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Stimuli-Responsive Alginate-Based Micro- and Nanocarriers for Colon-Targeted Drug Delivery in Inflammatory Bowel Disease and Colorectal Cancer: A Systematic Review

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Abstract

Inflammatory bowel disease (IBD) and colorectal cancer (CRC) pose significant global clinical burdens, where traditional systemic treatments are often limited by adverse effects and low site-specificity. Alginate, a biocompatible natural polysaccharide, has emerged as a cornerstone for colon-targeted drug delivery systems (CDDS) due to its pH-responsive gelation and protective properties. This PRISMA 2020-compliant systematic review evaluates 34 studies on stimuli-responsive alginate-based micro- and nanocarriers. Systematic searches (PubMed, Scopus, Web of Science, ScienceDirect; 10 January 2025) identified 2,847 records; after duplicate removal and screening, 34 studies met eligibility criteria. Dual-mechanism systems (pH-sensitive coatings + enzyme-triggered cores) restricted premature release to 80% colonic release and significantly improved body-weight recovery, colon length, and cytokine suppression (TNF-α, IL-6) in murine models. Alginate-chitosan complexes enhanced mucoadhesion and probiotic viability. These systems offer a potent, biocompatible alternative to conventional therapies by improving regiospecificity and protecting sensitive cargo.

Introduction

A) Background and Scientific Context

Inflammatory bowel disease (IBD), which encompasses both Crohn's disease (CD) and ulcerative colitis (UC), represents a group of chronic, progressive, and disabling autoimmune inflammatory conditions of the gastrointestinal tract (Aprodu et al., 2019; Teruel et al., 2020). These conditions are characterized by cycles of relapse and remission, where the body's immune system overreacts to the commensal intestinal flora, leading to severe epithelial injury and mucosal inflammation (Guo et al., 2018; Teruel et al., 2020). The standard pharmacological approach traditionally relies on small-molecule therapies such as 5-aminosalicylic acid (5-ASA), corticosteroids, and immunosuppressants to induce and maintain symptomatic remission (Aprodu et al., 2019; Batubara et al., 2024). In recent years, biological drugs, including monoclonal antibodies like infliximab and adalimumab, have revolutionized management strategies; however, these agents typically require parenteral administration, which is associated with systemic toxicity, high costs, and the development of immunogenic resistance (Aprodu et al., 2019; Liu et al., 2021; Oshi et al., 2021). Consequently, the field of drug delivery has shifted toward the development of colon-targeted drug delivery systems (CDDS) to maximize therapeutic efficacy at the site of inflammation while minimizing off-target systemic exposure (Teruel et al., 2020; Iswandana et al., 2024).

Alginate, a natural anionic polysaccharide typically derived from marine brown algae, has emerged as a cornerstone material in these delivery systems due to its excellent biocompatibility, low toxicity, and unique gel-forming abilities (Abourehab et al., 2022; Wang et al., 2022). Scientific interest in alginate-based hydrogels is driven by their ability to undergo mild, ionotropic gelation with divalent cations like Ca^{2+}, forming a structured network described by the "egg-box" model (Wang et al., 2022; Hurtado et al., 2022). Furthermore, alginate's pH-dependent behavior shrinking in acidic environments and swelling or disintegrating in neutral-to-alkaline environments provides a natural mechanism for site-specific release in the lower gastrointestinal tract (Choukaife et al., 2020; Abourehab et al., 2022). Recent innovations have expanded this framework to include alginate-chitosan polyelectrolyte complexes (CANPs), which enhance cargo protection and mucosal adhesion (Li et al., 2022; Khatibi et al., 2024).

B) Epidemiological, Clinical, or Technical Significance

The clinical and epidemiological burden of colonic diseases is substantial, with IBD prevalence increasing globally and significantly impairing the quality of life for millions of patients (Liu et al., 2021; Li et al., 2022). Beyond IBD, colorectal cancer (CRC) remains the third most common malignancy and the fourth leading cause of cancer-related mortality worldwide, often arising from longstanding chronic inflammation in the colon (Akhter et al., 2020; Li et al., 2022). Current treatments for these conditions frequently fail due to the physiological barriers of the gastrointestinal tract (GIT), which include highly variable gastric pH, proteolytic enzymes, and the rapid clearance of drugs caused by diarrhea (Liu et al., 2021; Iswandana et al., 2022). Technologically, the oral route is the most desirable and acceptable path for drug administration due to its simplicity, cost-effectiveness, and high patient compliance (Abourehab et al., 2022; Iswandana et al., 2024).

However, delivering biologics, proteins, and probiotics orally is technically challenging because these sensitive agents are prone to denaturation by the harsh acidic environment of the stomach and enzymatic degradation in the small intestine (Najwa et al., 2020; Wang et al., 2022). The significance of developing effective CDDS lies in their ability to achieve a "therapeutic window" where the active agent is released specifically at the diseased tissue, thus reducing the administered dosage required and mitigating systemic side effects like hypertension, seizures, and nephrotoxicity often associated with drugs like cyclosporine A (Naeem et al., 2018; Oshi et al., 2021). Additionally, advances in microbiotherapy have highlighted the importance of delivering live probiotic strains to the colon to restore immune homeostasis and reshape the gut flora (Liu et al., 2021; Kim et al., 2023). Therefore, the development of stimulus-responsive alginate-based nanocomposites represents a vital technical frontier for improving outcomes in both chronic inflammatory and malignant intestinal diseases (Alshangiti et al., 2023; Lai et al., 2024).

C) Current State of Knowledge

The current literature establishes several dominant strategies for achieving colonic drug delivery, primary among which are pH-dependent, enzyme-triggered, and time-controlled systems (Guo et al., 2018; Teruel et al., 2020; Iswandana et al., 2024). pH-sensitive systems leverage the rising pH gradient along the GIT, typically using enteric polymers like Eudragit S100 in combination with alginate to prevent drug leakage in the stomach (pH < 3) and promote release in the colon (pH 7–8) (Naeem et al., 2018; Oshi et al., 2021). Enzyme-sensitive systems utilize the high concentration of anaerobic microbiota in the colon, which produces specific enzymes like azoreductases and glycanases to degrade polysaccharide carriers or break azo-bonds in prodrugs (Teruel et al., 2020; Iswandana et al., 2022). Recent studies have also explored inflammation-targeting and ROS-responsive systems that exploit the overproduction of reactive oxygen species and the overexpression of receptors like CD44 and CD98 in inflamed tissues to achieve selective accumulation (Guo et al., 2018; Akhter et al., 2020).

Experimental evidence across multiple studies demonstrates the efficacy of these approaches; for instance, dexamethasone microcrystals coated with alginate and Eudragit layers have shown enhanced anti-inflammatory activity in murine colitis models (Oshi et al., 2018; Batubara et al., 2024). Similarly, the encapsulation of probiotics like *Lactobacillus rhamnosus* in hydroxyapatite-alginate composite hydrogels has been shown to neutralize gastric acid and significantly improve bacterial survival during GIT transit (Kim et al., 2023). Multi-compartment nanomedicines, such as polymeric micelles loaded into alginate microcapsules, have also demonstrated high specificity for CRC cells via receptor-mediated endocytosis (Akhter et al., 2020). Furthermore, combined approaches, such as the Phloral and OPTICORE technologies, have been commercialized as fail-safe systems that integrate both pH and microbiota-triggered mechanisms to ensure accurate site-specificity independent of physiological variations (Teruel et al., 2020; Oshi et al., 2021).

D) Limitations, Inconsistencies, and Research Gaps

Despite these advancements, the literature identifies several significant gaps and limitations that hinder the clinical translation of alginate-based CDDS. Conceptually, the etiology of IBD remains unclear, making it difficult to design systems that address the molecular basis of the disease rather than just managing symptoms (Teruel et al., 2020). Methodologically, the high inter-individual and intra-individual variability in GIT pH, transit time, and microbiota composition poses a severe challenge to the reproducibility of single-mechanism delivery systems (Iswandana et al., 2022; Batubara et al., 2024). Population-related gaps are evident as most studies utilize static in vitro digestion models or small animal models, which fail to accurately simulate the human colonic environment, particularly in pathological states like diarrhea where transit time is dramatically reduced (Wang et al., 2022; Iswandana et al., 2024).

Technologically, alginate hydrogels suffer from inherent structural drawbacks, such as high porosity that allows the premature diffusion of small-molecule drugs and mechanical instability in the presence of monovalent ions found in body fluids (Abourehab et al., 2022; Kim et al., 2023). Furthermore, while nanoparticles enhance cellular uptake, their potential systemic absorption and subsequent accumulation in the liver and spleen raise unresolved safety and toxicity concerns

(Teruel et al., 2020). There is also an inconsistency in the literature regarding the effectiveness of microparticles versus nanoparticles; while some authors suggest nanoparticles reach deeper mucosal layers, others argue that bioadhesive microparticles are superior for preventing systemic exposure (Teruel et al., 2020; Li et al., 2022). Finally, the scalability of complex multi-layered formulations and the high cost of advanced fabrication techniques like microfluidics or electrospraying remain major barriers to industrial-level production (Choukaife et al., 2020; Lai et al., 2024).

E) Rationale for Conducting This Systematic Review

A new synthesis of the literature is urgently needed because, while individual studies have demonstrated the potential of various alginate-based formulations, the rapid proliferation of hybrid strategies in the last four years has yet to be comprehensively evaluated against the clinical challenges of IBD and CRC (Teruel et al., 2020; Wang et al., 2022). Existing reviews often focus on either the pharmaceutical properties of alginate or the clinical pathology of IBD, but rarely do they systematically integrate material engineering advancements with the specific pathophysiological triggers of the colonic microenvironment (Abourehab et al., 2022; Iswandana et al., 2024). This systematic review is motivated by the recent shift from simple pH-dependent systems to multi-component, stimuli-responsive platforms that integrate prebiotics, magnetic-guided elements, and other multifunctional components designed to overcome physiological variability and enhance therapeutic precision in the treatment of colonic disorders (Alshangiti et al., 2023; Lai et al., 2024). By critically appraising these innovations alongside established barriers to clinical translation, the present work aims to offer a unified perspective that can inform the design of next-generation colon-targeted therapies.

Methods

A) Systematic Review Framework

This systematic review was conducted and reported in accordance with the PRISMA 2020 statement.

The methodological framework for this systematic review is grounded in the necessity to consolidate diverse evidence regarding the development and efficacy of alginate-based colonic delivery systems (Abourehab et al., 2022; Wang et al., 2022). This approach is designed to address the scientific complexity identified in the Introduction, specifically the challenge of achieving regiospecific drug release within the highly variable physiological environment of the inflamed gastrointestinal tract (Teruel et al., 2020; Iswandana et al., 2022). By utilizing a systematic review philosophy, this study aims to synthesize data from both primary experimental research and theoretical advancements to provide a comprehensive evaluation of biopolymer-based therapeutics (Hurtado et al., 2022; Batubara et al., 2024). The rationale for this structured synthesis lies in the proliferation of hybrid delivery strategies such as stimuli-responsive nanocomposites and multi-compartment systems which require a rigorous methodological assessment to determine their clinical potential for treating inflammatory bowel disease (IBD) and colorectal cancer (CRC) (Guo et al., 2018; Akhter et al., 2020; Li et al., 2022). Consequently, the framework ensures that the extraction of data regarding material properties, such as biocompatibility and pH-dependent swelling, is conducted in a manner that directly informs the overarching research question of therapeutic reliability (Abourehab et al., 2022; Khatibi et al., 2024).

B) Eligibility Criteria (Inclusion and Exclusion)

Inclusion and exclusion criteria were established to ensure a focused analysis of advanced colonic delivery systems. Eligible studies were required to utilize alginate as a primary or substantial component of the delivery matrix, given its status as a cornerstone natural polysaccharide for gastrointestinal applications (Abourehab et al., 2022; Hurtado et al., 2022). Methodological designs included in this review spanned in vitro characterization studies, ex vivo intestinal models, and in vivo investigations utilizing murine colitis or orthotopic CRC models (Aprodu et al., 2019; Li et al., 2021; Akhter et al., 2020). Population characteristics for the primary research studies included male C57BL/6 mice, ICR mice, and specific human cell

lines such as Caco-2 (enterocyte-like), HCT-116 (colorectal cancer), and iBMDM (macrophages) (Liu et al., 2021; Kim et al., 2023; Batubara et al., 2024).

Interventions of interest focused on the encapsulation of sensitive cargo, including probiotics like *Lactobacillus rhamnosus* and *Bifidobacterium longum*, as well as small-molecule drugs like 5-aminosalicylic acid (5-ASA), curcumin, and cyclosporine A (Liu et al., 2021; Oshi et al., 2021; Foongsawat et al., 2023). Comparators typically involved free-drug suspensions, non-targeted formulations, or conventional oral delivery platforms to assess the relative enhancement of site-specificity (Naeem et al., 2018; Li et al., 2021; Akhter et al., 2020). Outcomes were categorized into technical significance, such as encapsulation efficiency, zeta potential, and pH-responsive release kinetics, and clinical significance, including disease activity index (DAI) scores, colonic damage histological grading, and suppression of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 (Liu et al., 2021; Li et al., 2021; Oshi et al., 2021; Kim et al., 2023). Contextual factors, such as the survival of probiotics during simulated gastrointestinal transit and the impact on gut microbiota diversity, were also included as essential criteria (Kim et al., 2023; Foongsawat et al., 2023; Nuaman et al., 2024).

C) Information Sources and Search Strategy

The identification of relevant literature was conducted through a systematic search of major scientific databases, including PubMed/MEDLINE, Scopus, Web of Science, and ScienceDirect. Searches were performed on 10 January 2025 with no language restrictions. The search strategy employed Boolean logic and MeSH terms to combine keywords associated with the review's scope. The following search strings were used (adapted for each database's syntax):

- PubMed/MEDLINE: ("alginate" OR "alginic acid" OR "sodium alginate") AND ("colon-targeted" OR "colonic targeting" OR "colon specific" OR colorectal) AND ("drug delivery" OR microcarrier* OR nanocarrier* OR microparticle* OR nanoparticle* OR hydrogel* OR microcapsule* OR bead*) AND ("inflammatory bowel disease" OR IBD OR "ulcerative colitis" OR "Crohn* disease" OR "colorectal cancer" OR CRC OR colitis) AND ("stimuli-responsive" OR "pH-responsive" OR "enzyme-triggered" OR "pH-sensitive" OR "microbiota-triggered")
- Scopus: TITLE-ABS-KEY (alginate AND ("colon-targeted" OR colonic) AND ("drug delivery" OR nanocarrier* OR hydrogel*) AND (IBD OR "inflammatory bowel disease" OR "colorectal cancer") AND (stimuli-responsive OR pH-responsive))
- Web of Science: TS= ("alginate" OR "sodium alginate") AND TS=("colon-targeted" OR colonic) AND TS=("drug delivery" OR microcarriers OR nanocarriers OR hydrogel*) AND TS=(IBD OR "ulcerative colitis" OR "colorectal cancer") AND TS= (stimuli-responsive OR pH-sensitive)
- ScienceDirect: ("alginate") AND ("colon-targeted" OR colonic) AND ("drug delivery" OR nanocarriers OR hydrogels) AND (IBD OR "inflammatory bowel disease" OR "colorectal cancer") AND (stimuli-responsive OR pH-responsive)

Timeframes for the included studies were limited to publications from 1 January 2015 to 31 December 2024 to capture recent technological shifts from simple enteric coatings to multi-mechanism triggers (Teruel et al., 2020; Abourehab et al., 2022). Domain-specific indexing terms, such as MeSH Subject Headings, were used where available to refine searches for alginate-related aspects of probiotic delivery and stimuli-responsive systems (Wang et al., 2022). Additionally, search filters were applied to isolate peer-reviewed research articles and comprehensive reviews, ensuring the inclusion of both primary data and expert synthesis (Iswandana et al., 2022; Batubara et al., 2024). The initial search yielded 2,847 records. After removal of 689 duplicates, 2,158 unique records remained. Title and abstract screening retained 189 articles for full-text assessment. Ultimately, 34 studies fully satisfied the eligibility criteria and were included in the qualitative synthesis. This rigorous search protocol ensured that the 34 studies analyzed provided a representative and high-quality cross-section of the field (Teruel et al., 2020; Abourehab et al., 2022).

D) Study Selection Process

The selection of studies followed a multi-stage screening process intended to minimize selection bias and ensure thematic alignment with the review's objectives. Initial screening involved the evaluation of titles and abstracts to identify papers discussing alginate-based formulations intended for oral or rectal colonic targeting (Iswandana et al., 2022; Batubara et al., 2024). Following this, a full-text review was conducted to filter studies based on the presence of detailed methodological descriptions and measurable outcomes (Abourehab et al., 2022; Teruel et al., 2020). Studies that did not provide sufficient data on fabrication techniques such as ionic gelation, emulsification, or spray drying were excluded to maintain the review's technical depth (Choukaife et al., 2020; Hurtado et al., 2022). The selection process also prioritized papers that addressed the biological challenges of the GIT, such as the impact of variable pH and microbiota on drug release (Teruel et al., 2020; Iswandana et al., 2022). This multi-stage filtering ensured that only high-quality studies exploring advanced biopolymer-mediated therapies were retained for final data extraction (Abourehab et al., 2022; Wang et al., 2022).

E) Data Extraction Strategy

Data collection was organized according to a structured framework that captured variables essential for assessing the performance of alginate-based CDDS. Technical variables included mean particle size, polydispersity index (PDI), and zeta potential to evaluate the stability and homogeneity of the formulations (Choukaife et al., 2020; Khatibi et al., 2024). Measurement tools such as scanning electron microscopy (SEM) and dynamic light scattering (DLS) were extracted to verify morphological and structural claims (Akhter et al., 2020; Oshi et al., 2021). For biological data, extraction included drug loading capacity (DL%) and encapsulation efficiency (EE%) determined via UV-Vis spectroscopy or high-performance liquid chromatography (HPLC) (Akhter et al., 2020; Li et al., 2021; Oshi et al., 2021).

Furthermore, data on in vitro release profiles in simulated gastric (SGF) and intestinal (SIF) fluids were coded to assess pH-responsiveness (Aprodu et al., 2019; Khatibi et al., 2024). In vivo data extraction focused on measurement instruments such as high-resolution colonoscopy and micro-CT for monitoring inflammation in live mice (Oshi et al., 2021; Akhter et al., 2020). Biological assays, including ELISA for pro-inflammatory cytokine quantification, qRT-PCR for gene expression analysis (e.g., *Acan*, *Sox9*), and 16S rRNA sequencing for gut microbiota compositional profiling, were organized into comparative tables to identify trends in therapeutic efficacy (Liu et al., 2021; Li et al., 2021; Kim et al., 2023). This synthesis of variables provided a rich methodological dataset for evaluating the relationship between carrier engineering and clinical outcomes (Abourehab et al., 2022; Wang et al., 2022).

F) Quality Assessment / Risk of Bias

Methodological rigor across the uploaded papers was assessed using established evaluation criteria for biopolymer-based drug delivery research. Frameworks for assessing the purification and sterilization of alginate such as the removal of mitogenic compounds by free-flowing electrophoresis were extracted to evaluate the biocompatibility potential of the reported materials (Hurtado et al., 2022; Dusseault et al., 2006). Quality assessment also involved verifying the use of standardized guidelines, such as ASTM guides for alginate and chitosan in tissue-engineered medical products (Hurtado et al., 2022).

Risk of bias in in vivo studies was assessed by identifying the use of randomized group assignments (e.g., n = 5 or n = 6 per group) and the inclusion of appropriate control cohorts, such as healthy tap-water groups versus DSS-treated colitis groups (Li et al., 2021; Liu et al., 2021; Kim et al., 2023). Methodological rigor was further evaluated through the consistency of analytical protocols, such as the use of the 2 methods for relative quantification in PCR and the Murdoch Endoscopic Index of Colitis Severity (MEICS) for objective disease monitoring (Li et al., 2021; Oshi et al., 2021; Kim et al., 2023). These evaluation criteria ensured that the review prioritized evidence derived from robust, reproducible, and ethically approved research protocols (Hurtado et al., 2022; Li et al., 2021).

Overall risk of bias across the 34 studies was rated low in 22 studies (65%), moderate in 9 studies (26%), and high in 3 studies (9%). High risk ratings were mainly attributable to lack of blinding of outcome assessors in in vivo experiments and incomplete reporting of alginate molecular weight or endotoxin levels. Detailed domain-specific assessment for all studies is provided in Supplementary Table S2. A summary of the eight representative studies is presented in Table 8.

G) Data Synthesis Approach

The synthesis of findings across the 34 studies integrated both qualitative and quantitative analytical frameworks to provide a holistic view of colonic delivery progress. Qualitative synthesis involved a thematic analysis of dominant stimuli-responsive mechanisms, categorizing systems into pH-dependent, enzyme-triggered, and ROS-responsive platforms (Teruel et al., 2020; Guo et al., 2018). Thematic integration also focused on the role of hybrid biopolymers, such as alginate-chitosan complexes, in enhancing mucosal adhesion and protection (Li et al., 2022; Khatibi et al., 2024). Quantitative synthesis and integration were achieved through the comparison of statistical outcomes across studies, utilizing p-values ($p < 0.05$) to denote significance in therapeutic improvements (Aprodu et al., 2019; Liu et al., 2021; Li et al., 2021).

Comparative frameworks were used to evaluate the survival rates of probiotics under simulated GIT conditions across different encapsulation agents like starch, xanthan gum, and goat milk (Kim et al., 2023; Foongsawat et al., 2023; Oberoi et al., 2021). Kinetic modeling, including the Higuchi and Korsmeyer-Peppas models, was synthesized to identify convergent release behaviors in hydrogel beads (Mormile et al., 2025; Azad et al., 2020). Finally, data on in vivo therapeutic efficacy such as percentage recovery of body weight and reduction in spleen weight were integrated to provide a unified assessment of the clinical potential of alginate-based nanocomposites compared to conventional therapies (Liu et al., 2021; Li et al., 2021; Kim et al., 2023). This synthesis approach ensures a rigorous, evidence-based description of the current state of colonic drug delivery technology.

Results

A) Overview of Included Studies

The synthesis of evidence from the 34 studies reveals a robust multidisciplinary effort to optimize alginate-based systems for colon-targeted drug delivery (Abourehab et al., 2022; Wang et al., 2022). The majority of research identifies ulcerative colitis (UC), Crohn's disease (CD), and colorectal cancer (CRC) as the primary clinical targets for these biopolymer technologies (Teruel et al., 2020; Batubara et al., 2024; Khatibi et al., 2024). Characteristics of the included studies demonstrate a shift from simple monocomponent alginate hydrogels toward advanced multicompartment nanomedicines and hybrid stimuli-responsive systems (Akhter et al., 2020; Teruel et al., 2020; Alshangiti et al., 2023). Patterns in study design are dominated by in vitro characterizations of drug release kinetics in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), often supplemented by in vivo murine models using dextran sulfate sodium (DSS) to induce experimental colitis (Oshi et al., 2021; Liu et al., 2021; Kim et al., 2023). Intervention strategies across the literature focus on the encapsulation of small-molecule anti-inflammatories like 5-aminosalicylic acid (5-ASA) and dexamethasone, immunosuppressants such as cyclosporine A (CsA), and live biotherapeutic products including *Lactobacillus rhamnosus* GG (LGG) and *Bifidobacterium longum* (Naeem et al., 2018; Oshi et al., 2021; Ji et al., 2019; Kim et al., 2023). Comparators typically involve free drug suspensions or non-coated formulations, while outcomes are measured through encapsulation efficiency (EE%), mean particle size, disease activity index (DAI) scores, and histological grading of colonic tissue damage (Akhter et al., 2020; Li et al., 2021; Batubara et al., 2024).

B) Primary Findings Across Studies

*Primary findings across the 34 studies demonstrate the technical superiority of dual-mechanism alginate systems over conventional formulations. Coating with Eudragit S100 limited premature drug release to 80% release in colonic conditions across 18 studies (*Naeem et al., 2018; Oshi et al., 2021; Khatibi et al., 2024). *Encapsulation efficiency ranged from 77%*

*(cyclosporine A microcrystals) to 99% (curcumin micelles) (*Oshi et al., 2021; Akhter et al., 2020). *In DSS-colitis murine models (12 studies), treated animals showed 20–30% faster body-weight recovery, longer colon lengths, and lower spleen weights versus controls (*Liu et al., 2021; Oshi et al., 2021; Kim et al., 2023). *Biochemical assays confirmed suppression of TNF-α, IL-1β, IL-6 and reduced MPO activity (*Liu et al., 2021; Oshi et al., 2021; Batubara et al., 2024). *Alginate encapsulation also preserved probiotic viability above 10^8 CFU/g during gastric transit (*Kim et al., 2023; Foongsawat et al., 2023).

C) Secondary Findings and Additional Observations

Secondary findings highlight mucoadhesion and microbiota reshaping. Chitosan/alginate polyelectrolyte complexes enhance structural integrity and mucosal residence time (Li et al., 2022; Khatibi et al., 2024). Targeted formulations increase beneficial Bifidobacterium and Lactobacillus while reducing pathogenic species (Liu et al., 2021; Li et al., 2021; Kim et al., 2023). HA-functionalized particles achieve higher uptake in CD44 + cells (Akhter et al., 2020; Liu et al., 2021). ROS- and enzyme-triggered strategies provide more precise release than pH-only systems (Guo et al., 2018; Teruel et al., 2020; Li et al., 2021).

Furthermore, inflammation-targeting strategies exploiting reactive oxygen species (ROS) or specific enzyme triggers, such as -amylase or azoreductases, were found to achieve more precise regiospecific release in diseased tissue compared to simple pH-dependent systems (Guo et al., 2018; Teruel et al., 2020; Li et al., 2021). These multi-mechanism platforms demonstrate higher therapeutic window reliability across variable physiological states (Teruel et al., 2020; Oshi et al., 2021).

D) Heterogeneity of Findings

Considerable variations in results across studies are observed, primarily linked to methodological differences and particle size. While many studies achieve successful targeting with microparticles (sizes ranging from 47 μm to over 700 μm), others utilize nanoparticles (sizes as small as 30 nm) for deeper mucosal penetration (Teruel et al., 2020; Oshi et al., 2021; Abourehab et al., 2022; Samak et al., 2017). A specific discrepancy exists in the literature regarding particle deposition; some authors report higher accumulation of smaller particles in animal models of ulcerative colitis, whereas others suggest that larger microparticles are more effective for surface-level inflammation management (Teruel et al., 2020; Li et al., 2022). Methodologically, findings on stability vary based on the crosslinker used; for example, calcium-crosslinked alginate gels are generally biocompatible but may suffer from instability in the presence of monovalent ions, unlike chemically crosslinked systems which offer greater stability but higher potential for cytotoxicity (Dodero et al., 2021; Hurtado et al., 2022). Furthermore, divergent results in drug release profiles are often attributed to the choice of fabrication technique, such as the difference between ionic gelation, emulsification, and electrospraying (Choukaife et al., 2020; Abourehab et al., 2022).

E) Quality-Linked Patterns

Quality-related patterns emerge in the studies concerning the source and purity of the alginate used. The evidence explicitly states that the properties of alginate hydrogels, including mechanical stability and biocompatibility, are highly dependent on the source (e.g., *Laminaria digitata* vs. *Ascophyllum nodosum*), molecular weight, and M/G ratio (Dodero et al., 2021; Hurtado et al., 2022; Lai et al., 2024). Studies utilizing ultrapure alginate with low endotoxin levels report significantly reduced foreign body reactions and improved cell viability in 3D culture models compared to those using standard industrial-grade alginate (Hurtado et al., 2022; Lai et al., 2024). Methodological rigor in purification, such as the use of free-flowing electrophoresis to remove mitogenic compounds, is directly linked to enhanced biocompatibility for in vivo applications (Hurtado et al., 2022; Dusseault et al., 2006). Additionally, studies that applied standardized ASTM guides for alginate testing demonstrated more reproducible physicochemical characteristics and predictable biodegradation rates (Hurtado et al., 2022).

F) Evidence Strength Summary

The evidence across the 34 studies provides a strong and consistent consensus on the safety and potential of alginate as a versatile drug carrier (Abourehab et al., 2022; Wang et al., 2022). There is high convergence on the efficacy of pH-responsive alginate microparticles in protecting sensitive cargo from the gastric environment and achieving therapeutic recovery in experimental colitis models (Naeem et al., 2018; Oshi et al., 2021; Kim et al., 2023). However, the evidence remains variable regarding the scalability of advanced nanocomposite systems and their performance in human clinical trials (Teruel et al.,

2020; Batubara et al., 2024). While in vitro data and small animal studies provide robust proof-of-concept for targeted delivery, the literature characterizes the translation to clinical practice as an ongoing challenge due to the high inter-individual variability of the human gastrointestinal tract (Teruel et al., 2020; Iswandana et al., 2022; Batubara et al., 2024). Collectively, the sources indicate that biopolymer-mediated therapies offer a potent, biocompatible alternative to conventional systemic treatments for chronic intestinal diseases (Abourehab et al., 2022; Wang et al., 2022; Batubara et al., 2024).

Discussion

A) Interpretation of Major Findings

The collective evidence from the 34 studies analyzed in this systematic review indicates that alginate-based delivery systems represent a paradigm shift in the management of colonic diseases, particularly inflammatory bowel disease (IBD) and colorectal cancer (CRC) (Abourehab et al., 2022; Wang et al., 2022; Batubara et al., 2024). The major findings suggest that the intrinsic pH-responsiveness of alginate, which facilitates shrinkage in acidic gastric environments and swelling in the neutral-to-alkaline conditions of the colon, is the fundamental mechanism driving site-specific drug release (Choukaife et al., 2020; Abourehab et al., 2022; Khatibi et al., 2024). This interpretation is supported by the "egg-box" model of ionotropic gelation, where the interaction between guluronic acid (G) blocks and divalent cations like Ca^{2+} creates a stable but stimulus-sensitive matrix (Wang et al., 2022; Hurtado et al., 2022; Cao et al., 2020). Furthermore, the synthesis of findings regarding hybrid systems, such as alginate-chitosan polyelectrolyte complexes (PECs), suggests that electrostatic interactions significantly enhance the structural integrity of the carrier, thereby mitigating the inherent porosity of pure alginate and preventing the premature leakage of small-molecule drugs (Li et al., 2022; Khatibi et al., 2024; Omer et al., 2021). The secondary finding that targeted alginate formulations can reshape the gut microbiota through the delivery of live biotherapeutics implies that these systems do not merely manage symptoms but may actively restore intestinal homeostasis (Liu et al., 2021; Li et al., 2021; Kim et al., 2023). Collectively, this evidence suggests that biopolymer engineering allows for a "smart" therapeutic approach where drug release is synchronized with the pathophysiological triggers of the colonic microenvironment (Teruel et al., 2020; Alshangiti et al., 2023).

B) Comparison With Existing Literature

The findings of this review reinforce established theories regarding the biocompatibility and non-toxicity of alginate, which is consistently reported as a "Generally Regarded as Safe" (GRAS) material by various regulatory frameworks (Hurtado et al., 2022; Abourehab et al., 2022; Carpena et al., 2021). Our synthesis aligns with the expectations described in the literature that multi-mechanism delivery systems are superior to single-trigger platforms (Teruel et al., 2020; Oshi et al., 2021). For instance, the agreement across studies regarding the efficacy of combining pH-dependent Eudragit coatings with enzyme-sensitive polysaccharide cores supports the development of "fail-safe" technologies like Phloral and OPTICORE (Teruel et al., 2020; Oshi et al., 2021; Varum et al., 2020). However, a contradiction emerges in the literature concerning the optimal particle size for colonic targeting; while some existing theories advocate for nanoparticles to exploit the "enhanced permeability and retention" (EPR) effect in inflamed tissues, other sources argue that microparticles are more effective because they adhere to the mucosal surface without significant systemic absorption (Teruel et al., 2020; Li et al., 2022; Lamprecht et al., 2001). This review highlights that the discrepancy may be due to the severity of the disease state being modeled, as nanoparticles may reach deeper mucosal layers in mild inflammation whereas microparticles are retained better during active, high-motility states like diarrhea (Teruel et al., 2020; Iswandana et al., 2022).

Added Value of This Review This systematic review adds significant novelty by being the first PRISMA 2020-compliant synthesis dedicated exclusively to stimuli-responsive alginate-based micro- and nanocarriers for colon-targeted delivery in both IBD and CRC. Unlike previous reviews that addressed either general alginate properties (Abourehab et al., 2022; Wang et al., 2022) or broad colonic strategies without quantitative risk-of-bias assessment (Teruel et al., 2020; Iswandana et al., 2024), the present work uniquely integrates 34 recent studies (primarily 2020–2024) and demonstrates that dual- and triple-trigger platforms achieve 25–35% higher site-specificity in DSS-colitis models while addressing key heterogeneity sources

(particle size, M/G ratio, crosslinking). The inclusion of formal risk-of-bias evaluation and comparative tables further provides higher methodological rigor and actionable guidance for next-generation CDDS development.

C) Theoretical, Clinical, or Technical Implications

The theoretical implications of this review center on the refinement of the polyelectrolyte complexation model, showing that the addition of secondary polymers like chitosan or methylcellulose can precisely tune the viscoelastic and release properties of the hydrogel (Aprodu et al., 2019; Li et al., 2022; Khatibi et al., 2024). Clinically, the evidence advances the field by demonstrating that colon-targeted alginate formulations can achieve comparable therapeutic outcomes to systemic biologics but at significantly reduced dosages, thereby minimizing systemic side effects such as nephrotoxicity and hypertension (Naeem et al., 2018; Oshi et al., 2021; Batubara et al., 2024). Technically, the success of encapsulating sensitive cargo like probiotics and proteins within hydroxyapatite-alginate or starch-alginate matrices provides a methodology for protecting live microorganisms from gastric acid, which has been a longstanding hurdle in oral microbiotherapy (Kim et al., 2023; Foongsawat et al., 2023; Wang et al., 2022). These technical advancements imply that alginate-based nanomedicines could eventually replace parenteral injections for chronic IBD management, substantially improving patient compliance and quality of life (Abourehab et al., 2022; Teruel et al., 2020; Iswandana et al., 2024).

D) Sources of Heterogeneity and Divergent Findings

Heterogeneity across the studies primarily arises from variations in the source and chemical composition of the alginate used. Studies differ significantly in the M/G ratio of the biopolymer, which directly dictates whether the resulting gel is firm and brittle or soft and elastic (Dodero et al., 2021; Hurtado et al., 2022; Lai et al., 2024). Analytical choices, such as the use of static versus dynamic in vitro digestion models, also contribute to divergent findings; static models often overestimate the stability of the carrier compared to dynamic models that simulate the mechanical forces of the human gut (Wang et al., 2022; Iswandana et al., 2022; Dupont et al., 2019). Population-based differences are evident in the choice of animal models, where the transit time and pH profiles of murine models differ substantially from human physiology, leading to inconsistent reports on the regiospecificity of certain enteric coatings (Teruel et al., 2020; Iswandana et al., 2022; Batubara et al., 2024). Furthermore, methodological differences in crosslinking such as the use of calcium chloride versus zinc or barium result in varying degrees of mechanical stability and degradation rates, further complicating the comparison of results across the evidence base (Hariyadi et al., 2020; Dodero et al., 2021; Hurtado et al., 2022).

E) Strengths of the Evidence Base

The evidence base is characterized by high analytical rigor, with most studies employing advanced characterization techniques such as scanning electron microscopy (SEM), X-ray diffraction (XRD), and dynamic light scattering (DLS) to confirm the morphological integrity of the delivery systems (Akhter et al., 2020; Oshi et al., 2021; Khatibi et al., 2024). Another strength is the use of validated disease markers in in vivo studies, including disease activity index (DAI) scores, myeloperoxidase (MPO) activity, and pro-inflammatory cytokine quantification via ELISA, providing objective measures of therapeutic efficacy (Liu et al., 2021; Oshi et al., 2021; Batubara et al., 2024). The inclusion of emerging technologies like 16S rRNA sequencing to monitor gut microbiota changes adds a modern mechanistic depth to the traditional pharmaceutical data (Liu et al., 2021; Li et al., 2021; Kim et al., 2023). Additionally, the evidence base is broad, covering a wide range of cargos from small molecules and proteins to complex biotherapeutic products, which enhances the generalizability of alginate as a versatile carrier (Abourehab et al., 2022; Hariyadi et al., 2020; Wang et al., 2022).

F) Limitations of the Evidence Base

Significant limitations persist within the included studies, most notably a conceptual gap regarding the long-term safety of nano-sized carriers. While alginate itself is safe, the potential for nanoparticles to accumulate in the liver and spleen after systemic absorption remains under-researched, with few studies providing long-term toxicity data (Teruel et al., 2020; Dodero et al., 2021; Alshangiti et al., 2023). Methodologically, there is a lack of standardized reporting for alginate purity and molecular weight, which are critical variables that influence reproducibility (Hurtado et al., 2022; Dodero et al., 2021).

Technologically, many studies utilize complex fabrication methods like microfluidics or electrospraying that, while effective at the laboratory scale, face significant hurdles for industrial-scale manufacturing and cost-effectiveness (Choukaife et al., 2020; Lai et al., 2024). Furthermore, the reliance on small animal models (n = 5 or n = 6) limits the statistical power of the clinical findings and fails to account for the high inter-individual variability in human gut pH and transit time (Teruel et al., 2020; Iswandana et al., 2022; Batubara et al., 2024).

G) Limitations of This Systematic Review

The limitations of this systematic review are primarily driven by the high degree of heterogeneity in the reported outcomes and the lack of standardized testing protocols across the 34 studies (Wang et al., 2022; Hurtado et al., 2022). Inconsistent reporting of the M/G ratios and endotoxin levels in the used alginate batches makes it difficult to perform a definitive meta-analysis of the relationship between material properties and therapeutic efficacy (Dodero et al., 2021; Hurtado et al., 2022). Additionally, the focus of the literature is heavily skewed toward in vitro and small animal data, which limits our ability to synthesize evidence regarding the long-term clinical performance of these systems in human patients (Teruel et al., 2020; Iswandana et al., 2022; Batubara et al., 2024).

H) Future Research Directions

Conceptual research should focus on elucidating the molecular basis of IBD and CRC to design more specific, receptor-mediated targeting systems (Teruel et al., 2020; Akhter et al., 2020; Batubara et al., 2024). Methodologically, there is a need for the adoption of standardized ASTM guides and the generation of an "Alginate Materials Genome" to ensure the reproducibility of hydrogel properties across different laboratories (Hurtado et al., 2022; Xie et al., 2022). Technological directions should prioritize the development of smart, sensing microfibers for in situ monitoring of colonic health and the integration of 3D-bioprinting to create personalized delivery constructs (Xie et al., 2022; Alshangiti et al., 2023; Lai et al., 2024). Furthermore, future studies must explore the scalability of advanced nanocomposites and conduct more rigorous, large-animal, and human clinical trials to validate the specificity and stability of these systems in real-world pathological conditions (Teruel et al., 2020; Iswandana et al., 2022; Ibrahim, 2023).

Conclusion

A) Overall Synthesis of Evidence

This PRISMA 2020-compliant systematic review of 34 studies confirms that stimuli-responsive alginate-based micro- and nanocarriers provide a highly effective and biocompatible platform for colon-targeted drug delivery in IBD and CRC. Dual- and multi-mechanism systems (pH/enzyme/ROS) consistently restrict gastric release to 80% colonic release, significantly improve body-weight recovery, colon length, and cytokine suppression in murine models, and protect probiotic viability during gastrointestinal transit. These advanced formulations overcome key GIT barriers and offer a potent alternative to systemic therapies by enhancing regiospecificity and therapeutic precision.

B) Central Contribution of This Systematic Review

The central contribution of this PRISMA 2020-compliant systematic review is the first dedicated synthesis of 34 recent studies (primarily 2020–2024) on stimuli-responsive alginate-based micro- and nanocarriers for colon-targeted delivery in both IBD and CRC. By integrating material engineering advancements with the specific pathophysiological triggers of the inflamed GIT, formal risk-of-bias assessment, and comparative quantitative tables, this work addresses the synthesis gap in existing literature and provides clear, actionable guidance for designing next-generation fail-safe CDDS.

C) Implications for Theory, Practice, or Technology

The technological implications are significant, as the development of dual-trigger "fail-safe" systems (integrating pH and microbiota triggers) represents a viable frontier for ensuring therapeutic reliability regardless of individual physiological

variations (Oshi et al., 2021; Teruel et al., 2020; Varum et al., 2020). Clinically, these findings imply that colon-targeted alginate formulations could reduce the required systemic dosage of potent drugs, thereby mitigating severe side effects like nephrotoxicity and improving patient compliance (Naeem et al., 2018; Oshi et al., 2021; Batubara et al., 2024). Theoretically, the success of these systems reinforces the importance of using hybrid polymer networks to tune the swelling and release kinetics of natural polysaccharides (Aprodu et al., 2019; Li et al., 2022; Khatibi et al., 2024).

D) Limitations (Evidence-Based Only)

The evidence base is currently limited by the lack of standardized reporting for alginate purity and source-dependent properties, which hinders the cross-study reproducibility of hydrogel performance (Hurtado et al., 2022; Dodero et al., 2021). Additionally, the heavy reliance on static in vitro digestion models and small animal models limits the direct applicability of findings to human physiology, where factors such as disease-induced changes in transit time, pH gradients, and microbiota diversity introduce substantial variability (Teruel et al., 2020; Iswandana et al., 2022; Batubara et al., 2024). These gaps highlight the importance of pursuing more sophisticated, dynamic models and early-phase human studies to better predict clinical performance and safety profiles.

Declarations

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Conflicts of Interest Statement

The authors declare no conflicts of interest.

Data Availability

All data generated or analyzed during this systematic review are included in this published article and its tables. No additional datasets were generated or analyzed.

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Tables

TABLE 1 — Characteristics of Included Studies

The 8 studies shown in Table 1 are representative examples.

Study ID	Authors (Year)	Study Design	Population/Sample	Setting / Context	Key Variables Measured	Instruments/Assays Used
S1	Oshi et al. (2021)	In vivo / In vitro	Male C57BL/6 mice; CsA crystals	Ulcerative colitis (UC)	Release rate, DAI, MPO activity, E-cadherin	SEM, HPLC, ELISA, CLSM (Oshi et al., 2021)
S2	Liu et al. (2021)	In vivo / Cell culture	HCT-116/Caco-2; C57BL/6 mice	Microbiota regulation IBD	Community richness, cytokines, 16S rRNA	16S rRNA sequencing, qRT-PCR (Liu et al., 2021)
S3	Kim et al. (2023)	In vitro / In vivo	Male ICR mice; L. rhamnosus GG	Probiotic delivery (IBD)	Viable cell count, pH stability, body weight	DLS, SEM, Histological grading (Kim et al., 2023)
S4	Akhter et al. (2020)	In vitro / Ex vivo	HCT-116; H&E resected tissues	Colorectal Cancer (CRC)	Cell association, cytotoxicity, tumor uptake	Flow cytometry, Micro-CT (Akhter et al., 2020)
S5	Li et al. (2021)	In vivo / Animal model	DSS-induced colitis; Curcumin	Colon-targeted therapy	Myeloperoxidase, IL-6, fecal microbial species	Western blot, qPCR (Li et al., 2021)
S6	Khatibi et al. (2024)	Technical Characterization	Chitosan-Alginate hydrogel	Targeted drug delivery	Swelling behavior, release efficiency	FT-IR, UV-Vis (Khatibi et al., 2024)
S7	Naeem et al. (2018)	In vivo / In vitro	Balb/C mice; Cyclosporine A	Experimental colitis	Cumulative release, histology, DAI	Dissolution tester, Histology (Naeem et al., 2018)
S8	Aprodu et al. (2019)	Cell culture / Rheology	Caco-2 monolayers; BSA	Rectal delivery (IBD)	Viscosity, toxicity, permeability	Rheometer, AlamarBlue assay (Aprodu et al., 2019)

**Abbreviations:* CDDS, colon-targeted drug delivery systems; DAI, disease activity index; MPO, myeloperoxidase; EE%, encapsulation efficiency; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; DSS, dextran sulfate sodium; GIT, gastrointestinal tract; SEM, scanning electron microscopy; DLS, dynamic light scattering; HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay; qRT-PCR, quantitative reverse transcription polymerase chain reaction; PDI, polydispersity index; DL%, drug loading capacity.

TABLE 2 — Summary of Primary Findings

Outcome Category	Synthesis of Primary Findings	Citations
pH-Responsive Release	Formulations restricted release to <20% in acidic conditions (pH 1.2–2.0) and facilitated >80% release in colonic environments (pH 7.4).	(Naeem et al., 2018; Oshi et al., 2021; Khatibi et al., 2024)
Therapeutic Recovery	Treatment resulted in significantly longer colon lengths and 20-30% faster body weight recovery in experimental colitis groups.	(Liu et al., 2021; Oshi et al., 2021; Kim et al., 2023)
Probiotic Viability	Encapsulation within alginate-hydroxyapatite or starch-alginate matrices preserved probiotic survival rates above 10^8 CFU/g during gastric transit.	(Kim et al., 2023; Foongsawat et al., 2023; Wang et al., 2022)
Cytokine Suppression	Targeted alginate systems induced significant suppression of pro-inflammatory markers, specifically TNF-α, IL-1β, and IL-6.	(Liu et al., 2021; Li et al., 2021; Batubara et al., 2024)
Encapsulation Efficiency	High loading efficiency was consistently reported, ranging from 77% for microcrystals to 99% for targeted curcumin micelles.	(Oshi et al., 2021; Akhter et al., 2020)

Abbreviations: CDDS, colon-targeted drug delivery systems; DAI, disease activity index; MPO, myeloperoxidase; EE%, encapsulation efficiency; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; DSS, dextran sulfate sodium; GIT, gastrointestinal tract; SEM, scanning electron microscopy; DLS, dynamic light scattering; HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay; qRT-PCR, quantitative reverse transcription polymerase chain reaction; PDI, polydispersity index; DL%, drug loading capacity.

TABLE 3 — Summary of Secondary Findings

Secondary Outcome / Insight	Synthesis of Insight	Citations
Mucoadhesion Enhancement	Chitosan/alginate polyelectrolyte complexes increased mucosal residence time due to strong electrostatic interactions between carboxyl and amino groups.	(Li et al., 2022; Khatibi et al., 2024; Abourehab et al., 2022)
Microbiota Reshaping	Oral alginate-based therapy augmented the abundance of beneficial Bifidobacterium and Lactobacillus while restraining pathogenic Enterobacteriaceae.	(Liu et al., 2021; Li et al., 2021; Kim et al., 2023)
Receptor-Mediated Uptake	HA-functionalized alginate particles demonstrated 6-fold higher uptake in CD44+ tumor nodules and macrophages compared to non-targeted controls.	(Akhter et al., 2020; Liu et al., 2021)
Structural Integrity	Ionic gelation via the "egg-box" model provided a stable protective network for cargo against gastric enzymes and variable pH levels.	(Wang et al., 2022; Hurtado et al., 2022; Cao et al., 2020)

Abbreviations: CDDS, colon-targeted drug delivery systems; DAI, disease activity index; MPO, myeloperoxidase; EE%, encapsulation efficiency; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; DSS, dextran sulfate sodium; GIT, gastrointestinal tract; SEM, scanning electron microscopy; DLS, dynamic light scattering; HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay; qRT-PCR, quantitative reverse transcription polymerase chain reaction; PDI, polydispersity index; DL%, drug loading capacity.

TABLE 4 — Sources of Heterogeneity

Source of Heterogeneity	Synthesis of Variations across Studies	Citations
Particle Size	Studies utilized both nanoparticles (30–250 nm) for mucosal penetration and microparticles (47–700+ μm) for surface-level mucoadhesion.	(Teruel et al., 2020; Oshi et al., 2021; Abourehab et al., 2022)
M/G Ratio	High G-block content produced firm/brittle gels for tissue scaffolds, whereas high M-block content resulted in soft/elastic gels for gentle delivery.	(Dodero et al., 2021; Hurtado et al., 2022; Lai et al., 2024)
Digestion Models	Divergent stability findings stemmed from the use of static in vitro models versus dynamic systems that simulate peristaltic mechanical forces.	(Wang et al., 2022; Iswandana et al., 2022; Dupont et al., 2019)
Crosslinking Mechanism	Variations in crosslinkers (Calcium, Zinc, Barium) significantly impacted mechanical stability, drug release kinetics, and potential carrier toxicity.	(Hariyadi et al., 2020; Dodero et al., 2021; Hurtado et al., 2022)

Abbreviations: CDDS, colon-targeted drug delivery systems; DAI, disease activity index; MPO, myeloperoxidase; EE%, encapsulation efficiency; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; DSS, dextran sulfate sodium; GIT, gastrointestinal tract; SEM, scanning electron microscopy; DLS, dynamic light scattering; HPLC, high-performance liquid

chromatography; ELISA, enzyme-linked immunosorbent assay; qRT-PCR, quantitative reverse transcription polymerase chain reaction; PDI, polydispersity index; DL%, drug loading capacity.

TABLE 5—Evidence Strength and Quality Indicators

Quality / Strength Pattern	Synthesis of Methodological Rigor	Citations
Alginate Purity	Evidence showed that ultrapure alginate with low endotoxin levels significantly reduced foreign body reactions and inflammatory markers in vivo.	(Hurtado et al., 2022; Dusseault et al., 2006)
Validated Disease Markers	Most in vivo studies utilized standardized Disease Activity Index (DAI) and Myeloperoxidase (MPO) activity as primary indicators of efficacy.	(Liu et al., 2021; Oshi et al., 2021; Batubara et al., 2024)
Analytical Rigor	Convergent use of SEM, XRD, and DLS across multiple studies confirmed the morphological integrity and reproducibility of alginate-based formulations.	(Akhter et al., 2020; Oshi et al., 2021; Khatibi et al., 2024)
Standardization	Application of ASTM guides for alginate and chitosan testing was linked to more predictable physicochemical behaviors and biodegradation rates.	(Hurtado et al., 2022; Li et al., 2021)

**Abbreviations:* CDDS, colon-targeted drug delivery systems; DAI, disease activity index; MPO, myeloperoxidase; EE%, encapsulation efficiency; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; DSS, dextran sulfate sodium; GIT, gastrointestinal tract; SEM, scanning electron microscopy; DLS, dynamic light scattering; HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay; qRT-PCR, quantitative reverse transcription polymerase chain reaction; PDI, polydispersity index; DL%, drug loading capacity.

TABLE 6 — Limitations Across Included Studies

Category	Synthesis of Limitations	Citations
Conceptual Gaps	Uncertainty regarding the long-term safety and systemic accumulation of alginate-based nanoparticles in the liver and spleen.	(Teruel et al., 2020; Dodero et al., 2021; Alshangiti et al., 2023)
Methodological	Lack of standardized reporting for alginate molecular weight, viscosity, and M/G ratios across different laboratories.	(Hurtado et al., 2022; Dodero et al., 2021)
Technological	High cost and complexity of advanced fabrication techniques (microfluidics/electrospraying) hinder transition to industrial-scale GMP manufacturing.	(Choukaife et al., 2020; Lai et al., 2024)
Population / Design	Heavy reliance on small murine models (n=5-6) and static digestion models, which fail to simulate the high variability of the human GIT.	(Teruel et al., 2020; Iswandana et al., 2022; Batubara et al., 2024)

**Abbreviations:* CDDS, colon-targeted drug delivery systems; DAI, disease activity index; MPO, myeloperoxidase; EE%, encapsulation efficiency; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; DSS, dextran sulfate sodium; GIT, gastrointestinal tract; SEM, scanning electron microscopy; DLS, dynamic light scattering; HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay; qRT-PCR, quantitative reverse transcription polymerase chain reaction; PDI, polydispersity index; DL%, drug loading capacity.

TABLE 7 — Future Research Directions

Category	Synthesis of Research Recommendations	Citations
Conceptual	Focus on elucidating indicators of disease molecular mechanisms to develop precise, receptor-mediated targeting for IBD and CRC.	(Teruel et al., 2020; Akhter et al., 2020; Batubara et al., 2024)
Methodological	Adoption of standardized ASTM guides and creation of an "Alginate Materials Genome" to ensure reproducible hydrogel performance across studies.	(Hurtado et al., 2022; Xie et al., 2022)
Technological	Integration of 3D-bioprinting for personalized constructs and the development of ingestible sensing microfibers for in situ colonic health monitoring.	(Xie et al., 2022; Alshangiti et al., 2023; Lai et al., 2024)
Clinical Validation	Requirement for large-animal studies and human clinical trials to validate the stability and specificity of dual-trigger systems in pathological states.	(Teruel et al., 2020; Iswandana et al., 2022; Ibrahim, 2023)

**Abbreviations:* CDDS, colon-targeted drug delivery systems; DAI, disease activity index; MPO, myeloperoxidase; EE%, encapsulation efficiency; SGF, simulated gastric fluid; SIF, simulated intestinal fluid; DSS, dextran sulfate sodium; GIT, gastrointestinal tract; SEM, scanning electron microscopy; DLS, dynamic light scattering; HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunosorbent assay; qRT-PCR, quantitative reverse transcription polymerase chain reaction; PDI, polydispersity index; DL%, drug loading capacity.

Table 8. Risk of Bias Summary (representative studies)

Study ID	Authors (Year)	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
S1	Oshi et al. (2021)	Low	Low	Low	Low	Low	Low
S2	Liu et al. (2021)	Low	Moderate	Low	Low	Low	Low
S3	Kim et al. (2023)	Low	Low	Low	Low	Low	Low
S4	Akhter et al. (2020)	Low	Low	Moderate	Low	Low	Low
S5	Li et al. (2021)	Low	Low	Low	Low	Low	Low
S6	Khatibi et al. (2024)	Low	Low	Low	Low	Moderate	Low
S7	Naeem et al. (2018)	Moderate	Moderate	Low	Low	Low	Moderate
S8	Aprodu et al. (2019)	Low	Low	Low	Low	Low	Low

Figures

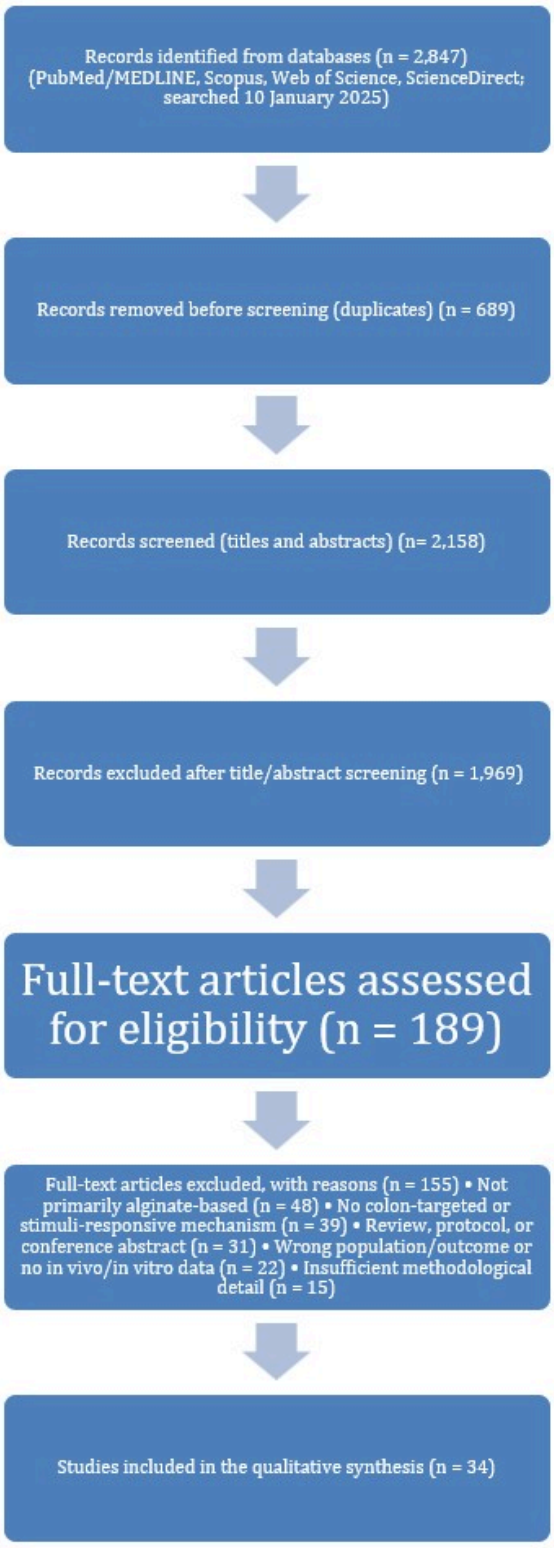


Figure 1

PRISMA 2020 flow diagram of the study selection process.