ISSN: 2349-5448

Intercontinental Journal of Pharmaceutical Investigations and Research (ICJPIR)

ICJPIR |Vol. 11 | Issue 4 | Oct – Dec 2024

www.icjpir.com

DOI: https://doi.org/10.61096/icjpir.v11.iss4.2024.197-211

Colon-Targeted Drug Delivery Systems: pH-Dependent, Enzyme-Responsive, Time-Controlled, and Microbiota-Triggered Release Platforms

N. Mahesh Kumar, R. Sathya sri

Scient Institute of Pharmacy
lbrahimpatnam, Ranga Reddy District - 501 506, Telangana
exambranch.ghip@gmail.com

Published on: 24.11.2024
Published by: Futuristic Publications

Abstract

Background: Colon-targeted drug delivery systems are designed to release their drug payload specifically in the large intestine while resisting premature drug release in the stomach and small intestine. The therapeutic rationale for colonic targeting encompasses two distinct but equally important goals: local therapy for diseases confined to the colonic mucosa — including inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, colorectal cancer, and colonic infections — and systemic drug delivery exploiting the colon's large absorptive surface area, reduced enzymatic activity compared to the small intestine, and prolonged transit time for drugs with absorption windows in the distal gut or requiring sustained release. The colon harbors a dense and metabolically active microbiota of approximately 10 to 100 billion bacteria per milliliter of luminal content, which produces a unique enzymatic environment exploitable as a biological trigger for site-specific drug release.

Objective: This review comprehensively examines the physiological basis of colon-targeted delivery, the classification and design principles of pH-dependent, time-controlled, enzyme-responsive, pressure-activated, and microbiota-triggered colon delivery systems, preparation and characterization methodologies, therapeutic applications in IBD, colorectal cancer, and chronic systemic diseases, and the critical translation barriers that distinguish successful from unsuccessful colon-targeting approaches in clinical practice.

Results and Discussion: pH-dependent polymer coating using Eudragit S100 and Eudragit FS 30D remains the most clinically established colon-targeting strategy, exploiting the pH gradient from 1.5 to 2.0 in the stomach through 6.0 to 6.5 in the terminal ileum to 6.5 to 7.5 in the colon. Microbiota-triggered release systems utilizing polysaccharide carriers including pectin, guar gum, chondroitin sulfate, and inulin that resist enzymatic digestion in the small intestine but are fermented by colonic bacteria represent an inherently specific triggering mechanism with compelling disease-relevant applications. Nanoparticle-based colon-targeted systems demonstrate superior mucosal penetration and uptake by intestinal macrophages compared to conventional coated tablets, with particular relevance for siRNA delivery to colonic immune cells in IBD.

Conclusion: Colon-targeted drug delivery has achieved substantial clinical validation through multiple approved products for IBD management, with ongoing research in microbiota-modulating delivery, colorectal cancer targeting, and next-generation biologic delivery establishing the continued pharmaceutical relevance of this delivery approach. Critical translation barriers including inter-individual GI pH variability, microbiome compositional heterogeneity, and the

poor permeability of the colonic epithelium to macromolecules remain active research priorities.

Keywords: *Colon-targeted drug delivery; pH-dependent coating; Eudragit; enzyme-triggered release; microbiota; inflammatory bowel disease; polysaccharide carriers; ulcerative colitis; 5-aminosalicylic acid; CODAS technology*

1. Introduction

The large intestine presents a pharmacologically distinctive environment that differs fundamentally from the stomach and small intestine in its physicochemical milieu, enzymatic landscape, microbial ecology, mucosal architecture, and drug absorption characteristics. Understanding these differences is prerequisite to rational design of colon-targeted drug delivery systems, which must exploit features of the colonic environment as selectivity mechanisms while resisting the quite different conditions of the upper gastrointestinal tract [1,2].

The clinical need for colon-targeted drug delivery is driven primarily by the high prevalence and therapeutic inadequacy of colonic diseases. Inflammatory bowel disease, comprising ulcerative colitis and Crohn's disease, affects approximately 6.8 million people globally with rapidly increasing incidence in newly industrialized countries, and is characterized by chronic immune-mediated inflammation of the gastrointestinal mucosa for which systemic corticosteroid therapy causes unacceptable long-term toxicity while local colonic delivery of anti-inflammatory drugs offers effective disease control with minimal systemic exposure. Colorectal cancer is the third most common cancer and second leading cause of cancer death globally, with 1.9 million new cases annually, representing a compelling oncological target for local chemotherapy delivery that maximizes intratumoral drug concentration while limiting systemic toxicity [3,4].

Beyond local colonic therapy, the colon offers several pharmacokinetic advantages for systemic drug delivery that have motivated development of colonic targeting for circadian rhythm-dependent drug therapy. Drugs requiring nighttime plasma peaks for optimal efficacy — including corticosteroids for morning symptom control in rheumatoid arthritis, antihypertensives for circadian blood pressure management, and statins for nocturnal hepatic cholesterol synthesis inhibition — can be formulated as colon-targeted systems that delay drug release until the drug reaches the colon several hours after administration, effectively creating a timed-release delivery mechanism synchronized with the patient's circadian pharmacokinetic requirements [5,6].

The gut microbiota — the 10 to 100 trillion bacteria collectively inhabiting the large intestine — produces a biochemically rich enzymatic environment capable of hydrolyzing polysaccharides, reducing azo bonds, deconjugating bile acids, and performing numerous other biotransformations that are absent in the sterile upper GI tract. This unique enzymatic activity provides the basis for microbiota-triggered drug delivery systems that remain intact through the stomach and small intestine but are specifically activated by bacterial enzymes in the colon, providing a biologically inherent mechanism for colonic drug release that is independent of pH or transit time and therefore potentially more robust across the inter-individual variability that limits pH-dependent and time-controlled approaches [7].

This review systematically examines the physiological basis of colon-targeted drug delivery, the four principal triggering mechanisms used in colon-targeted formulations, the materials and preparation methods for each approach, characterization and evaluation strategies, therapeutic applications, and a critical analysis of the translational challenges that distinguish successful colon-targeting from failed approaches in clinical development.

2. Scientific Background

2.1 Gastrointestinal Physiology Relevant to Colon Targeting

The gastrointestinal tract from stomach to rectum presents a continuous but regionally heterogeneous environment for oral drug delivery. The stomach maintains a highly acidic pH between 1.5 and 3.5 in the fasted state, substantially increasing to 4.0 to 5.0 postprandially due to buffering by food. Gastric emptying of solid dosage forms in the fasted state typically occurs over 0.5 to 2 hours but is markedly delayed by food intake, with a high-fat meal extending gastric emptying time by 3 to 5 hours. The proximal small intestine receives bicarbonate secreted by the pancreas and bile, raising pH to approximately 5.5 to 6.5 in the duodenum and jejunum. The terminal ileum maintains pH values of 6.0 to 7.5. The colon receives ileal effluent at a pH of 6.0 to 6.8, which may temporarily decrease to 5.5 to 6.0 in the proximal colon due to fermentation of carbohydrates by saccharolytic bacteria, and increases to 6.5 to 7.5 in the distal colon and rectum [8,9].

Small intestinal transit time from pylorus to ileocecal valve is approximately 3 to 4 hours in healthy volunteers, remarkably consistent across individuals despite substantial variability in gastric emptying time. Colonic transit time in contrast is highly variable — typically 20 to 60 hours in healthy adults but reduced to 10 to 20 hours in patients with inflammatory bowel disease with diarrheal predominance, and substantially prolonged in constipation-predominant conditions. Drug absorption from the colon is generally lower than from the small intestine due to the reduced surface area from the absence of villi, thicker mucus layer, and lower permeability of the colonic epithelium, though significant absorption of certain lipophilic small molecules does occur from the colon during the extended transit time [10].

2.2 The Colonic Microbiota as a Drug Delivery Target

The human colon harbors a microbial community of extraordinary complexity and metabolic diversity, comprising approximately 500 to 1000 bacterial species at a density of 10 to 100 billion organisms per milliliter of luminal content. The dominant bacterial phyla are Firmicutes (40 to 60%) and Bacteroidetes (20 to 40%), with Actinobacteria, Proteobacteria, and other phyla comprising the remainder. The collective genome of the gut microbiota — the gut metagenome — encodes enzymatic capabilities not present in the human genome, including carbohydrate-active enzymes that degrade dietary fiber and polysaccharides, beta-glucuronidase that deconjugates biliary glucuronide conjugates, azoreductases that cleave azo bonds, and numerous other biotransforming enzymes [11,12].

The metabolic activity of colonic bacteria creates a distinctive chemical environment with therapeutic relevance beyond their role as drug delivery triggers. Short-chain fatty acids produced by bacterial fermentation of dietary fiber — acetate, propionate, and butyrate — serve as energy substrates for colonocytes and exert anti-inflammatory and anti-proliferative effects on colonic epithelium. Dysbiosis — altered microbiota composition characteristic of IBD, colorectal cancer, and metabolic syndrome — provides both a therapeutic target for microbiota-modulating drug delivery and a variable that may affect the reliability of microbiota-triggered drug release across patient populations [13].

3. Classification of Colon-Targeted Drug Delivery Systems

3.1 pH-Dependent Systems

pH-dependent colon-targeting exploits the ascending pH gradient of the gastrointestinal tract, using polymeric coatings that dissolve at pH values characteristic of the terminal ileum and colon (pH ≥ 6.5 to 7.0) while remaining intact at the lower pH values of the stomach (pH 1.5 to 3.5) and proximal small intestine (pH 5.5 to 6.5). Eudragit S100 (poly(methacrylic acid-co-methyl methacrylate) 1:2, dissolution pH ≥ 7.0) and Eudragit L100-55 (dissolution pH ≥ 5.5) are the most extensively used pH-sensitive polymers for enteric and colon-specific coating respectively. The pH-responsive dissolution of these polymers occurs when the carboxylic acid groups on the polymer backbone become ionized (pKa approximately 5.5 to 7.0 depending on composition), converting the hydrophobic polymer to a water-soluble polycarboxylate that dissolves from the tablet surface, releasing the enclosed drug [14,15].

Eudragit FS 30D (poly(methacrylic acid-co-methyl acrylate-co-methyl methacrylate), dissolution pH ≥ 6.8), specifically developed for colon targeting, provides more reliable colon-specific release than Eudragit S100 in patients with intestinal diseases in which luminal pH may be altered. The PENTASA (mesalamine) and ASACOL (mesalamine) formulations use Eudragit coatings for pH-triggered mesalamine release in the small intestine and colon respectively, and are among the most commercially successful implementations of pH-dependent colonic drug delivery [16].

3.2 Time-Controlled Release Systems

Time-controlled systems exploit the relatively consistent small intestinal transit time of 3 to 4 hours to design oral formulations that release drug after a lag time corresponding to the time required for transit from the duodenum to the cecum. Pulsatile release capsule technologies including the PORT system, the Chronotropic system, and the CTDDS (Colon-Targeted Drug Delivery System) use swellable or erodible plug materials within a hard capsule body that maintain capsule integrity during gastric and small intestinal transit and dissolve or erode over a programmed lag time to release drug in the colon. The TIME CLOCK technology combines a hydrophobic surfactant coating with HPMC to produce a time-dependent porous membrane that gradually takes up water and eventually disrupts, releasing drug after a programmed lag time [17,18].

The CODAS (Chronotherapeutic Oral Drug Absorption System) technology, used commercially in the verapamil product Verelan PM for nocturnal angina and hypertension management, incorporates a combination of water-permeable and water-insoluble polymer coatings on drug pellets to achieve a lag time

of 4 to 5 hours followed by sustained drug release — timed such that when the capsule is taken at bedtime, drug reaches the systemic circulation during the early morning hours when cardiovascular events peak [19].

3.3 Enzyme-Responsive (Microbiota-Triggered) Systems

Microbiota-triggered colon delivery systems use carriers that resist enzymatic digestion by mammalian pancreatic and brush border enzymes in the small intestine but are degraded by the colonic bacterial enzymatic machinery to release drug in the colon. The primary polysaccharide carriers in this category include pectin (degraded by bacterial pectinases), guar gum (degraded by beta-mannanase and beta-galactosidase), chondroitin sulfate (degraded by chondroitin lyase), inulin (degraded by bacterial inulinase), amylose (degraded by amylase-producing bacteria), and dextran (degraded by dextranase). These natural polysaccharides are incorporated as tablet matrix materials, coating agents, or micro- and nanoparticle carriers [20,21].

Azo-crosslinked polymer systems provide an alternative enzyme-responsive triggering mechanism based on azo bond (–N=N–) reduction by bacterial azoreductases. Azo bonds incorporated into polymer backbone or crosslinks are cleaved by colonic azoreductase-producing bacteria, dissolving crosslinks or breaking polymer chains to release encapsulated drug. Olsalazine and balsalazide, clinically approved prodrugs for ulcerative colitis, are aminosalicylate compounds linked through azo bonds to carrier molecules that are cleaved by colonic bacteria to release the active 5-aminosalicylic acid in situ [22].

3.4 Pressure-Controlled and Osmotic Systems

The pressure-controlled colon delivery system (PCDS) exploits the higher intraluminal pressure in the colon compared to the small intestine — resulting from segmental contractions of the colonic musculature during propulsion — to rupture an ethylcellulose capsule shell when the capsule enters the colon. Drug dissolved or suspended in lipid within the capsule is released upon capsule rupture triggered by the elevated colonic pressure. This elegant design does not rely on pH or enzyme activity, making it potentially more robust across pathological conditions that alter luminal pH or microbiota composition [23].

3.5 Multi-Mechanism Combined Systems

Dual-mechanism colon delivery systems combine two independent targeting strategies to improve selectivity and reliability of drug release in the colon. pH-dependent outer coating with time-controlled inner core provides sequential protection: the enteric coating prevents drug release in the acidic stomach, while the timed-release core ensures additional delay beyond the enteric coating dissolution to prevent premature drug release in the jejunum and ileum during periods of elevated small intestinal pH. Combination pH-responsive and polysaccharide-coated systems provide dual protection against both small intestinal pH and enzymatic attack [24].

Table 1: Classification of colon-targeted drug delivery systems by triggering mechanism, materials, release trigger, and representative products

System Type	Key Materials	Trigger Mechanism	Limitations	Examples / Products
pH-dependent coating	Eudragit L100, S100, FS 30D	pH ≥ 6.8–7.0 polymer dissolution	GI pH variability in disease	Asacol (mesalamine), Lialda, Pentasa
Time-controlled	HPMC, Eudragit RS, ethylcellulose	5–6 h lag post-dosing	Rapid GI transit variability	CODAS (Verelan PM), PORT system, Chronotropic
Polysaccharide/enzyme-responsive	Pectin, guar gum, chondroitin, inulin	Colonic bacterial degradation	Microbiome variability across patients	Experimental; azo prodrugs (Olsalazine)
Azo-crosslinked polymer	Azo-crosslinked dextran, polyacrylate	Azoreductase cleavage (bacteria)	Variable azoreductase activity	Olsalazine, balsalazide (prodrug mechanism)

Pressure-controlled	Ethylcellulose capsule + lipid fill	Colonic intraluminal pressure	Requires intact colonic motility	PCDS (investigational)
Osmotic / expandable	Semipermeable cellulose membrane	Osmotic pressure gradient	Fluid-dependent performance	OROS technology variants
Dual-mechanism (pH + enzyme)	Eudragit S100 + pectin/amylose	Sequential pH and enzymatic	Complex manufacturing	Experimental multi-layer coatings

HPMC: hydroxypropyl methylcellulose; CODAS: Chronotherapeutic Oral Drug Absorption System; PCDS: pressure-controlled colon delivery system; OROS: oral osmotic system.

4. Formulation Design and Development

4.1 pH-Responsive Polymer Selection and Coating Thickness

Selection of the appropriate pH-responsive polymer requires matching the polymer dissolution pH threshold to the intended drug release site in the gastrointestinal tract. For ileal drug release, Eudragit L100-55 (dissolution pH $\geq$ 5.5) or Eudragit L100 (dissolution pH $\geq$ 6.0) is appropriate, while for colonic drug release, Eudragit S100 (dissolution pH $\geq$ 7.0) or Eudragit FS 30D (dissolution pH $\geq$ 6.8) is required. Coating thickness critically determines the lag time before coating dissolution and the completeness of coating integrity during upper GI transit; typical coating weight gain for colon-targeted tablets ranges from 8 to 15% of the uncoated tablet weight. The aqueous dispersion Eudragit FS 30D enables coating at lower processing temperatures than solvent-based Eudragit systems, reducing the risk of drug thermal degradation during coating [25,26].

4.2 Polysaccharide Matrix Design

Polysaccharide-based colon targeting requires selection of polysaccharides with appropriate resistance to pancreatic and brush border enzyme digestion in the small intestine and susceptibility to colonic bacterial enzymes. Pectin, a heterogeneous polysaccharide from plant cell walls, is degraded by pectinases produced by Bacteroides and Bifidobacterium species in the colon but is partially solubilized by the neutral pH of the small intestine, reducing its site-specificity as a single coating agent. Coating pectin with calcium ions (calcium-crosslinked pectin) or incorporating it into a HPMC or chitosan matrix reduces its solubility in the small intestine while preserving its susceptibility to colonic bacterial pectinase, improving site-specificity [27].

Amylose, the linear polymer of glucose linked by alpha-1,4 bonds that comprises approximately 25% of natural starch, is resistant to small intestinal amylases in its native compact helical form but is fermented by colonic bacteria producing amylolytic enzymes. Amylose combined with ethylcellulose to form a compressed film provides a colon-specific coating that resists dissolution in simulated gastric and intestinal fluids but erodes in simulated colonic environments, enabling colonic drug release from coated tablets [28].

4.3 Nanoparticle Design for Colonic Mucosa Targeting

Nanoparticle-based colon delivery must overcome the colonic mucus barrier — a 100 to 500 micrometer thick viscoelastic gel layer overlying the colonocyte epithelium — to achieve drug delivery to the mucosal immune cells and epithelium that are the therapeutic targets in IBD. Nanoparticles of 200 to 500 nm demonstrate the greatest penetration through the colonic mucus layer, with size below 200 nm enabling faster diffusion through mucus pores and size above 500 nm causing significant mucus trapping. Chitosan-coated nanoparticles demonstrate enhanced mucoadhesion to colonic mucin through electrostatic interaction, prolonging mucosal contact time and improving drug deposition in the colonic mucosa relative to uncoated nanoparticles [29,30].

4.4 Prodrug Design for Colonic Activation

Azo-bond prodrug design exploits the high azoreductase activity of colonic anaerobes to release active drug from inactive prodrug precursors in a site-specific manner. Balsalazide (5-ASA linked to 4-aminobenzoyl-beta-alanine by an azo bond) and olsalazine (two 5-ASA molecules linked by an azo bond) are approved prodrugs that deliver mesalamine (5-ASA) specifically to the colon with substantially lower systemic absorption than free mesalamine formulations, exploiting the colonic bacterial azoreductase activity for both site-specific delivery and reduced systemic toxicity [31].

5. Preparation Methods

5.1 Aqueous Film Coating for pH-Dependent Systems

Aqueous film coating of tablets or pellets with Eudragit FS 30D or Eudragit S100 is performed using fluidized bed coating equipment (Wurster bottom-spray or top-spray configuration) or pan coating systems. The coating dispersion typically contains the polymer dispersion, plasticizer (triethyl citrate at 10 to 25% of dry polymer weight for Eudragits, dibutyl sebacate for ethylcellulose), and optionally anti-tacking agents such as talc or glyceryl monostearate to prevent particle agglomeration during coating. Inlet air temperature, atomization air pressure, spray rate, and product temperature are the critical process parameters that determine coating uniformity, tablet surface roughness, and coating efficiency [32].

5.2 Compression Coating for Colon Targeting

Compression coating involves compressing a drug-containing tablet core within a shell of colonic targeting polymer material using a specially designed compression coating machine or a conventional two-stage compression process. The outer compression-coated shell of polysaccharide or pH-sensitive polymer material surrounds the drug core without the temperature exposure of film coating processes, making it suitable for thermolabile drugs. The weight ratio of shell to core, shell polymer composition, and compression force determine the release lag time and drug release kinetics [33].

5.3 Preparation of Polysaccharide Matrix Tablets

Polysaccharide matrix tablets for colon-targeted delivery are prepared by direct compression or wet granulation of drug-polysaccharide mixtures. Guar gum, pectin, locust bean gum, and inulin are incorporated as matrix-forming agents at concentrations of 20 to 60% of tablet weight. Direct compression produces tablets with adequate hardness if the polysaccharide exhibits sufficient compressibility, which is the case for guar gum and pectin in a wide concentration range. The addition of cross-linking agents including calcium chloride (for pectin) or borax (for guar gum) reduces the swelling and disintegration rate of the polysaccharide matrix in upper GI fluids, improving colonic selectivity [34].

5.4 Preparation of Nanoparticles for Colonic Drug Delivery

PLGA nanoparticles for colon-targeted IBD drug delivery are prepared by double emulsion-solvent evaporation for hydrophilic drugs or single emulsion for lipophilic drugs. For oral colon delivery, the nanoparticles are typically incorporated into a pH-responsive polymer coated capsule or tablet that protects the particles during upper GI transit and releases them in the colon as a nanoparticle suspension. Alternatively, nanoparticles can be incorporated into a hydrogel matrix that swells and releases particles in the colon, or spray-dried with mannitol and sodium carboxymethylcellulose to produce a solid nanoparticle composite powder for reconstitution before administration as an oral suspension or enema [35].

6. Characterization and Evaluation

6.1 In Vitro Drug Release in Simulated GI Fluids

Drug release from colon-targeted formulations is evaluated sequentially in simulated gastric fluid (SGF, pH 1.2, 2 hours), simulated intestinal fluid (SIF, pH 6.8, 3 hours), and simulated colonic fluid (SCF, pH 7.4 or pH 6.8, remainder of study) using USP apparatus II (paddle) or apparatus I (basket). For polysaccharide-based systems, the addition of rat cecal contents or commercially available colonic bacterial enzyme mixtures (pectinase, inulinase, or mixed microbial enzyme extracts) to the SCF is required to demonstrate enzyme-triggered drug release, as the buffers alone cannot recapitulate the enzymatic environment of the colon [36].

6.2 High-Performance Liquid Chromatography Drug Quantification

HPLC with UV detection at appropriate wavelength (typically 303 nm for mesalamine/5-ASA, 254 nm for budesonide, or drug-specific wavelength) is used to quantify drug released at each stage of the sequential dissolution test. The dissolution acceptance criteria typically require less than 10% drug release in SGF after 2 hours and less than 20% release in SIF after 3 hours, with at least 70 to 80% drug release in colonic fluid within 12 to 24 hours, providing a quantitative benchmark for site-specificity [37].

6.3 Ex Vivo Mucoadhesion and Mucosal Penetration

Mucoadhesion of nanoparticle-based colon delivery systems is evaluated using freshly excised rat or porcine colon mucosa. The formulation is applied to the mucosal surface, incubated for defined times, and the amount of drug or

nanoparticles retained on the mucosa after washing is quantified as a percentage of the applied amount to calculate mucoadhesive efficiency. Confocal laser scanning microscopy of fluorescent nanoparticle-treated colon tissue sections visualizes penetration depth of nanoparticles into the mucus layer and epithelium, providing quantitative measurement of mucosal penetration efficiency as a function of particle size and surface properties [38].

6.4 In Vivo Gastrointestinal Transit Scintigraphy

Gamma scintigraphy using technetium-99m-labeled tablets or capsules provides definitive real-time visualization of formulation transit through the human GI tract, enabling determination of the time and location of tablet disintegration or coating dissolution. For pH-dependent colon-targeted formulations, scintigraphic studies in healthy volunteers and patients with IBD have demonstrated the impact of intestinal pH variability on coating dissolution timing, with Eudragit S100 coatings dissolving in the terminal ileum or ascending colon in most healthy subjects but potentially dissolving earlier in patients with elevated small intestinal pH due to bacterial overgrowth [39].

7. Mechanism of Drug Delivery to the Colon

7.1 pH-Triggered Polymer Dissolution

The mechanism of pH-triggered dissolution of Eudragit and cellulose acetate phthalate coatings involves ionization of pendant carboxylic acid groups on the polymer backbone as luminal pH rises above the polymer pKa. At gastric pH 1.5 to 3.5, the carboxylic acid groups are protonated and uncharged, maintaining the polymer in a hydrophobic, water-insoluble state that prevents water penetration and drug dissolution. As luminal pH rises to 6.8 to 7.0 in the terminal ileum and colon, carboxylate ionization converts the polymer to a hydrophilic polyelectrolyte that rapidly takes up water, swells, and dissolves from the tablet surface, exposing the drug to colonic fluid [40].

7.2 Bacterial Fermentation and Enzymatic Cleavage

Polysaccharide-based colon-targeting formulations depend on the metabolic activity of colonic bacteria for drug release. Saccharolytic bacteria including Bacteroides, Bifidobacterium, Lactobacillus, Roseburia, and Ruminococcus species produce glycoside hydrolases and polysaccharide lyases that degrade the polysaccharide carrier matrix through sequential hydrolysis of glycosidic bonds. The rate of degradation depends on polysaccharide chemical structure, microbial community composition, and luminal substrate availability. Pectin degradation begins within 2 to 4 hours of cecal entry in the human colon, while the more resistant amylose-ethylcellulose matrix requires 6 to 12 hours for complete degradation [41].

7.3 Prodrug Activation by Azoreductase

Azo bond-containing prodrugs including olsalazine and balsalazide are transported through the upper GI tract intact due to the absence of azoreductase activity in mammalian upper GI tissues. Upon reaching the colon, the reducing environment maintained by strictly anaerobic bacteria and the azoreductase activity of Clostridium, Bacteroides, and Fusobacterium species cleave the azo bond (–N=N–) through sequential one-electron reduction to produce the corresponding amine metabolites plus free 5-aminosalicylic acid. For olsalazine (two 5-ASA molecules linked by an azo bond), equimolar release of two 5-ASA molecules from a single prodrug molecule provides double the molar drug delivery per prodrug molecule compared to single carrier-linked systems [42].

8. Therapeutic Applications

8.1 Ulcerative Colitis and Inflammatory Bowel Disease

Ulcerative colitis, limited to the colon and rectum, is the most precisely targeted indication for colon-specific drug delivery, as the inflamed mucosa requiring treatment is entirely within the colonic compartment. Aminosalicylate (5-ASA/mesalamine) therapy is the mainstay of mild-to-moderate ulcerative colitis management, with several colon-targeted formulations demonstrating superior mucosal 5-ASA concentrations and equivalent or superior clinical efficacy to systemic corticosteroids with substantially reduced systemic side effects. Asacol (mesalamine with Eudragit S100 coating), Lialda (mesalamine multimatrix MMX technology), and PENTASA (mesalamine ethylcellulose microgranules releasing throughout the gut) represent distinct colon-targeting strategies for mesalamine delivery, each with distinct pharmacokinetic profiles and efficacy data [43,44].

Corticosteroid colon-targeted delivery using budesonide with pH-dependent coating (Entocort EC, Cortiment MMX) achieves high mucosal drug concentrations at the site of inflammation while limiting

systemic corticosteroid exposure through extensive hepatic first-pass metabolism of absorbed budesonide, providing effective induction of remission in Crohn's disease and microscopic colitis with substantially reduced systemic corticosteroid adverse effects compared to conventional prednisolone. The MMX (Multi-Matrix System) technology used in Cortiment and Lialda employs a three-layer controlled-release system combining a hydrophilic matrix, lipophilic matrix, and outer delayed-release coating to produce a once-daily tablet that distributes drug release throughout the colon [45].

8.2 Colorectal Cancer

Colon-targeted delivery of chemotherapeutic agents offers the theoretical advantage of achieving high intraluminal drug concentrations at the tumor site with lower systemic plasma concentrations than conventional intravenous administration, potentially improving the therapeutic index of cytotoxic agents. Nanoparticle-based oral colon-targeted delivery of 5-fluorouracil, oxaliplatin, curcumin, and the topoisomerase inhibitor SN-38 have been investigated in preclinical colorectal cancer models, with pH-responsive PLGA nanoparticles demonstrating threefold higher tumor drug concentrations compared to equivalent intravenous doses in orthotopic colon cancer mouse models. CD44-targeted hyaluronic acid-coated nanoparticles delivered specifically to CD44-overexpressing colorectal cancer cells demonstrate superior tumor cell uptake and cytotoxicity compared to non-targeted nanoparticles [46].

8.3 Chronotherapeutic Systemic Drug Delivery

The CODAS technology for verapamil delivers the calcium channel blocker with a 4 to 5 hour delay after a once-daily evening dose, achieving peak plasma concentrations in the early morning hours (4 to 7 AM) when blood pressure surge and cardiovascular event risk are highest. Phase 3 clinical trials of Verelan PM demonstrated equivalent blood pressure control to conventional immediate-release verapamil three-times-daily with superior morning blood pressure coverage and reduced 24-hour blood pressure variability. This chronotherapeutic advantage — delivering drug when the patient needs it most rather than when they take it — demonstrates the clinical utility of time-controlled colon delivery beyond gastrointestinal disease [47].

8.4 Vaccine and Immunotherapy Delivery

The colon-associated lymphoid tissue (CALT), comprising lymphoid aggregates, macrophages, and dendritic cells distributed throughout the colonic mucosa, represents an immunologically active site for vaccine antigen delivery. Oral colon-targeted delivery of vaccine antigens using polysaccharide nanoparticles or pH-responsive polymer microparticles deposits antigens in proximity to CALT immune cells, activating mucosal secretory IgA immune responses that provide both systemic and mucosal immunity. Guar gum-coated nanoparticles loaded with tetanus toxoid demonstrated colonic antigen delivery with measurable mucosal and systemic IgA and IgG responses in animal models, establishing proof-of-concept for oral mucosal vaccination via colon targeting [48].

9. Recent Advances

9.1 Microbiome-Modulating Drug Delivery

Beyond exploiting the microbiota as a drug release trigger, advanced colon-targeted systems have been developed to deliver therapeutics specifically designed to modulate microbiota composition for treatment of dysbiosis-associated conditions. Fecal microbiota transplantation (FMT), delivered as an encapsulated lyophilized fecal microbiota preparation (SER-109, Ferring Pharmaceuticals), received FDA approval in November 2022 for prevention of recurrent Clostridioides difficile infection, representing the first microbiome therapeutic approved by a regulatory agency. The formulation challenge of oral microbiome therapeutics — protecting viable bacteria through gastric acid and small intestinal bile to deliver them to the colon — has been addressed by acid-resistant enteric capsules and lyophilization formulation with cryoprotectants [49].

9.2 siRNA and Nucleic Acid Delivery to the Colon

RNA interference-based therapy for IBD, delivering siRNA targeting pro-inflammatory genes including TNF-alpha, NF-kappaB, and SMAD7 specifically to colonic macrophages and epithelial cells, represents a molecularly precise approach to IBD management that complements conventional pharmacotherapy. Lipid nanoparticles and chitosan nanoparticles loaded with siRNA or antisense oligonucleotides have been formulated with pH-responsive Eudragit S100 coatings for oral colon-targeted delivery, demonstrating specific target gene knockdown in colonic macrophages of dextran sulfate sodium-induced colitis mouse

models. The siRNA-based drug mongersen (GED-0301, antisense oligonucleotide against SMAD7) advanced through phase 2 clinical trials for Crohn's disease with promising results before phase 3 discontinuation due to manufacturing and efficacy endpoint challenges [50].

9.3 Nanoparticle-Mediated Macrophage Targeting in IBD

Colonic macrophages play a central role in the pathogenesis of IBD through production of pro-inflammatory cytokines including TNF-alpha, IL-6, IL-12, and IL-23. Nanoparticles of 200 to 500 nm are preferentially taken up by macrophages through phagocytosis, making nanoparticle-based drug delivery an inherently macrophage-targeted approach for anti-inflammatory drug delivery in the inflamed colon. Mannose receptor-targeted nanoparticles exploit the high mannose receptor expression on M1 (pro-inflammatory) macrophages in the inflamed colonic mucosa for selective drug delivery, achieving macrophage drug concentrations tenfold higher than non-targeted nanoparticles of equivalent size and drug loading in IBD mouse models [51].

9.4 Gut-on-a-Chip for Colon Delivery Testing

Organ-on-a-chip microfluidic devices replicating the colon microenvironment — including columnar epithelial cells, Caco-2 cells, intestinal organoids, and commensal bacteria in a co-culture under controlled luminal flow — have been developed as more physiologically relevant testing platforms for colon-targeted formulations than conventional static cell culture. The colon-on-a-chip enables simultaneous evaluation of drug transport across the epithelial barrier, mucosal permeation, and microbial drug metabolism in a single in vitro system that captures the dynamic interactions absent from conventional dissolution testing. Published colon-on-a-chip systems have demonstrated bacterial colonization, mucus production, and drug metabolism profiles consistent with in vivo measurements, providing a promising next-generation preclinical testing platform [52].

10. Comparative Analysis

The selection of a colon-targeting strategy requires consideration of the robustness of the targeting mechanism across the inter-individual variability in gastrointestinal pH, transit time, and microbiota composition that characterize real patient populations. pH-dependent coating is the most clinically established approach with the best regulatory precedent, but is limited by the substantial inter-individual variability in luminal pH — particularly in IBD patients where mucosal inflammation alters local pH gradients — and by the risk of premature coating dissolution in patients with elevated small intestinal pH due to bacterial overgrowth or altered acid secretion [53].

Microbiota-triggered systems provide a potentially more robust targeting mechanism in healthy subjects, as the colonic bacterial enzymatic activity is less affected by luminal pH than polymer dissolution, but are more vulnerable to inter-individual microbiome compositional differences. Patients with IBD, which is itself characterized by microbiota dysbiosis with reduced abundance of saccharolytic Bacteroides and Bifidobacterium species, may have diminished capacity to trigger polysaccharide-based colon delivery, ironically reducing the targeting efficacy precisely in the patient population most in need of treatment [54].

Table 2: Comparative evaluation of colon-targeting mechanisms across key performance parameters

Parameter	pH-Dependent	Time-Controlled	Enzyme-Responsive	Azo Prodrug	Pressure-Controlled
Site specificity	Moderate	Low–moderate	High	High	Moderate
Robustness in IBD	Reduced (pH alteration)	Reduced (rapid transit)	Reduced (dysbiosis)	Reduced (dysbiosis)	Good (motility preserved)
Drug loading versatility	High	High	Moderate	Low (requires azo synthesis)	Moderate
Manufacturing complexity	Low–moderate	Moderate	Moderate	High (synthesis)	High
Regulatory precedent	Well established	Established (CODAS)	Limited	Established (olsalazine)	Investigational
Clinical products	Asacol, Lialda, Entocort	Verelan PM	Experimental	Olsalazine, balsalazide	None approved

IBD: inflammatory bowel disease.

11. Advantages and Limitations

11.1 Advantages

- Local drug delivery to colonic mucosa achieves high mucosal drug concentrations at the site of disease in ulcerative colitis and Crohn's disease while minimizing systemic drug exposure and associated adverse effects, improving the therapeutic index of aminosalicylates and corticosteroids

- The colon's large absorptive surface area (approximately 1.5 meters in length) and prolonged transit time (20 to 60 hours) provide a large window for drug absorption, beneficial for systemic drug delivery via colonic targeting and for sustained drug exposure to the colonic mucosa

- pH-dependent colon targeting offers a well-established, commercially validated, and regulatory-precedented delivery strategy with multiple approved products demonstrating clinical safety and efficacy across large patient populations

- Polysaccharide-based enzyme-triggered systems provide inherent biological selectivity through microbial specificity, exploiting the presence of saccharolytic bacteria exclusively in the colon as the release trigger without relying on potentially variable luminal pH

- Nanoparticle-based colon delivery achieves preferential uptake by colonic macrophages through phagocytosis, enabling macrophage-targeted anti-inflammatory therapy relevant to the pathophysiology of IBD where macrophage activation drives mucosal inflammation

- Chronotherapeutic colon-targeted systems (CODAS technology) achieve pharmacokinetic synchronization with circadian disease rhythms, providing clinical benefits in blood pressure management and cardiovascular risk reduction not achievable by conventional immediate-release formulations

- Prodrug strategies (olsalazine, balsalazide) exploit bacterial azoreductase activity for both site-specific activation and reduced systemic drug exposure, providing a chemically elegant solution to colon-specific drug delivery

11.2 Limitations

- Substantial inter-individual variability in colonic luminal pH — particularly in IBD patients where mucosal inflammation and bacterial overgrowth alter local pH gradients — reduces the reliability of pH-dependent colon targeting precisely in the patient population for which it is intended

- Accelerated GI transit in IBD patients with diarrheal predominance reduces the contact time between pH-sensitive coatings and colonic luminal pH, potentially resulting in premature or delayed drug release relative to the healthy volunteer pharmacokinetic data used to develop the formulation

- Microbiome-triggered colon delivery is vulnerable to the dysbiotic microbiome composition characteristic of IBD, with reduced abundance of saccharolytic bacteria potentially limiting enzyme-triggered drug release in active disease

- Drug absorption from the colon is significantly lower than from the small intestine due to reduced surface area, thicker mucus layer, and lower paracellular permeability, restricting the range of drugs that can achieve adequate systemic bioavailability through colonic absorption

- The limited permeability of the colonic epithelium to macromolecules including peptides, proteins, and nucleic acids substantially restricts colon-targeted delivery of biologic drugs to local mucosal applications, with systemic biologic delivery via the colon remaining an unresolved challenge

- Colonic drug delivery systems require validation of release specificity in simulated colonic fluids with appropriate enzymatic content, and there is no universally standardized in vitro test method that reliably predicts in vivo colonic drug release across the full range of colon-targeting technologies

12. Clinical Translation and Marketed Products

Colon-targeted drug delivery has one of the strongest clinical validation records among advanced drug delivery technologies, with multiple approved products in widespread clinical use demonstrating efficacy and safety across large patient populations with IBD, colorectal disease, and cardiovascular conditions. The commercial aminosalicylate market for ulcerative colitis — comprising mesalamine formulations including Asacol, Lialda, Mezavant, Pentasa, Salofalk, and several generic equivalents — represents one of the most commercially important applications of pH-dependent and controlled-release colon targeting in clinical practice [55].

The approval of SER-109 (VOWST, Ferring Pharmaceuticals) in May 2023 by the FDA for prevention of recurrent Clostridioides difficile infection represents a landmark extension of the colon-targeted delivery concept to live biotherapeutic products (LBPs), establishing the regulatory precedent for oral spore-based microbiome therapeutics formulated in acid-resistant capsules for colon-targeted delivery of therapeutic bacteria. This approval catalyzed a wave of development of additional oral microbiome therapeutics for IBD, metabolic syndrome, and oncology support in clinical development programs [56].

Table 3: Clinically approved colon-targeted drug delivery products and selected clinical programmes (as of 2023)

Product	Drug	Technology	Indication	Clinical Status / Key Data
Asacol / Asacol HD	Mesalamine	Eudragit S100 coating	Ulcerative colitis	FDA approved; widely used; multiple Phase 3 trials
Lialda / Mezavant	Mesalamine	MMX multimatrix system	Ulcerative colitis	FDA approved 2007; once-daily dosing; CORE I/II trials
Entocort EC	Budesonide	pH-dependent coating (Eudragit L)	Crohn's disease (ileum/colon)	FDA approved; superior systemic safety vs prednisolone
Cortiment MMX	Budesonide	MMX multimatrix (colonic)	Ulcerative colitis	FDA approved 2013; once-daily full colon distribution
Verelan PM	Verapamil	CODAS (time-controlled pellets)	Hypertension, angina	FDA approved; chronotherapeutic morning BP control
Olsalazine (Dipentum)	5-ASA prodrug	Azo bond prodrug	Ulcerative colitis	FDA approved; colonic azo-cleavage releases 2× 5-ASA
VOWST / SER-109	Live biotherapeutic (spores)	Enteric capsule (colon-targeted)	Recurrent C. difficile	FDA approved May 2023 — first oral FMT product

MMX: Multi-Matrix System; 5-ASA: 5-aminosalicylic acid (mesalamine); CODAS: Chronotherapeutic Oral Drug Absorption System; BP: blood pressure; FMT: fecal microbiota transplantation.

13. Critical Analysis

The established clinical success of pH-dependent and prodrug-based colon delivery technologies for IBD therapy provides a reassuring foundation for confidence in the colon-targeting concept. However, several important methodological and translational issues in the colon-targeted delivery literature merit critical examination that the field has not uniformly applied.

The most clinically significant limitation of pH-dependent colon targeting — inter-individual GI pH variability — is systematically underestimated in most preclinical and clinical pharmacokinetic publications due to the standard use of mean pH data from literature sources rather than individual pH measurements in study participants. A critical analysis of 24 published pH profiles of individual human volunteers and patients collected by Intestinal pH telemetry capsule (Heidelberg capsule or Bravo pH probe) demonstrates that small intestinal pH in individual subjects varies from 5.5 to 7.8 throughout the day, with postprandial pH elevation to 6.8 to 7.5 in the ileum creating a window during which Eudragit S100 coating (designed to dissolve at pH

≥ 7.0) would dissolve in the ileum rather than the colon. This premature dissolution, observed clinically in mesalamine scintigraphy studies, is rarely discussed in the context of dose-response failures in IBD clinical trials [57].

The animal models used to evaluate colon-targeted drug delivery systems in preclinical studies — predominantly rat, mouse, and rabbit — have GI anatomical and physiological characteristics that differ substantially from the human gastrointestinal tract in ways that affect the validity of drug release and bioavailability data. The rat cecum is disproportionately large relative to total gut volume and contains a substantially different microbial community than the human colon, including higher abundance of certain carbohydrate-fermenting bacteria that may accelerate polysaccharide-triggered drug release relative to humans. Mouse colonic transit time is approximately 2 to 4 hours — dramatically shorter than the 20 to 60 hour human colonic transit — providing substantially less time for colon-targeted drug delivery to achieve effective mucosal concentrations. These species differences are well-documented in the comparative physiology literature but are rarely explicitly discussed in colon-targeted drug delivery publications [58].

The SMAD7 antisense oligonucleotide mongersen (GED-0301), which showed promising efficacy signals in a phase 2 trial for Crohn's disease with a 55% remission rate at the highest dose, failed to demonstrate efficacy in two phase 3 trials despite similar formulation and dosing approaches. Post-hoc analysis suggested that the formulation may have achieved sub-therapeutic mucosal drug concentrations in the heterogeneous Crohn's disease patient population due to variable colonic transit and pH in severely inflamed bowel. This high-profile clinical failure illustrates that formulation performance observed in relatively homogeneous phase 2 populations does not guarantee reproducibility in the more diverse and severely ill phase 3 populations for whom the drug is ultimately intended [59].

Finally, the comparative clinical superiority of different mesalamine colon-targeted formulations — Asacol versus Lialda versus Pentasa versus Salofalk — has never been definitively established in head-to-head randomized controlled trials powered for superiority. Published network meta-analyses suggest similar efficacy across formulations, yet the commercial success of each product's distinctive targeting technology has driven continued investment in formulation differentiation despite the lack of clear clinical superiority evidence. This suggests that the pharmacokinetic distinctions between these formulations — differences in drug release site, rate, and extent — may be clinically irrelevant for the majority of IBD patients with disease extending throughout the colon, where any mesalamine that reaches the colon (regardless of the exact release location) provides therapeutic benefit [60].

14. Conclusion

Colon-targeted drug delivery has demonstrated genuine clinical value across a range of therapeutic applications, with the aminosalicylate formulations for ulcerative colitis, budesonide for Crohn's disease, chronotherapeutic verapamil for cardiovascular disease, and — most recently — oral microbiome therapeutics for recurrent Clostridioides difficile infection providing compelling evidence that targeting drug release to the large intestine can be achieved by diverse pharmaceutical mechanisms and can translate into clinically meaningful patient benefits.

The field has also produced important lessons about the limits of in vitro and animal model-based formulation development for predicting clinical performance. The variability of luminal pH in disease states, the acceleration of GI transit in active IBD, the compositional heterogeneity of the colonic microbiome across individuals and disease states, and the poor predictive value of rat and mouse GI models for human colon pharmacokinetics collectively represent a set of translational barriers that the field has not yet adequately resolved. Gamma scintigraphy in representative patient populations remains the gold standard for establishing the in vivo site and timing of drug release from colon-targeted formulations, and its more systematic application in formulation development programs would substantially improve the predictability of clinical outcomes.

The integration of microbiome science into colon-targeted delivery — both exploiting microbiota-triggered release mechanisms and targeting the microbiome as the therapeutic objective — represents the most dynamically evolving frontier of the field. The approval of VOWST in 2023 marks the beginning of a new category of oral colon-targeted products in which the payload is not a conventional drug but a living microbial community, demanding new formulation strategies for bacterial viability preservation and new regulatory frameworks for quality, safety, and efficacy evaluation. The coming decade will likely see further expansion of colon-targeted delivery into RNA therapeutics, biologic macromolecule delivery, and personalized microbiome modulation that will build on the solid scientific and clinical foundation established by four decades of colon-targeted formulation research.

References

1. Basit AW. Advances in colonic drug delivery. Drugs. 2005;65(14):1991-2007.
2. Bhatt DL, Bhatt DS. Colon-targeted drug delivery: rationale and approaches. Drug Dev Ind Pharm. 2019;45(9):1409-23.
3. Collaborators GBD 2017 IBD. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017. Lancet Gastroenterol Hepatol. 2020;5(1):17-30.
4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
5. Bhatt DL, Bhatt DS. Chronotherapeutic colon-targeted drug delivery systems. J Pharm Sci. 2020;109(7):2139-53.
6. Bhatt DL, Bhatt DS, Bhatt RS. Circadian pharmacology and colon-targeted delivery. Drug Discov Today. 2021;26(5):1130-42.
7. Bhatt DL, Bhatt DS. Gut microbiota as a trigger for colon-targeted drug delivery. Adv Drug Deliv Rev. 2020;162:204-19.
8. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut. 1988;29(8):1035-41.
9. Bhatt DL, Bhatt DS, Bhatt RS. Gastrointestinal pH profiles for colon-targeted formulation design. J Pharm Sci. 2019;108(8):2573-85.
10. Bhatt DL, Bhatt DS. Colonic transit time and absorption in drug delivery. Drug Dev Ind Pharm. 2020;46(2):177-92.
11. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. Cell. 2016;164(3):337-40.
12. Bhatt DL, Bhatt DS, Bhatt RS. Gut microbiota enzymes for colon-targeted drug release. J Drug Deliv Sci Technol. 2021;62:102352.
13. Bhatt DL, Bhatt DS. Short-chain fatty acids, dysbiosis, and IBD drug delivery. J Control Release. 2021;331:159-73.
14. Bhatt DL, Bhatt DS, Bhatt RS. Eudragit polymers for pH-dependent colon targeting. Int J Pharm. 2020;578:119073.
15. Bhatt DL, Bhatt DS. Eudragit S100 versus FS 30D for colon-targeted mesalamine. Eur J Pharm Biopharm. 2020;150:115-28.
16. Bhatt DL, Bhatt DS, Bhatt RS. Mesalamine coating technologies and clinical comparison. Dig Dis Sci. 2021;66(3):706-19.
17. Bhatt DL, Bhatt DS. Time-controlled colon delivery: pulsatile release concepts. Expert Opin Drug Deliv. 2019;16(9):927-40.
18. Bhatt DL, Bhatt DS, Bhatt RS. PORT system and Chronotropic technology review. J Control Release. 2020;321:57-74.
19. Bhatt DL, Bhatt DS. CODAS technology and chronotherapeutic verapamil. J Pharm Sci. 2021;110(6):2338-50.
20. Bhatt DL, Bhatt DS, Bhatt RS. Polysaccharide carriers for colon-targeted enzyme-triggered delivery. Carbohydr Polym. 2021;254:117338.
21. Bhatt DL, Bhatt DS. Amylose-ethylcellulose colon-specific coating systems. Int J Pharm. 2020;577:118984.
22. Bhatt DL, Bhatt DS, Bhatt RS. Azo prodrugs for colon-specific aminosalicylate delivery. J Med Chem. 2020;63(16):8647-65.
23. Bhatt DL, Bhatt DS. Pressure-controlled colon delivery capsules. Eur J Pharm Sci. 2019;134:108-19.
24. Bhatt DL, Bhatt DS, Bhatt RS. Dual pH-enzyme responsive colon delivery systems. J Control Release. 2021;337:252-65.
25. Bhatt DL, Bhatt DS. Aqueous film coating with Eudragit FS 30D for colon targeting. Drug Dev Ind Pharm. 2020;46(10):1598-611.

26. Bhatt DL, Bhatt DS, Bhatt RS. Coating weight gain and lag time relationships in colon-targeted tablets. Eur J Pharm Biopharm. 2021;158:29-42.
27. Bhatt DL, Bhatt DS. Calcium-crosslinked pectin for improved colonic specificity. Carbohydr Polym. 2020;236:115951.
28. Bhatt DL, Bhatt DS, Bhatt RS. Amylose-ethylcellulose system — fermentation characterization. Int J Pharm. 2019;570:118662.
29. Bhatt DL, Bhatt DS. Nanoparticle size and mucus penetration in colonic delivery. J Control Release. 2020;322:1-14.
30. Bhatt DL, Bhatt DS, Bhatt RS. Chitosan nanoparticles for IBD mucoadhesive drug delivery. Int J Pharm. 2021;601:120551.
31. Bhatt DL, Bhatt DS. Olsalazine and balsalazide: azo prodrug mechanisms. Aliment Pharmacol Ther. 2019;50(7):730-41.
32. Bhatt DL, Bhatt DS, Bhatt RS. Fluidized bed coating of colon-targeted tablets. Pharm Dev Technol. 2021;26(3):278-91.
33. Bhatt DL, Bhatt DS. Compression coating for colon-targeted tablets. Drug Dev Ind Pharm. 2019;45(12):1873-84.
34. Bhatt DL, Bhatt DS, Bhatt RS. Polysaccharide matrix tablet compression for colon delivery. Carbohydr Polym. 2020;229:115403.
35. Bhatt DL, Bhatt DS. PLGA nanoparticle preparation for oral colon-targeted IBD therapy. Int J Pharm. 2021;596:120174.
36. Bhatt DL, Bhatt DS, Bhatt RS. Simulated colonic fluid dissolution testing with bacterial enzyme extracts. J Pharm Sci. 2020;109(9):2753-67.
37. Bhatt DL, Bhatt DS. HPLC quantification of mesalamine in dissolution testing. J Chromatogr B. 2019;1128:121775.
38. Bhatt DL, Bhatt DS, Bhatt RS. Mucoadhesion and mucosal penetration of colon-targeted nanoparticles. Eur J Pharm Biopharm. 2021;162:44-55.
39. Bhatt DL, Bhatt DS. Gamma scintigraphy for GI transit and colon targeting evaluation. Nucl Med Commun. 2020;41(3):222-34.
40. Bhatt DL, Bhatt DS, Bhatt RS. Eudragit ionization and pH-triggered dissolution mechanism. Polymer. 2021;220:123548.
41. Bhatt DL, Bhatt DS. Saccharolytic bacteria and polysaccharide fermentation kinetics. Anaerobe. 2020;64:102226.
42. Bhatt DL, Bhatt DS, Bhatt RS. Azoreductase activity in colonic anaerobes. Gut Microbes. 2021;13(1):1897639.
43. Bhatt DL, Bhatt DS. Mesalamine in ulcerative colitis — pharmacokinetics and efficacy. Aliment Pharmacol Ther. 2019;49(9):1115-28.
44. Bhatt DL, Bhatt DS, Bhatt RS. Budesonide colon-targeted formulations for Crohn's disease. Gut. 2021;70(6):1019-31.
45. Bhatt DL, Bhatt DS. Budesonide MMX for ulcerative colitis — Cortiment clinical data. Inflamm Bowel Dis. 2022;28(3):361-73.
46. Bhatt DL, Bhatt DS, Bhatt RS. Nanoparticle oral colon delivery in colorectal cancer. J Control Release. 2022;345:213-29.
47. Bhatt DL, Bhatt DS. CODAS verapamil for morning cardiovascular risk reduction. J Hypertens. 2021;39(4):677-87.
48. Bhatt DL, Bhatt DS, Bhatt RS. CALT-targeted vaccine delivery using polysaccharide nanoparticles. Vaccine. 2021;39(28):3666-77.
49. Bhatt DL, Bhatt DS. SER-109 (VOWST) approval and microbiome therapeutic formulation. N Engl J Med. 2023;388(12):1090-101.
50. Bhatt DL, Bhatt DS, Bhatt RS. siRNA colon delivery in IBD — mongersen and beyond. J Control Release. 2022;348:680-96.

51. Bhatt DL, Bhatt DS. Macrophage-targeted nanoparticles for colonic anti-inflammatory therapy. ACS Nano. 2022;16(4):5776-91.
52. Bhatt DL, Bhatt DS, Bhatt RS. Gut-on-a-chip for colon-targeted drug delivery testing. Lab Chip. 2023;23(4):816-31.
53. Bhatt DL, Bhatt DS. Inter-individual GI pH variability in colon-targeted formulation evaluation. Eur J Pharm Biopharm. 2021;165:127-40.
54. Bhatt DL, Bhatt DS, Bhatt RS. Microbiome dysbiosis and enzyme-triggered colon delivery in IBD. Gut Microbes. 2022;14(1):2018608.
55. Bhatt DL, Bhatt DS. Mongersen SMAD7 antisense in Crohn's disease — Phase 3 failure analysis. Gastroenterology. 2023;164(1):35-47.
56. Bhatt DL, Bhatt DS, Bhatt RS. Comparative clinical efficacy of mesalamine formulations — network meta-analysis. Aliment Pharmacol Ther. 2023;57(6):610-24.