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ANALYSIS OF MODERN DRUG DELIVERY SYSTEMS FOR THE TREATMENT OF CROHN'S DISEASE

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ABSTRACT

Crohn's disease is a chronic relapsing inflammatory bowel disease characterized by segmental, transmural inflammation that can affect any part of the gastrointestinal tract, but most commonly involves the terminal ileum and colon. Despite the availability of conventional small-molecule drugs and advanced biologics, long-term disease control remains suboptimal for a large proportion of patients due in part to limited drug exposure at the sites of intestinal inflammation and systemic adverse effects. Modern drug delivery systems aim to improve the therapeutic index of established and emerging agents by enhancing colonic targeting, prolonging mucosal residence, and enabling local or cellularly specific delivery. A wide range of platforms has been investigated, including pH-, time- and microbiota-triggered oral formulations, nanocarriers, liposomes, hydrogels, and device-based systems, many of which are tailored to the unique pathophysiology of Crohn's disease, such as increased permeability, altered microbiota, and elevated levels of reactive oxygen species. This review summarizes current problems in drug delivery for Crohn's disease and approaches to address them, analyzes existing and potential delivery systems, and discusses their relative advantages, limitations, and future perspectives.

1. INTRODUCTION

Crohn's disease (CD) is a chronic, idiopathic inflammatory bowel disease (IBD) characterized by relapsing–remitting inflammation of the gastrointestinal tract, often leading to strictures, fistulas and the need for surgical intervention.[1,2] Current pharmacotherapy includes aminosalicylates, corticosteroids, immunomodulators, small-molecule inhibitors and biologic agents such as anti-TNF antibodies, anti-integrins and anti-interleukin agents.[3,4] Although biologics and targeted small molecules have markedly improved clinical outcomes, primary non-response and loss of response are common, and many patients still require surgery over the course of their disease.[5,6]

A central challenge in treating Crohn's disease is delivering adequate drug concentrations to inflamed intestinal segments while minimizing systemic exposure and off-target toxicity.[7,8] Conventional oral formulations often undergo extensive absorption in the upper gastrointestinal tract, resulting in insufficient drug levels in the distal ileum and colon, where inflammation frequently predominates.[9 - 11] Moreover, the disrupted mucosal barrier, altered pH profile and accelerated or irregular transit associated with active inflammation complicate attempts at predictable local delivery.[12 - 14]

These limitations have prompted intensive research into colon-targeted and inflammation-responsive drug delivery systems that more precisely match the spatial and temporal pattern of disease activity.[15] Strategies include pH- and time-dependent coatings, microbiota-triggered release, nanoparticles and liposomes with mucoadhesive or ligand-directed targeting, and ingestible devices that mechanically deploy drugs at predefined intestinal sites.[16 - 18] The aim of this review is to analyze modern drug delivery systems for the treatment of Crohn's disease, focusing on existing challenges, current and emerging technologies, and their potential to transform long-term disease management.

2. Current problems in drug delivery for Crohn's disease and approaches to their resolution

2.1 Inadequate colonic targeting and premature upper-GI absorption

A major problem of conventional oral therapies is premature absorption or release in the stomach and small intestine, leading to low drug concentrations at colonic sites of inflammation and systemic adverse effects.[19] This

is particularly relevant for drugs intended for local action in the terminal ileum and colon, such as corticosteroids or small-molecule immunomodulators, which may be mostly absorbed before reaching diseased segments.[20,21]
To address this issue, several classes of colon-targeted oral drug delivery systems have been developed, including pH-dependent coatings that dissolve at higher pH values, time-controlled release systems and formulations that rely on enzymatic degradation by colonic microbiota.[22 - 24] pH-dependent systems typically use polymers such as Eudragit that remain intact at gastric pH and dissolve in the more alkaline environment of the distal small intestine and colon, but inter-individual pH variability can result in unpredictable release.[25,26] Time-controlled systems introduce a lag phase before release and may be combined with pH sensitivity, yet they remain susceptible to variation in gastrointestinal transit time.[27]
Microbiota-triggered systems exploit enzymes produced by colonic bacteria to cleave polysaccharide or other biodegradable carriers, thereby initiating drug release predominantly in the colon.[28] Recent work on glycopolymer-based and "glyco-caged" systems illustrates how carbohydrate conjugation can protect active ingredients from absorption in the upper GI tract and enable selective release in the lower GI, potentially improving the effectiveness of oral therapies for IBD.[29]

2.2 Unfavorable pharmacokinetics and systemic toxicity

Systemically administered biologics and small molecules often show wide inter-patient variability in pharmacokinetics, which can contribute to subtherapeutic exposure, immunogenicity and toxicity.[30 - 32] High systemic doses are frequently required to achieve sufficient drug levels at the intestinal mucosa, increasing the risk of infections, malignancy and other adverse events associated with chronic immunosuppression.[33 - 36]
Advanced delivery systems seek to optimize pharmacokinetics by improving local drug retention at the intestinal wall, reducing systemic absorption or enabling controlled release over extended periods.[37, 38] Nanoparticle-based carriers, for example, can modify the distribution and clearance of encapsulated drugs, enhancing stability in the gastrointestinal environment and facilitating mucosal uptake or adhesion to inflamed tissue.[39 - 41] Liposomal formulations and hydrogels have likewise been employed to provide sustained local exposure and to shield vulnerable macromolecules, such as peptides and nucleic acids, from degradation.[42, 43] These approaches aim to enhance the therapeutic index of existing agents by decoupling local efficacy from systemic exposure.[44]

2.3 Barriers from intestinal pathophysiology: pH, enzymes and permeability

The inflamed intestine in Crohn's disease presents a complex and dynamic environment, including altered luminal pH, changes in digestive enzyme composition, mucus layer disruption and increased intestinal permeability.[45] These factors can interfere with conventional delayed-release formulations that rely on relatively stable pH gradients, as well as with carriers that are susceptible to enzymatic degradation in non-target regions.[46, 47]
Modern drug delivery strategies increasingly integrate multiple trigger mechanisms to cope with this variability.[48, 49] For example, colonic drug delivery systems may incorporate pH-sensitive polymers together with enzyme-degradable linkers or encapsulate nanoparticles within protective hydrogels that erode preferentially in inflamed tissue.[50, 51] By designing systems that respond to a combination of environmental cues, such as pH, redox status and enzyme activity, researchers aim to achieve more robust and selective drug release in diseased intestinal segments despite pathophysiological heterogeneity.[52, 53]

2.4 Targeting inflamed tissue and immune cells

Another challenge is the preferential targeting of drugs to inflamed mucosa and key immune cell populations, such as macrophages, T cells and dendritic cells, which orchestrate Crohn's disease pathogenesis.[54] Passive diffusion of small molecules or conventional biologics offers limited selectivity, resulting in drug distribution throughout healthy and diseased tissues alike.[55]
Nanoparticle-mediated delivery has emerged as a promising solution due to the enhanced permeability and retention-like effect observed in inflamed intestinal tissue and the ability of particles to be taken up by activated immune cells.[56, 57] Surface modification of nanoparticles with ligands such as antibodies, sugars (e.g. mannose, galactose) or other targeting moieties can further direct them to specific cell types or receptors, thereby increasing local drug concentration where it is most needed.[58] In addition, inflammation-responsive carriers that degrade in the presence of high levels of reactive oxygen species (ROS) or other inflammatory mediators enable on-demand drug release within diseased segments while sparing healthy tissue.[59, 60]

2.5 Protection and oral delivery of biologics

Many of the most effective therapies for Crohn's disease are biologics—large proteins or nucleic acid-based agents—that are typically administered parenterally due to degradation in the gastrointestinal tract and poor oral bioavailability.[61, 62] However, chronic injections reduce patient convenience and adherence and limit the ability to directly target intestinal lesions via the luminal route.[63]
To overcome these obstacles, several technologies are being developed to enable oral delivery of biologics for IBD, including enteric-coated capsules, nanoparticle and liposome carriers, engineered bacteria and micro- or nano-needle-equipped ingestible devices that inject drugs into the intestinal wall from within the lumen.[64, 65] These systems aim to protect biologics from gastric acid and proteases, promote trans-epithelial transport or deliver them

directly beyond the mucosal barrier, potentially transforming long-term management of Crohn's disease by combining the benefits of biologic specificity with the convenience of oral administration.[66, 67"]

Table 1. Summary of key problems and solutions in drug delivery for Crohn's disease

Problem	Consequence in Crohn's disease	Main technological approaches	Representative examples
Premature upper-GI absorption	Low colonic drug levels, systemic side effects	pH-dependent coatings, time-controlled release, microbiota-triggered systems	Eudragit-coated tablets, time-controlled release systems, polysaccharide-based coatings, glyco-caging[3–6,9–11,21–23]
Variable intestinal environment	Unpredictable release, reduced efficacy	Multi-trigger systems (pH, enzymes, ROS), protective hydrogels	pH- and enzyme-responsive polymers, ROS-sensitive nanoparticles in hydrogels
Systemic toxicity and PK variability	Adverse events, non-response	Localized delivery, sustained-release carriers	Nanoparticles, liposomes, controlled-release matrices
Poor targeting of inflamed tissue and immune cells	Off-target exposure, reduced local efficacy	Mucoadhesive and ligand-targeted nanoparticles	Mannosylated and galactose-modified nanoparticles, inflammation-directed carriers
Oral delivery of biologics	Need for injections, adherence issues	Protected oral formulations, bacterial vectors, device-based systems	Nanomedicine for oral biologics, engineered bacteria, autonomous mechanical capsules

3. Existing and potential drug delivery systems for Crohn's disease

3.1 Existing drug delivery systems

3.1.1 Conventional delayed-release oral formulations

Several approved oral therapies for Crohn's disease rely on conventional delayed-release mechanisms, including pH-dependent coatings and multi-matrix systems designed to modulate the site and rate of release.[68 - 70] These formulations typically aim to bypass the stomach and proximal small intestine, releasing active drug in the distal small intestine and colon to treat local inflammation while reducing systemic exposure. [68 - 70]

pH-dependent systems are relatively simple and scalable, and they have demonstrated clinical utility in ulcerative colitis and Crohn's disease for drugs such as mesalamine and corticosteroids.[71] However, their performance can be compromised by intra- and inter-patient variability in luminal pH and transit time, particularly during disease flares.[72] Time-controlled or multi-matrix systems may partially mitigate this variability but remain dependent on physiological factors and can still lead to premature or delayed release in some patients.[73] Thus, while these formulations represent an important baseline technology, they leave substantial room for improvement in precision targeting.[74]

3.1.2 Colon-targeted oral drug delivery systems (CDDS)

Colon-specific drug delivery systems have been extensively investigated for local treatment of IBD, including Crohn's disease, because they can achieve high drug concentrations at inflamed colonic sites while minimizing systemic exposure.[75, 76] Design strategies include pH-sensitive polymers, time-dependent coatings, enzyme-degradable linkers, pressure-controlled systems and combinations of these triggers.[77 - 79]

Recent reviews highlight that CDDS based on microbiota-triggered release, such as those using polysaccharide carriers degraded by colonic bacteria, show particular promise due to the density and metabolic activity of the colonic microbiome.[80, 81] However, dysbiosis in Crohn's disease may alter enzymatic activity and thus influence release profiles, emphasizing the need for robust multi-trigger designs.[82] Novel concepts like glyco-caging, in which therapeutic molecules are conjugated to sugar moieties that are selectively cleaved by bacterial enzymes in the lower GI tract, exemplify how microbiome-responsive systems can enhance colonic targeting of existing drugs.[83, 84]

3.1.3 Nanoparticle-mediated delivery systems

Nanoparticle-mediated drug delivery systems, including polymeric nanoparticles, lipid nanoparticles and nanoemulsions, have been widely explored for the treatment of IBD because they can enhance mucosal adhesion, protect drugs from degradation and exploit the increased permeability of inflamed tissues.[85, 86] In Crohn's disease models, nanoparticles loaded with corticosteroids, immunomodulators or nucleic acids have shown improved localization to inflamed colon segments and reduced systemic toxicity compared with free drugs.[87 - 89]

The physicochemical properties of nanoparticles—including size, surface charge, hydrophobicity and the presence of targeting ligands—strongly influence their interaction with the mucus layer and intestinal

epithelium.[90, 91] Surface modification with ligands such as mannose, galactose or antibodies can direct nanoparticles to specific cell types (e.g. macrophages or dendritic cells) or to receptors overexpressed in inflamed tissue, thereby increasing cellular uptake and therapeutic efficacy. [92, 93] Nevertheless, challenges remain regarding large-scale manufacturing, long-term safety and potential immunogenicity of particular nanomaterials.[94]

3.1.4 Liposomes, hydrogels and other colloidal systems

Liposomes and related vesicular systems offer another established platform for delivering drugs to the inflamed intestine.[95] Liposomes can encapsulate both hydrophilic and hydrophobic molecules, protect them from gastric and enzymatic degradation and be coated with pH-sensitive polymers such as Eudragit to delay release until the colon.[95] Experimental studies have demonstrated that liposomes coated with pH-responsive polymers show minimal drug release under gastric and small-intestinal conditions but release their payload at colonic pH, leading to enhanced local drug levels and reduced systemic exposure.[96, 97]

Hydrogels and hydrogel-nanoparticle hybrids have been developed to further improve colonic retention and inflammation-responsive drug release.[98, 99] In preclinical models of colitis, nanoparticles embedded in ROS-degradable hydrogels have shown targeted degradation and drug release within inflamed colon tissue, accompanied by reduced disease activity and histologic inflammation.[100, 101] These systems can be administered orally or rectally and may be particularly useful for delivering nucleic acid therapeutics or other labile molecules that benefit from multilayer protection.[102, 103]

3.1.5 Device-based oral systems

Beyond conventional formulations, device-based oral systems such as autonomous mechanical capsules are under development to deliver drugs to specific regions of the gastrointestinal tract.[104] These capsules use sensor algorithms (e.g. based on reflected light or luminal conditions) to determine their location in the GI tract and then deploy liquid formulations or micro-needles that inject drugs directly into the intestinal wall.[105]

Such systems have several proposed advantages in IBD, including independence from physiological variables like pH and transit time, the ability to deliver biologics or other large molecules that would otherwise be degraded and predictable high local exposure with limited systemic absorption.[106] Early studies suggest that these approaches could be particularly beneficial for delivering biologics or high-cost agents where maximizing local efficacy and minimizing systemic waste are critical.[107] However, they are still in early stages of clinical development and require careful evaluation of safety, patient acceptability and cost-effectiveness.[108, 109]

3.2 Potential and emerging systems

3.2.1 Inflammation- and ROS-responsive nanomedicine

Emerging strategies for Crohn's disease increasingly focus on inflammation-responsive and ROS-responsive nanomedicine that exploits the biochemical milieu of inflamed tissues to trigger drug release.[110 - 112] Experimental systems include thioketal-linked nanoparticles that degrade in the presence of high ROS levels, thereby releasing encapsulated drugs or siRNA specifically within inflamed segments while remaining stable in healthy tissues.[113, 114]

Preclinical studies in murine models of colitis have demonstrated that ROS-responsive nanoparticles delivering siRNA against pro-inflammatory targets such as TNF-α or signaling kinases can reduce inflammatory markers, preserve colon length and improve histologic scores compared with controls.[115, 116] These systems illustrate how disease-specific triggers can be harnessed for highly localized therapy and may be adapted in the future for Crohn's disease-specific targets or combined with existing biologics to enhance local action.[117]

3.2.2 Oral delivery of biologics and nucleic acids

The oral delivery of biologics, including monoclonal antibodies, peptides and nucleic acids, is a rapidly evolving field with significant implications for IBD management.[118] Nanoparticle carriers, liposomes, engineered bacteria and protective capsules are being engineered to shield biologics from gastric acid and proteases, facilitate trans-epithelial transport or deliver them directly into the intestinal wall or lymphoid tissue.[119]

Recent reviews emphasize that nanomedicine can enhance the stability, permeability and cellular targeting of orally administered biologics in IBD models.[120] For example, nanoparticles loaded with siRNA directed against inflammatory mediators have been shown to accumulate in inflamed colon tissue and to suppress target gene expression, resulting in reduced inflammation in animal models.[121, 122] While clinical translation is still limited, these approaches represent a promising future direction for more convenient, patient-friendly delivery of advanced therapies for Crohn's disease.[123]

3.2.3 Microbiome-integrated and smart systems

Given the central role of the gut microbiome in Crohn's disease pathogenesis, there is growing interest in drug delivery systems that explicitly integrate microbiome interactions into their design.[124 - 126] Microbiota-triggered systems not only use bacterial enzymes to initiate drug release but may also be combined with microbiome-modulating agents such as prebiotics, probiotics, bacteriophages or cytokine-expressing bacteria to simultaneously deliver therapeutics and shape the microbial ecosystem.[127 - 129]

"Smart" systems that incorporate sensors, feedback mechanisms or external control (e.g. via imaging, magnetic fields or ultrasound) are also being explored to achieve spatiotemporally precise drug delivery.[130 - 133] While many such concepts remain at a preclinical or early clinical stage, they highlight a trajectory toward increasingly

System type	Status	Key features	Advantages	Limitations
pH-/time-dependent oral formulations	Existing, clinical	Enteric coatings, time-lag release	Simple, scalable, some clinical success	Sensitive to pH and transit variability, imperfect targeting[3–6,8–10,21]
Microbiota-triggered CDDS	Existing/advanced preclinical	Enzyme-degradable carriers, glyco-caging	Colonic specificity, microbiome-based release	Influence of dysbiosis, inter-patient variability[5–6,22–23,49–50]
Nanoparticles (polymeric, lipid)	Advanced preclinical	Mucoadhesive, ligand-targeted, stimuli-responsive	Improved local delivery, lower systemic toxicity	Scale-up, material safety, regulatory complexity
Liposomes and hydrogels	Advanced preclinical	Vesicular and gel matrices, ROS-responsive hybrids	Protection of labile drugs, sustained local release	Manufacturing complexity, stability issues
Device-based capsules	Early clinical/preclinical	Location-sensing, mechanical deployment	pH-independent targeting, oral delivery of biologics	Cost, safety, patient acceptance[8,16–18]
ROS-responsive and smart systems	Preclinical	Inflammation-triggered release, sensor-guided delivery	High specificity to inflamed tissue, personalized potential	Technical complexity, early development stage[12,14,16,30–31]
Oral biologics/nucleic acids	Preclinical/early clinical	Protected carriers, bacterial vectors, trans-epithelial delivery	Non-invasive administration of advanced therapies	Low bioavailability, stringent stability requirements[15–17,26,28–29,35–37]

sophisticated, personalized drug delivery that responds dynamically to disease activity and individual patient characteristics.[134 – 137]

Table 2. Summary of existing and potential drug delivery systems for Crohn's disease treatment

4. DISCUSSION

Comparative analyses of available data suggest that no single drug delivery platform currently satisfies all requirements for optimal Crohn's disease management; instead, each class offers distinct strengths and weaknesses.[138, 139] Conventional pH- and time-dependent formulations are clinically established and relatively easy to manufacture but provide limited precision and are vulnerable to physiological variability.[140] In contrast, nanoparticle-based and inflammation-responsive systems demonstrate superior targeting and pharmacokinetic control in preclinical models but face challenges related to safety evaluation, regulatory approval and large-scale production.[141 - 143]

From a translational perspective, incremental improvements to existing technologies—such as combining pH, time and microbiota triggers or embedding nanoparticles within traditional CDDS frameworks—may offer a pragmatic path toward better outcomes in the near term.[144 - 146] At the same time, more disruptive innovations, including ROS-responsive nanocarriers, oral biologic delivery systems and device-based capsules, hold the

potential to fundamentally reshape therapeutic strategies by providing highly localized, patient-friendly and possibly personalized treatment options.[147 - 149]

It is also important to consider how drug delivery advances align with evolving therapeutic landscapes, including new biologics, small-molecule inhibitors, cell- or gene-based therapies and microbiome-targeted interventions.[150,151] Effective integration will require interdisciplinary collaboration between gastroenterologists, pharmacologists, materials scientists and engineers to ensure that delivery platforms are tailored to the pharmacology of emerging agents and to the heterogeneous manifestations of Crohn's disease.[152] Future clinical trials should incorporate delivery-specific endpoints, such as mucosal drug concentrations, tissue-level pharmacodynamic markers and microbiome signatures, to more directly evaluate the benefits of advanced delivery technologies beyond systemic pharmacokinetics and traditional clinical scores.[153 - 155]

5. Conclusions

Modern drug delivery systems for Crohn's disease aim to overcome long-standing limitations of conventional therapies by improving colonic targeting, enhancing local exposure and reducing systemic toxicity. Existing technologies, including colon-targeted oral formulations, nanoparticles, liposomes and hydrogels, provide a foundation for more precise therapy but remain constrained by physiological variability, manufacturing challenges and limited clinical validation. Emerging approaches—such as inflammation-responsive nanomedicine, oral delivery of biologics and nucleic acids, microbiome-integrated systems and device-based capsules—offer promising avenues for more effective and patient-centered treatment but require rigorous preclinical and clinical evaluation. Progress in this field will depend on integrating advances in materials science, pharmaceutics and gastroenterology to develop robust, scalable and personalized delivery platforms that can be seamlessly incorporated into evolving therapeutic strategies for Crohn's disease.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed Consent

The authors declare that no patients were used in this study.

Availability of data and material

Not applicable.

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