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Review Article

A Review on: Advances in colon targeted drug delivery system for oral site specific Therapeutics

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A B S T R A C T

Colon-targeted drug delivery has attracted significant attention due to its potential to achieve site-specific and controlled therapeutic action within the large intestine. The unique physiological environment of the colon—neutral to slightly alkaline pH, long transit time, dense microbial population, and selective permeability—offers several exploitable triggers for localized drug release. Conventional approaches such as prodrug systems, pH-dependent coatings, time-controlled release, and polysaccharide-based carriers utilize physiological variations along the gastrointestinal tract but face limitations due to inter- and intra-patient variability, disease-induced alterations, and inconsistent release profiles. Recent advances have focused on multifunctional and adaptive delivery systems integrating nanotechnology, smart polymers, and disease-responsive triggers to enhance precision and therapeutic efficiency. Developments such as multi-trigger systems, osmotic and pressure-controlled capsules, nanoparticles, and intelligent stimuli-responsive platforms have demonstrated improved localization, sustained release, and minimized systemic toxicity in conditions like inflammatory bowel disease, colorectal cancer, and other colonic disorders. Emerging ligand-mediated and externally triggered systems further enhance specificity through receptor targeting and controlled external modulation. Collectively, these innovations mark a shift toward next-generation colon-targeted drug delivery paradigms incorporating personalized, intelligent, and multi-responsive formulations for superior clinical outcomes.

Key words: Colon-targeted drug delivery system ,Site-specific oral therapeutics ,pH-dependent drug delivery Microbially triggered polysaccharide systems ,Nanoparticle-based colon delivery ,Stimuli-responsive smart systems.

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INTRODUCTION

Colon-targeted drug delivery has become one of the most popular fields of pharmaceutics, as the large intestine presents unique physiological and pathological conditions, which can be used to gain site-specific and, in certain instances, systemic therapeutic outcomes[1].The colon is the final segment of the gastrointestinal (GI) tract, being made up of the ascending, transverse, descending, and sigmoid colon with the attachments of the rectum and is charged with the responsibility of absorbing water and electrolytes, fermentation of the undigested carbohydrates and also storing the fecal matter[2]. The colon relative to the stomach and small intestine is typified by relatively neutral to slightly alkaline pH, higher transit time, lower fluid content, abundant and heterogenous microbiota, and a thick mucus layer, which all contribute significantly to drug dissolution, stability, and absorption.These attributes form the basis of current colon -targeted delivery approaches[3]. The luminal pH is generally in the range of approximately 6 to 7.5, but this may be changed by a significant amount between individuals and through various parts hence should be taken into account when engineering pH-dependent systems. In this physiological context, colon-specific drug delivery systems may be generally characterized as a dosage form designed to release the drug minimally in the stomach and small intestine but be able to react to specific colonic microenvironmental conditions, through any of a variety of triggering mechanisms, including pH changes, transit time, the activity of intestinal microorganisms, luminal pressure, or disease-specific biochemical signals[4]. Colon-specific systems have

been broadly described as systems where the drug release is controlled, and preferably predictable, on reaching the colon, with may triggering the classical colon targeting strategies were mostly limited to spatial targeting, ensuring that drugs destined to treat colonic diseases are not degraded in the upper GI tract, but rather released in the colon under specific pH conditions associated with the distal ileum or colon[5]. Examples of classic methods of colon targeting include prodrugs of 5 -aminosalicylic acid (5 -ASA) conjugated to azo bonds, which are cleaved by colonic microbes, and tablets coated with pH-sensitive polymers, engineered to dissolve at pH conditions Colon-targeted systems have been shown to have disease-relevant applications, particularly in inflammatory bowel diseases such as ulcerative colitis and Crohn disease: These diseases are chronic relapsing disorders, with inflammation and ulceration of the intestinal mucosa, and often including the colon and rectum[6]. Inflammatory bowel disease Colon-targeted delivery has been demonstrated to have considerable disease relevance, as these diseases are chronic relapsing conditions, accompanied by inflammation and ulceration of the intestinal mucosa, and often involving Non-targeted oral or parenteral administration of standard drugs like aminosalicylates, corticosteroids, immunosuppressants, and biologic agents can be effective but often cause serious side effects systemically and result in adverse systemic reactions and are more useful when localized to the diseased colonic region[7].Colon-specific formulations of drugs, such as mesalazine and budesonide, have shown that localization of drug release to the diseased column leads to much lower systemic drug effects, better clinical output, and less toxic systemic reactions and adverse[7,8]. A good example is pH-modified and multi-layered based systems, which have been clinically applied to deliver mesalazine selectively to the colon to achieve better control of inflammation with reduced systemic toxicity than non-targeted regimens[9].Colorectal cancer is another critical area of therapeutic interest in which colonic-targeted delivery has been demonstrated to be more effective than non-targeted-controlled systems. The application of nanoparticles, prodrug, and polymer-based systems to deliver drugs selectively to the colon has been shown to be more successful than non In addition to the IBD and the treatment of colorectal cancer, colon-targeted systems have been investigated in the treatment of irritable bowel syndrome and in infectious colitis and other localized colonic disease where localized drug concentrations would be preferable[10]. Delivery to sites can enable lower total doses, less frequent dosing and better adherence by reducing upper GI side effects and systemic toxicity[11].

Colon physiology relevant to targeting

Colon physiology critically determines whether colon-targeted systems release drug at the right site and time.Key factors are pH profile, transit behavior, colonic microbiota, and how disease alters these parameters.Colonic pHIn healthy adults, colonic pH is usually near neutral, roughly 6.0–7.5, and tends to increase from proximal to distal segments, but there is large inter- and intra-individual variability[12].In active ulcerative colitis or Crohn's colitis, the lumen often becomes more acidic due to fermentation changes and inflammation, which can delay or prevent dissolution of pH-dependent coatings designed to open above about pH 7.Transit and motility small intestinal transit is relatively predictable (about 3–4 hours), whereas colonic transit can range from roughly 20 to over 40 hours, providing a long window for local action and controlled release.Disease states such as severe diarrhea or constipation shorten or prolong colonic transit, respectively, which can cause premature washout or prolonged retention of colon-targeted dosage forms and complicate time-dependent systems[13]. In IBD or after antibiotic therapy, bacterial composition and enzymatic activity can be markedly reduced or shifted, potentially slowing degradation of polysaccharide-based carriers and leading to incomplete drug release.Disease-related changes and targetingInflammation, ulcers, and tumors increase mucosal permeability, alter mucus thickness, and may generate excess reactive oxygen species, which can be exploited by permeability-enhancing or ROS-responsive systems.However, combined changes in pH, transit, and microbiota during disease often reduce the reliability of single-trigger pH- or microbially responsive systems, supporting the trend toward multi-trigger and adaptive colon-targeted designs[14].

Conventional targeting approaches

Conventional colon-targeting approaches rely on physiological differences between the upper GI tract and colon to trigger site-specific drug release[15].The four classic strategies are prodrug design, pH-dependent systems, time-dependent systems, and microbially triggered polysaccharide-based systems, each with clear advantages and important limitations[16].

Prodrug-based systems

Drug is covalently linked to a carrier (e.g., azo, glycosidic, amide bond) that is stable in the stomach and small intestine but cleaved by colonic bacterial enzymes (e.g., azoreductases, glycosidases). Classic examples include azo-linked 5-aminosalicylic acid prodrugs for IBD[17].High selectivity when target enzymes are abundant; minimal release in upper GI; possibility to tailor linkers to specific bacterial enzymes and improve colonic localization[18].Requires chemical modification and full toxicological evaluation of the promoiety; inter-individual variability in microbiota and enzyme levels can cause under- or over-release; difficult to apply to all drug classes[19].

pH-dependent systems

Dosage forms are coated with polymers that remain intact at low pH (stomach, proximal small intestine) and dissolve when luminal pH exceeds a threshold typical of distal ileum/colon (often around pH 6–7).Methacrylic acid copolymers and other enteric polymers with defined dissolution pH; sometimes combined in multi-layer coatings to tune the release site[20].Technologically straightforward and scalable; established regulatory experience; good protection against gastric acid.Large inter- and intra-patient variability in GI pH and disease-induced acidification of the colon can cause premature opening in distal small intestine or failure to dissolve; food effects may further change pH profile and compromise targeting[21].

Time-dependent (chronotropic) systems

Drug is protected by an outer layer (often enteric) and an additional barrier that imposes a lag time before release; the lag is designed to match average small intestinal transit so that release begins around colonic entry.Variations include hydrophobic or swellable barriers, plug-containing capsules, and layered tablets engineered for a predetermined delay[22].Do not rely on local pH or microbiota; conceptually simple; can be tuned to deliver drug after a programmed time, enabling chronotherapy (e.g., symptoms peaking at night or early morning).GI transit times show high variability with food, disease, and individual physiology, so a fixed lag time cannot guarantee colonic release; premature or delayed release is common in vivo; dose dumping is possible if barrier fails[23].

Microbially triggered polysaccharide systems

Dosage forms are prepared with natural or modified polysaccharides (e.g., pectin, guar gum, chitosan, inulin, dextran, amylose) that resist digestion in the stomach and small intestine but are degraded by colonic bacterial enzymes[24].Matrix tablets, coated cores, hydrogels, and nano-/micro-particles where the polysaccharide forms a major structural component[25].Exploit the unique, dense colonic microbiota; minimal reliance on pH; use of generally recognized as safe (GRAS) materials; potential for high specificity when microbiota is intact.Natural polymers show batch variability; premature swelling/erosion in small intestine can occur; disease, antibiotics, or diet can reduce bacterial populations and slow carrier degradation, leading to incomplete or delayed drug release[26].

Advanced and emerging systems

Advanced and emerging colon-targeted delivery systems build on conventional pH, time and microbially triggered designs by integrating multiple triggers, nanotechnology, and disease-responsive materials to improve precision, efficacy and safety. These systems aim to overcome variability in pH, transit and microbiota and to exploit pathophysiological features of inflamed or cancerous colon such as altered permeability, receptor overexpression and elevated reactive oxygen species (ROS).

Multi-trigger and hybrid systems

Modern colon-targeted formulations often incorporate more than one triggering mechanism to reduce the chance of premature release or non-release[27]. A typical strategy is to combine an enteric coating (protecting against gastric acid) with an internal layer containing organic acids or polysaccharides that modulate local pH and/or undergo microbial degradation, followed by a core designed for controlled release.Such “hybrid” systems may rely simultaneously on pH elevation in the distal gut, specific transit time, and enzymatic activity of colonic microbiota, providing higher robustness than single-trigger designs in the face of inter-patient variability[28].Recent work also explores co-processed excipients and interpenetrating polymer networks that can respond to both pH and enzymes, tuning swelling and erosion profiles for more reliable colon opening[29].

Osmotic and pressure-controlled capsules

Osmotic and pressure-controlled systems use mechanical forces within the colon rather than only chemical cues to trigger drug release[30].Osmotic capsules typically consist of a semi-permeable membrane surrounding an osmogen-containing core with a delivery orifice; as fluid enters, internal pressure builds until it pushes drug solution or suspension out at a controlled rate. For colon targeting, such devices are often coated with an enteric layer to delay activation until after gastric emptying, and the formulation is tuned so that meaningful osmotic pumping begins around the ileocolonic region[31]. Pressure-controlled capsules are designed to rupture or open when exposed to the higher intraluminal pressure characteristic of the colon, caused by viscous contents and segmental contractions, which is typically greater than in the small intestine.These mechanical approaches are less dependent on luminal pH and microbiota, but they still face inter-subject variability in GI motility and luminal contents, and their complexity can pose manufacturing and cost challenges[32].

Nanoparticles and nano-in-micro systems

Nanotechnology has become a central theme in advanced colon-targeted delivery, with polymeric nanoparticles, lipid nanoparticles, micelles and nano-in-micro systems used to improve mucosal retention, tissue penetration and cellular uptake[33]. Polymeric nanoparticles based on PLGA, PCL and modified polysaccharides can be engineered for stability in upper GI fluids, followed by controlled degradation or surface charge changes in the colonic environment, enabling sustained local release. Surface modification with hydrophilic polymers such as PEG or with targeting ligands helps nanoparticles navigate the mucus barrier and selectively bind to inflamed or cancerous tissue. Lipid-based systems, including solid lipid nanoparticles and nanostructured lipid carriers, offer high loading of lipophilic drugs and can be incorporated into colon-specific tablets or capsules via coatings or microencapsulation. Nano-in-micro platforms, where nanoparticles are embedded within a larger pH- or microbially responsive microparticle, provide an additional level of protection and allow more accurate colonic positioning before nanoparticle release[34].In inflammatory bowel disease models, nanoparticles carrying corticosteroids, immunosuppressants or natural anti-inflammatories (e.g., curcumin) have shown enhanced accumulation at inflamed sites, improved disease scores and reduced systemic toxicity relative to conventional formulations. Similarly, nano-formulations of chemotherapeutic agents such as 5-fluorouracil or irinotecan for colorectal cancer have demonstrated better tumor localization and antitumor efficacy in preclinical studies, especially when combined with targeting ligands or stimuli-responsive elements[35].

Stimuli-responsive and “intelligent” systems

Stimuli-responsive systems are designed to sense and react to specific physicochemical changes associated with the colonic environment or disease states, earning the label “intelligent” or “smart” carriers. Enzyme-responsive hydrogels and nanogels incorporate linkages or cross-links cleavable by enzymes overexpressed in colonic microbiota or in inflamed tissues, such as azoreductases, glycosidases, matrix metalloproteinases or proteases[36]. ROS-responsive polymers

contain groups that degrade or change hydrophilicity in the presence of high ROS levels, which are characteristic of inflamed colonic mucosa, leading to triggered release of anti-oxidant or anti-inflammatory drugs at disease sites. Dual- or multi-responsive systems may respond to combinations of pH, temperature, redox state, and enzymes, allowing finely tuned release profiles that better match complex pathophysiology[37].In IBD models, ROS-responsive nano-carriers have been shown to preferentially release drugs in inflamed areas while limiting release in healthy tissue, thereby improving local efficacy and minimizing off-target effects. In cancer, pH- and enzyme-responsive systems exploit the mildly acidic and protease-rich tumor microenvironment, combined with colon targeting, to concentrate cytotoxic agents in colorectal tumors.These stimuli-responsive designs represent an evolution from passive to active environmental sensing, aligning drug release more closely with disease activity[38].

Ligand-mediated and cell-targeted delivery

Ligand-mediated systems enhance specificity by decorating carriers with molecules that bind receptors or adhesion molecules overexpressed in diseased colonic tissues[39].In IBD, integrins, selectins, and cell surface markers on activated immune cells can be targeted with peptides, antibodies or carbohydrate ligands to direct nanoparticles or liposomes to inflamed mucosa or to specific immune cell populations. In colorectal cancer, ligands such as folate, hyaluronic acid (for CD44), RGD peptides (for integrins), and antibodies against tumor-associated antigens have been used to guide nanocarriers to tumor cells, improving uptake and intracellular delivery[40].By combining colon targeting (through pH, microbial or time triggers) with molecular targeting (through ligands), these systems can achieve dual-level specificity: first ensuring arrival in the colonic region, then preferential accumulation in diseased tissue or specific cell types. This strategy has shown promising preclinical results in enhancing therapeutic index for both anti-inflammatory and anticancer agents, although manufacturing complexity and cost remain important considerations for translation[41].

Magnetically and externally triggered systems

Magnetically guided systems incorporate magnetic nanoparticles within oral dosage forms, which can be held or concentrated in the colon using an external magnetic field, increasing local residence time and drug exposure[42].In experimental studies, such systems have demonstrated improved colonic retention and localized drug release, but clinical application is challenged by practical issues such as field generation, patient convenience and safety[43].Other externally triggered approaches, including ultrasound or light-responsive materials, have been explored mainly in preclinical settings and could, in principle, allow on-demand drug release once a dosage form reaches the colon[44].

Future-oriented integrated platforms

The latest trend is toward integrated platforms that combine multiple advanced features: nano-scale carriers with stimuli-responsive matrices, ligand targeting, and multi-trigger colon positioning, often guided by in silico modeling and microbiome profiling[44],[45]. For example, a single system might use an enteric coat plus a microbial-degradable layer for colon entry, release muco-penetrating nanoparticles that carry ROS-responsive cores, and present surface ligands for inflamed or tumor tissue targeting[46].Such designs seek not only to localize drugs but also to adapt dynamically to local conditions, potentially supporting personalized therapy when combined with patient-specific data on microbiota and disease activity[47],[48].

Formulation strategies

Formulation strategies for colon-targeted delivery focus on choosing and engineering materials whose structure and properties align with specific colonic triggers (pH, time, microbiota, enzymes, ROS, receptors). These include pH-sensitive polymers, polysaccharides, biodegradable synthetic polymers, lipids/surfactants, and newer stimuli-responsive and hybrid networks.

pH-sensitive synthetic polymers

Structurally, classic pH-sensitive polymers are weak polyacids (e.g., methacrylic acid copolymers) or polybases with ionizable groups that remain unionized and insoluble in gastric/upper small-intestinal pH but ionize and dissolve above a threshold pH typical of distal ileum/colon. These are usually used as coatings on tablets, pellets or capsules to create enteric and delayed-release layers[49]. The trigger mechanism is ionization-induced dissolution or swelling once luminal pH exceeds about 6–7, exposing the drug core and initiating release.Advantages include well-established processing (solution or dispersion coating), scalable manufacturing, robust gastric protection, and extensive regulatory experience for many grades[50].Challenges are large inter-patient variability in GI pH, disease-induced acidification of the colon (especially in active IBD), and food effects, all of which can cause premature dissolution in distal small intestine or failure to dissolve in the colon.Recent modifications focus on fine-tuning copolymer composition and molecular weight to adjust dissolution pH windows, developing aqueous dispersions with better film quality, and combining pH-sensitive polymers with enzymatically degradable or hydrophobic components to create multi-trigger coatings (e.g., pH plus microbial or time triggers)[51].

Polysaccharides and microbially degradable matrices

Natural polysaccharides (pectin, guar gum, chitosan, inulin, dextran, amylose, xanthan gum) are widely used because their glycosidic linkages and high molecular weight confer resistance to digestion in the upper GI tract but susceptibility to fermentation and enzymatic degradation by colonic microbiota. They can serve as matrix formers, coating materials, or hydrogel networks in tablets, pellets, capsules, and nano/microparticles[52]. The primary trigger is microbial degradation of the polysaccharide backbone by colonic bacteria (glycosidases, pectinases, dextranases), leading to erosion or pore formation and subsequent drug release.Advantages include biocompatibility, availability, many with GRAS status, and direct exploitation of the dense colonic microbiota, making them intrinsically colon-biased. Challenges include batch-to-batch variability, sensitivity to processing (hydration, compression), premature swelling/erosion in upper GI, and the fact that microbiota

composition/activity is altered by disease, antibiotics, and diet, which can slow degradation and produce incomplete or delayed release[53].Recent formulation strategies involve chemical modification (cross-linking, grafting with synthetic monomers, thiolation, hydrophobic modification) to control swelling, reduce early dissolution, and tailor degradation rates; creating interpenetrating networks with pH-sensitive acrylics; and using polysaccharide-based nanogels or nano-in-micro systems to combine microbial triggering with better mucosal interaction and drug protection[54].

Biodegradable synthetic polyesters (e.g., PLGA, PCL)

Poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and related biodegradable polyesters contain hydrolyzable ester linkages that undergo bulk or surface erosion in aqueous media, enabling prolonged, diffusion-plus erosion-controlled release. They are primarily used as nanoparticle or microparticle matrices, sometimes embedded into colon-specific tablets or capsules that provide the initial GI protection.The intrinsic trigger is hydrolytic degradation (time-dependent), but in colon-targeted systems they are often combined with external triggers such as pH-sensitive coats or microbially degradable outer shells[55].Advantages include good control over release kinetics via polymer composition (lactide:glycolide ratio, molecular weight, end-group chemistry), established safety for parenteral use, and suitability for nano- and micro-sized carriers that enhance mucosal retention and cellular uptake[56]. Challenges include potential burst release, acidic microenvironment from degradation products (for PLGA) that can destabilize sensitive actives, and more stringent regulatory scrutiny for oral nano-systems.Recent modifications involve surface PEGylation or coating with mucoadhesive/mucus-penetrating polymers, conjugation of targeting ligands (folate, antibodies, peptides), and blending with polysaccharides or pH-sensitive polymers to create multi-responsive nano-systems tailored for inflamed or tumor tissue in the colon[57].

Lipids and surfactants (SLNs, NLCs, SEDDS)

Lipid-based carriers such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and self-emulsifying drug delivery systems (SEDDS) rely on lipid matrices and surfactants that solubilize lipophilic drugs and can form colloidal dispersions in GI fluids. Structurally, SLNs use solid lipids, NLCs mix solid and liquid lipids to improve loading and reduce crystallinity, while SEDDS are isotropic mixtures of lipid/surfactant/co-solvent that spontaneously form emulsions upon dilution.For colon targeting, these carriers are typically incorporated into pH- or polysaccharide-coated tablets/capsules or microencapsulated in polymer shells so that the lipid structures are only released in the colon[58].Advantages are high loading of poorly soluble drugs, protection from hydrolysis and enzymatic degradation, and potential for lymphatic transport or enhanced mucosal uptake once released[59].Challenges include physical instability (polymorphic transitions, aggregation), surfactant-related irritation, and complex in vivo behavior, especially when combined with colon-specific coatings.Recent approaches include hybrid lipid–polymer nanoparticles, where a lipid core is coated with polymers responsive to pH or ROS, and ligand-decorated lipid carriers for targeted colorectal cancer or inflamed mucosa therapy[60].

Stimuli-responsive and “smart” polymers

Stimuli-responsive polymers are engineered with functional groups or cross-links that react to specific stimuli such as enzymes, ROS, pH shifts, or temperature changes.Examples include azo cross-linked networks cleaved by bacterial azoreductases, polysaccharide- or peptide-cross-linked hydrogels sensitive to bacterial glycosidases or proteases, and ROS-responsive polymers containing thioketal, boronic ester, or disulfide linkages that break in oxidative environments.The trigger mechanism is structural transformation of the network (de-cross-linking, sol–gel transition, or charge alteration) at the disease site, causing pronounced swelling or erosion and releasing drug[61].Advantages are high specificity toward diseased tissue (inflamed IBD mucosa or tumors), which helps limit off-target release and reduce systemic side effects[62].Challenges include synthetic complexity, potential variability of stimulus intensity among patients, and the need for comprehensive safety and degradation-product evaluation.Recent modifications focus on multi-stimuli-responsive designs (e.g., pH plus ROS or enzyme plus temperature), incorporation into nanoparticles or nano-in-micro structures to combine macro-level colon targeting with micro-level disease responsiveness, and integration with imaging agents to enable theranostic applications[63].

Mucoadhesive and mucus-penetrating coatings

Mucoadhesive materials such as chitosan, carbomers, polycarbophil, and thiolated polymers have functional groups that can form hydrogen bonds, ionic interactions or even covalent bonds (e.g., disulfide with mucin cysteines) with mucus, increasing residence time at the colonic wall. By contrast, mucus-penetrating systems use low-adhesion, hydrophilic coatings (often PEGylation) and optimized particle size/charge to diffuse through mucus and reach the epithelial surface.Mucoadhesive formulations can prolong contact at inflamed sites, improving local drug concentrations but risk entrapment in the outer, fast-shedding mucus layer[65]. Mucus-penetrating formulations can reach deeper mucus and epithelium but may have shorter overall residence time[65].Recent trends include designing “adaptive” carriers that initially penetrate mucus and then become more adhesive upon reaching inflamed tissue (e.g., charge-switchable or enzyme-activated mucoadhesion), and combining mucoadhesive polymers with stimuli-responsive matrices to localize and retain drug specifically at diseased colonic areas[66].

Ligands and targeting moieties

Targeting ligands such as folic acid, hyaluronic acid (for CD44), RGD peptides, antibodies, or carbohydrates can be covalently attached to polymer or lipid surfaces to recognize overexpressed receptors on inflamed or cancerous colonic cells.Structurally, this involves functionalization of carrier surfaces with reactive groups (carboxyl, amine, maleimide) and coupling of ligands through stable linkers.The trigger mechanism is receptor-mediated binding and uptake, which acts downstream of macro-level colon targeting provided by

coatings or matrices[67].Advantages are increased accumulation in diseased tissues and cells, improved internalization of nano-carriers, and potential reduction in off-target toxicity[68].Challenges include maintaining ligand activity during processing, potential immunogenicity, and cost and regulatory complexity for ligand-modified oral products.Recent work explores multi-ligand carriers (targeting multiple receptors), cleavable linkers that expose ligands only in the colon, and integration of targeting moieties into stimuli-responsive nanocarriers for dual spatial and cellular specificity[69].

Advance Approaches

Future perspectives in colon-targeted drug delivery emphasize microbiome-informed personalization, multi-responsive intelligent systems, AI-optimized designs, and integrated theranostics to overcome current limitations in precision and translation.

Microbiome-informed personalization

Individual microbiota profiles influence how fast polysaccharide carriers (e.g., pectin, dextran, inulin, guar gum) are degraded, which directly affects colon release.Recent reviews show microbiota-sensitive systems where natural polysaccharides act both as matrix and microbiome-active excipient, allowing adjustment of polymer type and content to patient-specific dysbiosis patterns in IBD[70].Microbiome-active drug delivery systems (MADDS) are being categorized into fermentable carriers and prodrug/polymer–drug conjugates activated by microbial enzymes, offering a framework for personalized selection based on fecal enzyme profiles[71].Machine-learning analysis of fecal microbiota and enzyme activity is being explored to predict degradation kinetics of carriers and refine dosing for IBD patients, although most work is at the modeling and ex vivo level. Probiotic and prebiotic co-administration is increasingly integrated into formulations: some polysaccharide matrices show intrinsic prebiotic activity that can help normalize dysbiosis while also serving as a colon-specific trigger[73].

Multi-stimuli “smart” platforms

Multi-stimuli hydrogels and nanoparticles that respond to combinations of pH, enzymes, redox and ROS are progressing from proof-of-concept to disease-model validation. Dual pH/enzyme-responsive hydrogels based on methacrylate copolymers with enzyme-cleavable crosslinkers have already been shown to remain stable in gastric conditions but swell and release drug faster in the presence of colonic microbial enzymes (rat cecal content), illustrating how multi-trigger logic can sharpen colon selectivity[74]. New pH/ROS-responsive hydrogels (e.g., GBR hydrogel) tested in DSS-induced colitis mice reduce disease activity index and improve weight, demonstrating inflammation-amplified release by exploiting elevated ROS in inflamed colon.Broader overviews of smart and multi-responsive hydrogels highlight materials that combine temperature, pH and redox sensitivity, and propose self-regulating systems where higher inflammatory signals accelerate degradation and drug liberation.Reviews of stimulus-responsive hydrogels for IBD and cancer describe concepts akin to “nanoparticle swarms” that disassemble or penetrate more deeply only under tumor-like pH/ROS conditions, aligning with the idea of autonomous, disease-adaptive delivery[75].

AI/ML and computational design

AI and ML are being implemented to optimize colon-targeted formulations by predicting coating thickness, polymer blends and lag times that match desired colonic arrival windows. Recent work specifically discusses AI’s role in colon-targeted drug delivery, emphasizing supervised and reinforcement learning to refine release profiles and formulation design before manufacturing, thereby reducing experimental burden.Broader AI/ML in drug delivery also uses models trained on physicochemical properties, in vitro dissolution, and in vivo PK/PD to suggest optimal excipient ratios and structural parameters for carriers[76].Digital-twin concepts of the GI tract are emerging from the convergence of ingestible sensors and computational modeling: ingestible electronic microsystems can continuously transmit GI pH, temperature, pressure and sometimes motility data, which can feed into individualized models of transit and local environment. Smart ingestible capsules with highly sensitive pH sensors have been demonstrated for real-time mapping of pH patterns in GI disorders such as IBD and ulcerative colitis, providing the type of data stream that could enable future closed-loop, adaptive dosing systems[77].

Theranostic and combination systems

Advances in colon-targeted nanocarriers increasingly combine therapeutic and diagnostic functions, embedding imaging agents such as fluorescent dyes or MRI contrast moieties into nanoparticles for real-time tracking of colonic delivery and tissue accumulation. Reviews of colon-targeted drug technologies highlight nanoparticle and microparticle systems capable of carrying both small molecules and biologics, and note that adding imaging payloads can support non-invasive assessment of mucosal distribution in IBD[78]. Multi-drug platforms are being designed for sequential or site-overlapping delivery, such as combinations of anti-inflammatory drugs with microbiome-modulating agents or chemotherapy with immunotherapies for colorectal cancer, although most remain at preclinical stages.An example of a “theranostic-like” strategy is DAV132, a colon-targeted adsorbent that captures residual antibiotics in the colon to protect the microbiota; recent human data show that DAV132 can modulate antibiotic-related dysbiosis without interfering with systemic antibiotic exposure, illustrating how colon-targeted systems can act both protectively and as a monitoring platform[79].

Advanced manufacturing and regulation

3D printing is being actively investigated to fabricate oral dosage forms with complex geometries and spatially programmed release regions tailored to colonic targeting.Recent reviews on colon-targeted drug delivery and advanced oral technologies emphasize that additive manufacturing allows patient-specific adjustment of shape, internal structure, and layer composition to tune transit times and site of release[79]. There is also progress in 3D-printed pulsatile and multi-compartment tablets that can mimic programmed lag times aligned with expected small-intestinal transit to achieve colonic arrival.On the regulatory side, agencies and academic–industry consortia are developing

more predictive in vitro and ex vivo models that incorporate human fecal microbiota and diseased tissue conditions to better evaluate colon-targeted systems. Recent reviews stress the need to harmonize dissolution and performance testing for microbiota-responsive systems, including the use of human fecal slurries and inflammation-mimicking media, to support approval of advanced smart carriers[80].

Gene therapy, microbiome editing and wearables

Colon-targeted gene therapy concepts involve viral and non-viral nanoparticles engineered for local delivery of CRISPR/Cas systems to colonic epithelial or immune cells to modulate inflammatory pathways in IBD or correct oncogenic mutations in colorectal cancer; current work is largely in preclinical models but shows feasibility of local GI gene editing with reduced systemic exposure[80].Reviews of stimuli-responsive nanomaterials discuss how pH and enzyme triggers can be combined with nucleic-acid cargoes for localized gene regulation in GI diseases.Microbiome-editing strategies are moving toward encapsulated engineered bacteria and bacteriophages for colon release, using pH- and microbiota-sensitive coatings to protect the biological agents through the upper GI tract. Encapsulated live biotherapeutic products designed for colon targeting are in early clinical development for IBD and metabolic disorders, illustrating the translational potential of immunomodulatory microbiome delivery[81].Wearable and ingestible GI monitoring is rapidly advancing: ingestible sensor capsules now capture multi-parameter data (pH, temperature, pressure, sometimes gas composition), while external wearables and IoT frameworks provide continuous monitoring and cloud-based analytics. Recent reports describe autonomous ingestible pH biosensing systems and biomechanical energy-harvesting devices to power ingestible electronics, pointing toward long-term, feedback-controlled platforms where real-time GI data could modulate colon-targeted drug release in a closed loop[82].

CONCLUSION

Colon-specific drug delivery continues to evolve from simple pH- or time-dependent systems toward complex and integrated platforms capable of responding dynamically to the heterogeneous colonic environment. While traditional designs laid the foundation for localized therapy, their limitations under pathological conditions have prompted the development of advanced systems that combine physical, chemical, and biological triggers. Nanotechnology and stimuli-responsive materials now enable precise release, improved mucosal interaction, and targeted accumulation in diseased tissues, reducing systemic side effects and enhancing therapeutic efficacy. The future of colon-targeted drug delivery lies in hybrid and personalized formulations that exploit patient-specific microbiome, disease biomarkers, and computational modeling to optimize drug localization and response. Ultimately, these advanced systems offer promising opportunities for effective, safe, and patient-tailored therapies for both local and systemic treatment of colonic diseases.

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