

Multiparticulate Pellet Systems and Extended-Release Coating Strategies for Targeted Therapy in Ulcerative Colitis: A Review

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Abstract

Ulcerative colitis (UC) is a chronic, recurring inflammatory bowel disease confined to the colon and rectum's mucosal lining. A key formulation challenge is delivering therapeutic drug concentrations directly to the colonic mucosa while preventing premature release in the upper gastrointestinal tract. Multiparticulate pellet systems offer significant biopharmaceutical advantages over single-unit monolithic dosage forms, including consistent gastrointestinal transit, a lower risk of dose dumping, and predictable dispersion within the colon. This review explores the physiological changes in the UC gastrointestinal tract, production techniques for functional multiparticulates (like extrusion-spheronization and fluid-bed coating), and targeted extended-release coating mechanisms. It emphasizes pH-dependent, time-dependent, microbial enzyme-triggered, and hybrid dual-mechanism coating platforms. Preclinical and clinical performance, regulatory considerations, and emerging nano-in-micro multiparticulate platforms are highlighted to outline future clinical applications.

Keywords: Ulcerative colitis; Multiparticulates; Pellets; Extrusion-spheronization; Extended-release coating; Colon-targeted drug delivery; Inflammatory bowel disease.

1. Introduction

1.1 Pathophysiology of Ulcerative Colitis and Current Clinical Gaps

Ulcerative colitis (UC) is a chronic inflammatory condition marked by continuous, confluent ulcerations of the colonic mucosa, starting from the rectum and extending proximally.¹ Clinically, it presents with bloody diarrhea, severe abdominal cramping, tenesmus, and weight loss, often alternating between remission and relapse.² Current treatments include oral anti-inflammatory agents like 5-aminosalicylic acid (mesalamine), corticosteroids, immunosuppressants, and targeted biologics.³ However, conventional oral monolithic formulations face significant pharmacokinetic issues, such as absorption in the stomach or systemic exposure before reaching the inflamed colonic mucosa.⁴ High systemic absorption can lead to dose-dependent adverse effects, including kidney damage, increased infection risk, and suppression of the hypothalamic-pituitary-adrenal axis, while leaving the colonic lesions inadequately treated.⁵

1.2 Rationale for Colonic Targeting

Directly delivering therapeutic agents to the inflamed colonic epithelium enhances local tissue exposure while minimizing off-target systemic distribution.⁶ Achieving predictable colonic targeting necessitates

an oral dosage form that can withstand the stomach's acidic environment and resist degradation in the enzyme-rich upper small intestine.⁷ Delivery systems must be engineered to release active compounds precisely at the ileocecal junction or throughout the colonic lumen.⁸

1.3 Advantages of Multiparticulate Pellet Dosage Forms

Oral multiparticulate pellet formulations offer distinct pharmacokinetic and physiological benefits over single-unit tablets or capsules.^{9,10} Due to their small size (typically 0.5 to 1.5 mm), individual pellets pass gradually and continuously through the pyloric sphincter into the duodenum, independent of phase III migrating motor complexes.¹¹ Multiparticulates distribute widely across the colonic mucosal surface, preventing localized drug accumulation and subsequent irritation.¹¹ Furthermore, dividing the total drug dose among numerous coated subunits significantly reduces the risk of severe dose dumping due to mechanical coating failure.¹²

2. Gastrointestinal Physiology and Pathological Variations in UC

2.1 Luminal pH Shifts Along the Gastrointestinal Axis

The healthy gastrointestinal tract exhibits a distinct pH gradient, moving from highly acidic conditions in the stomach (pH 1.0–2.5) to neutral-to-alkaline levels in the terminal ileum (pH 7.0–7.5), and then slightly declining to pH 6.0–6.5 in the cecum due to bacterial fermentation.¹³ In active UC, mucosal inflammation and impaired bicarbonate secretion lead to significantly more acidic conditions in the colonic lumen, sometimes dropping below pH 5.5.¹⁴ Formulations relying solely on standard pH-triggered dissolution thresholds may not dissolve completely in inflamed segments, resulting in the excretion of intact units in feces.¹⁵

2.2 Alterations in Motility and Transit Times

Small intestinal transit time is relatively consistent among individuals (approximately 3 to 4 hours), whereas colonic transit time varies considerably under normal conditions (20 to 48 hours).¹⁶ During active UC flares, significantly increased propulsive colonic motor activity drastically shortens residence time, often reducing it to less than 6 hours.¹⁷ Rapid transit, coupled with voluminous diarrheal fluid, requires controlled-release multiparticulates to hydrate and release their drug load quickly upon reaching the target segment.¹⁸

2.3 The Colonic Mucus Barrier and Dysbiosis

In healthy individuals, the colonic mucosa is protected by a continuous, layered mucus barrier composed of mucin polymers (primarily MUC2), which maintains physical separation between the commensal microflora and the underlying lamina propria.¹⁹ In UC patients, defective goblet cell synthesis results in an attenuated, discontinuous mucus layer with reduced cross-linking density.²⁰ Microbial diversity is also decreased; there are marked decreases in obligate anaerobic species such as *Bacteroides* and *Faecalibacterium prausnitzii*, and short-chain fatty acid metabolites, as well as reductions in bacterial azoreductases and polysaccharidases.²¹

3. Engineering and Fabrication of Core Pellets

3.1 Extrusion-Spheronization

Extrusion-spheronization is considered to be the standard wet-granulation technique for the manufacture of highly spherical, mechanically robust pellet cores with a narrow particle-size distribution.²² The method consists of dry blending the active ingredients with functional binders (primarily microcrystalline cellulose), followed by uniform wet massing, followed by continuous axial or radial screw extrusion and

friction rounding on a spinning grooved friction plate.²³ The resulting pellets are characterized by a high bulk density, low surface friability and excellent core sphericity, all critical prerequisites for applying defect-free functional polymer films.²⁴

3.2 Solution, Suspension, and Powder Layering

Drug layering onto inert nonpareil seed cores, typically composed of microcrystalline cellulose or sugar spheres, by fluidized-bed techniques is another alternative method for multiparticulate assembly.²⁵ The active ingredients are dissolved or suspended together with film-forming polymers and atomized from bottom-spray Wurster nozzles onto agitated starter cores under controlled thermal conditions.²⁶ This approach is particularly suitable for potent or thermally sensitive drugs that require very tight control of layer thickness and drug loading uniformity.²⁷ Table 1 compares these two techniques with hot-melt extrusion (HME) in terms of excipients, drug loading, advantages and limitations.

Table 1: Comparison of Core Pellet Fabrication Techniques

Technique	Common Starters / Excipients	Drug Loading	Key Advantage	Main Limitation
Extrusion-Spheronization	MCC, water, PVP	High (85%)	High mechanical strength and density	Multi-step process; sensitive to moisture
Fluid-Bed Layering (Wurster)	Sugar or MCC starter cores, HPMC	Moderate (10–50%)	Excellent batch uniformity and sphericity	Longer run times; risk of nozzle clogging
Hot-Melt Extrusion (HME)	Thermoplastic polymers, plasticizers	Moderate (30–60%)	Solvent-free; enhances poorly soluble APIs	Thermal stress; unsuitable for heat-sensitive drugs

4. Extended-Release and Targeted Coating Strategies

The overall strategy for colonic targeting of coated multiparticulates, from gastric transit to dual-trigger release at the inflamed colon, is illustrated in Figure 1. The individual coating platforms are discussed in Sections 4.1–4.4 and compared in Table 2.

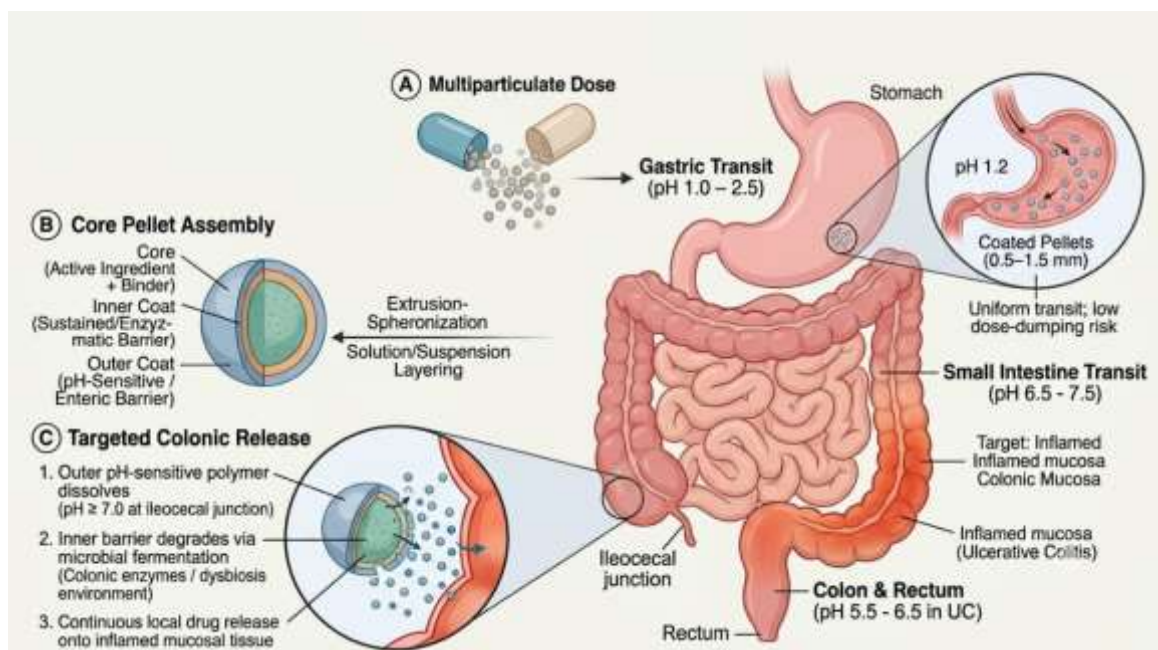


Figure 1. Anatomical transit and dual-trigger targeted release of oral multiparticulate pellets in ulcerative colitis. The journey of the multiparticulate dose (A) through the gastric ($\text{pH} 1.0\text{--}2.5$) and small intestinal environments to reach the diseased colon. View of the Core Pellet Assembly (B) fabricated via extrusion-spheronization or layering, illustrating its multi-barrier coating. Zoom-in of the Targeted Colonic Release (C) depicts the sequential dissolution of the outer pH-sensitive polymer at the ileocecal junction followed by microbiome-triggered degradation of the inner coat, facilitating continuous local drug release onto the inflamed colonic mucosa ($\text{pH} 5.5\text{--}6.5$).

4.1 pH-Dependent Enteric and Colonic Polymers

pH responsive coatings exploit the physiological gradient of luminal pH from the stomach to the distal ileum by utilizing synthetic polymethacrylate copolymers.²⁸ Copolymers of polymethacrylic acid and methyl methacrylate bearing free carboxylic acid groups (methacrylic acid-methyl methacrylate copolymer 1:2, commercially designated as Eudragit® S100), are unionized and insoluble in acidic media but dissolve in the intestinal lumen at a $\text{pH} > 7.0$.²⁹ Given that the distal colonic lumen pH often falls below 6.5 during UC flares, formulators often blend such polymers with Eudragit® L100 (dissolved at $\text{pH} \geq 6.0$) or utilize poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) dispersion (Eudragit® FS 30D, dissolved at $\text{pH} \geq 7.0$ with higher film flexibility) to manipulate the release threshold.³⁰

4.2 Time-Dependent Sustained-Release Systems

Time-controlled multiparticulate devices exploit water-insoluble polymers with pH-independent swelling and diffusion properties to delay drug release.^{31,32} Water-insoluble, hydrophobic polymers such as ethylcellulose plasticized with hydrophobic agents like triethyl citrate or dibutyl sebacate are employed to fabricate strong diffusion limiting membrane coats over active cores.³³ Hydrophilic channeling agents (hypromellose or polyethylene glycol) are physically mixed along with ethylcellulose in the membrane solution; upon exposure to aqueous media, the channeling agents dissolve to generate water-filled pores that enable a sustained, diffusion-controlled drug release mechanism.³⁴

4.3 Microbiome-Triggered and Biodegradable Polymers

Microbiome-responsive systems employ naturally-occurring polysaccharides that are resistant to hydrolysis or enzymatic digestion in the human upper gastrointestinal tract yet biodegrade in response to

colonic microflora.³⁵ The biopolymer chains of amylose, pectin, guar gum, inulin and chitosan are subjected to enzymatic degradation through glycosidases, xylanases and pectinases secreted by the microbial consortium inhabiting the cecal and colonic lumen.³⁶ However, being hydrophilic polysaccharides, rapid swelling in aqueous media in the upper gastrointestinal tract can result in premature leaching. To circumvent this, such hydrophilic polymers are often cross-linked with metal ions (zinc pectinate) or blended with ethylcellulose to prepare composite membranes that remain intact in the upper gastrointestinal tract and degrade upon reaching the cecum.³⁷

4.4 Dual and Multi-Triggered Hybrid Coating Systems

In order to overcome the physiological unpredictability of UC (such as altered acid pH profile or dysbiosis), formulators have employed dual mechanism-based coating technologies.^{38,39} A combination of an outer pH-responsive polymer coat (Eudragit® S100) and an inner water-insoluble carbohydrate polymer matrix (ethylcellulose blended with glassy amylose) is a popular strategy that has been employed.⁴⁰ While the outer polymer coat prevents premature swelling in the stomach and small intestine, the inner composite matrix enzymatically degrades or dissolves in the cecum and ascending colon after the dosage form reaches the distal ileum.⁴⁰ The key polymers, trigger mechanisms, advantages and limitations of the four platforms are summarised in Table 2.

Table 2: Comparative Summary of Extended-Release and Targeted Coating Strategies for Colonic Drug Delivery in Ulcerative Colitis

Coating Platform	Key Polymeric Excipients	Primary Trigger Mechanism	Key Advantages	Formulation Limitations in Active UC
pH-Dependent	Eudragit® S100, L100, FS 30D	Luminal pH elevation (pH $\geq$ 6.0–7.0)	High manufacturing throughput; well-defined regulatory history	Incomplete drug dissolution caused by acidic pH drops (pH < 6.0) in inflamed colonic mucosa
Time-Dependent	Ethylcellulose + HPMC, Eudragit® RS/RL	Controlled swelling and pore diffusion	Independent of inter-individual luminal pH variations	Rigid transit time assumptions; accelerated colonic transit causes incomplete release
Microbiome-Triggered	Pectin, Inulin, Chitosan, Amylose	Microbial fermentation by colonic enzymes	Highly colon-specific degradation profile	Hydrophilic swelling requires hydrophobic blending; severe dysbiosis decreases enzyme activity

Dual/Hybrid Multi-Trigger	Eudragit® combined with Amylose/Ethylcellulose	S100 with	Synchronized pH dissolution and microfloral digestion	Failsafe multi-barrier protection; avoids release failure	Complex multi-layer fluid-bed coating; strict process parameter control required
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5. In Vitro and In Vivo Characterization Techniques

5.1 Biorelevant Dissolution Methodologies

Standard compendial dissolution apparatuses (USP Apparatus I, II, or III) using static pH buffer stages often fail to predict in vivo release behavior in inflammatory bowel disease.⁴¹ Modern biorelevant protocols employ multi-stage media cascades, which transition through simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8), followed by modified colonic buffers (pH 6.0-6.5) enriched with fecal slurries or purified microbial enzymes (pectinase, galactomannanase, azoreductase).⁴² Automated dynamic gut models such as TIM-2 allow physiological hydrodynamics, shear stresses, and anaerobic microbiota fermentation to deliver improved IVIVC.⁴³

5.2 Animal Models of Colitis and In Vivo Imaging

Efficacy testing for colonic drug delivery systems is reliant on chemically induced rodent colitis models such as dextran sulfate sodium (DSS) and 2,4,6-trinitrobenzenesulfonic acid (TNBS).⁴⁴ The DSS model disrupts the intestinal mucosal barrier to simulate acute epithelial ulceration whereas the TNBS model elicits a T-cell driven transmural inflammation mimicking Crohn's-like or severe ulcerative phenotypes.⁴⁵ Longitudinal tracking of multi-unit formulations in vivo is routinely achieved by non-invasive gamma scintigraphy, micro-computed tomography (micro-CT) and magnetic resonance imaging (MRI).⁴⁶

6. Clinical Applications, Regulatory Challenges, and Emerging Trends

6.1 Translation from Bench to Bedside

The development of commercial colonic formulation products (e.g., mesalamine-loaded microgranules and multi-matrix tablets) is a significant proof of concept for the success of delayed-release therapeutics in the maintenance of remission in patients with mild-to-moderate UC.⁴⁷ Indeed, interindividual variability in gut transit time, pH, and enzymatic activity dictates differing responses to therapy.⁴⁸ Multiparticulate pellets appear to be the dosage form of choice for future drug delivery to the gastrointestinal tract, providing consistent gastric emptying as well as an adaptable and patient-specific dose of API.⁴⁹

6.2 Nano-in-Micro Composite Delivery Systems

One of the most promising formulations currently investigated for the treatment of mucosal diseases is the development of 'nano-in-micro' formulations, in which drug-containing nanoparticles are encapsulated within a functional enteric-coated micro-pellet structure.⁵⁰ Nanocarriers made from poly(lactic-co-glycolic acid) (PLGA), solid lipid nanoparticles, or lipid nanocapsules, are known to selectively accumulate at sites of inflammation through enhanced permeability and retention (EPR) effect.⁵¹ At the site of inflammation, the outer enteric micro-pellet is disintegrated by the low pH or specific enzymes in the terminal ileum or colon, thereby releasing the enclosed nanoparticles directly on the inflamed tissue, promoting their targeting and subsequent cellular internalization by macrophages and mucosal epithelial cells.⁵²

7. Conclusion

Targeted delivery of the drug to the affected part of the colon is crucial for the effective treatment of ulcerative colitis, as well as for reducing systemic side effects. Multiparticulate systems seem to overcome most of the barriers related to single-unit dosage forms, providing consistent drug release in the stomach and the entire area of the colon. The simplest way to achieve targeting is to use conventional single-unit tablets with a pH-dependent coating. However, UC-associated changes in the colon environment can affect the mechanical and chemical integrity of the coating and lead to dose dumping. A promising approach is to use tablets with dual-coating technology: an external coating that responds to the pH of the intestine and an internal layer that is recognized by the UC microbiota. The use of intelligent polymers, bioadhesive excipients, and miniaturized multilayer structures in multiparticulate systems seems to be the way to heal mucosal ulcers and improve the quality of life of patients with inflammatory bowel disease.

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