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Targeting the Colon: Advances in Oral and Site-Specific Drug Delivery.

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Abstract:

Colon-targeted drug delivery has effective approach to address the clinical need for localized treatment of colonic diseases while reducing systemic side effects and improving therapeutic outcomes. Advances in understanding colonic anatomy, physiology, gastrointestinal transit, and the role of microbiota have enabled the development of site-specific delivery strategies such as pH-dependent, time-controlled, enzyme-responsive, and microbiota-activated systems. The use of advanced carrier systems, including polymers, micro- and nanoparticles, lipid-based carriers, and hybrid platforms, has further enhanced drug stability, controlled release, and targeting precision. These technologies have shown significant therapeutic benefits in the management of inflammatory bowel disease, Crohn's disease, colorectal cancer, and microbiome-related and systemic applications. Despite promising preclinical and clinical outcomes, challenges such as formulation stability, physiological variability, regulatory complexity, and scalable manufacturing remain. Emerging trends focusing on smart multi-responsive systems, integration with microbiome-based therapies, and personalized medicine are expected to overcome existing limitations and drive the future clinical translation of colon-specific drug delivery systems.

Keywords: Colon-Targeted Drug Delivery, pH-Dependent, Microbiota-Activated, Crohn's Disease, Colorectal Cancer, Inflammatory Bowel Disease (IBD).

1. INTRODUCTION

1.1 Clinical Need for Colon-Targeted Drug Delivery

Colon-targeted drug delivery systems are designed to ensure that therapeutic agents are released specifically in the large intestine rather than earlier in the gastrointestinal tract, because many orally administered drugs are degraded or absorbed before they reach the colon, limiting their effectiveness against colonic diseases [1]. Targeting the colon is particularly important for treating local conditions such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, and colorectal cancer (Fig.1) where high local drug concentrations directly at the disease site can improve therapeutic outcomes while reducing systemic toxicity. Furthermore, the colon offers opportunities for systemic delivery of

drugs that are poorly absorbed or unstable in the stomach and small intestine by protecting them until they reach the distal gut. Effective colon targeting must account for unique physiological features such as variable pH, microbial flora, and transit times, necessitating specialized formulation strategies to protect drugs during transit and trigger release in the colon [2].

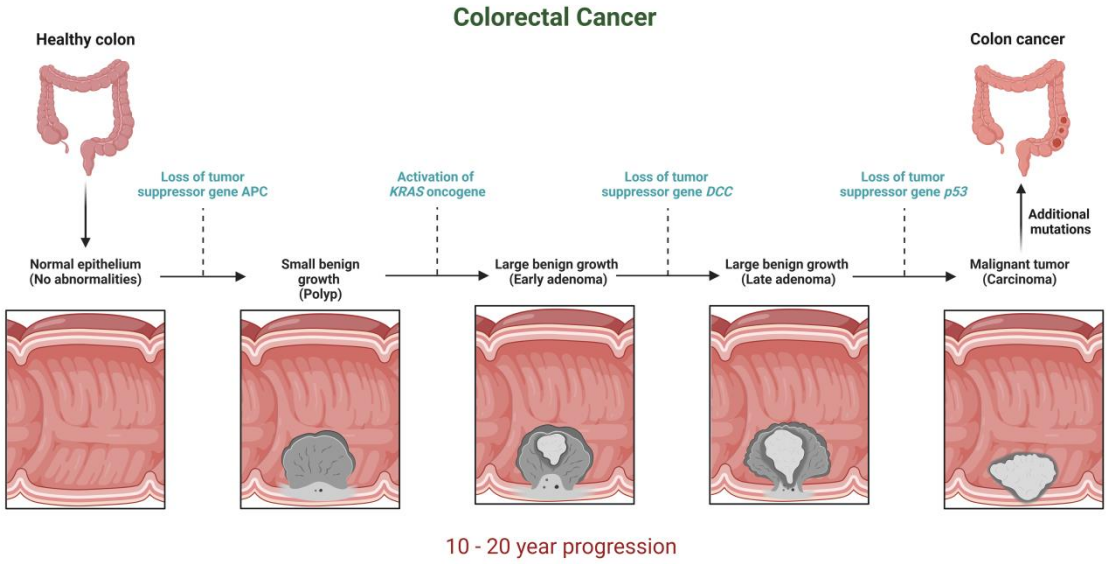

Fig.1 Colorectal Cancer

1.2 Advantages and Challenges of Colon-Specific Therapy

Colon-specific therapy provides several advantages over conventional oral administration by enabling higher local drug concentrations, reducing systemic side effects, avoiding first-pass hepatic metabolism, and improving bioavailability of labile drugs such as proteins and peptides. Localized release in the colon may also allow lower drug doses and better patient compliance due to targeted action with minimized off-target exposure [3].

However, this approach faces significant challenges, including physiological variability in pH and transit time among individuals, premature drug release before reaching the colon, degradation by digestive enzymes, barriers posed by the mucosal layer, and complex manufacturing requirements. Furthermore, producing predictable and reproducible drug release at the specific colonic site requires careful selection of polymers, excipients, and triggering mechanisms such as pH-sensitivity, time-dependence, or microflora responsiveness [4].

1.3 Scope and Objectives of the Review

The scope of this review is to provide a comprehensive overview of the design principles, formulation strategies, and advanced technologies used in oral colon-targeted drug delivery, covering both traditional approaches such as pH-dependent and time-dependent systems, as well as innovative techniques like hot-melt extrusion, three-dimensional printing, and microbiota-responsive carriers. By critically evaluating both the advantages and limitations of existing systems, the review aims to highlight how various methods can be tailored to ensure site-specific delivery with controlled release, improved therapeutic outcomes, and reduced side effects

Specific objectives include summarizing the role of physiological factors in colon targeting, comparing conventional and novel delivery systems, discussing relevant diseases that necessitate targeted therapy, addressing formulation challenges, and outlining future research directions for translating innovative delivery platforms into effective clinical applications.

2. PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL CONSIDERATIONS

2.1. Anatomy and Physiology of the Colon

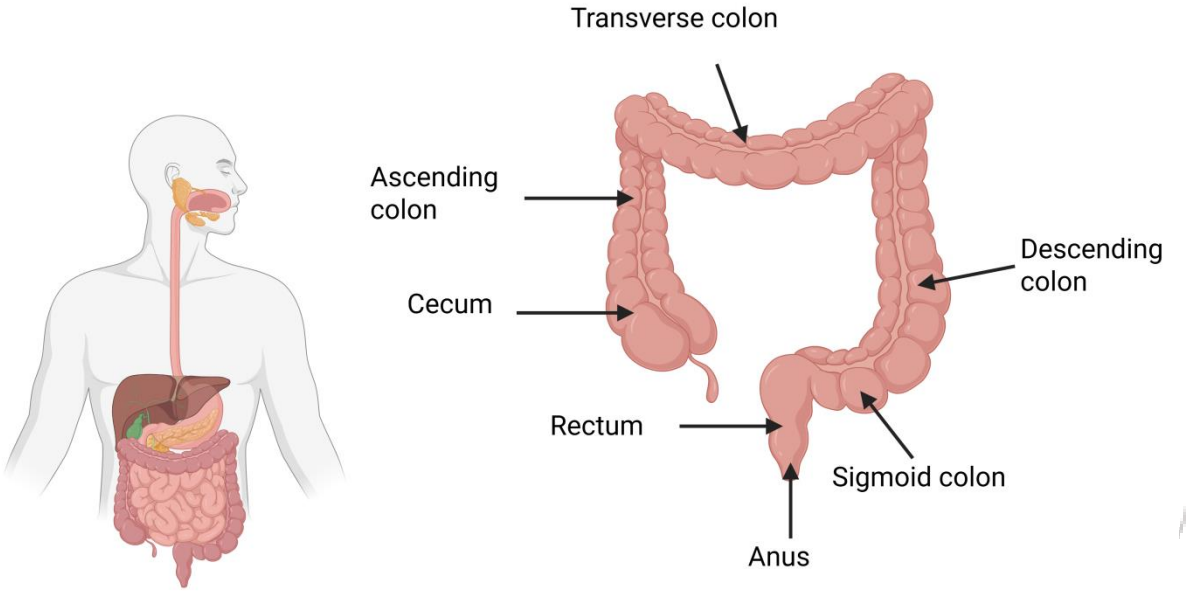

Fig.2 Anatomy and Physiology of the Colon

The colon is the terminal part of the gastrointestinal tract and consists of the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anus with an average length of approximately meters (Fig.2). Unlike the small intestine, the colon has a relatively smooth mucosal surface without villi, resulting in a smaller absorptive area; however, it plays a vital role in water and electrolyte absorption (Fig.2). The colonic wall is composed of mucosa, submucosa, with goblet cells producing large amounts of mucus that form a protective barrier [5]. Blood flow and enzymatic activity in the colon are lower than in the upper gastrointestinal tract, which can be advantageous for site-specific drug delivery. These anatomical and physiological characteristics influence drug residence time, permeability, and release behaviour, making the colon an attractive yet challenging target for oral drug delivery systems [6].

2.2 Gastrointestinal Transit and pH Gradients

Gastrointestinal transit time and pH variation play a crucial role in the design of colon-targeted drug delivery systems. After oral administration, dosage forms typically pass through the stomach within 0.5–2 hours and the small intestine within 3–4 hours, while residence time in the colon can extend from 20 to 30 hours, offering prolonged exposure for drug absorption or local action [7]. The pH of the gastrointestinal tract gradually increases from acidic conditions in the stomach (pH 1–3) to near neutral or slightly alkaline values in the small intestine (pH 6–7.5), followed by a decrease or stabilization in the colon (pH 6–7). However, these pH values vary significantly depending on diet, disease state, and individual physiology. This variability poses challenges for pH-dependent delivery

systems but also provides opportunities to design formulations that remain intact in the upper tract and release drugs upon encountering colonic conditions [8].

2.3 Role of Colonic Microbiota in Drug Activation

The colon harbors a dense and diverse population of anaerobic microorganisms that produce enzymes such as azoreductases, glycosidases, esterases, and nitroreductases, which are largely absent in the upper gastrointestinal tract. These microbial enzymes play a significant role in drug activation by degrading specific carrier materials or cleaving prodrugs designed for colon targeting [9]. Polysaccharides such as chitosan, pectin, guar gum, dextran, and inulin are commonly used in colon-specific formulations because they are resistant to digestion in the stomach and small intestine but are readily metabolized by colonic bacteria. This microflora-triggered approach enables highly site-specific drug release and is particularly useful for treating colonic diseases. However, variations in microbial composition among individuals and disease conditions can influence drug activation and therapeutic outcomes, necessitating careful formulation design and evaluation [10, 11].

3. STRATEGIES FOR COLON-TARGETED DRUG DELIVERY

3.1 pH-Dependent Delivery Systems

pH-Dependent delivery systems are among the most widely explored strategies for colon targeting, as they exploit the gradual increase in pH along the gastrointestinal tract. These systems typically use enteric polymers that remain intact in the acidic environment of the stomach and the mildly acidic to neutral conditions of the small intestine but dissolve at higher pH values encountered in the distal ileum and colon [12]. Commonly used polymers include methacrylate copolymers, cellulose acetate phthalate, and hydroxypropyl methylcellulose phthalate. The primary advantage of this approach lies in its simplicity and ease of formulation. However, variability in gastrointestinal pH due to diet, disease state, and interindividual differences may lead to premature or incomplete drug release, limiting the reliability of purely pH-based colon-targeted systems [13].

3.2 Time-Dependent and Pulsatile Release Systems

Time-dependent and pulsatile release systems are designed to deliver drugs to the colon based on the predictable transit time of dosage forms through the gastrointestinal tract. These systems rely on polymer coatings or matrices that gradually erode, swell, or dissolve over a predefined lag time, ensuring drug release occurs after passage through the stomach and small intestine [14].

Pulsatile systems, in particular, are useful for diseases exhibiting circadian rhythms, as they provide a rapid release of the drug following a programmed delay. Although this strategy does not depend on pH or enzymatic triggers, its effectiveness may be compromised by variability in gastric emptying time, intestinal motility, and physiological conditions among patients. Consequently, time-controlled systems are often combined with other targeting mechanisms to improve site specificity [15, 16].

3.3 Enzyme-Responsive Prodrugs and Carriers

Enzyme-responsive systems utilize the metabolic activity of colonic enzymes to achieve site-specific drug release. In this strategy, drugs are chemically modified into inactive prodrugs or encapsulated within carriers that remain stable in the upper gastrointestinal tract but are selectively degraded by enzymes present in the colon [17]. Prodrug approaches often involve linking the active drug to a promoiety via azo, glycosidic, ester, or amide bonds, which are cleaved by colonic enzymes to release the active compound. Similarly, enzyme-degradable carriers made from natural polysaccharides such as dextran, pectin, and chitosan are commonly employed. These systems offer high specificity for the

colon; however, variability in enzyme activity and formulation complexity can influence drug release consistency [18].

3.4 Microbiota-Activated Drug Delivery Systems

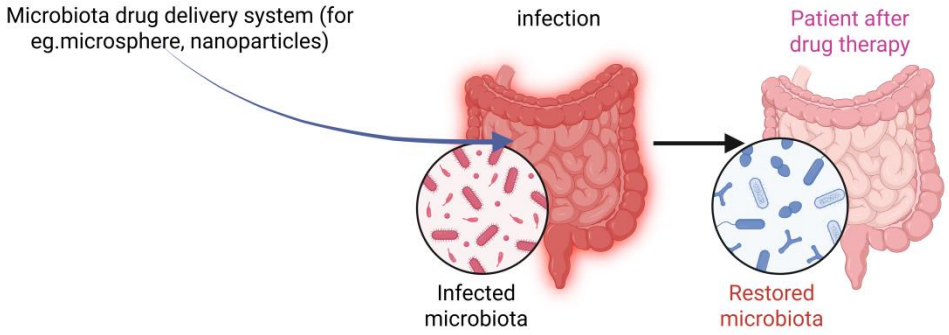

Fig.3 Microbiota-Activated Drug Delivery Systems

Microbiota-activated drug delivery systems rely on the dense and metabolically active microbial population in the colon to trigger drug release. The colonic micro biota produces a variety of enzymes capable of degrading specific polymers, nanoparticles (Fig.3) and conjugates that are resistant to digestion in the upper gastrointestinal tract [19]. Polysaccharides such as guar gum, insulin, amylose, and xanthan gum are frequently used as carriers because they are selectively fermented by colonic bacteria. This strategy enables highly localized drug release and is particularly effective for treating inflammatory and infectious diseases of the colon. However, differences in microbial composition between individuals, as well as alterations caused by disease or antibiotic use, may affect the predictability and performance of micro biota-activated systems [20].

4. CARRIER SYSTEMS AND FORMULATION APPROACHES

4.1 Polymers and Coatings for Site-Specific Delivery

Polymers and polymeric coatings form the foundation of many colon-targeted drug delivery systems due to their ability to control the timing and location of drug release. Enteric coatings using polymers such as methacrylic acid copolymers, cellulose acetate phthalate, and hydroxypropyl methylcellulose phthalate remain intact in the acidic stomach environment and dissolve at the higher pH of the distal small intestine or colon [21]. Natural polysaccharides like pectin, guar gum, inulin, and chitosan are also employed because they resist enzymatic degradation in the upper gastrointestinal tract but are metabolized by colonic bacteria. Combining synthetic and natural polymers enables formulation flexibility, enhances stability, and allows for tailored release profiles, making polymer-based carriers highly versatile for site-specific drug delivery [22, 23].

4.2 Micro and Nanoparticles for Colon Targeting

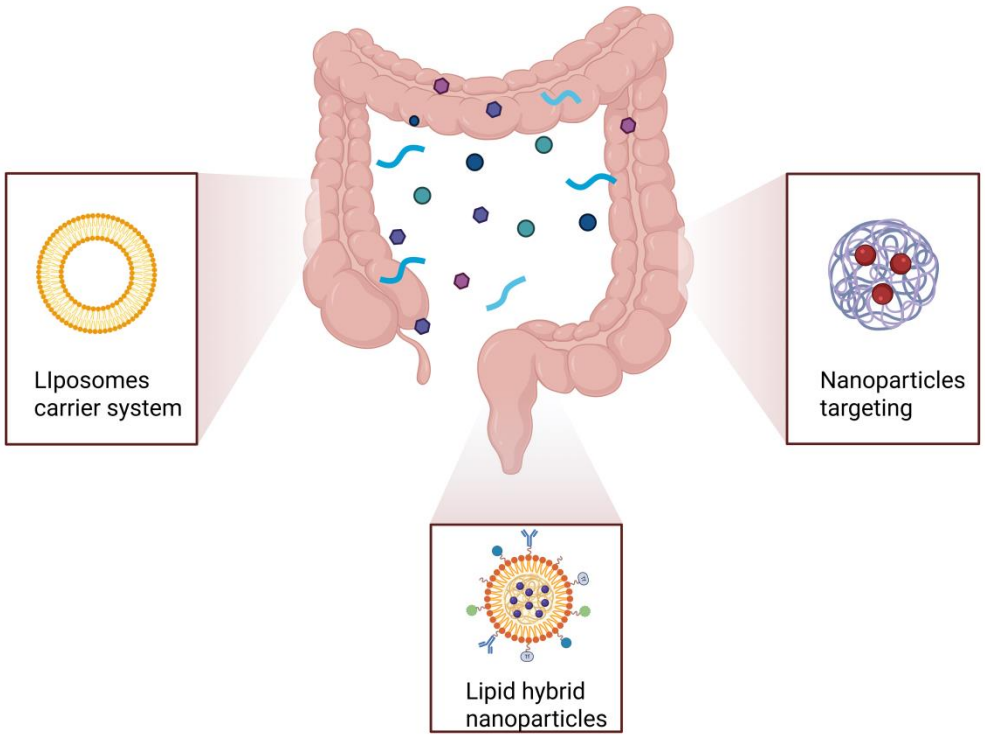

Fig.4 Carrier Systems for Colon Targeting

Micro- and nanoparticulate systems have gained attention due to their ability to improve drug solubility, stability, and bioavailability, while enabling precise targeting to the colon (Fig.4). These systems can be fabricated using biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA), chitosan, and alginate, which provide protection against the harsh gastrointestinal environment and allow controlled or stimuli-responsive drug release [24]. Nanoparticles can also enhance mucosal adhesion and cellular uptake, providing a therapeutic advantage in inflammatory bowel diseases and colorectal cancer. Surface functionalization with ligands or pH-sensitive coatings further improves site specificity, reducing systemic exposure and improving therapeutic outcomes [25, 26].

4.3 Lipid-Based Carriers and Liposomes

Lipid-based carriers, including liposomes, solid lipid nanoparticles, and self-emulsifying drug delivery systems, are used to enhance the solubility and stability of poorly water-soluble drugs (Fig.4). Liposomes are vesicular systems composed of phospholipids bilayers that can encapsulate hydrophilic and hydrophobic drugs and can be modified with pH-sensitive or polysaccharide coatings to achieve colon-specific delivery [27]. Lipid-based carriers also offer biocompatibility, protection from enzymatic degradation, and the potential for targeted drug release through passive accumulation or microbiota-responsive triggers. These systems are particularly advantageous for delivering biologics, peptides, or drugs with poor stability in the upper gastrointestinal tract [28, 29].

4.4 Hybrid and Multifunctional Delivery Platforms

Hybrid and multifunctional systems combine multiple strategies to overcome the limitations of single-mode delivery systems. For example, polymer-lipid hybrid nanoparticles (Fig.4) or polysaccharide-coated nanocarriers integrate the advantages of both pH-responsiveness and microbial degradation triggers, allowing highly controlled and site-specific drug release. Multifunctional platforms may incorporate targeting ligands, imaging agents, or stimuli-responsive elements to improve therapeutic precision and monitor drug distribution [30]. These platforms are particularly promising for complex diseases such as colorectal cancer and inflammatory bowel disease, where targeted, controlled, and sustained drug release is essential for optimal efficacy [31, 32].

5. THERAPEUTIC APPLICATIONS

Table.1 Therapeutic Applications of Colon-Targeted Drug Delivery

Condition	Drug Delivery System	Description / Mechanism	Reference no
5.1 Inflammatory Bowel Disease (IBD) & Ulcerative Colitis	Mesalamine-loaded pH-sensitive polymeric tablets	pH-sensitive polymers release mesalamine in the colon to reduce inflammation locally while minimizing systemic exposure	[33, 34]
	Budesonide microgranules coated with polysaccharides	Polysaccharide coating resists upper GI digestion and releases budesonide in the colon for targeted anti-inflammatory effect	
5.2 Crohn's Disease	5-Aminosalicylic acid (5-ASA) prodrugs	Enzyme-responsive prodrugs cleaved by colonic enzymes to release active 5-ASA specifically at the diseased site	[35, 36]
	Nanoparticle-loaded corticosteroids	Biodegradable nanoparticles enhance mucosal adhesion and prolong drug residence time for targeted therapy	
5.3 Colorectal Cancer (Fig.1)	Curcumin-loaded PLGA nanoparticles	Nanoparticles protect curcumin from degradation and improve colonic bioavailability for anti-cancer activity	[37, 38]
	Liposomal irinotecan	Lipid-based carriers enhance drug stability and allow site-specific release at the tumor site in the colon	

5.4 Microbiome-targeted therapies & Systemic applications	Probiotic-loaded polysaccharide microparticles Antibiotic-loaded enzyme-sensitive carriers	Polysaccharides degrade in response to colonic microbiota, releasing probiotics or drugs selectively in the colon Enzyme-responsive carriers release antibiotics specifically in the colon to modulate microbiota or treat local infections	[39, 40]

6. PRECLINICAL AND CLINICAL EVALUATION

6.1 In Vitro Dissolution and Release Testing

In vitro dissolution and release testing is an essential first step in evaluating colon-targeted drug delivery systems. These studies simulate the conditions of the gastrointestinal tract, including variations in pH, enzyme content, and transit times, to predict where and when the drug will be released. Standard dissolution apparatus, such as the USP type I or II systems can be modified to include sequential media representing gastric, intestinal, and colonic environments. Additionally, enzyme-containing media, such as those supplemented with bacterial azoreductases or polysaccharidases, are employed to assess the responsiveness of microflora-activated carriers or enzyme-degradable prodrugs [41, 42].

In vitro testing provides critical information on drug release kinetics, lag time, and stability, guiding formulation optimization before in vivo studies [43].

6.2. In Vivo Animal Models for Colon Delivery

Animal models play a crucial role in evaluating the pharmacokinetics, bio distribution, and therapeutic efficacy of colon-targeted formulations. Commonly used models include rats, rabbits, and dogs due to their well-characterized gastrointestinal physiology and ease of handling [44, 45]. Techniques such as radiolabeling, gamma scintigraphy, or fluorescent imaging allow non-invasive tracking of dosage forms through the gastrointestinal tract. Disease-specific models, such as chemically induced colitis in rodents, are frequently used to assess the therapeutic performance of anti-inflammatory or anticancer agents. While animal studies provide valuable insight, differences in gastrointestinal transit, pH, enzyme activity, and microbiota composition compared to humans must be considered when interpreting results [46, 47].

6.3 Clinical Trials and Translational Considerations

Clinical trials are the ultimate step to validate colon-targeted drug delivery systems. Early-phase studies focus on safety, tolerability, pharmacokinetics, and site-specific drug release in healthy volunteers, often using imaging techniques or biomarker analysis to confirm colon targeting. Subsequent trials evaluate therapeutic efficacy in patient populations with diseases such as ulcerative colitis, Crohn's disease, or colorectal cancer (Fig.1) [48].

Translational challenges include inter individual variability in colonic pH, micro biota composition, and gastrointestinal transit times, which can affect drug release and bioavailability. Regulatory considerations require thorough in vitro-in vivo correlation (IVIVC) studies and evidence of consistent

site-specific delivery across populations. These factors collectively determine the success of translating preclinical formulations into effective clinical therapies [49].

7. CHALLENGES IN COLON-TARGETED DELIVERY

Table.2 Challenges in Colon-Targeted Drug Delivery

Section	Key Challenges	Description on Colon Targeting	Reference no.
7.1 Formulation Stability and Reproducibility	Drug and carrier Instability	Colon-targeted formulations must withstand acidic gastric conditions, digestive enzymes, and mechanical stress during transit. Instability of polymers, degradation of drugs, or premature erosion of coatings can lead to early drug release and loss of site specificity.	[50]
	Batch-to-batch variability	Complex formulations using natural polymers or multilayer coatings often show variability in physicochemical properties, affecting reproducibility, scalability, and consistent in vivo performance.	
7.2 Variability in Gastrointestinal Physiology	pH and transit time variability	Differences in gastrointestinal pH, motility, and residence time among individuals—and between healthy and diseased states—can significantly influence the reliability of pH- or time-dependent colon-targeted systems.	[51, 52]
	Microbiota heterogeneity	Variations in colonic microflora composition due to diet, disease, antibiotics, or age can alter enzymatic activity, leading to unpredictable drug release from microbiota-activated systems.	
7.3 Regulatory and Manufacturing Considerations	Lack of standardized evaluation methods	There is no universally accepted in vitro or in vivo model that accurately predicts human colonic drug release, complicating regulatory approval and in vitro–in vivo correlation.	[53, 54]

	Manufacturing complexity and cost	Multi-unit systems, advanced coatings, and hybrid carriers require sophisticated manufacturing processes, increasing production costs and posing challenges for large-scale commercial manufacturing and quality control	

8. EMERGING TRENDS AND FUTURE PERSPECTIVES

8.1 Smart and Multi-Responsive Delivery Systems

Smart and multi-responsive drug delivery systems represent a significant advancement in colon-targeted therapy by responding to multiple physiological triggers simultaneously, such as pH changes, enzymatic activity, redox conditions, or microbial metabolism. Unlike conventional single-trigger systems, these platforms are designed to improve precision by minimizing premature drug release and enhancing site specificity within the colon [55].

Examples include polymeric carriers that combine pH-sensitive coatings with enzyme-degradable cores or nanoparticles that respond to both inflammatory markers and colonic conditions. These systems offer improved therapeutic efficacy, particularly for complex diseases such as inflammatory bowel disease and colorectal cancer (Fig.1) where localized and controlled drug release is critical. Continued research into smart materials and responsive polymers is expected to further enhance the reliability and clinical translation of colon-targeted formulations [56].

8.2 Integration with Microbiome-Based Therapies

The growing understanding of the gut microbiome has opened new opportunities for integrating colon-targeted drug delivery with microbiome-based therapeutic strategies. Advanced delivery systems are being developed to selectively release drugs, probiotics, prebiotics, or microbiota-modulating agents in response to colonic microbial activity [57]. Such approaches aim not only to treat disease symptoms but also to restore microbial balance, which plays a crucial role in gastrointestinal health and immune regulation. Microbiota-activated carriers using fermentable polysaccharides or enzyme-cleavable linkages allow precise interaction with colonic bacteria, enhancing therapeutic selectivity. Future developments are likely to focus on co-delivery systems that combine conventional drugs with microbiome-modulating agents for synergistic therapeutic outcomes [58, 59].

8.3 Personalized Medicine Approaches

Personalized medicine is emerging as a promising direction in colon-targeted drug delivery, driven by increasing recognition of interindividual variability in gastrointestinal physiology, microbiota composition, disease progression, and treatment response [60, 61]. Tailoring drug delivery systems based on patient-specific factors such as colonic pH, transit time, microbial profile, and genetic background may significantly improve therapeutic efficacy and safety. Advances in diagnostic tools, computational modeling, and formulation technologies such as three-dimensional printing enable the customization of dosage forms with precise release characteristics. Personalized colon-targeted therapies hold the potential to optimize treatment outcomes in chronic and heterogeneous conditions, including inflammatory bowel disease and colorectal cancer, while reducing adverse effects associated with generalized treatment strategies [62, 63].

9. CONCLUSIONS

Colon-targeted drug delivery has emerged as a highly promising approach for improving the treatment of localized colonic disorders and enabling systemic delivery of drugs with limited stability or absorption in the upper gastrointestinal tract. Advances in formulation science have led to the development of diverse delivery strategies, including pH-dependent, time-controlled, enzyme-responsive, microbiota-activated, and multi-responsive systems that enhance site specificity and therapeutic efficacy. The integration of novel carriers such as nanoparticles, lipid-based systems, hybrid platforms, and smart polymers has further improved drug protection, controlled release, and targeting precision. Despite these advancements, challenges related to formulation stability, physiological variability, scalability, and regulatory translation remain significant. Ongoing progress in microbiome research, personalized medicine, and advanced manufacturing technologies is expected to address these limitations and drive the successful clinical translation of colon-targeted therapies. Continued interdisciplinary research and standardized evaluation methods will be essential to fully realize the clinical potential of colon-specific drug delivery systems and to establish them as reliable tools for managing complex gastrointestinal and systemic diseases.

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