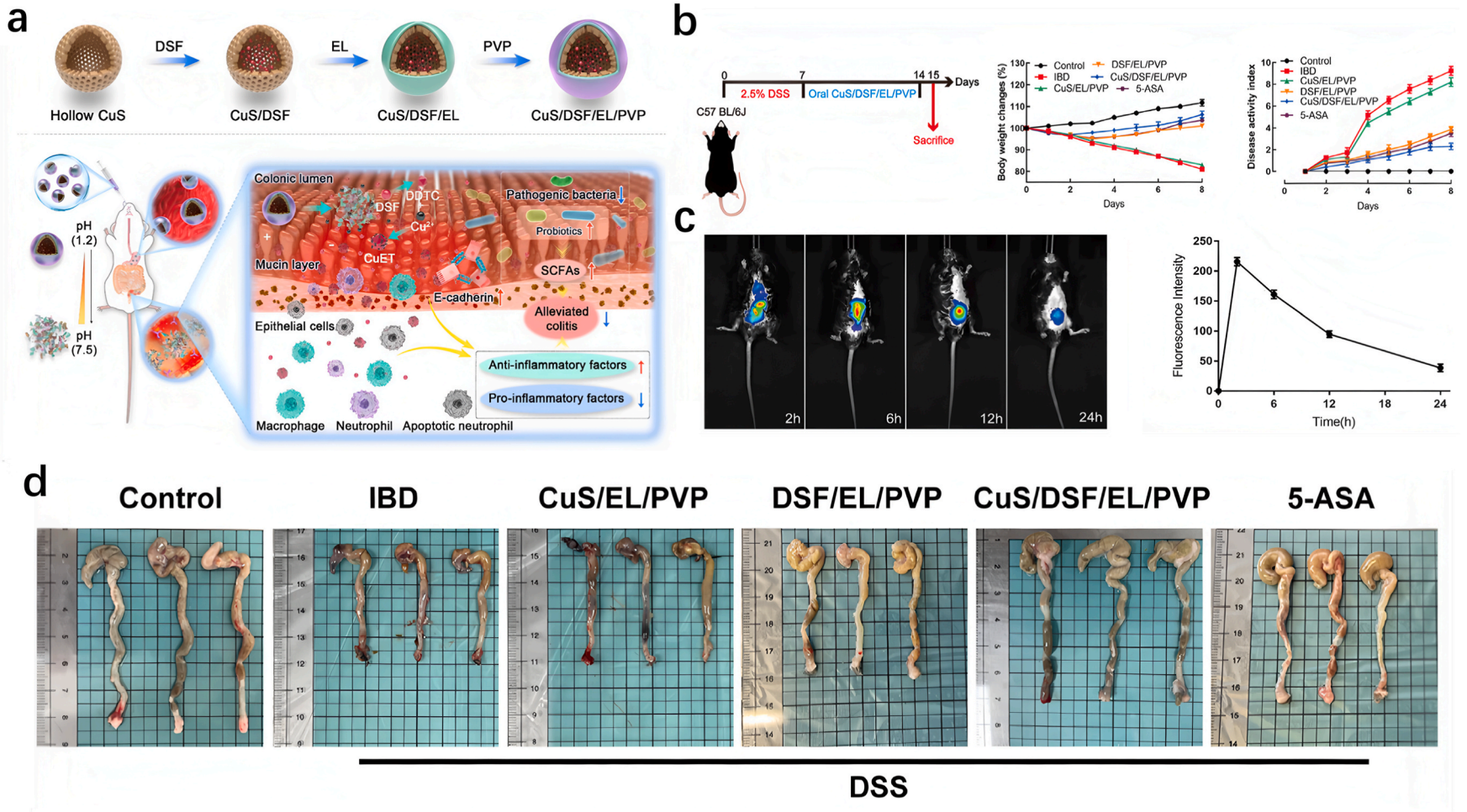


Fig. 6. A pH-responsive CuS/DSF/EL/PVP nanoplatform for regulating gut immunity and microbiota. pH-responsive CuS/DSF/EL/PVP nanoplatform alleviates inflammatory bowel disease in mice via regulating gut immunity and microbiota (a) A schematic depiction illustrates the synthesis process of the CuS/DSF/EL/PVP nanoplatform, its targeted delivery system, and therapeutic mechanism. (b) The construction and treatment of an acute colitis model in mice are visualized schematically, and the weight change, DAI after treatment. (c) Fluorescence imaging of the gastrointestinal tract in colitis-induced mice, taken at various time intervals after oral administration of the nanoplatform, confirmed that the EL coating effectively shielded the nanoplatform. This protection facilitated targeted drug accumulation in the intestine via pH-sensitive mechanisms. (d) Administration of the CuS/DSF/EL/PVP nanoplatform significantly reduced inflammation and restored colon length compared to the untreated colitis group, further validating its therapeutic potential. Reproduced with permission [133]. Copyright 2024, Elsevier BV.

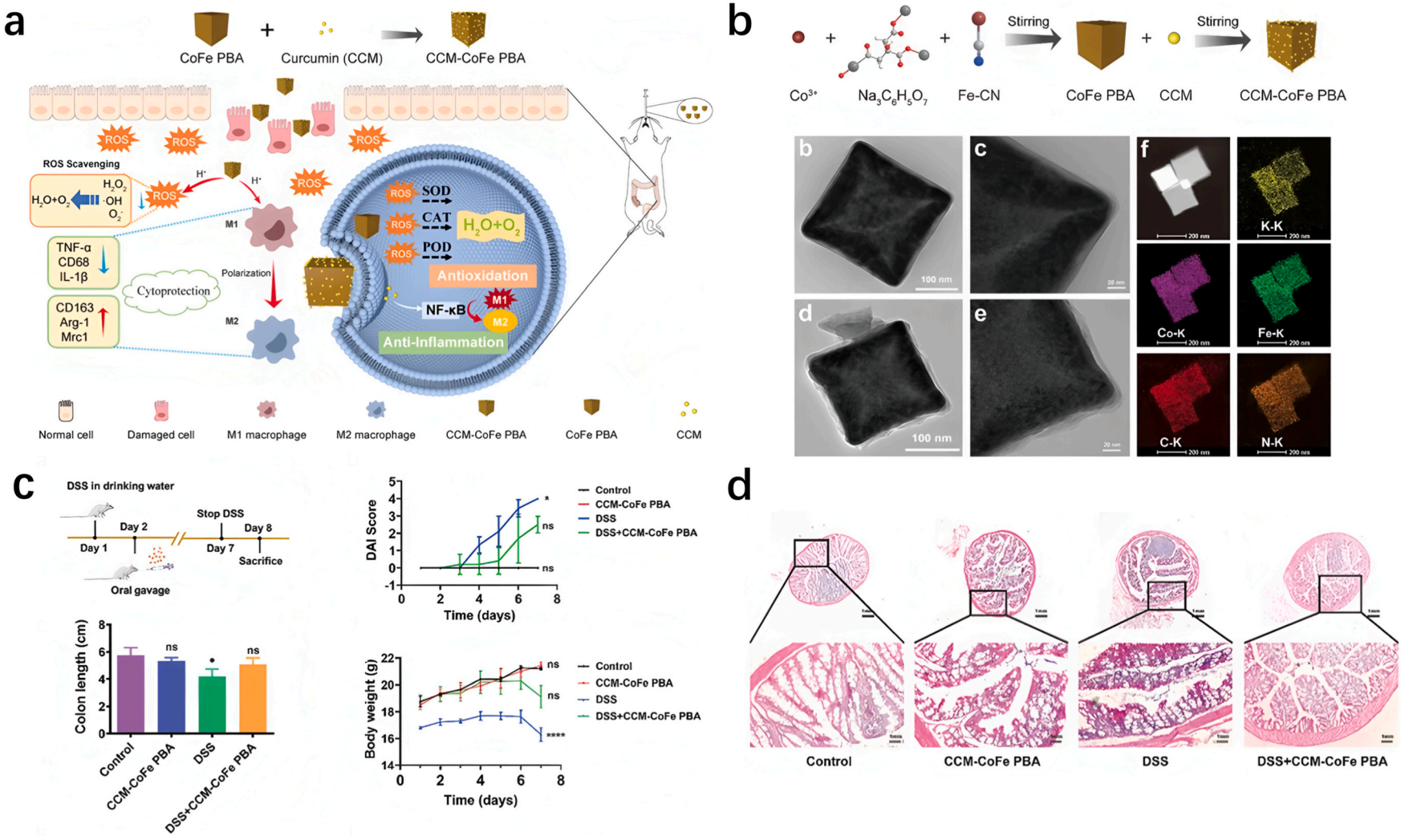


Fig. 7. A curcumin-modified coordination polymers for ROS scavenging and macrophage phenotype regulating properties. (a) A schematic illustration presents the oral administration of CCM-CoFe PBA for treating UC in a mouse model. (b) Characterization and fabrication of CoFe PBA and CCM-CoFe PBA. (c) Comprehensive evaluations were performed, including measurements of body weight, colon length, bleeding incidence, DAI, histological markers of inflammation, and levels of inflammatory cytokines. (d) CCM-CoFe PBA effectively alleviated DSS-induced colitis by limiting macrophage infiltration and controlling their proliferation at the site of inflammation, thereby reducing the production of inflammatory mediators. Reproduced with permission [136]. Copyright 2023, Wiley.

and curcumin-conjugated polymers. A key feature of this system is its exceptional stability under acidic gastric conditions, while being specifically engineered to degrade in the presence of elevated α-amylase levels in the inflamed colon, ensuring site-specific drug release and enhanced therapeutic efficacy. Similarly, Li et al. [143] created a controlled release system with a curcumin-cyclodextrin core and a chitosan and sodium alginate shell. A unique aspect of this design is its structural simplicity and cost-effectiveness, which also utilizes α-amylase to trigger the degradation of the shell, releasing the active drug directly at the inflamed sites, thereby promoting mucosal healing and modulating inflammatory responses. Beyond drug release, the enzymes themselves can serve as therapeutic agents. For instance, Liang et al. [183] introduced an innovative strategy for creating enzyme-based nano-carriers with excellent therapeutic performance and biocompatibility. A major highlight of this study is that it leverages the cascade catalytic activity of SOD and CAT to directly eliminate intracellular ROS, addressing the root cause of inflammation rather than merely delivering a therapeutic agent. This method holds significant promise for treating gastrointestinal disorders through oral delivery. Fig. 8 illustrates how enzyme-based nano-carriers directly eliminate ROS and promote mucosal healing, reinforcing their therapeutic potential.Further illustrating the versatility of enzyme-responsive mechanisms, other studies have tailored nanoparticle systems to respond to different enzymes associated with inflammation. Tiruppathi et al. [144] utilized human serum albumin NPs conjugated with 5-ASA, targeting myeloperoxidase, an enzyme abundantly expressed in inflamed IBD tissues. A notable achievement of this strategy is its ability to enhance the anti-inflammatory properties of 5-ASA by over a thousand times, significantly boosting the drug's potency. Additionally, Chen et al. [145] designed lipid nanoparticles modified with chitosan and loaded with dexamethasone, which respond to esterase enzymes in the inflamed colon to release the drug. While this system has the advantage of simultaneously mitigating colonic atrophy and improving cellular adhesion, its limitation is that esterase expression may not be confined to the site of inflammation, posing a potential risk of non-specific release. From these findings, it is evident that enzyme-responsive systems can be tailored to different enzymatic triggers, broadening their applicability in IBD therapy.

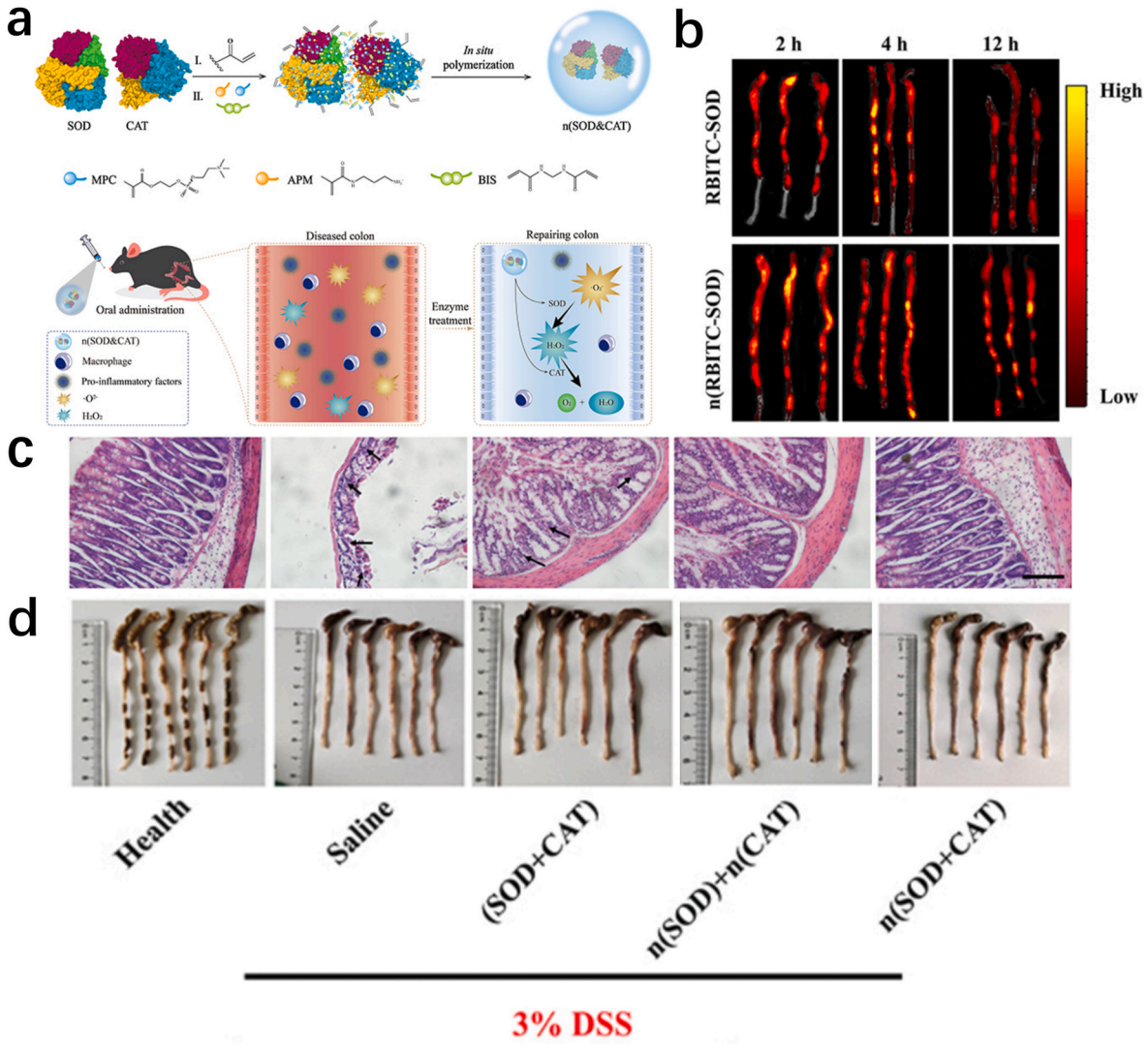


Fig. 8. An enzyme capsule engineered to promote the targeted accumulation of enzymes in inflamed colon tissues. (a) Schematic illustration of the synthesis procedure for the n(SOD&CAT) capsule and its mechanism of action in vivo. (b) In DSS-induced colitis mice, oral administration of n(RBITC-SOD) resulted in markedly increased fluorescence in colon tissues 12 h post-treatment, indicating efficient enzyme delivery to the site of inflammation. (c) H&E staining of colonic tissue sections was conducted to assess the pathological changes in mice treated with different formulations. (d) Treatment with both n(SOD) + n(CAT) and n (SOD&CAT) significantly alleviated inflammation and led to an increase in colon length compared to the untreated colitis group. Reproduced with permission [183]. Copyright 2022, Dove Press.

Despite the great therapeutic promise of enzyme-responsive systems, their clinical application still faces challenges. The main obstacle is the complex and precise control required over drug release kinetics. Due to the immense variability of enzyme levels between different patients, as well as the dynamic changes in enzyme levels in the same individual at different stages of the disease, consistent drug release can be difficult to maintain [145]. These issues underline that enzyme-responsiveness alone may not achieve the precision required for clinical translation. Moreover, many enzymes involved are not uniquely upregulated in inflamed tissues, raising concerns about off-target drug release and safety in clinical translation. For example, esterase and myeloperoxidase are also expressed in non-inflamed tissues, which may compromise targeting accuracy. These limitations suggest that relying solely on a single enzyme as a trigger may be insufficient to meet clinical demands for drug delivery precision and reliability. Therefore, multi-responsive strategies that combine enzyme-responsiveness with other triggers (e.g., pH or ROS-responsiveness) are expected to provide more robust solutions for future IBD treatment, in order to cope with the complexity and variability of the physiological environment. Meta-analyses of enzyme-targeted systems indicate substantial heterogeneity in preclinical outcomes, suggesting that translation into reliable human therapies remains challenging.

4.1.4. Receptor-responsive strategies

Receptor-responsive strategies epitomize an advanced method within the sphere of targeted drug delivery, notably in the treatment of IBD, such as ulcerative colitis. Compared with pH-, ROS-, or enzyme-responsive systems that rely on indirect biochemical cues, receptor-responsive strategies directly leverage overexpressed membrane receptors (CD44, mannose receptor, CD98, etc.) on inflamed colonic cells as "molecular zip codes," thereby offering a higher level of precision.

Surface plasmon resonance data reveal that HA–CD44 affinity increases linearly with receptor density: KD $\approx 10^{-8}$ M at CD44 $\geq 10^5$ copies per cell, but rises by one order of magnitude when expression drops by 50 % [184]. This density-dependent interaction illustrates why receptor targeting is particularly advantageous in inflamed mucosa, where receptor upregulation amplifies nanoparticle retention. Similarly, the mannose receptor maintains an optimal conformation at pH 6.2–6.8; protonation at pH < 6 closes the binding pocket, increasing KD ~20-fold [185], highlighting an intrinsic "pH threshold" as a physiological gatekeeper. This also suggests that receptor-based targeting can be further reinforced when combined with microenvironmental triggers such as pH.

HA-PLGA-Cur nanoparticles accumulate 5.8-fold in DSS-colitis colons versus only 1.9-fold in adjacent healthy tissue, directly validating that receptor density dictates targeting accuracy [38]. Mannose-PLGA-OVA nanoparticles achieve 92 % uptake by macrophages in vitro, yet their rapid mannose loss in acidic conditions (≈40 % within 2 h at pH 2) underscores a key limitation—ligand degradation in the stomach. This challenge is particularly critical for oral formulations, where gastric acidity accelerates ligand degradation before reaching colonic targets. This instability poses a major translational challenge, particularly for oral delivery systems, where premature ligand degradation may lead to inconsistent targeting outcomes across patient populations, thereby undermining clinical reproducibility.

CD98 Fab'-conjugated nanoparticles co-target Caco-2 cells and macrophages, showing broader targeting potential than HA or mannose ligands. However, Fab' fragments cost 7–10 × more than HA, and CD98 is also expressed on healthy epithelia, posing an off-target risk [148]. Kawabata et al. further demonstrated that CD98 expression fluctuates significantly across inflammatory stages [149], suggesting that "one--size-fits-all" targeting is unrealistic. Overall, receptor-targeted systems enhance lesion accumulation, but each ligand entails trade-offs between stability, cost, and off-target effects. Consequently, although antibody-based ligands improve in vitro selectivity, their reproducibility and cost-effectiveness in vivo remain limited.

To overcome such single-ligand limitations, multi-responsive systems are being explored. For instance, Zhang's RH-F/C-NPs couple receptor recognition with pH/ROS dual triggers: drug release is contingent upon high CD44 expression, pH 7.4, and ROS ≥100 μM, achieving 80 % release within 6 h [173]. Similarly, AA/CDM-BT-ALG microparticle-in-nanoparticle systems first lock onto CD44 on macrophages and then disintegrate via intracellular ROS, evading lysosomal degradation and improving in vivo efficacy 1.7-fold over single-target controls [148]. As shown in Fig. 9, dual-responsive receptor-targeted systems achieved significantly higher macrophage targeting and therapeutic efficacy compared with single-ligand controls, underscoring a broader trend toward integrating receptor specificity with environmental responsiveness.

Despite superior lesion accumulation, three major translational barriers persist: (1) receptor heterogeneity across patients and disease stages, (2) susceptibility of ligands to enzymatic or acidic degradation during oral delivery, and (3) high production costs, especially for antibody-modified nanoparticles. Future work should therefore establish quantitative "receptor-density vs ligand-affinity" models and rationally integrate receptor cues with pH, ROS, or enzyme responsiveness into multi-modal platforms, aiming to balance targeting precision with scalability and long-term biosafety. Although receptor targeting shows promising selectivity, systematic reviews highlight inconsistent efficacy across preclinical designs, underscoring the need for more standardized evaluation before clinical translation.

4.1.5. Microbiota-responsive strategies

Microbiota-dependent NP drug delivery systems are emerging as a significant advancement in the treatment of IBD by targeting the unique ecosystem of the gut microbiota. Unlike conventional probiotic supplementation that passively modulates intestinal flora, microbiota-responsive DDS exploit bacterial enzymes, metabolic activity, and colonization capacity as active "biological triggers" for drug release and mucosal repair [150].

Recent innovations have introduced engineered probiotics, such as *Escherichia coli* Nissle 1917 (EcN) [151], coated with nano-enzymes or encapsulated in protective hydrogels, to enhance colonization rates and retention time in the gut. For instance, a Pt-Lipid@EcN system demonstrated significant increases in gut microbiota colonization rates [152], while an HPN-NE-EcN system, involving hyaluronic acid-polythiophene nanoparticles coupled to EcN, showed a synergistic effect in clearing ROS and stabilizing the microbial community [153]. These findings indicate that microbiota-based carriers function not only as passive transporters but also as active modulators reshaping the inflammatory microenvironment.

Integration of therapeutic agents into microbiota-dependent nanoparticle drug delivery systems further enhances therapeutic outcomes. For example, EcN/5-ASA@Alg systems improved both microbial diversity and mucosal barrier integrity [154]. Expanding beyond native strains, a humanized variant of *Bifidobacterium longum* (BL@B-SA50) employed single-atom catalytic artificial enzymes (SAzymes) to mimic antioxidant enzyme activity, thereby attenuating inflammation and oxidative stress in the colon [155]. Fig. 10 demonstrates that multi-responsive nano-systems integrate complementary triggers to achieve superior site-specific drug release, offering a promising blueprint for next-generation IBD therapy. This marks a paradigm shift from traditional probiotic therapy toward "living DDS," where engineered bacteria function simultaneously as vehicles and as bioactive modulators.

Despite these advances, several challenges remain. First, the gut microbiota is highly heterogeneous among individuals and fluctuates dynamically with diet, antibiotics, and disease stage, leading to unpredictable efficacy. Second, ensuring biosafety of genetically engineered strains and preventing horizontal gene transfer are critical translational hurdles. Third, large-scale production, quality control, and regulatory approval of live-bacteria DDS remain underdeveloped compared with

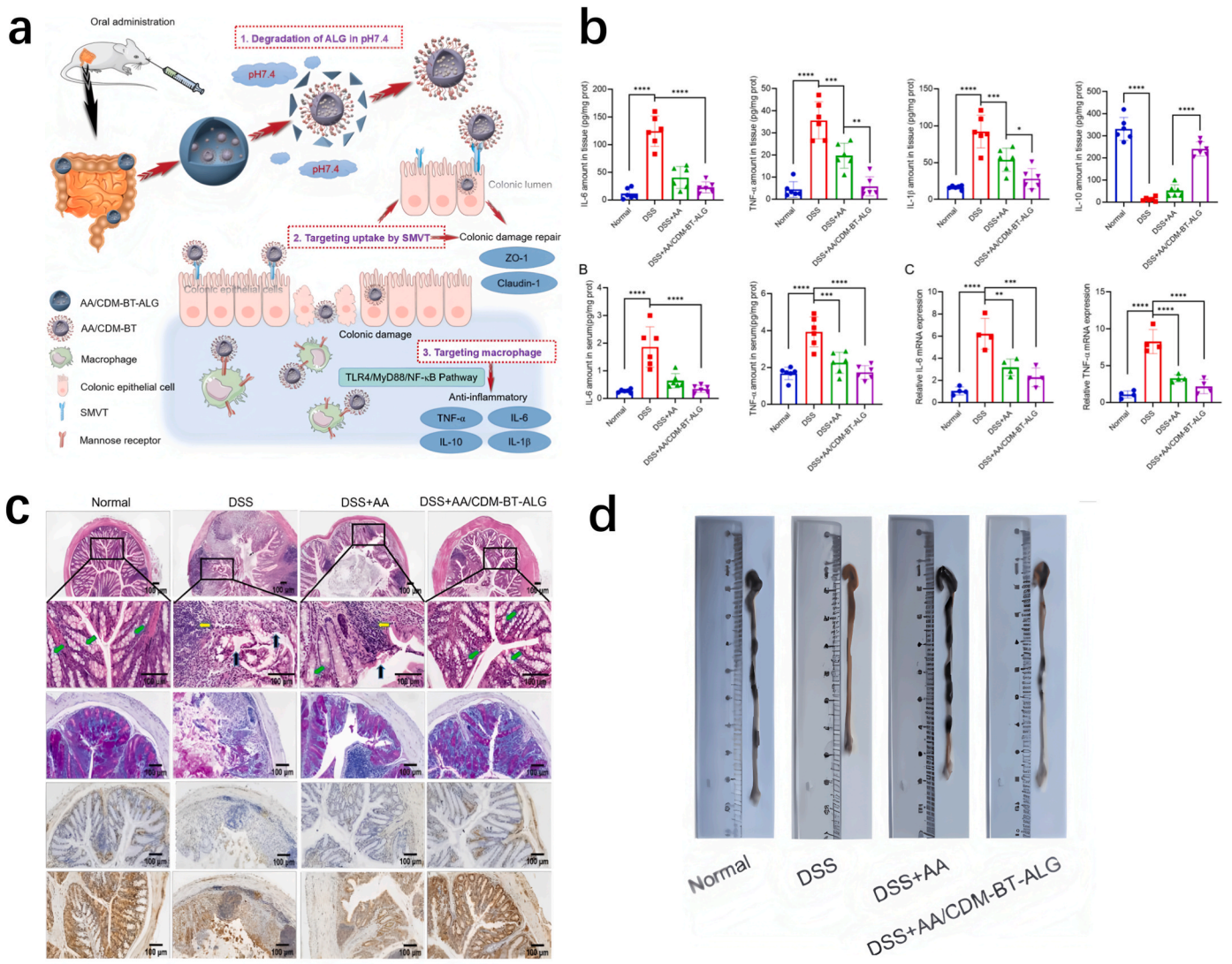


Fig. 9. AA/CDM-BT-ALG achieves targeted uptake by macrophages and Caco-2 cells through mannose receptor- and biotin-mediated endocytosis, respectively. **(a)** A schematic diagram illustrates the dual-targeted nanoparticle-in-microparticle system designed for treating UC. **(b)** The impact of AA/CDM-BT-ALG on inflammatory cytokine production and protein expression following UC therapy is evaluated. **(c)** H&E-stained colonic tissue sections from mice treated with various formulations provide insights into the pathological changes. **(d)** Treatment with AA/CDM-BT-ALG significantly alleviated inflammation and restored colon length compared to the untreated UC group. Reproduced with permission [148]. Copyright 2023, John Wiley and Sons Ltd.

chemical nanocarriers. Systematic reviews published in recent years also emphasize that while preclinical results are encouraging, clinical validation in IBD patients is still scarce, limiting their immediate translational potential [186].

Taken together, microbiota-responsive strategies offer a promising path forward by directly addressing dysbiosis and intestinal inflammation. However, their future success will depend on combining microbial engineering with multi-stimuli nanotechnology (pH, ROS, or receptor targeting), thereby ensuring both precision and robustness in complex gastrointestinal environment.

4.2. *External stimuli-responsive strategies*

Unlike internal stimuli-responsive drug carriers, exogenous responsive smart drug carriers are triggered by external environmental stimuli. They require an external specific source (such as magnetic fields, near-infrared light, ultrasound, or exogenous temperature) to enhance drug release and are insensitive to changes in the body's physiological characteristics. Numerous studies have explored this field, developing a wide range of drug delivery systems utilizing these strategies. In the following section, we summarize and discuss various external stimuli-responsive approaches.

4.2.1. *Magnetic-response strategies*

Magnetic-responsive drug delivery offers an externally guided approach, where applied magnetic fields can rapidly modulate carrier behavior to achieve precise drug targeting. This technique involves stabilizing magnetic nanoparticles through surface modification, which are then conjugated with therapeutic agents to form a stable drug carrier system. Typically, when an external magnetic field is applied, certain magnetic-responsive carriers containing metallic substances exhibit targeting, heat generation, and shape changes. A key strength of magnetic systems is their capacity for instantaneous response to external field modulation, enabling real-time control over carrier localization and drug release.

Several preclinical studies have explored the therapeutic potential of magnetic-responsive nanocarriers in IBD, with promising results across different formulations. For example, SPION–drug conjugates have shown promise in improving colonic targeting in IBD models, SPION–mesalamine composites demonstrated preferential

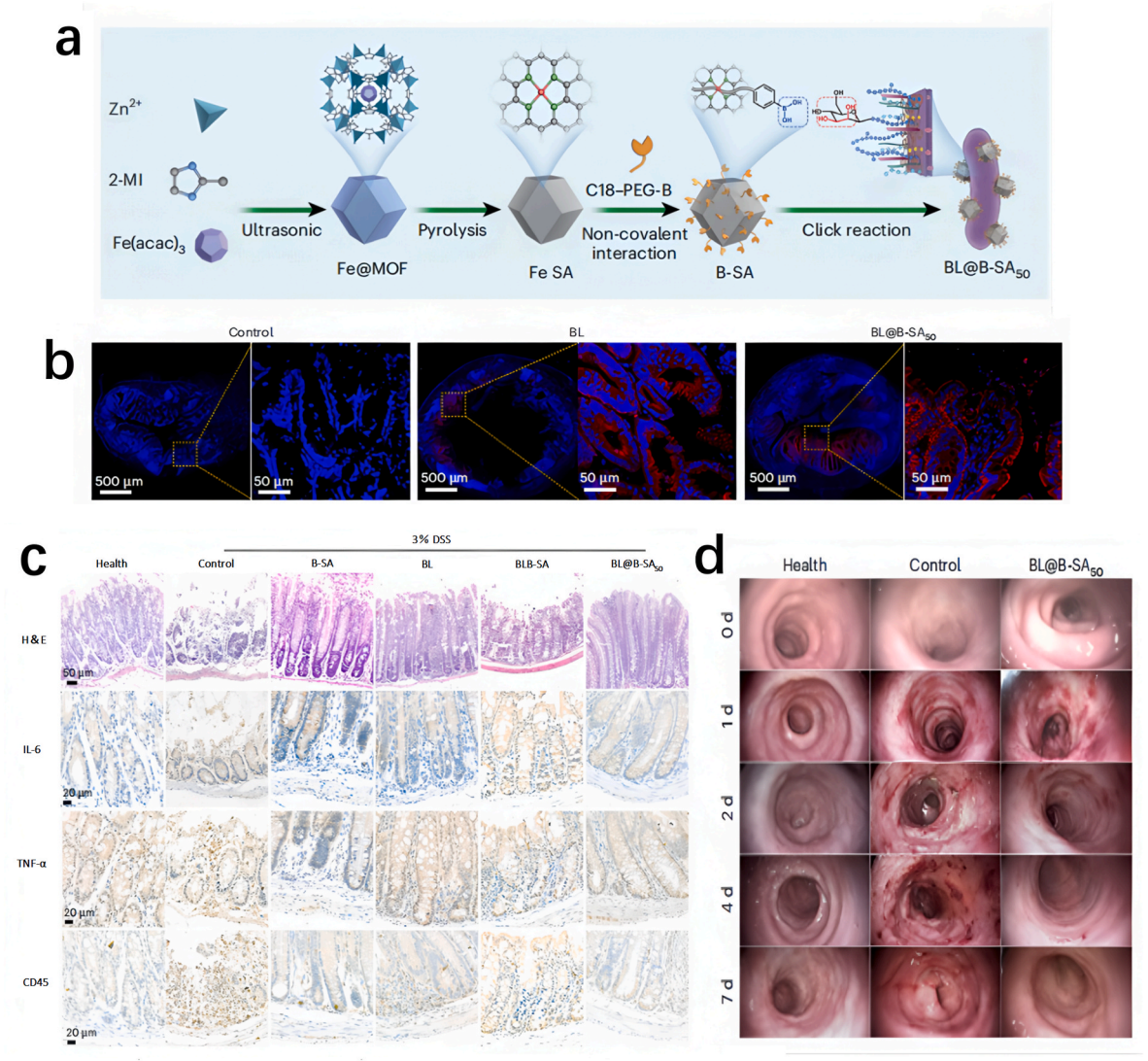


Fig. 10. An artificial-enzyme-equipped *Bifidobacterium longum* probiotic designed to mitigate intestinal inflammation and restore microbiota balance. **(a)** A schematic representation illustrates the artificial-enzyme-enhanced probiotic, BL@B-SA_{50}. **(b)** Fluorescence in situ hybridization (FISH) assays show the levels of *Bifidobacterium longum* in the colons of UC mice treated with BL and BL@B-SA_{50}. **(c)** Colonic tissue sections from treated mice were analyzed using H&E staining to evaluate histopathological changes. **(d)** Endoscopic images from canine models highlight differences in outcomes across various treatments. Reproduced with permission [155]. Copyright 2023, Springer Nature.

accumulation in DSS-colitis lesions under magnetic guidance, reaching 3.5-fold higher drug concentration compared with free mesalamine [157]. Together, these studies indicate that magnetic guidance markedly enhances colonic drug accumulation relative to free formulations. Moreover, magnetic nanogels co-loaded with dexamethasone achieved sustained release and reduced systemic exposure, suggesting their dual benefit of local enrichment and controlled delivery [156]. As shown in Fig. 11, SPION-based systems achieved preferential accumulation in inflamed colonic tissue under magnetic guidance, directly validating the feasibility of externally controlled targeting. These findings confirm that magnetic guidance can improve drug accumulation specifically at colitis lesions, but it is important to note that nearly all evidence so far has been generated in DSS-induced colitis rodent models, and no clinical investigations in IBD patients have been reported. Moreover, efficacy has been shown almost exclusively in DSS colitis models, raising concerns about reproducibility across other IBD subtypes and patient-specific conditions. This underscores that progress in this field remains at a preclinical stage.

However, significant translational barriers remain. First, external magnetic fields show limited penetration depth in abdominal tissues, especially in humans, which may reduce targeting efficiency compared to small-animal models. Second, prolonged or repeated magnetic exposure raises concerns of local heating and biosafety. Third, high costs and lack of standardized magnetic field devices hinder clinical adoption.

Future efforts should integrate magnetic guidance with complementary triggers (e.g., pH, ROS, enzymatic cues) to enhance selectivity, while advancing minimally invasive platforms such as capsule robots to accelerate translation from preclinical models to clinical application.

4.2.2. *Light-responsive strategies*

Photodynamic therapy (PDT) is a minimally invasive method recognized for its effectiveness in treating inflammatory diseases. This technique is characterized by its high efficacy, minimal toxicity, and suitability for repeated applications [187]. PDT employs a photosensitizer (PS) applied to the affected area, which is activated using light of specific wavelengths [158]. By selectively targeting rapidly dividing cells, PDT presents a flexible and promising therapeutic approach for various medical conditions [187,188], Photoreactive carriers offer numerous advantages including biocompatibility, biodegradability, easily accessible and clean light sources, strong remote operability, and

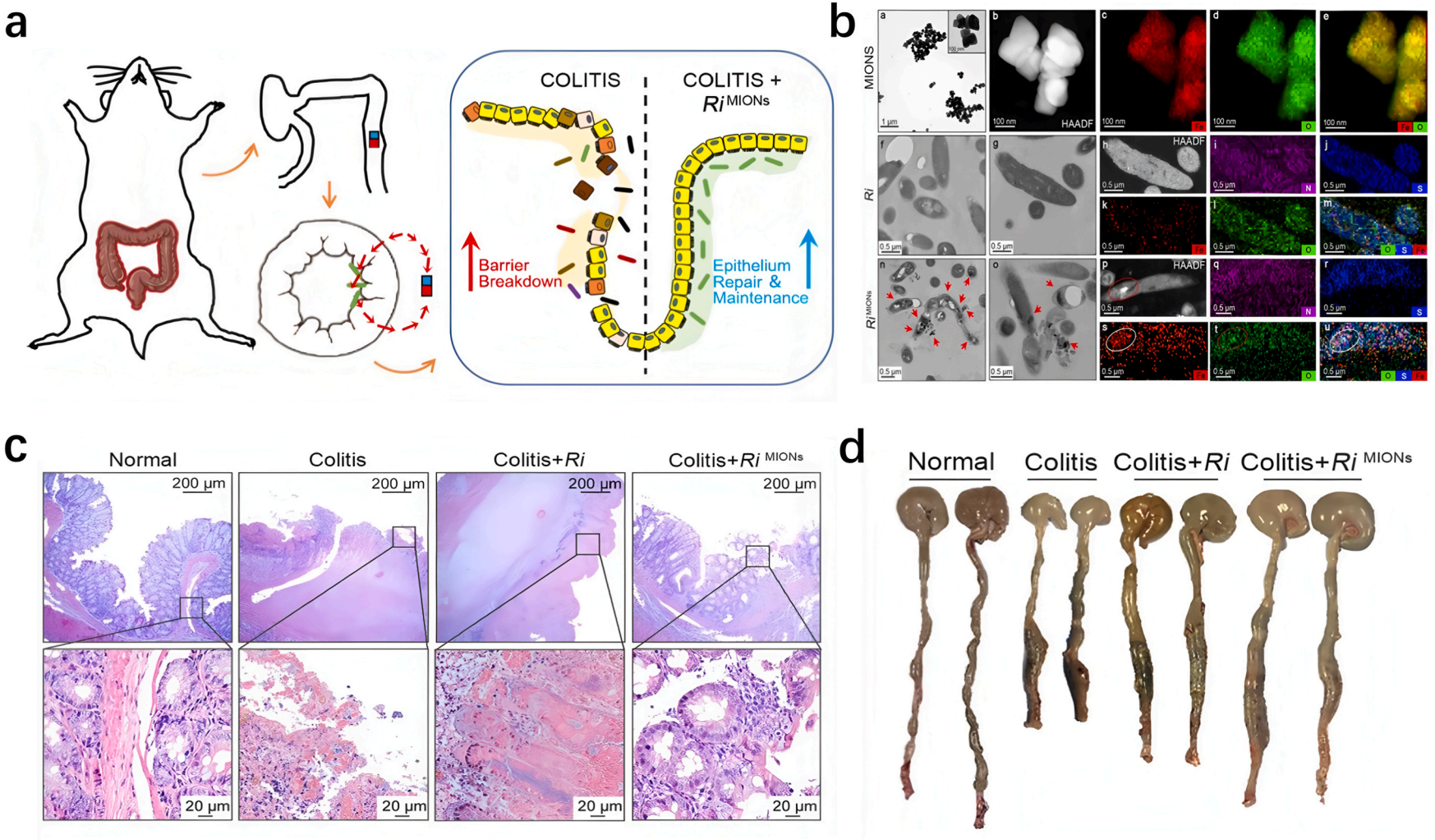


Fig. 11. A *Roseburia intestinalis* strain internalized with MIONs for precise colon targeting. **(a)** A schematic diagram outlining the experimental framework. **(b)** *Roseburia intestinalis* was engineered to incorporate MIONs. **(c)** H&E staining of colonic tissue sections in a rat colitis model was conducted to assess pathological changes following various treatments. **(d)** Treatment with *R. intestinalis* loaded with MIONs significantly alleviated inflammation and restored colon length compared to the untreated group. Reproduced with permission [157]. Copyright 2019, Royal Society of Chemistry.

precise and rapid responsiveness. These attributes have paved a new pathway for the development of SDDSs. Photoreactive drug carriers can undergo reversible structural changes through the modulation of light stimuli, such as toggling the light source on and off, altering wavelengths, and adjusting the duration of irradiation. These changes allow for the controlled, pulsed release of medications. This innovative approach not only enhances the efficacy of drug delivery but also maximizes the therapeutic potential while minimizing side effects, thereby aligning with the goals of modern, targeted therapy. Photoreactive carriers are primarily composed of photosensitive polymers, typically containing photosensitive groups such as azobenzene, spiropyran, diarylethene, triphenylmethane, azidonaphthoquinone, cinnamate esters, and coumarin [159]. They achieve phototriggered phototherapy through three main mechanisms: (1) light-induced hydrophobic-hydrophilic transitions, (2) photolysis reactions, and (3) photothermal therapy (PTT) [160]. This non-invasive drug delivery technique operates by responding to specific light wavelengths, enabling a controlled, on-demand drug release process that can be activated either once or multiple times. Considering safety and availability, ultraviolet light ranging from 250 to 380 nm and near-infrared light from 700 to 900 nm are commonly used to induce photo responses [161].

IBD is recognized as a contributing factor to the development of colorectal cancer (CRC) [185], and PDT has demonstrated efficacy as a palliative treatment for advanced CRC, offering a minimally invasive option to manage the disease [189,190]. Moreover, recent studies highlight PDT's potential in mitigating IBD by suppressing pro-inflammatory cytokines [191], modulating the intestinal microbiota [192], and influencing the expression of miRNAs [193]. Recent research has demonstrated that PDT can alleviate IBD by reducing pro-inflammatory cytokines [191], influencing the composition of intestinal microbiota [192], and modulating miRNAs [193]. Liu et al. [162] demonstrated that PPARGC1A, a gene downregulated in both DSS-induced acute colitis and DSS-stimulated colonic epithelial cells, can be restored through PDT. Furthermore, silencing PPARGC1A was found to diminish the therapeutic effects of PDT in these models, underscoring its pivotal role in mediating PDT's efficacy. Another study revealed that ALA-PDT induces apoptosis and necrosis in targeted lesions. It also examined the impact of ALA-PDT on peripheral blood mononuclear cell (PBMC) subsets in patients with active CD, shedding light on its immunomodulatory mechanisms. Post-treatment analysis showed a significant downregulation of cytokines and inflammation-associated exosomes at the subcellular level, consistent with previous findings in PBMCs from healthy individuals. These findings suggest that ALA-PDT holds potential as a therapeutic option for CD and other immune-mediated diseases [163]. Additionally, LD_4-mediated photodynamic therapy (LD_4-PDT) [194] has been shown to improve survival rates in rats with UC induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS). Collectively, these studies highlight PDT's potential as a groundbreaking approach for treating gastrointestinal diseases, particularly IBD. The treatment significantly reduces the levels of pro-inflammatory markers, including interleukin IL-6, IL-1, and tumor necrosis factor TNF-α, as well as oxidative stress indicators such as malondialdehyde (MDA) and myeloperoxidase (MPO). Simultaneously, it increases the expression of antioxidant markers like glutathione (GSH) and superoxide dismutase (SOD), while preserving the integrity of the intestinal epithelium. These findings suggest that LD_4-PDT is an effective

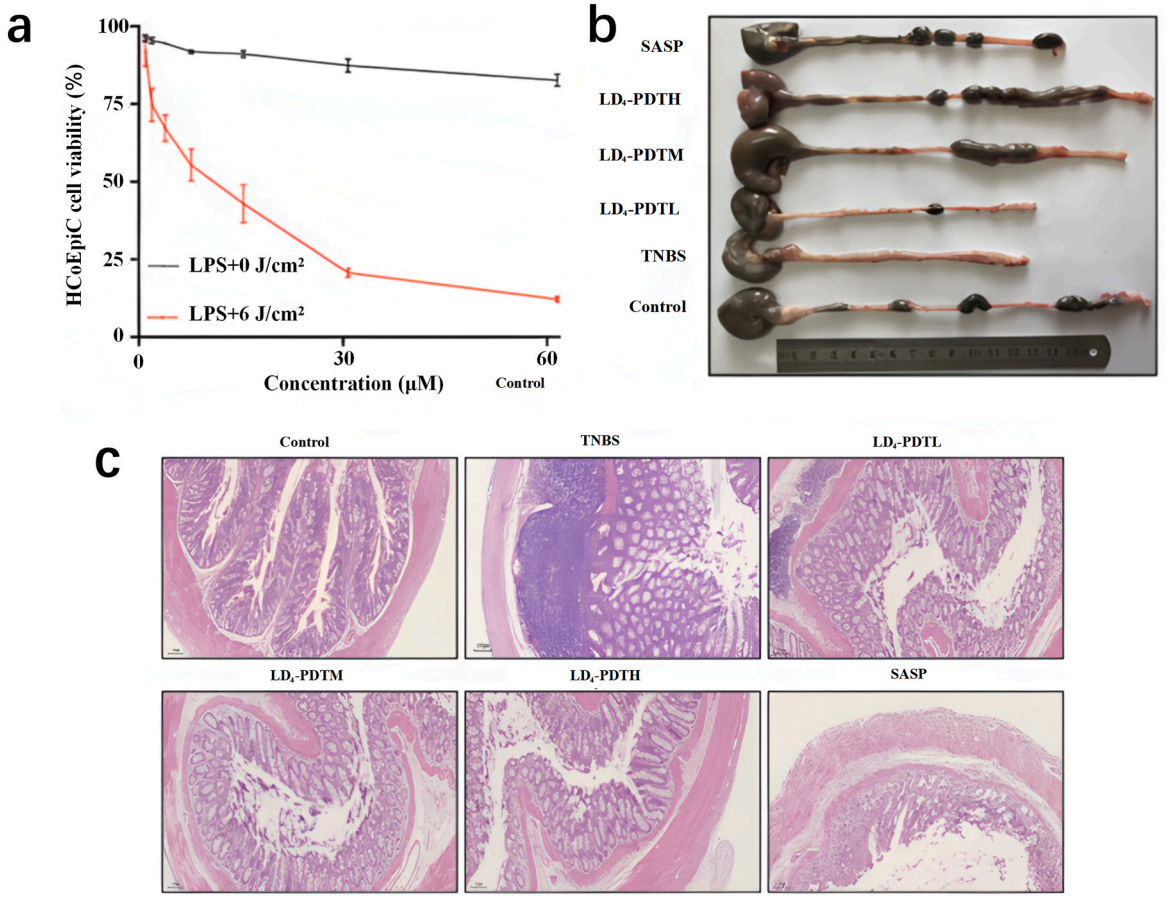


Fig. 12. A Photodynamic Therapy Using a Novel Photosensitizer Alleviates TNBS-Induced Ulcerative Colitis via AOC_1 Inhibition (a) MTT assay demonstrates that LD_4-PDT effectively reduces inflammation in LPS-induced HCoEpiC cells. (b) Treatment with LD_4-PDT significantly mitigated inflammation, leading to an increase in colon length compared to the untreated group. (c) H&E staining of colonic tissue sections in the rat colitis model reveals improved pathological outcomes following treatment with various formulations, highlighting the efficacy of LD_4-PDT. Reproduced with permission [194].Copyright 2021, Rong, Hong, Zhu, Liu, Jiang and Liu.

therapeutic strategy for UC, with AOC_1 identified as a potential therapeutic target (Fig. 12).

PDT faces several challenges. The effectiveness of PDT relies heavily on the selective uptake of the photosensitizing agent by target cells [164]. However, precise targeting remains a significant challenge, particularly when treating diffuse or extensive lesions [165]. Moreover, the standardization and optimization of PDT protocols and parameters across different diseases are still unresolved issues [166]. Further research is urgently needed to identify ideal photosensitizers, refine light dosimetry, and develop tailored treatment regimens to improve therapeutic outcomes [195]. PDT, while complex and requiring specialized equipment and expertise, often faces barriers in terms of cost and accessibility, particularly in resource-limited environments. Although generally well-tolerated, PDT can cause side effects, including skin photosensitivity, pain during light activation, and potential damage to adjacent healthy tissues. Future research directions should focus on combining light responsiveness with other stimuli (e.g., pH or ROS triggers) to improve selectivity and overcome penetration depth limitations. At the same time, the development of minimally invasive light delivery tools suitable for gastrointestinal application is crucial for clinical translation [167].

4.2.3. *Ultrasound-responsive strategies*

Ultrasound-responsive systems harness the mechanical and thermal effects of ultrasound to promote drug release or enhance penetration into diseased tissues. This approach is particularly attractive because ultrasound is non-invasive, clinically established, and capable of reaching deeper tissues, making it promising for gastrointestinal diseases including IBD. Unlike light, which has limited penetration depth, ultrasound can reach deeper intestinal regions, potentially improving the treatment of lesions located beyond the mucosal surface [196].

The release of drugs triggered by ultrasound cavitation results from the oscillation and collapse of bubbles in the acoustic field. The implosion of these microbubbles not only liberates the drug payload but also causes the endothelial gaps in the vascular system of inflamed colonic tissues to expand, thereby increasing tissue permeability [197]. By tuning the acoustic frequency and pressure (intensity) and controlling exposure time (duty cycle), the penetration depth into tissues can be regulated, thereby improving the permeation and retention of drug carriers in diseased sites. Another advantage of ultrasound-assisted therapy is its ability to enhance permeability through non-degradable polymers and the accelerated degradation of degradable polymers [198]. This approach not only improves drug delivery efficacy but also minimizes potential damage to healthy tissues, aligning with the principles of precision medicine [168]. At present, however, the administration of ultrasound-responsive drug delivery systems is somewhat restricted in scope, with applications primarily focused on diseases that necessitate rectal delivery.

Schoellhammer et al. [199] emphasized the potential of ultrasound as an innovative technique to improve drug delivery within the GI tract, particularly for rectal administration (Fig. 13). Their findings revealed that it can increase the absorption of model drugs such as inulin, hydrocortisone, and mesalamine by two-to ten-fold in ex vivo tissues, with effectiveness varying by gastrointestinal tract location. This approach also facilitated the systemic delivery of insulin, triggering the anticipated hypoglycemic effect. In a rodent model of chemically induced acute colitis, the combination of ultrasound and daily mesalamine enemas led to markedly better clinical and histological outcomes than mesalamine alone. This demonstrates that ultrasound can improve the local availability of conventional drugs, thereby enhancing their

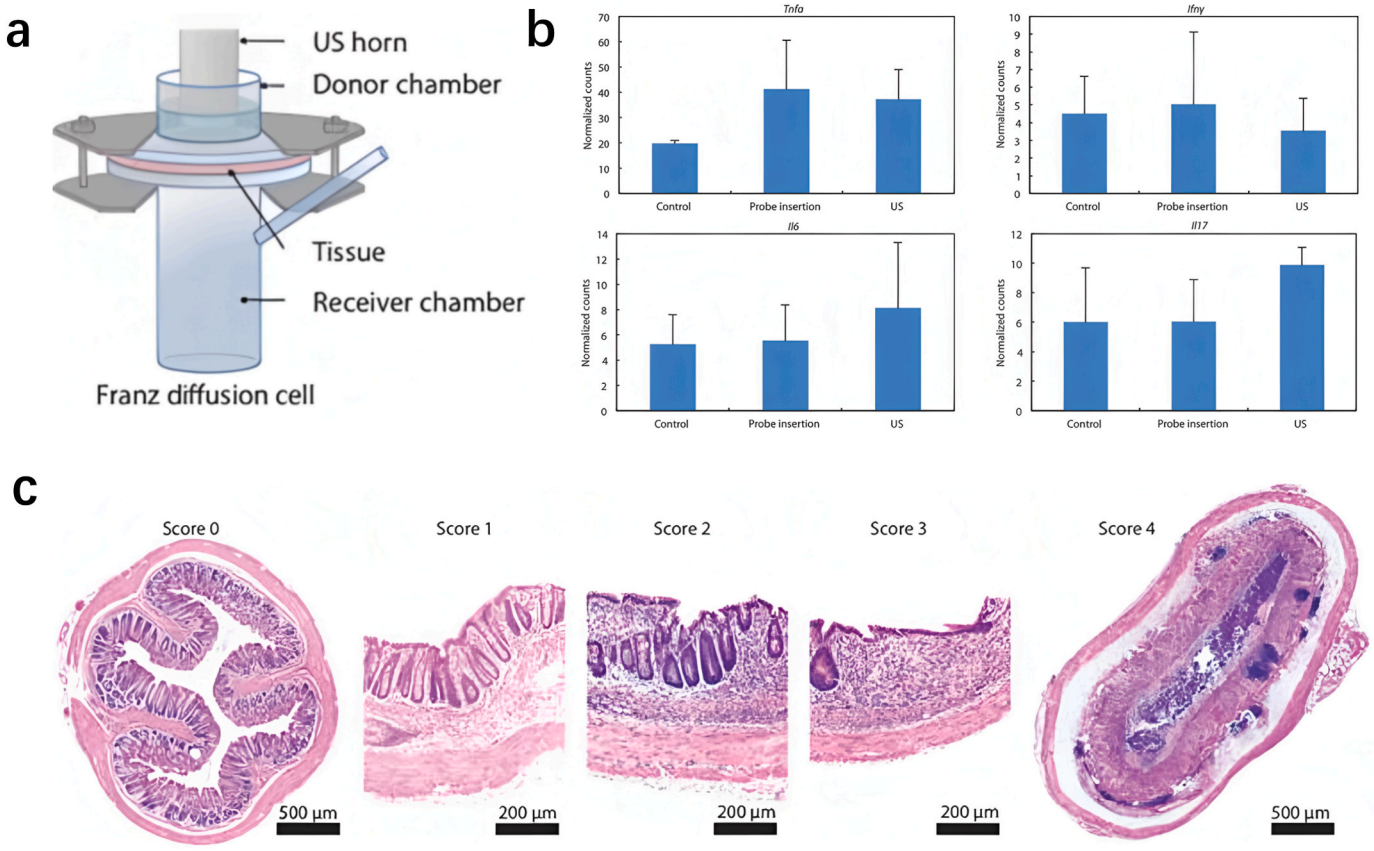


Fig. 13. An ultrasound-mediated GI delivery (UMGID) for augmenting the efficacy of GI therapies. (a)schematic depiction of the ex vivo characterization of UMGID. (b)Cytokine mRNA levels in colonic tissue samples. (c) H&E staining of colonic tissue sections in the rat colitis model reveals improved pathological outcomes following treatment with various formulations. Reproduced with permission [199]. Copyright 2015, American Association for the Advancement of Science.

therapeutic efficacy without requiring structural modification of the drug itself. However, concerns persist regarding the stability of liposomal formulations under repeated insonation and the potential for off-target drug release. Moreover, the inconsistency of therapeutic benefits across different preclinical models raises questions about the reproducibility and predictability of these findings in clinical settings.

Building on this principle, Li et al. [200] highlighted the potential of Perfluorooctylbromide nanoparticles (PFOB NPs) as efficient carriers for delivering therapeutic agents in IBD. These nanoparticles can transport various drug payloads effectively, offering versatility in treatment applications. Compared with Schoellhammer's liposomal system, PFOB NPs-assisted delivery provides stronger penetration across the intestinal barrier, but it requires specialized formulation of contrast-like agents and raises potential biosafety questions related to cavitation. Furthermore, ultrasound has demonstrated the ability to deliver mRNAs and siRNAs to the colonic mucosa in mice, successfully silencing target mRNA expression [201].

Ultrasound-responsive materials hold significant promise for drug delivery in IBD but face substantial hurdles. Their clinical translation is limited by a lack of human safety and efficacy data, coupled with low drug loading capacities. To advance this technology, future efforts must focus on enhancing loading efficiency, expanding clinical trials, and fostering greater collaboration to enable broader therapeutic application beyond current preclinical and rectal delivery methods. Future efforts should integrate ultrasound responsiveness with other stimuli (e.g., ROS or pH triggers) to achieve multi-level precision, while simultaneously developing minimally invasive ultrasound delivery devices such as capsule-based or endoscopic systems. Only with such innovations can ultrasound-responsive DDS move beyond preclinical demonstrations toward clinical translation in IBD therapy. In addition, the lack of standardized ultrasound equipment and regulatory guidelines for ultrasound-mediated DDS significantly delays clinical translation.

4.2.4. Temperature-responsive strategies

Temperature-responsive drug delivery systems exploit the changes in the solubility or phase transition of polymers in response to temperature variation. In the context of IBD, inflamed tissue is often characterized by a mild elevation in temperature, typically around 1–2 °C higher than healthy mucosa. Although this temperature gradient is relatively small, it has been exploited as a trigger for localized drug release [169]. Carone et al. [170] demonstrated a temperature-triggered in situ forming lipid mesophase gel's ability to encapsulate and release drugs with varying polarities, such as tofacitinib and tacrolimus, in a controlled manner (Fig. 14). The gel adheres to the colonic wall for at least 6 h, enhancing drug bioavailability by preventing leakage. Crucially, incorporating known colitis treatments into the gel has been shown to improve outcomes in two acute colitis mouse models. This temperature-responsive gel holds potential for treating colitis more effectively while reducing the side effects linked with systemic administration of immunosuppressants. In a similar vein, Guo et al. [171] explored the use of an injectable thermosensitive copolymer hydrogel for IBD treatment, with a focus on UC. This localized formulation creates a protective barrier over ulcerated regions while serving as a sustained drug release system. The hydrogel is composed of a poly (aliphatic ester)-based triblock copolymer, poly (dl-lactic acid)-poly(ethylene glycol)-poly(dl-lactic acid) (PDLLA-PEG-PDLLA), which transitions from a liquid state at room temperature to a gel at body temperature when its concentration exceeds 11 %. It provides dual benefits: shielding ulcerated sites from bacterial intrusion and acting as a reservoir for mesalazine, enhancing drug retention and enabling prolonged localized release in the colon. Both systems rely on temperature variation to achieve controlled drug release, with Guo et al.'s approach extending this concept further by providing sustained drug release through localized temperature triggers, thus enhancing treatment duration and effectiveness. However, despite their promising localized treatment effects, both systems still rely on external heat sources or temperature gradients, posing challenges for broader clinical application.

These studies suggest that exogenous temperature-responsive DDS hold potential for localized treatment of colitis, but their insensitivity to physiological temperature changes and dependence on external devices may limit their wider application. Future work will need to address the complexity of production and device dependency to enable clinical translation.

4.3. Multiple stimuli-responsive strategies

Designing drug delivery systems that respond to a single physiological trigger (e.g., pH, one enzyme, or redox state) often proves insufficient for reliable colon targeting. Biological conditions in the gastrointestinal tract vary greatly between and within individuals, especially in disease states. For example, a pH-dependent release coating may fail if a patient's intestinal pH never reaches the preset threshold (a common issue in ulcerative colitis where colonic pH is reduced). Likewise, relying on one enzymatic trigger can be problematic due to interpatient differences in enzyme expression or gut transit times. These limitations mean single-trigger systems risk premature drug release or lack of release altogether in some patients, undermining therapeutic efficacy and safety.

Multiple stimuli-responsive drug delivery systems are designed to address the above shortcomings by incorporating two or more independent triggers into one platform. In these systems, an additional stimulus serves as a secondary or simultaneous signal to initiate drug release, creating a built-in “backup” or synergistic mechanism. Release can thus be programmed to occur only when at least one (fail-safe mode) or all (coincidence mode) of the targeted conditions are met, dramatically improving site-specific precision. This strategy compensates for physiological variability; if one trigger is insufficient due to an abnormal GI environment, the other trigger can still ensure the drug is released at the intended site. Moreover, combining triggers can effectively narrow the release window both spatially and temporally, since the unique concurrence of multiple conditions (e.g., a specific pH range and the presence of a certain enzyme) is more exclusive to the disease microenvironment than any single factor alone. The net result is enhanced specificity of drug release to the colon (or even to inflamed lesions within the colon), reducing off-target drug loss and side effects, while maximizing therapeutic concentration where it's needed. Evidence from recent designs confirms that multi-trigger systems can achieve more reliable and efficient drug delivery compared to single trigger counterparts.Advancements in materials science have driven growing interest in dual- and multi-responsive systems for applications in drug delivery and tissue engineering [202,203].

A notable example is OPTICORE™ [204,205], a clinically validated drug delivery system that combines pH- and bacteria-triggered release mechanisms. This system has demonstrated effective drug release upon reaching the colon and has achieved market approval, illustrating the practical viability of multi-trigger designs. Beyond proof-of-concept, this platform reduces “too-early/too-late” release risk inherent to single-trigger systems and provides a regulatory precedent for the class. Similarly, Rabeh et al. [206] developed a copolymer of 2-hydroxyethyl methacrylate and methacrylic acid, crosslinked with an azobenzyl linker, which exhibits dual pH- and enzyme-responsive properties. The swelling and drug release characteristics of the hydrogel were tested in buffers at pH 1.2, 6.5, and 7.4, as well as in the presence of rat cecal matter. Metronidazole and mesalamine were used as model drugs of BCS Class I and IV drugs, respectively. The hydrogel showed significant swelling at pH 7.4 (69 %) and minimal swelling at pH 1.2 (32 %), with drug liberation accelerated in the presence of colonic enzymes (rat cecal contents), supporting colon specificity. Mechanistically, the pH window gates transit through the upper GI tract, while azobenzyl cleavage by bacterial azoreductases provides lesion-site activation—together mitigating inter-patient variability in pH or enzyme levels seen with single-trigger carriers. Functionally, this design is well-suited for BCS IV

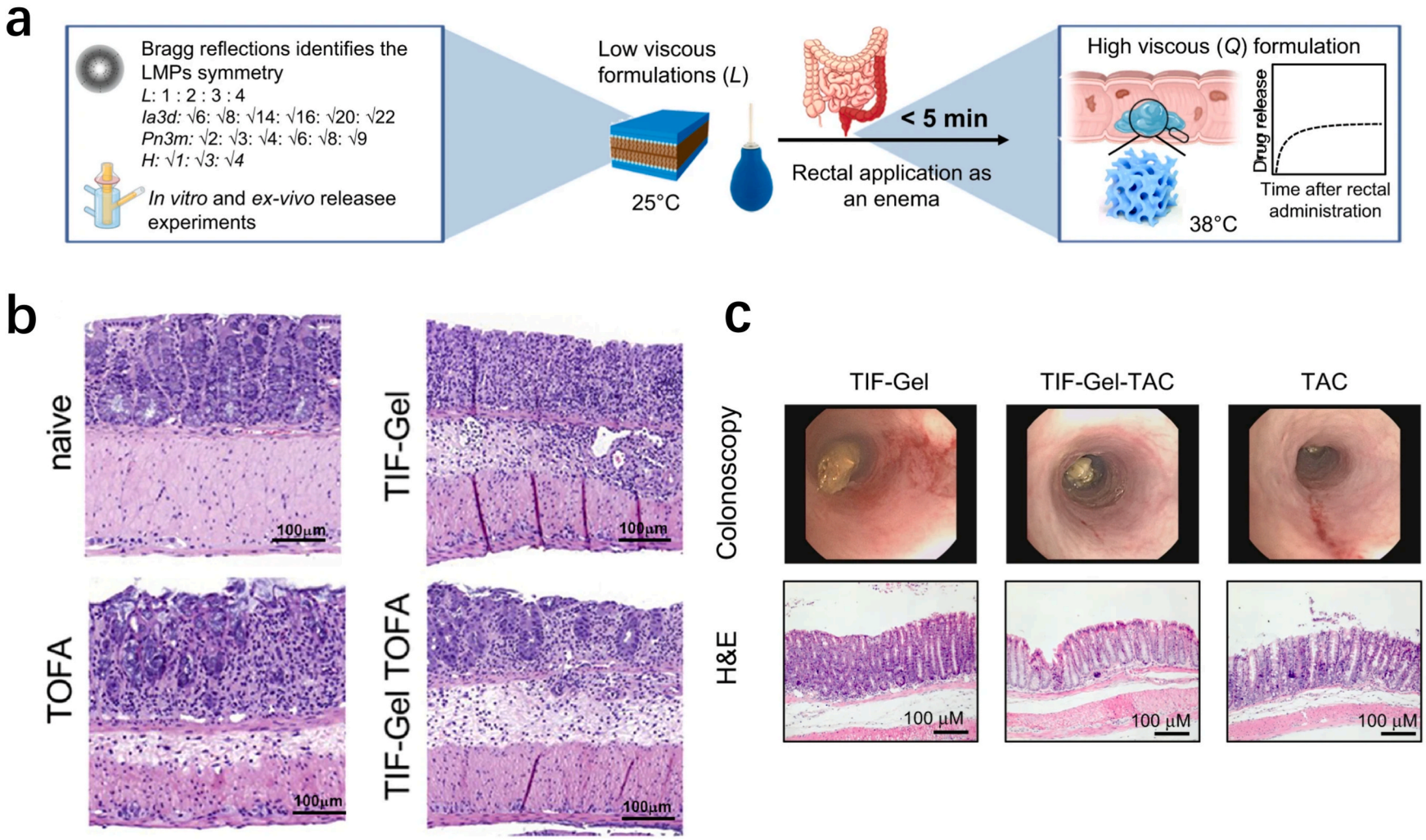


Fig. 14. A temperature-triggered in situ forming lipid mesophase gel for UC treatment. (a) A schematic diagram illustrates the in vitro characterization and the gel formation mechanism, highlighting the temperature-sensitive process. (b) The TIF-Gel-TOFA formulation demonstrates significant efficacy in reducing intestinal inflammation and alleviating disease symptoms in a DSS-induced colitis mouse model. (c) The therapeutic impact of TAC-loaded TIF-Gel was evaluated in a T cell-mediated colitis model, demonstrating its potential efficacy in modulating immune responses. Reproduced with permission [170]. Copyright 2023, Springer Nature.

payloads, where poor solubility often limits mucosal exposure. Nevertheless, its validation remains largely in vitro, and the complexity of synthesis still poses challenges for broader translation. Additionally, Yang et al. [207] created a thermosensitive hydrogel-based nanozyme for IBD therapy. This formulation incorporated a manganese oxide (Mn_3O_4) nanozyme with multi-enzyme activity into a thermosensitive hydrogel made from a poly (d, l-lactide)-poly (ethylene glycol)-poly(d, l-lactide) (PDLLA-PEG-PDLLA) triblock copolymer. The sharp gelation transition of PDLLA-PEG-PDLLA at body temperature allowed the Mn3O4-loaded hydrogel (MLPPP) to efficiently target the inflamed colon when administered rectally. Here, the thermogel provides mucoadhesive retention and on-site depot formation, while the Mn3O4 nanozyme offers cascade-like ROS-scavenging, together restoring epithelial redox homeostasis and dampening cytokine production in DSS colitis. However, its reliance on rectal administration may limit general clinical applicability, highlighting the need for more versatile delivery formats. Compared with single-stimulus platforms, these dual/multi-responsive systems improve spatiotemporal control, buffer biological variability (pH, enzyme activity), and reduce off-target exposure—yet scale-up complexity and device-assisted administration (e.g., rectal delivery) remain practical hurdles that future work should address.

Together, these examples reveal a clear progression—from a clinically implemented system (OPTICORE™) to advanced preclinical hydrogels (Rabeh), and finally to innovative dual-functional nanozymes (Yang). This trajectory illustrates the growing sophistication of multi-stimuli strategies, moving beyond proof-of-concept toward more robust and clinically relevant designs.

Gut microbiota-responsive mechanisms have emerged as a particularly powerful element in multi-stimuli delivery systems for colon targeting. The dense microbial population in the colon provides a unique trigger through enzymes (glycosidases, azoreductases, proteases, etc.) that are largely absent in the upper GI tract. Incorporating a microbiota-sensitive component (such as a bacterially fermentable polysaccharide or azo-bond linker) into drug carriers thus endows them with site-selectivity: significant degradation and drug release occur only upon reaching the colon where these microbes thrive. Used alone, this strategy can be effective but might be influenced by interindividual differences in microbiota composition or activity. However, when combined with other triggers (like pH or time-delay coatings), microbiota-activated release forms a synergistic system that is more robust against variability, thereby compensating for the limitations of single-trigger strategies. For example, the dual-trigger Phloral™ coating (basis of the OPTICORE technology) uses a pH-sensitive polymer together with a resistant starch that bacteria can digest; this ensures drug release in the colon even if colonic pH is lower than expected. Conversely, if pH is sufficient but a patient's microbial enzyme activity is reduced, the pH trigger alone can still effect release – the two cues provide mutual reinforcement or redundancy as needed. In essence, the microbiota trigger acts as an AND/OR gate with other signals: some formulations require both pH and microbial action in sequence (enhancing specificity to the distal colon), whereas others will release if either condition is met (enhancing reliability) – both design logics have been employed successfully. This redundancy and synergy directly address the shortcomings of single-trigger systems, offering greater consistency and precision in drug delivery.

Notably, leveraging the microbiota in multi-trigger platforms can improve not just site-specificity but also disease-specificity. In inflammatory conditions like IBD, the gut microbiome and its enzymatic profile can shift, but certain enzymatic activities (e.g., glycosidic breakdown of dietary fibers or azo bond reduction) generally persist and can be targeted. This provides a biological selectivity that purely physicochemical triggers (e.g., pH, ROS) cannot reliably guarantee. By calibrating drug matrices to these activities, one can achieve drug release that coincides with regions of microbial proliferation, which often correspond to the colon and dysbiotic/inflamed segments. Recently, researchers demonstrated a sophisticated triple-trigger oral delivery system that responds to pH, microbiota, and transit time in tandem. This formulation remained intact through the stomach and small intestine (requiring a prolonged transit and pH rise), then underwent microbial degradation in the colon, effectively ensuring that release occurred only after all three conditions were satisfied, achieving unprecedented spatial precision [208]. Compared with dual-trigger systems, this "three-layer safeguard" further minimizes premature leakage, although it also increases formulation complexity and may pose manufacturing challenges. This underscores that while layering additional triggers can improve precision, it also amplifies hurdles in scalability and patient compliance.

Taken together, microbiota-sensitive cues serve as natural "gatekeepers" that can be seamlessly integrated with other signals. When functioning as AND gates, they enhance specificity for distal colon targeting; when acting as OR gates, they increase reliability across patient variability. The advantage of including a microbiota-responsive element is clear: it leverages an intrinsic, self-regulating feature of the colon that is difficult to replicate synthetically. Yet, its dependence on microbial activity also introduces variability, underscoring the need for careful patient stratification and further clinical validation. The net result, when optimized, is a more efficacious therapy that concentrates drug action at diseased sites while reducing systemic exposure.

Multiple stimuli-responsive delivery systems represent one of the most promising frontiers in IBD therapy and gastrointestinal drug delivery. By integrating cues from the disease microenvironment (pH shifts, enzymatic activity of the microbiota, oxidative stress from ROS, etc.) with engineered triggers (such as time-dependent coatings or thermosensitive matrices), these carriers achieve a level of precision rarely attainable with single-trigger designs (Fig. 15). Importantly, combining triggers provides built-in redundancy and synergy: if one cue is inconsistent across patients (e.g., variable pH or microbiota activity), additional signals ensure reliable release. This directly addresses the shortcomings of earlier approaches and enhances both site- and disease-specific targeting. Recent advances even point toward personalized systems, where polymers are tailored to an individual's microbial or inflammatory profile, paving the way for patient-specific therapy. The modular nature of these designs also extends their relevance beyond IBD. Similar principles can guide selective drug release in colorectal

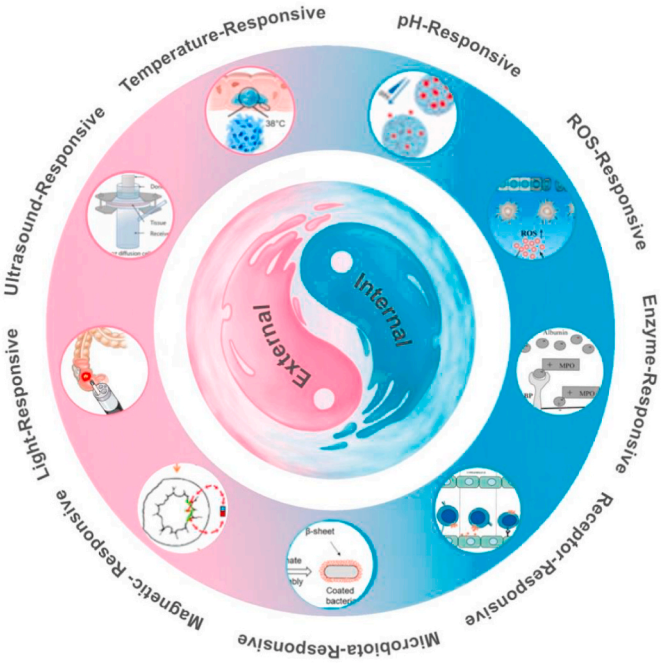


Fig. 15. Yin-yang representation of stimuli-responsive drug delivery strategies.

cancer, infectious diseases, or even systemic conditions where oral drugs must be protected until reaching a defined GI region. Encouragingly, the clinical success of dual-trigger coatings such as OPTICORE™ has demonstrated that multi-stimuli systems can be both safe and reliable, setting a regulatory precedent for future platforms.

Nevertheless, challenges remain. Manufacturing complexity, quality control, and regulatory validation of multi-trigger systems are non-trivial, and their increased structural sophistication can complicate large-scale production. In addition, interpatient variability in microbiota or immune status highlights the need for careful stratification in clinical trials. In a broader perspective, the convergence of microbiota science with materials engineering offers a unique synergy—enabling not only improved colonic targeting but also opening avenues for novel modalities, such as orally delivered biologics or live microbial therapies with protective multi-responsive coatings. In summary, multi-trigger platforms stand out as a rational solution to the limitations of single-stimulus systems, offering greater precision, reliability, and translational potential. Their continued development is poised to significantly improve outcomes in IBD and inspire next-generation drug delivery strategies across diverse gastrointestinal and systemic diseases. Ultimately, multi-stimuli systems represent not only a rational solution to single-trigger limitations but also a cornerstone for the next generation of precision gastrointestinal therapeutics.

5. Conclusions and perspectives

Within this work, recent progress in the design and construction of smart stimuli responsive DDSs was summarized, as well as their applications in the treatment of IBD. Generally, frequently used responsive strategies have improved drug bioavailability with diverse functional properties, including acid resistance, ROS clearance, precise drug release, and mucosal repair. Regarding internal stimuli, pH-responsive SDDSs have been designed to employ the gastrointestinal pH changes. They shield loaded drugs under harsh acidic conditions while passing the stomach and upper intestine, and then release drugs in the higher pH environment of colon for therapeutic purposes. Clinical observations, however, show that colonic pH is often reduced in ulcerative colitis, which can compromise the reliability of this approach. ROS-responsive NPs offer a targeted therapeutic approach to intestinal high ROS environment, ensuring the release of drugs directly at the inflammation sites. Still, the degree of ROS elevation is highly variable between patients and disease stages, raising concerns about its consistency. Enzyme-responsive SDDSs utilize the unique enzymatic environment of the inflammatory intestinal tract (α-amylase, superoxide dismutase, catalase, myeloperoxidase, esterase, etc.) to facilitate precise drug release. In practice, enzyme levels differ markedly across individuals, and non-specific enzyme activity may also trigger premature release. Receptor-responsive SDDSs exploit ligands (saccharides, peptides, antibodies, etc.) on the surfaces to targeted bind molecules (mannose receptors, galactose receptor, CD44, etc.) that are overexpressed on the surface of inflammatory intestinal cells, achieving receptor-mediated endocytosis. Yet, fluctuations in receptor expression and the instability of ligands reduce the reproducibility and translational potential of this strategy. Microbiota-responsive NPs take advantage of the microbiota or engineered probiotics to deliver drugs directly to the inflamed colon, alleviate inflammatory symptoms and rebuild intestinal balance. Nevertheless, since the gut microbiome is highly heterogeneous, the therapeutic effect may not be equally robust in all patients. As for external stimuli, external specific sources (such as magnetic fields, near-infrared light, ultrasound, or exogenous temperature) to enhance drug release and are insensitive to changes in the body's physiological characteristics. However, sensitivity to external stimuli requires the use of environmental remote-control devices, which could potentially be less convenient for autonomous operation. Moreover, the reliance on specialized external devices limits their practicality in routine clinical settings. This could be the reason why only a few studies focus on external stimuli alone.

The key therapeutic benefits that SDDSs offer for the treatment of IBD include: (1) Enhanced Localized Drug Concentration: SDDSs enable the delivery of a high concentration of medication directly to inflamed colonic tissues, resulting in improved therapeutic outcomes. (2) Minimized Systemic Side Effects: By reducing the systemic absorption of active compounds, SDDSs help to lower the likelihood of adverse effects commonly associated with conventional drug delivery methods. (3) Improved Drug Efficiency: Due to their ability to achieve high localized concentrations, SDDSs require smaller doses of active agents to achieve the desired therapeutic impact, enhancing overall treatment efficiency. (4) Increased Patient Compliance: The oral administration route, combined with reduced dosing frequency enabled by SDDSs, offers greater convenience and comfort for patients, promoting adherence to treatment regimens. (5) Cost-Effectiveness: By optimizing drug usage and minimizing side effects, SDDSs contribute to reduced healthcare costs, making them a more economical option for managing IBD.

The main therapeutic advantages that SDDSs for can provide for IBD treatment are (1) high drug concentration in the colonic inflamed tissues that implies better therapeutic effects, (2) a reduction of adverse effects by a decreased systemic absorption of active agents, (3) smaller amounts of active agents necessary to reach the desirable therapeutic effects since high local concentrations are attained, (4) a high compliance of patients due to the comfort of the oral route and the reduced frequency of drug administration, and (5) savings in health economic resources.

The advancement of SDDSs for IBD marks a significant step forward in enhancing therapeutic efficacy and patient compliance. Despite these advancements, several issues persist. The harsh conditions of the gastrointestinal tract, including acidic environments, proteolytic enzymes, and varying bacterial populations, continue to challenge the stability and efficacy of orally administered drugs. Additionally, disease-induced physiological changes such as altered pH, microbiome composition, and barrier integrity further complicate drug delivery. Therefore, developing formulations that can withstand these conditions, reach the target site reliably, and release the drug in a smarter manner is crucial.

Strategies such as pH-sensitive coatings, encapsulation techniques, and prodrugs activated by colonic bacteria offer potential solutions to these issues. The future of SDDS in IBD treatment lies in the integration of advanced nanotechnology and a deeper understanding of pathophysiological changes. Innovations in stimuli-responsive nano-carriers, particularly those responsive to internal stimuli such as pH, ROS, and enzymes, hold significant promise. Compared with previous reviews, this article uniquely integrates cytokine pathways and genetic susceptibility with stimuli-responsive carrier design, providing a mechanistic framework rather than a descriptive summary. These systems can leverage the unique pathological conditions of IBD to achieve precise and controlled drug release, enhancing therapeutic outcomes while minimizing systemic side effects. Yet, most investigations remain restricted to DSS or TNBS colitis models, and the variability of ROS levels across different disease states raises concerns about their generalizability to clinical settings. Moreover, the development of dual or multi-responsive systems represents a burgeoning area of research. By combining multiple triggers, these systems can offer even greater specificity and efficiency in drug delivery. Indeed, by layering triggers, multi-stimuli systems provide both backup and synergy, making them the most promising candidates for robust precision therapy in IBD. For instance, systems that respond to both pH and bacterial enzymes could ensure more precise targeting and controlled release in the inflamed colon. Furthermore, the exploration of microbiota-responsive strategies opens new avenues for IBD treatment. By utilizing engineered probiotics or microbiota-dependent NPs, these systems can restore intestinal balance and enhance therapeutic efficacy. The integration of these strategies with conventional therapies could lead to more holistic and effective treatment regimens. Lastly, addressing the remaining challenges will require a multidisciplinary approach. Collaborations between researchers in nanotechnology, microbiology, and clinical

sciences are essential to develop and refine these advanced delivery systems. Regulatory support and comprehensive in vivo studies will also be critical in translating these innovations from the laboratory to clinical practice. In summary, while significant progress has been made, the journey towards fully optimized SDDS for IBD treatment continues. Despite encouraging preclinical data, clinical validation remains scarce, and regulatory pathways for live-bacteria DDS or multi-responsive nanoplatforms are not yet standardized, representing major translational bottlenecks. Future research should focus on overcoming existing barriers, exploring novel strategies, and ensuring the safe and effective translation of these technologies to improve patient outcomes. At the same time, a universal limitation of current SDDSs is the scarcity of human clinical trial data and unresolved regulatory hurdles, which continue to impede clinical translation. Looking ahead, more well-designed human studies and regulatory-focused investigations are eagerly anticipated to validate safety, efficacy, and scalability, ultimately paving the way for broader adoption in clinical practice.

Compared with previously published reviews, this work offers several unique contributions. First, it systematically integrates both internal and external stimuli-responsive strategies into a unified framework, highlighting not only individual advantages but also their inherent limitations. Second, it provides a comprehensive and forward-looking discussion of multi-stimuli systems, emphasizing how redundancy and synergy can compensate for patient variability and ensure more robust therapeutic precision. Finally, unlike earlier reviews that mainly catalog mechanisms, this article bridges mechanistic insights with translational considerations by addressing regulatory hurdles, reproducibility, and the path toward clinical validation. Together, these features position this review as a more practice-oriented and clinically relevant resource for advancing smart drug delivery in IBD.

CRediT authorship contribution statement

Jiabin Xu: Writing – original draft, Validation, Methodology, Investigation, Funding acquisition. **Peiyu Tang:** Writing – original draft, Validation, Methodology, Investigation. **Xiaoyi Sun:** Validation, Investigation. **Yihan Song:** Validation, Investigation. **Kaili Lin:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Shan Jiang:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Changyong Yuan:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Ethics approval and consent to participate

This study did not involve human or animal subjects, and thus, no ethical approval was required. The review study protocol adhered to the guidelines established by the journal.

Consent for publication

We confirm the manuscript we are submitting has never been published before. Also, it is not currently being considered for publication in any other journal. All the listed authors have carefully reviewed and approved this manuscript. We all agree to submit it to Journal of Biomedical Science for publication and are aware of and accept the journal's publication policies.

Availability of data and material

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Declaration of competing interest

The authors declare no conflict of interest.

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Data availability

No data was used for the research described in the article.

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