Journal of Applied Pharmacology and Toxicology
Volume 1 Issue 1, Year of Publication 2025, Page 48 – 63
DOI: https://doi.org/10.69857/joapt.v1i1.3

Review Article

JOURNAL OF APPLIED PHARMACOLOGY AND TOXICOLOGY | JOAPT
www.joaptonline.com

CHALLENGES AND BENEFITS FOR ORAL COLON-TARGETED NANOPARTICULATE DRUG DELIVERY SYSTEM: A BRIEF REVIEW

Debgopal Ganguly[1], Ananta Choudhury[1*], Himangshu Deka[1], Jahnabi Sarmah[1], Kousik Mahanti[2], Sk Farin Rahaman[3], Debasmita Ghosh[3]

Article Information
Received: 16th June 2025
Revised: 31st August 2025
Accepted: 29th September 2025
Published: 15th December 2025

Keywords
Oral colon delivery, nanoparticles, targeted drug delivery, polymeric carriers, lipid nanoparticles, gastrointestinal barriers, translational nano-medicine.

ABSTRACT
Oral colon-targeted drug delivery systems (OCTDDS) are increasingly recognized for their therapeutic potential in both local conditions, such as inflammatory bowel disease, colorectal cancer, and intestinal infections, and systemic disorders in which colonic absorption is advantageous. Nanoparticulate carriers have gained particular attention because they offer several advantages over conventional systems, including improved stability, protection from enzymatic degradation, controlled drug release, and enhanced bioavailability. Despite these benefits, the gastrointestinal environment presents significant challenges to selective colon delivery. Variability in pH, digestive enzymes, mucus layering, and the influence of gut microbiota often hinder predictable performance. To overcome these barriers, diverse nanoscale platforms—such as polymeric nanoparticles, lipid-based systems, dendrimers, and hybrid nano-in-micro carriers—have been developed, each offering unique mechanisms to optimize targeting and therapeutic outcomes. This review brings together recent advances in nanoparticle-mediated colon targeting, highlighting design principles, advantages, and translational prospects. Regulatory considerations and early clinical findings are also discussed, emphasizing the importance of bridging laboratory innovation with clinical application to realize the full potential of these emerging systems.

INTRODUCTION

Oral drug administration remains the dominant approach in pharmaceutical delivery systems, primarily due to its simplicity, safety, and widespread patient acceptance. Among all available administration routes, the oral pathway is considered the most convenient for both patients and healthcare providers. Its non-invasive nature, compatibility with self-administration, cost-effectiveness & ease of manufacturing have made it the preferred choice in the treatment of both chronic and acute conditions. However, despite these advantages, the oral route faces significant challenges, especially when precise site-specific drug delivery within the gastrointestinal (GI) tract is required [1]. One such challenge involves the targeted delivery of drugs to the colon, the distal portion of the GI tract. Conventional oral formulations typically release the active pharmaceutical ingredient (API) in the stomach or small

[1]*Assam down town University, Sankar Madhab Path Gandhi Nagar, Panikhaiti, Guwahati, Assam 781026, India.*
[2]*Calcutta Institute of Pharmaceutical Technology & Allied Health Sciences,Banitabla,Uluberia,Howrah 711316, India.*
[3]*East West Education Institute,Talit,Burdwan,West Bengal,India.*

For Correspondence:** **anantachoudhury@gmail.com

intestine. This premature release may result in subtherapeutic concentrations of the drug reaching the colon, particularly in diseases in which localized drug action is essential. Moreover, systemic absorption in the upper gastrointestinal tract can lead to adverse effects and reduced therapeutic efficacy. Hence, there is an increasing need for drug delivery systems that can bypass the upper GI tract and specifically release the drug in the colon [2].

This need is particularly significant in the treatment of colonic disorders such as ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), colorectal cancer, and certain parasitic infections. These conditions often require the delivery of anti-inflammatory agents, anticancer drugs, antibiotics, or biologics directly to the site of inflammation or tumor growth in the colon. Localized delivery minimizes systemic exposure, enhances therapeutic outcomes, and reduces adverse effects associated with conventional drug administration [3].

In response to these therapeutic demands, Colon-Targeted Drug Delivery Systems (CTDDS) have been developed. These systems are engineered to ensure that the drug remains protected as it transits through the stomach and small intestine and only releases the payload upon reaching the colon. Various design strategies have been explored for colon targeting, including pH-sensitive coatings, enzyme-responsive materials, time-dependent systems, and pressure-controlled devices. While each of these has demonstrated varying degrees of success, achieving reliable and reproducible colon-specific delivery remains a significant challenge in pharmaceutical science [4-7].

In recent years, the emergence of nanoparticulate drug delivery systems has opened new avenues for addressing the limitations of conventional CTDDS. Nanoparticles—defined as submicron-sized carriers ranging typically from 10 to 1000 nanometers—possess unique physicochemical properties that make them highly suitable for site-specific drug delivery. Their high surface-area-to-volume ratio, ability to encapsulate both hydrophilic and hydrophobic drugs, and surface-modification capability make them versatile platforms for tailored therapy. Furthermore, nanoparticles can be designed to respond to specific stimuli present in the colonic environment, such as changes in pH, redox conditions, or enzymatic activity, enabling triggered and controlled drug release [8]. The integration of nanotechnology with CTDDS offers several advantages. Firstly, nanoparticles enhance drug stability by protecting the API from harsh acidic conditions and digestive enzymes encountered during GI transit. Secondly, their small size allows for better mucosal penetration and intimate contact with colonic tissues, which may lead to improved drug absorption and retention at the target site. Thirdly, by functionalizing nanoparticles with targeting ligands or surface polymers, they can be guided to specific cell types, such as cancer cells or inflamed tissues, thereby enhancing therapeutic precision [9].

Additionally, the use of polymeric nanoparticles, lipid-based nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and nano-in-micro formulations has broadened the scope of colon-targeted therapy. Nano-in-micro systems, for instance, involve embedding nanoparticles within larger microparticles, thereby providing dual-layer protection and improved control over release kinetics. This design is particularly effective in preventing premature drug release and ensuring that a higher drug concentration reaches the colon intact [10].

Despite these promising developments, several barriers still impede the full realization of nanoparticle-based CTDDS. Biological factors such as variable GI transit times, fluctuating pH levels, presence of the mucus barrier, and inter-patient variability in colonic microbiota and enzyme activity can affect the performance of these systems. Moreover, manufacturing challenges, regulatory constraints, and the need for robust characterization techniques add layers of complexity to product development [11].

Nevertheless, the clinical potential of nanoparticulate colon-targeted systems continues to grow, supported by encouraging data from preclinical and early clinical studies. With advances in materials science, polymer chemistry, and nanotechnology, future systems may be more responsive, more targeted, and more customizable than ever before. Additionally, integrating these systems with digital health tools and biosensors could enable personalised colon-targeted therapy, adapting the drug release profile based on real-time physiological cues [12].

In conclusion, although oral drug administration remains the most preferred route for patient compliance and cost-effectiveness, effective colon-specific delivery remains challenging. Nanoparticulate drug delivery systems represent a

transformative advancement in overcoming the physiological and technological barriers associated with CTDDS. As research continues to refine these systems, they are expected to play an increasingly vital role in the treatment of colonic diseases, revolutionizing site-specific therapy and enhancing patient outcomes [13–16].

2. Benefits and Challenges of Oral Colon-Targeted Drug Delivery

2.1 Therapeutic Advantages of Colonic Targeting

Colon-targeted drug delivery systems (CTDDS) offer numerous therapeutic benefits, particularly in the treatment of localized diseases such as inflammatory bowel disease (IBD), colorectal cancer, and parasitic infections. One of the primary advantages is localized treatment, wherein the drug is released directly at the disease site in the colon. This targeted approach results in higher local drug concentrations, which enhances therapeutic efficacy while significantly reducing systemic side effects. For instance, in conditions such as ulcerative colitis or Crohn's disease, localized delivery ensures that anti-inflammatory or immunosuppressive agents act directly on the inflamed mucosa, minimizing systemic exposure. Another key benefit is the reduction in dosing frequency. Many colon-targeted formulations are designed for controlled or sustained drug release, allowing the medication to act over an extended period. This reduces the need for frequent dosing, thereby enhancing patient compliance and maintaining more consistent drug levels at the target site, leading to improved therapeutic outcomes.

Improved bioavailability is also a significant advantage of nanoparticulate systems used for colon targeting [17]. Many drugs intended for colonic diseases are poorly water-soluble or have limited permeability across biological membranes. Nanoparticles help overcome these challenges by enhancing drug solubility, facilitating absorption through the colonic epithelium, and promoting effective drug distribution within the mucosal layers. This leads to higher bioavailability and better pharmacological action, even at lower doses. Colonic targeting offers improved stability of sensitive drug molecules [18]. The upper gastrointestinal tract—comprising the stomach and small intestine presents a harsh environment for many drugs due to low pH, enzymatic activity, and digestive processes. Colon-targeted systems, particularly those using nanoparticles, are designed to protect the drug during transit through these regions. By shielding the active pharmaceutical ingredient from degradation until it reaches the colon, the system ensures that a higher proportion of the drug remains active and therapeutically effective at the site of release [19].

2.2 Key Challenges in Oral Colon Delivery

Despite the therapeutic advantages of colon-targeted drug delivery, several physiological and formulation-related challenges hinder its effective implementation. One of the major issues is premature drug release. Colon-targeted systems often rely on pH-sensitive coatings or polymers that are designed to dissolve at the higher pH of the colon. However, the pH of the gastrointestinal (GI) tract can vary significantly between individuals and under different physiological conditions. For instance, the small intestine may reach a pH similar to that of the colon, leading to early dissolution of the coating and unintended drug release before the drug reaches the target site. Another significant challenge is enzymatic degradation. The upper GI tract, particularly the stomach and small intestine, is rich in digestive enzymes, including proteases and lipases. These enzymes can degrade drugs, especially biologics and peptides, before they reach the colon. As a result, a large portion of the active drug may be lost during transit, reducing therapeutic efficacy and necessitating higher doses or more frequent administration. Variable transit time through the GI tract also complicates colon-targeted delivery. The time required for a dosage form to transit from the mouth to the colon varies widely with factors such as food intake, individual metabolism, and disease status. Variations in gastric emptying and intestinal motility can lead to unpredictable drug-release profiles, making it difficult to ensure precise colonic delivery. This inconsistency poses a major obstacle to designing reliable & effective delivery systems [20].

Additionally, the mucus layer and microbial environment of the colon present both physical and biochemical barriers. The thick mucus lining of the intestinal tract can trap nanoparticles, preventing them from reaching the epithelial surface where drug absorption occurs. Moreover, the colonic microbiota, while essential for triggering certain enzyme-responsive delivery systems, can also degrade the drug or the nanocarrier prematurely. These interactions can reduce drug availability and complicate the design of stable, responsive delivery platforms. In summary, while oral colon-targeted drug delivery systems hold great potential, their success depends on overcoming these complex challenges. Strategies to address pH variability,

enzymatic degradation, transit-time variability, and biological barriers are critical to developing more effective and reliable formulations [21]. An overview of the challenges in Oral Colon-Targeted Delivery is presented in Table 1.

Table 1: Overview of Challenges in Oral Colon-Targeted Delivery

Barrier Type	Description	Effect on Drug Delivery	Ref.
pH Variation	pH fluctuates from highly acidic (stomach) to near neutral (colon)	Premature drug release in the stomach or small intestine; instability of pH-sensitive carriers	[22]
Enzymatic Degradation	Presence of proteolytic enzymes (e.g., pepsin, trypsin, lipases) in upper GIT	Degradation of drug or nanoparticle components before reaching the colon	[23]
Microbiota Metabolism	A diverse microbial population in the colon metabolizes polysaccharides and drugs	Enables targeted release via microbiota-activated systems; may also lead to drug degradation	[24]
Mucus Barrier	A thick mucus layer in the GI tract traps and clears foreign particles	Hinders nanoparticle penetration and mucoadhesion; reduces bioavailability	[25]
Variable Transit Time	Gastric emptying and intestinal motility differ among individuals	Inconsistent drug arrival time at the colon affects controlled-release systems	[26]
Limited Absorptive Surface	Colon has fewer villi and transporters compared to the small intestine	Lower absorption efficiency: challenges for systemic drug delivery from the colon	[27]
Peristaltic Movement	Rhythmic contractions propel content through the GI tract	Mechanical stress may disrupt nanoparticle structure or trigger early release	[28]
Immune Surveillance	Presence of Peyer's patches and immune cells	May lead to uptake and clearance of nanoparticles by the immune system	[29]

3. Biological Barriers in Gastrointestinal Transit

Effective oral colon-targeted drug delivery must overcome several biological barriers encountered throughout the gastrointestinal (GI) tract. One of the primary barriers is the stomach's harsh, acidic environment, which can rapidly degrade acid-sensitive drugs and disrupt the integrity of certain delivery systems. This acidic pH, combined with the presence of potent digestive enzymes such as pepsin, poses a significant risk to drug stability during the early phase of GI transit. Following the stomach, the small intestine presents additional challenges, including a neutral-to-slightly alkaline pH and a complex mixture of digestive enzymes, such as trypsin, chymotrypsin, and lipases [30]. These enzymes can degrade proteins, peptides, and lipids, making the delivery of sensitive biomolecules particularly difficult. In addition, the small intestine has a large absorptive surface area and high permeability, which may result in the premature absorption of drugs before they reach the colon. Another critical barrier is the mucus layer that lines the entire GI tract. While this layer serves a protective role by trapping pathogens and facilitating food transport, it can also impede the transport and retention of drug-loaded nanoparticles. Nanocarriers may become trapped in mucus and be eliminated before reaching the epithelial surface, reducing the amount of drug that actually reaches the target site. Designing mucus-penetrating nanoparticles is therefore essential for enhancing colonic drug delivery. Moreover, the gut-associated immune system, including Peyer's patches and M-cells in the small intestine, can recognize and clear foreign particles, including drug carriers. This immune surveillance mechanism, while protective, poses a barrier to nanoparticulate systems intended for colonic delivery, as it can lead to premature clearance from the GI tract. Lastly, the colonic microbiota, while beneficial in triggering enzymatic release from certain prodrugs or biodegradable carriers, can also metabolize or degrade drugs and nanocarriers unintentionally, thereby impacting the stability and performance of the delivery system. The variability in microbial composition among individuals further complicates the predictability of these interactions [31]. Biological barriers, including acidic pH, enzymatic activity, mucus obstruction, immune recognition, and microbial variability, collectively pose substantial obstacles to the efficient delivery of drugs to the colon via the oral route. A thorough understanding of these barriers is essential for the rational design of advanced colon-targeted drug delivery systems [32].

3.1 pH Variation along the GI Tract and Colon

The gastrointestinal (GI) tract is characterized by distinct and dynamic pH gradients, which play a crucial role in influencing drug solubility, stability, and release profiles. The stomach maintains a highly acidic environment, with a pH of 1.0-3.0, primarily due to hydrochloric acid secretion. This acidic condition aids digestion but poses significant challenges for acid-sensitive drugs and pH-responsive delivery systems. As the dosage form enters the small intestine, the pH gradually

increases to approximately 6.0-7.5, influenced by bile and pancreatic secretions. The pH in the colon typically ranges from 6.5 to 7.0, although this can vary with diet, microbial activity, and disease state [33].

This spatial pH variation complicates the development of pH-sensitive nanoparticulate drug delivery systems designed for colon targeting. Suppose the nanoparticle formulation relies solely on pH-triggered mechanisms for drug release. In that case, there is a risk of premature drug release in the small intestine, where the pH may overlap with the threshold for activation. As a result, the drug may be released and absorbed before reaching the colon, compromising its therapeutic efficacy. Therefore, careful selection of pH-sensitive polymers with precise dissolution thresholds and the incorporation of dual- or multi-triggered systems (e.g., pH plus enzymatic or redox triggers) are often required to ensure targeted release specifically within the colonic environment (34). Anatomy of the lower gastrointestinal tract, highlighting two distinct pH regions located in the ascending colon and the sigmoid colon in Figure 1.

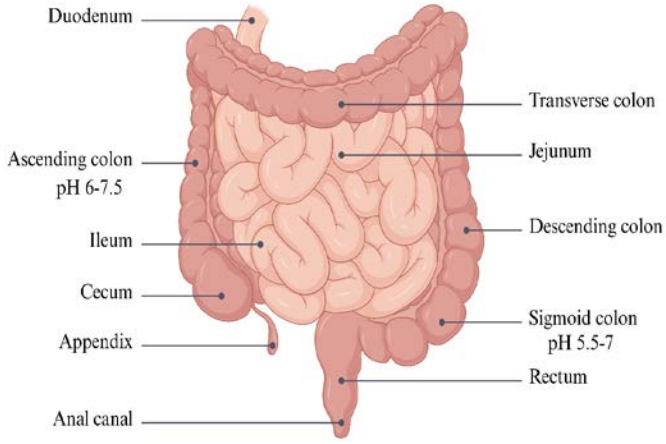

Figure 1: Anatomical structure of the lower gastrointestinal tract with indication of two distinct pH zones, one in the ascending colon and another in the sigmoid colon.

3.2 Enzymatic Degradation and Microbiota Interaction

Another significant challenge in oral colon-targeted drug delivery is the extensive enzymatic activity encountered in the upper GI tract. Enzymes such as pepsin in the stomach and trypsin, chymotrypsin, amylases, and lipases in the small intestine can degrade both the drug molecule and its carrier, particularly when the carrier is composed of proteins, peptides, or lipid-based materials. This enzymatic degradation may significantly reduce drug bioavailability, especially for macromolecules and biologics that are inherently unstable in the digestive environment [35].

In contrast, the colon has a relatively low concentration of digestive enzymes. Still, it is rich in resident microbiota that play a pivotal role in fermenting non-digestible dietary fibres and polysaccharides. This unique enzymatic profile of the colon can be exploited for site-specific drug release. For example, nanocarriers made from polysaccharides such as chitosan, pectin, or dextran can be degraded by colonic bacterial enzymes, thereby releasing the encapsulated drug selectively at the target site. This approach is particularly promising for designing microbiota-responsive nanoparticle systems that remain stable in the stomach and small intestine but are triggered by colonic microbial enzymatic activity. However, inter-individual variability in microbial composition and enzyme expression remains a challenge that may affect the consistency and predictability of drug release among patients [36–41].

3.3 Mucus Barrier and Colonic Mucosal Transport

The mucus layer that lines the GI tract serves as a critical biological defence mechanism, trapping pathogens, facilitating lubrication, and maintaining hydration of the underlying epithelium. However, this protective barrier also presents a major obstacle to drug delivery, especially for nanoparticulate systems. The mucus is composed of a dense network of mucin glycoproteins, lipids, and salts that can trap and immobilise nanoparticles via adhesive interactions, thereby promoting their premature clearance from the lumen before they reach the epithelial surface [42].

To address this challenge, researchers have developed mucus-penetrating nanoparticles (MPNPs) by modifying the carrier surface with hydrophilic and muco-inert polymers, such as polyethylene glycol (PEG)—a process commonly referred to as PEGylation. These surface modifications help nanoparticles to navigate through the mucus layer without being trapped, allowing them to reach and interact with the colonic mucosa. Additionally, some formulations are engineered to exhibit mucoadhesive properties to prolong residence time in the colon, thereby enhancing drug absorption [43]. Despite these innovations, drug absorption in the colon is inherently limited by its relatively low surface area and tighter epithelial junctions compared with those of the small intestine. The absence of villi and reduced expression of transport proteins further constrain

the bioavailability of many drugs. Therefore, optimising nanoparticle design to improve mucus penetration and epithelial transport remains a crucial focus for enhancing the effectiveness of colon-targeted therapies [40–43].

4. Polymeric Nanoparticle Systems for Colon Targeting

Polymeric nanoparticles have emerged as a highly promising platform for colon-targeted drug delivery owing to their versatility in surface modification, controlled-release capabilities, and responsiveness to specific physiological triggers. These Nanoparticulate carriers can be broadly classified based on the nature of the polymer used—synthetic or natural (polysaccharide-based). Both types offer unique advantages for achieving precise and efficient drug release in the colon while overcoming the challenges posed by the GI tract [1].

4.1 Synthetic Polymer Nanoparticles

Synthetic polymers are extensively utilised in the formulation of colon-targeted drug delivery systems due to their predictable physicochemical properties, stability, and ease of modification. Some of the most commonly used synthetic polymers include Eudragit series polymers, poly (lactic-co-glycolic acid) (PLGA), and polymethacrylates. These polymers are typically engineered to be pH-sensitive, making them suitable for oral colon delivery applications [44]. One notable example is Eudragit S100, a methacrylic acid copolymer that dissolves above pH 7.0. This feature allows the drug-loaded nanoparticles to remain intact during passage through the acidic stomach and mildly basic small intestine, releasing their payload only upon reaching the higher-pH environment of the colon. This pH-dependent solubility ensures that the therapeutic agent is delivered precisely where it is needed, enhancing local efficacy and minimizing systemic side effects [45–47].

Similarly, PLGA is a biodegradable and biocompatible polymer that has been used to develop sustained-release nanoparticle systems. Although it is not inherently pH-sensitive, PLGA can be combined with enteric coatings or other functional polymers to achieve targeted release. Moreover, PLGA nanoparticles can encapsulate a wide range of hydrophilic & hydrophobic drugs, offering a flexible platform for colon-targeted formulations [48–50]. The main advantage of using synthetic polymers lies in their high reproducibility, mechanical strength, and tunable degradation rates, enabling formulators to tailor the drug-release profile precisely. However, the potential for toxicity from residual monomers and limited responsiveness to biological triggers, such as enzymes or the microbiota, must be considered during formulation development [51].

4.2 Natural Polysaccharide Nanoparticles

Natural polysaccharides have attracted substantial interest for colon-targeted drug delivery owing to their biodegradability, biocompatibility, and responsiveness to colonic microbial enzymes. Polymers such as chitosan, pectin, guar gum, dextran, inulin, and alginate serve as excellent candidates for developing microbiota-sensitive Nanoparticulate systems [52].

One of the most widely used polysaccharides is chitosan, a cationic polymer derived from chitin. Chitosan-based nanoparticles exhibit mucoadhesive properties that enhance their adherence to the colonic mucosa, thereby prolonging residence time and improving drug absorption. Although chitosan is soluble in acidic environments, it can be chemically modified (e.g., by crosslinking or by coating with anionic polymers) to enhance its stability and enable colon-specific drug release [53]. Pectin and guar gum are examples of non-starch polysaccharides that are resistant to digestion in the upper GI tract but are readily degraded by the colonic microbiota. This feature makes them ideal carriers for microbiota-triggered drug delivery. Upon reaching the colon, these polysaccharides are degraded by bacterial enzymes such as pectinase or galactomannanase, thereby enabling the controlled release of the encapsulated drug [54]. Dextran, another polysaccharide, is particularly useful in forming enzyme-degradable linkages within the nanoparticle matrix or conjugate. It can be functionalized with drug molecules or used to fabricate nanoparticles that degrade specifically in the presence of colonic dextranases [55].

The natural origin and low toxicity of polysaccharide-based nanoparticles make them highly favorable for oral drug delivery. Moreover, these polymers can be engineered to form hydrogels, coated particles, or core-shell structures for more advanced delivery systems. However, challenges such as batch-to-batch variability, reduced mechanical strength, and limited control over degradation kinetics must be addressed to ensure consistent in vivo performance [56].

5. Lipid-Based Nanoparticle Carriers

Lipid-based nanocarriers are a promising class of systems for colon-targeted drug delivery owing to their biocompatibility,

high drug-loading capacity, protection against harsh gastrointestinal conditions, and the potential for modification in response to physiological triggers. These carriers are especially beneficial for encapsulating poorly water-soluble drugs and macromolecules susceptible to degradation. Among lipid-based nanoparticles, liposomes, niosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have demonstrated significant potential for improving the effectiveness and selectivity of colonic drug delivery [57–60].

5.1 Liposome and Niosome

Liposomes are spherical vesicles composed of one or more phospholipid bilayers surrounding aqueous compartments. This unique structure allows liposomes to encapsulate both hydrophilic drugs (within the aqueous core) and lipophilic drugs (within the lipid bilayer), making them versatile carriers for a wide range of therapeutic agents. Liposomes are particularly advantageous for protecting drugs from enzymatic degradation in the stomach and small intestine, thereby increasing the likelihood that the drug reaches the colon intact [34]. In the context of colon-targeting, surface modification of liposomes with polymers such as Polyethylene Glycol (PEG), ligands, or antibodies can be employed to enhance mucus penetration, bioadhesion, or active targeting to inflamed or cancerous colonic tissues. Furthermore, liposomes can be coated with pH-sensitive or enzyme-responsive polymers, enabling selective release in the colonic environment [61].

Niosomes, by contrast, are nonionic surfactant-based vesicles that offer several advantages over liposomes, including greater physical and chemical stability, lower production costs, and enhanced shelf life. Composed of surfactants such as Span or Tween, often in combination with cholesterol, niosomes are similarly capable of encapsulating both hydrophilic and hydrophobic drugs. Their robust structure makes them less prone to oxidative degradation and aggregation, which are common limitations of conventional liposomes [62]. Both liposomes and niosomes can be tailored for colon-specific delivery through appropriate formulation strategies. For instance, coating these vesicles with enteric polymers or embedding them in larger pH-responsive or enzymatically degradable matrices enables triggered release specifically in the colon, making them highly effective for treating localized diseases such as inflammatory bowel disease (IBD), colorectal cancer, and parasitic infections [63].

5.2 Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Solid Lipid Nanoparticles (SLNs) are submicron-sized particles composed of lipids that remain solid at both room and body temperatures. These particles offer controlled and sustained drug release, enhanced physical stability, protection of labile drugs & improved oral bioavailability. SLNs have a solid lipid core in which the drug is dispersed or embedded, and this core is typically stabilized with emulsifiers. SLNs are particularly effective at improving the oral delivery of poorly water-soluble drugs, a major limitation in conventional colon-targeted therapies [64]. However, one limitation of SLNs is their low drug-loading capacity, owing to the highly ordered crystalline structure of the lipid matrix. To overcome this issue, Nanostructured Lipid Carriers (NLCs) were developed. NLCs are second-generation lipid nanoparticle systems composed of a mixture of solid and liquid lipids that form an imperfect crystal structure. This structural imperfection enables greater accommodation of drug molecules, thereby enhancing drug-loading efficiency and reducing the risk of drug expulsion during storage [65]. Both SLNs and NLCs can be further optimized for colon-specific delivery by integrating pH-sensitive coatings or enzymatically degradable outer layers that prevent drug release in the upper gastrointestinal tract. Upon reaching the colon, these coatings degrade in response to local pH changes or colonic microbiota activity, thereby facilitating site-specific drug release. This approach ensures that the therapeutic agent is delivered directly to the diseased region, enhancing treatment efficacy and reducing systemic exposure [66]. Additionally, SLNs and NLCs exhibit superior mucosal adhesion, which can further strengthen retention at the colonic site, thereby improving therapeutic outcomes in conditions such as ulcerative colitis and colorectal cancer. These systems are being increasingly explored in preclinical and clinical studies, underscoring their potential as next-generation colon-targeted delivery platforms [67].

6. Emerging and Hybrid Nanoparticle Platforms

As the field of nano-medicine evolves, novel and hybrid nanoparticle-based drug delivery systems are being developed to overcome the multifaceted barriers associated with oral colon-targeted drug delivery. These innovative systems are designed to offer improved control over drug release, enhanced bioavailability, and greater selectivity for colonic tissues. This section outlines some of the most promising emerging

nanotechnologies, including polymeric micelles, dendrimers, inorganic nanoparticles, carbon-based carriers, and nano-in-micro systems, which are advancing current colon-targeting strategies [68].

6.1 Polymeric Micelles and Dendrimers

Polymeric micelles are nanosized colloidal carriers formed through the self-assembly of amphiphilic block copolymers in aqueous solutions. These systems consist of a hydrophobic core that encapsulates poorly water-soluble drugs and a hydrophilic shell, often composed of polyethylene glycol (PEG), that imparts stealth properties and improves stability in the gastrointestinal environment. Due to their small size, high drug-loading efficiency, and modifiable surface, polymeric micelles are increasingly being explored for site-specific delivery to the colon. Additionally, they can be engineered to respond to pH changes or to enzymatic activity, thereby enabling precise control over the timing and location of drug release [69]. Dendrimers, such as polyamidoamine (PAMAM) dendrimers, are highly branched, monodisperse macromolecules with well-defined architecture and multiple surface functional groups. Their unique structure enables fine-tuned control over size, shape, and surface chemistry, making them highly effective at penetrating biological barriers, such as the mucus layer of the gastrointestinal tract. Dendrimers can be conjugated with ligands for targeted delivery, modified with polymers for enhanced mucosal transport, and loaded with both hydrophilic and hydrophobic drugs. Their modularity and multifunctionality make them a powerful tool for next-generation colon-targeted therapies [70–74].

6.2 Inorganic Nanoparticles

Inorganic nanoparticles, particularly mesoporous silica nanoparticles (MSNs) and gold nanoparticles (AuNPs), have gained attention due to their stability, tunable size and pore structure, and ease of surface functionalization. MSNs are characterized by their high surface area and porous framework, allowing for substantial drug loading and controlled release. By modifying their surface with pH-sensitive gates or enzyme-cleavable linkers, MSNs can be programmed to release their cargo specifically in the colonic environment. For instance, coatings that degrade in the presence of colonic enzymes, such as azoreductases or glycosidases, enable microbiota-triggered drug release [75–78]. Gold nanoparticles, known for their biocompatibility and optical properties, are also being explored for colon-specific delivery. These particles can be conjugated with targeting ligands or responsive coatings to facilitate site-specific accumulation and controlled drug release. Furthermore, gold nanoparticles have been investigated for combined diagnostic and therapeutic (theranostic) applications, such as imaging-guided therapy in colorectal cancer [79–82].

6.3 Carbon-Based Nanocarriers

Carbon-based nanocarriers, including carbon nanotubes (CNTs) and graphene oxide (GO), are emerging as innovative platforms for colon-targeted drug delivery owing to their exceptional surface area, mechanical strength, and drug-loading capacity. CNTs possess a tubular structure that can encapsulate or adsorb therapeutic agents, whereas GO sheets can be functionalized with polymers and biomolecules to enhance solubility and biocompatibility. Despite their potential, these systems raise concerns related to long-term toxicity, immunogenicity, and regulatory acceptance. Studies are ongoing to understand their interactions with the gastrointestinal tract better and to optimize their physicochemical properties for safe and effective use. Nevertheless, their unique structural & functional characteristics position them as strong candidates for future colon-targeted nanomedicines, especially for conditions requiring sustained drug delivery and high local concentrations [3,6].

6.4 Nano-in-Micro Delivery Systems (NiMOS)

Nano-in-Micro Delivery Systems (NiMOS) represent a hybrid strategy that integrates the advantages of both nanoparticulate and microparticulate technologies. In this approach, nanoparticles are encapsulated within a larger biodegradable microparticle matrix, typically composed of natural or synthetic polymers. The outer microparticle acts as a protective shell, shielding the inner nanoparticles from degradation in the acidic stomach and enzymatic activity in the small intestine. Upon reaching the colon, the outer layer dissolves or degrades—either via pH-responsive mechanisms or enzymatic digestion by the colonic microbiota—thereby releasing the embedded nanoparticles directly at the target site. This dual-barrier system enhances the stability and specificity of drug delivery, particularly for labile or sensitive therapeutic agents. NiMOS platforms can be further optimized by modifying the surfaces of both the nano- and microcomponents to enhance mucosal adhesion, penetration, and controlled release. NiMOS has shown significant promise in preclinical models of inflammatory bowel diseases and colorectal cancer, offering enhanced therapeutic

efficacy and reduced systemic exposure. As formulation science advances, these systems are expected to play a vital role in the next generation of colon-targeted drug delivery platforms. The classification of nanoparticles used in colon-targeted drug delivery is presented in Table 2. Figure 2 represents various nanoparticles and their advantages in colon-targeted drug delivery [16,35,36].

Table 2: Classification of nanoparticles used in colon-targeting drug development

Type	Materials Used	Advantages	Representative Examples	Ref.
Polymeric NPs	PLGA, Eudragit S100, Chitosan, Pectin, Guar Gum	Biodegradable, pH-sensitive, enzyme-responsive, sustained release	Budesonide-loaded PLGA NPs; 5-ASA in Eudragit-S100	[17]
Lipid-Based NPs	Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), Liposomes, Niosomes	High drug loading, protection from enzymes, and improved solubility	Curcumin-SLN; Cyclosporine-liposomes; Prednisolone-NLC	[83]
Dendrimers	PAMAM, PPI	Precise size and surface functionality, multivalency, mucoadhesion	PAMAM–5-ASA conjugates; Dendrimer–Camptothecin complex	[43]
Inorganic NPs	Mesoporous Silica Nanoparticles (MSNs), Gold NPs, ZnO NPs	High surface area, stability, tunable pore size, and imaging capability	MSNs for 5-FU; Gold NPs for colon cancer imaging and delivery	[37]
Polymeric Micelles	PEG-PLA, Poloxamers	Self-assembly in aqueous media, good solubilization of hydrophobic drugs	Paclitaxel-loaded micelles; Micellar curcumin	[38]
Carbon-Based NPs	Carbon Nanotubes (CNTs), Graphene Oxide (GO)	High surface area, potential for functionalization, targeting ability	CNTs for Doxorubicin; GO for IBD-targeted delivery	[84]
Hybrid Systems	Nano-in-Micro (NiMOS), polymer-lipid hybrids	Dual protection, colon-specific release, improved GI stability	NiMOS for Insulin; Chitosan-lipid hybrid for 5-ASA	[21]
Stimuli-Responsive NPs	Enzyme-sensitive, redox-responsive, pH/time dual-sensitive systems	Triggered release at the target site, increased precision and efficacy	pH/enzyme dual-responsive NPs for IBD therapy	[23]

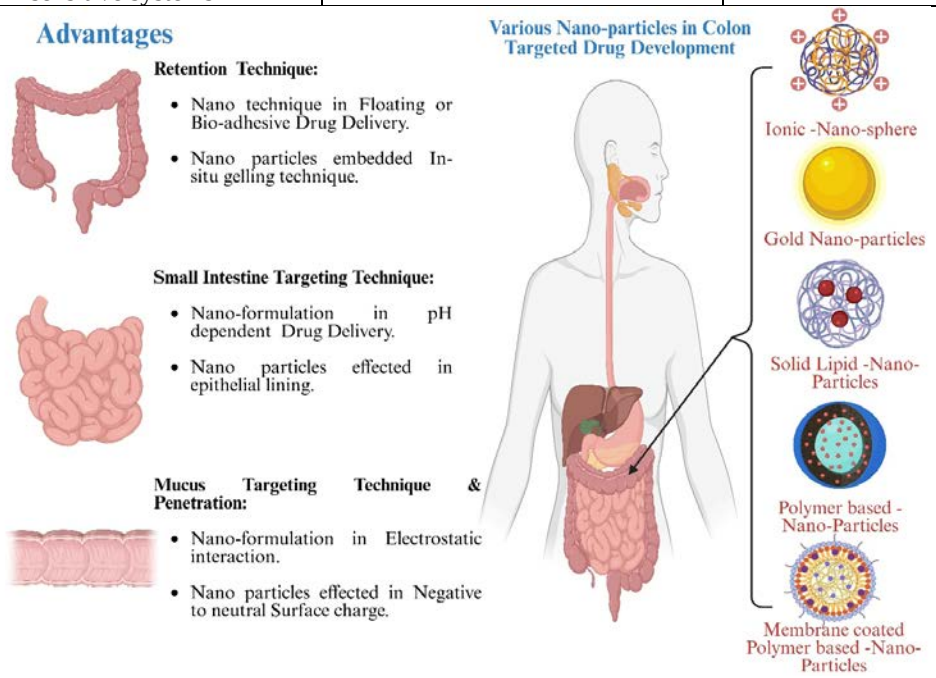

Figure 2: Various nanoparticles and their advantages in colon-targeted drug delivery

7. Formulation Complexities and Optimisation Strategies

The development of effective colon-targeted Nanoparticulate drug delivery systems is a sophisticated process that involves overcoming multiple formulation challenges. These complexities stem from the need to maintain nanoparticle integrity during gastrointestinal transit, achieve adequate drug loading and encapsulation efficiency, and ensure scalability and reproducibility of the manufacturing process [24].

7.1 Stability during GI Transit

One of the primary formulation hurdles is ensuring that the nanoparticles remain stable and intact during passage through the upper gastrointestinal (GI) tract, where acidic pH and enzymatic activity can degrade both the carrier and the active pharmaceutical ingredient. To mitigate this, formulation scientists employ enteric coatings that dissolve only at higher pH levels typically found in the colon. Coatings made from pH-sensitive polymers such as Eudragit S100 or Eudragit L100 prevent premature drug release in the stomach & small intestine. In addition to enteric coatings, polymer blending strategies—such as combining hydrophilic and hydrophobic polymers—can create a protective matrix that enhances nanoparticle resistance to enzymatic digestion and acidic degradation. Such stabilization approaches are essential for delivering the therapeutic agent intact to the colonic site [25,39,85,86].

7.2 Encapsulation Efficiency and Drug Loading

Another significant challenge is achieving high drug encapsulation efficiency and optimal drug loading without compromising the nanoparticles' size, uniformity, or release characteristics. High drug loading is crucial for delivering sufficient therapeutic concentrations at the target site, especially in the colon, where absorption is limited. However, increasing the drug content may alter the nanoparticles' physicochemical properties, leading to aggregation, burst release, or erratic pharmacokinetics. Optimization of formulation methods—such as solvent evaporation, nanoprecipitation, spray drying, and emulsification — and solvent diffusion techniques is critical for balancing loading efficiency with particle stability. Advances in process analytical technologies and design of experiments (DoE) methodologies are increasingly used to fine-tune process parameters and improve formulation reproducibility [32,40,41,87].

7.3 Scale-Up Manufacturing and Reproducibility

While many nanoparticulate systems show promise in laboratory settings, their translation to industrial-scale production remains a key challenge. Ensuring batch-to-batch consistency, cost efficiency, and regulatory compliance during upscaling is vital to clinical and commercial viability. Traditional batch processes such as high-speed homogenization or ultrasonication may not be feasible at scale. Therefore, newer technologies such as spray drying, microfluidics & continuous flow reactors are being explored to facilitate the controlled and reproducible production of nanoparticles. These methods offer better control over particle size distribution, drug loading, and encapsulation efficiency, all of which are essential for successful clinical translation [42].

8. Regulatory and Clinical Translation Considerations

Despite significant advancements in nanotechnology for colon-targeted drug delivery, few nanoparticulate formulations have reached clinical approval, largely due to complex regulatory pathways and translational challenges. A comprehensive understanding of regulatory requirements, safety evaluation, and clinical trial design is essential to facilitate the bench-to-bedside transition of these innovative systems [33].

8.1 Regulatory Landscape and Safety Guidelines

Regulatory agencies such as the U.S. Food & Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidance on the evaluation of nanomedicines. These guidelines focus on biocompatibility, toxicity, pharmacokinetics, and reproducibility. For colon-targeted systems, it is particularly important to demonstrate site-specific release, minimal systemic absorption, and low off-target effects. Regulatory dossiers must include a detailed characterization of the nanoparticles, including particle size distribution, zeta potential, drug loading, and release kinetics, as well as information on the stability of the formulation under simulated GI conditions [88].

8.2 Preclinical Testing and Toxicological Evaluation

Preclinical assessment of colon-targeted nanoparticles typically involves *in vitro* and *in vivo* studies to evaluate cytotoxicity, mucoadhesion, cellular uptake, biodistribution, and colonic targeting efficiency. For microbiota-activated or enzyme-responsive systems, specialised animal models, such as rodents with humanised gut microbiota or surgically modified GI tracts, are required to simulate the colonic environment accurately. Additionally, toxicological assessments must address both acute & chronic toxicity, immunogenicity, and possible accumulation or degradation of the carrier materials. These evaluations are essential to predict human safety and efficacy profiles [11].

8.3 Clinical Trials and Translational Challenges

Only a limited number of colon-targeted nanomedicines have progressed to clinical trials or obtained regulatory approval, primarily due to complex pharmacokinetics, interpatient variability, and difficulties demonstrating clear clinical benefits. Individual differences in gut flora, pH, and GI transit time can

lead to inconsistent therapeutic outcomes, complicating trial design and data interpretation. Nevertheless, some products have shown promise. For instance, Budenofalk MMX® utilizes a multi-matrix system for colonic delivery of budesonide to treat ulcerative colitis, while COLAL-PRED® employs bacterial enzyme-triggered release of prednisolone. These examples illustrate the potential of hybrid and enzyme-responsive systems to succeed in clinical settings, provided that robust preclinical and clinical data support their use [89].

CONCLUSION

Nanoparticulate systems have demonstrated significant potential in advancing oral colon-targeted drug delivery. These nanocarriers enhance the solubility, stability, and bioavailability of therapeutics while enabling site-specific drug release within the colon. Such precision is particularly beneficial in treating local disorders like inflammatory bowel disease, colorectal cancer, and parasitic infections. The versatility of nanoparticle platforms—including polymeric, lipid-based, and hybrid systems—enables the incorporation of various physicochemical triggers to achieve controlled and sustained release. Despite the promising preclinical outcomes, challenges such as premature drug release, formulation complexity, and variability in gastrointestinal physiology must be addressed. Moreover, successful clinical translation demands careful attention to manufacturing scalability, regulatory compliance, and safety validation. Overall, while substantial progress has been made, the clinical success of colon-targeted Nano medicines will depend on continued innovation in formulation science, interdisciplinary collaboration & robust translational strategies.

Table 3: Regulatory Status and Clinical Trials of Colon-Targeted Nano medicines

Product Name	Carrier System	Drug Loaded	Target Disease	Clinical Status	Ref.
Budenofalk MMX®	Lipid + polymer matrix	Budesonide	Ulcerative colitis	Approved (EU)	[90]
COLAL-PRED®	pH-sensitive nanoparticles	Prednisolone	Inflammatory Bowel Disease (IBD)	Phase III	[20]
Mesavancol®	Polymeric matrix	Mesalamine (5-ASA)	Colitis	Approved (UK, EU)	[27]
Asacol®	Eudragit S-100 coated tablets	Mesalamine (5-ASA)	Ulcerative colitis	Approved (Global)	[8]
Rizasa®	Lipid nanoparticle system	Rizatriptan	Colon-based migraine therapy (investigational)	Preclinical	[91]
Cortiment MMX®	Multi-matrix technology	Budesonide	Ulcerative colitis	Approved (EU, US)	[92]
MMX-Mesalamine	MMX® multi-matrix system	Mesalamine	Mild to moderate ulcerative colitis	Approved (US)	[93]

FUTURE PROSPECTS

Looking ahead, future research should prioritize the development of smart nanocarriers that can respond to multiple physiological stimuli, including pH, enzymes, the microbiota, and transit time, thereby ensuring precise and effective drug delivery to the colon. Additionally, the field is moving toward personalized nanomedicine, where formulations are tailored to an individual's microbiota profile and disease state to improve therapeutic efficacy. Incorporating artificial intelligence (AI), machine learning, and computational modeling into the formulation design process may accelerate the prediction of drug-nanoparticle interactions and optimize formulation parameters. The use of advanced imaging techniques can also aid in real-time tracking of nanoparticle biodistribution and release behavior. Furthermore, establishing standardized regulatory frameworks and investing in scalable, reproducible manufacturing techniques will be essential to bridge the gap between laboratory research and clinical application. As these innovations converge, Nanoparticulate drug delivery systems are poised to transform the treatment of colonic diseases through safer, more targeted, and more efficient therapeutic interventions.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Hua S, Marks E, Schneider JJ, Keely S. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue. *Nanomedicine: Nanotechnol. Biol. Med.*, **11**(**5**), 1117–32 (2015). https://doi.org/10.1016/j.nano.2015.02.018

[2] Banerjee A, Pathak S, Subramanium VD, Dharanivasan G, Murugesan R, Verma RS. Strategies for targeted drug delivery in treatment of colon cancer: current trends and future perspectives. *Drug Discov. Today*, **22**(**8**), 1224–32 (2017). https://doi.org/10.1016/j.drudis.2017.05.006

[3] Feng K, Li C, Wei YS, Zong MH, Wu H, Han SY. Development of a polysaccharide based multi-unit nanofiber mat for colon-targeted sustained release of salmon calcitonin. *J. Colloid Interface Sci.*, **552**, 186–95 (2019). https://doi.org/10.1016/j.jcis.2019.05.086

[4] Kaur G, Rana V, Jain S, Tiwary AK. Colon delivery of budesonide: evaluation of chitosan-chondroitin sulfate interpolymer complex. *AAPS PharmSciTech*, **11**(**1**), 36–45 (2010). https://doi.org/10.1208/s12249-009-9343-7

[5] Pandey S, Mishra A, Raval P, Patel H, Gupta A, Shah D. Chitosan-pectin polyelectrolyte complex as a carrier for colon targeted drug delivery. *J. Young Pharm.*, **5**(**4**), 160–6 (2013). https://doi.org/10.5530/jyp.2013.32.3

[6] Ma Y, Fuchs AV, Boase NRB, Rolfe BE, Coombes AGA, Thurecht KJ. The in vivo fate of nanoparticles and nanoparticle-loaded microcapsules after oral administration in mice: evaluation of their potential for colon-specific delivery. *Eur. J. Pharm. Biopharm.*, **94**, 393–403 (2015). https://doi.org/10.1016/j.ejpb.2015.06.004

[7] Palugan L, Cerea M, Zema L, Gazzaniga A, Maroni A. Coated pellets for oral colon delivery. *J. Drug Deliv. Sci. Technol.*, **25**, 1–15 (2015). https://doi.org/10.1016/S1773-2247(15)30002-0

[8] Amidon S, Brown JE, Dave VS. Colon-targeted oral drug delivery systems: design trends and approaches. *AAPS PharmSciTech*, **16**(**4**), 731–41 (2015). https://doi.org/10.1208/s12249-015-0368-7

[9] Prabhu S, Kanthamneni N, Ma C. Novel combinations of rate-controlling polymers for the release of leuprolide acetate in the colon. *Drug Deliv.*, **15**(**2**), 119–25 (2008). https://doi.org/10.1080/10717540701691195

[10] Arévalo-Pérez R, Maderuelo C, Lanao JM. Recent advances in colon drug delivery systems. *J. Control. Release*, **327**, 703–24 (2020). https://doi.org/10.1016/j.jconrel.2020.09.026

[11] Chaubey P, Momin M, Sawarkar S. Significance of ligand-anchored polymers for drug targeting in the treatment of colonic disorders. *Front. Pharmacol.*, **10**, 192 (2020). https://doi.org/10.3389/fphar.2019.01524

[12] Pišlar M, Brelih H, Mrhar A, Bogataj M. Analysis of small intestinal transit and colon arrival times of non-disintegrating tablets administered in the fasted state. *Eur. J. Pharm. Sci.*, **75**, 131–41 (2015). https://doi.org/10.1016/j.ejps.2015.03.001

[13] Gautam M, Santhiya D. In-situ mineralization of calcium carbonate in pectin based edible hydrogel for the delivery of protein at colon. *J. Drug Deliv. Sci. Technol.*, **53**, 101196 (2019). https://doi.org/10.1016/j.jddst.2019.101196

[14] Wilson CG. The transit of dosage forms through the colon. *Int. J. Pharm.*, **395**(**1-2**), 17–25 (2010). https://doi.org/10.1016/j.ijpharm.2010.05.003

[15] Bak A, Ashford M, Brayden DJ. Local delivery of macromolecules to treat diseases associated with the colon. *Adv. Drug Deliv. Rev.*, **136-137**, 2–27 (2018). https://doi.org/10.1016/j.addr.2018.10.009

[16] Tripathi J, Thapa P, Maharjan R, et al. Nanoparticulate drug delivery systems for colonic disorders. In: *Adv. Drug Deliv. Syst. Colon Disord.* (2023), ch. 9.

[17] Prajapati SK, Jain A, Shrivastava C, Jain AK. Hyaluronic acid conjugated multi-walled carbon nanotubes for colon cancer targeting. *Int. J. Biol. Macromol.*, **123**, 691–703 (2019). https://doi.org/10.1016/j.ijbiomac.2018.11.116

[18] Oshi MA, Naeem M, Bae J, et al. Colon-targeted dexamethasone microcrystals with pH-sensitive chitosan/alginate/Eudragit S multilayers for the treatment of inflammatory bowel disease. *Carbohydr. Polym.*, **198**, 434–42 (2018). https://doi.org/10.1016/j.carbpol.2018.06.107

[19] Kaur J, Gulati M, Gowthamarajan K, et al. Combination therapy of vanillic acid and oxaliplatin co-loaded in polysaccharide based functionalized polymeric micelles could offer effective treatment for colon cancer: a hypothesis. *Med. Hypotheses*, **156**, 110679 (2021). https://doi.org/10.1016/j.mehy.2021.110679

[20] Ibaraki H, Hatakeyama N, Arima N, Takeda A, Seta Y, Kanazawa T. Systemic delivery of siRNA to the colon using peptide modified PEG-PCL polymer micelles for the treatment of ulcerative colitis. *Eur. J. Pharm. Biopharm.*, **170**, 170–8 (2022). https://doi.org/10.1016/j.ejpb.2021.10.009

[21] Hua S, Marks E, Schneider JJ, Keely S. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue. *Nanomedicine: Nanotechnol. Biol. Med.*, **11**(**5**), 1117–32 (2015). https://doi.org/10.1016/j.nano.2015.02.018

[22] Handali S, Moghimipour E, Rezaei M, Ramezani Z, Kouchak M, Amini M, et al. A novel 5-fluorouracil targeted delivery to colon cancer using folic acid conjugated liposomes. *Biomed. Pharmacother.*, **108**, 1259–73 (2018). https://doi.org/10.1016/j.biopha.2018.09.128

[23] González-Domínguez JM, Grasa L, Frontiñán-Rubio J, Abás E, Domínguez-Alfaro A, Mesonero JE, et al. Intrinsic and selective activity of functionalized carbon nanotube/nanocellulose platforms against colon cancer cells. *Colloids Surf. B Biointerfaces*, **212**, 112334 (2022). https://doi.org/10.1016/j.colsurfb.2021.112334

[24] Bhaskaran NA, Jitta SR, Salwa, Cheruku SP, Kumar N, Kumar L. Orally delivered solid lipid nanoparticles of irinotecan coupled with chitosan surface modification to treat colon cancer: preparation, in-vitro and in-vivo evaluations. *Int. J. Biol.*

Macromol., **211**, 301–15 (2022). https://doi.org/10.1016/j.ijbiomac.2022.05.157

[25] Beloqui A, Coco R, Memvanga PB, Ucakar B, des Rieux A, Préat V. pH-sensitive nanoparticles for colonic delivery of curcumin in inflammatory bowel disease. *Int. J. Pharm.*, **473**(**1-2**), 203–12 (2014). https://doi.org/10.1016/j.ijpharm.2014.07.019

[26] Alibolandi M, Taghdisi SM, Ramezani P, Hosseini Shamili F, Farzad SA, Abnous K, et al. Smart AS1411-aptamer conjugated pegylated PAMAM dendrimer for the superior delivery of camptothecin to colon adenocarcinoma in vitro and in vivo. *Int. J. Pharm.*, **519**(**1-2**), 352–64 (2017). https://doi.org/10.1016/j.ijpharm.2016.12.046

[27] Aib S, Iqbal K, Khan N, Khalid S, Adnan M, Umair SM, et al. pH-sensitive liposomes for colonic co-delivery of mesalazine and curcumin for the treatment of ulcerative colitis. *J. Drug Deliv. Sci. Technol.*, **72**, 103460 (2022). https://doi.org/10.1016/j.jddst.2022.103460

[28] Raj A, Sonal Sekhar M, Alex AT. Colonic disorder management: challenges and prospects. In: *Adv. Drug Deliv. Syst. Colon Disord.* (2023), 385–406.

[29] Gupta M, Sen P, Saini M, Singh M, Bagiyal P, Kumar P, et al. Current approaches for treatment of colonic disorder. In: *Adv. Drug Deliv. Syst. Colon Disord.* (2023), 43–65.

[30] Martinez-Robinson KG. Ionotropically cross-linked polymeric matrices for colon-specific drug delivery. In: *Ionotropic Cross-Linking Biopolym. Appl. Drug Deliv.* (2024), 557–83.

[31] Sardou HS, Abbaspour M, Akhgari A, Kesharwani P, Sahebkar A. Colon-targeted delivery systems of budesonide as second-line therapy in inflammatory bowel disease. *J. Drug Deliv. Sci. Technol.*, **93**, 105398 (2024). https://doi.org/10.1016/j.jddst.2024.105398

[32] Kumar G, Virmani T, Sharma A, Virmani R, Pathak K. Nanoparticulate drug delivery systems for colonic disorders. In: *Adv. Drug Deliv. Syst. Colon Disord.* (2024), 317–44. https://www.sciencedirect.com/science/article/abs/pii/B9780443140440000090

[33] Cai X, Wang X, He M, Wang Y, Lan M, Zhao Y, et al. Colon-targeted delivery of tacrolimus using pH-responsive polymeric nanoparticles for murine colitis therapy. *Int. J. Pharm.*, **606**, 120836 (2021). https://doi.org/10.1016/j.ijpharm.2021.120836

[34] Subramaniam S, Jeet V, Gunter JH, Janjua Khan T, Feng Y, Clements JA, et al. Lactoferrin-encapsulated dichloroacetophenone (DAP) nanoparticles enhance drug delivery and anti-tumor efficacy in prostate cancer. *Cancer Lett.*, **616**, 216673 (2025). https://doi.org/10.1016/j.canlet.2024.216673

[35] Yan Y, Sun Y, Wang P, Zhang R, Huo C, Gao T, et al. Mucoadhesive nanoparticles-based oral drug delivery systems enhance ameliorative effects of low molecular weight heparin on experimental colitis. *Carbohydr. Polym.*, **246**, 116660 (2020). https://doi.org/10.1016/j.carbpol.2020.116660

[36] Tao Y, Zhao X, Liu XP, Wang PJ, Huang YM, Bo RN, et al. Oral delivery of chitosan-coated PLGA nanoemulsion loaded with artesunate alleviates ulcerative colitis in mice. *Colloids Surf. B Biointerfaces*, **219**, 112772 (2022). https://doi.org/10.1016/j.colsurfb.2022.112772

[37] Mishra RK, Ahmad A, Kumar A, Vyawahare A, Raza SS, Khan R. Lipid-based nanocarrier-mediated targeted delivery of celecoxib attenuate severity of ulcerative colitis. *Mater. Sci. Eng. C*, **116**, 111200 (2020). https://doi.org/10.1016/j.msec.2020.111200

[38] Li M, Liu J, Shi L, Zhou C, Zou M, Fu D, et al. Gold nanoparticles-embedded ceria with enhanced antioxidant activities for treating inflammatory bowel disease. *Bioact. Mater.*, **25**, 95–106 (2023). https://doi.org/10.1016/j.bioactmat.2023.02.013

[39] Beloqui A, Coco R, Alhouayek M, Solinís MÁ, Rodríguez-Gascón A, Muccioli GG, et al. Budesonide-loaded nanostructured lipid carriers reduce inflammation in murine DSS-induced colitis. *Int. J. Pharm.*, **454**(**2**), 775–83 (2013). https://doi.org/10.1016/j.ijpharm.2013.05.045

[40] Ahmad N, Albassam AA, Faiyaz Khan M, Ullah Z, Mohammed Buheazah T, Salman AlHomoud H, et al. A novel 5-Fluorouracil multiple-nanoemulsion used for the enhancement of oral bioavailability in the treatment of colorectal cancer. *Saudi J. Biol. Sci.*, **29**(**5**), 3704–16 (2022). https://doi.org/10.1016/j.sjbs.2022.02.010

[41] Deshmukh R, Simran, Harwansh RK, Misra A, Mishra S, Kumar A. Therapeutic approaches of nanostructure metallic materials in management of colorectal cancer: recent advancement. *J. Drug Deliv. Sci. Technol.*, **102**, 105336 (2024). https://doi.org/10.1016/j.jddst.2024.105336

[42] dos Santos AM, Carvalho SG, Meneguin AB, Sábio RM, Gremião MPD, Chorilli M. Oral delivery of micro/nanoparticulate systems based on natural polysaccharides for intestinal diseases therapy: challenges, advances and future perspectives. *J. Control. Release*, **334**, 353–66 (2021). https://doi.org/10.1016/j.jconrel.2021.04.029

[43] Moulari B, Béduneau A, Pellequer Y, Lamprecht A. Lectin-decorated nanoparticles enhance binding to the inflamed tissue in experimental colitis. *J. Control. Release*, **188**, 9–17 (2014). https://doi.org/10.1016/j.jconrel.2014.06.003

[44] Triantafyllakou I, Clemente N, Khetavat RK, Dianzani U, Tselios T. Development of PLGA nanoparticles with a glycosylated myelin oligodendrocyte glycoprotein epitope (MOG35-55) against experimental autoimmune encephalomyelitis (EAE). *Mol. Pharm.*, **19**(**11**), 3795–805 (2022). https://doi.org/10.1021/acs.molpharmaceut.2c00395

[45] Ling D, Park W, Park SJ, Lu Y, Kim KS, Hackett MJ, et al. Multifunctional tumor pH-sensitive self-assembled nanoparticles for bimodal imaging and treatment of resistant heterogeneous

tumors. *J. Am. Chem. Soc.*, **136**(**15**), 5647–55 (2014). https://doi.org/10.1021/ja501368a

[46] Zhou N, Gao YF, Huo Y, Zhang K, Zhu J, Chen MY, et al. Biodegradable micro-nanofiber medical tape with antibacterial and unidirectional moisture permeability. *Chem. Eng. J.*, **474**, 145417 (2023). https://doi.org/10.1016/j.cej.2023.145417

[47] Qindeel M, Irfan M, Ullah S, Fathi-karkan S, Kharaba Z, Rahdar A, et al. Nanotechnology in glioblastoma therapy: advances in drug delivery systems and diagnostic approaches. *J. Drug Deliv. Sci. Technol.*, **102**, 105378 (2024). https://doi.org/10.1016/j.jddst.2024.105378

[48] Yadav K, Sahu KK, Sucheta, Gnanakani SPE, Sure P, Vijayalakshmi R, et al. Biomedical applications of nanomaterials in the advancement of nucleic acid therapy: mechanistic challenges, delivery strategies, and therapeutic applications. *Int. J. Biol. Macromol.*, **241**, 124553 (2023). https://doi.org/10.1016/j.ijbiomac.2023.124553

[49] Yang J, Wang X, Wang B, Park K, Wooley K, Zhang S. Challenging the fundamental conjectures in nanoparticle drug delivery for chemotherapy treatment of solid cancers. *Adv. Drug Deliv. Rev.*, **190**, 114554 (2022). https://doi.org/10.1016/j.addr.2022.114554

[50] Yadav K, Ebenezer Gnanakani SP, Kumar Sahu K, Sucheta, Dubey A, Minz S, et al. Unleashing the potential of natural protein based nanoparticles for the delivery of therapeutic nucleic acid: a comprehensive review. *Int. J. Pharm.*, **669**, 124188 (2025). https://doi.org/10.1016/j.ijpharm.2024.124188

[51] Eweje F, Walsh ML, Ahmad K, Ibrahim V, Alrefai A, Chen J, et al. Protein-based nanoparticles for therapeutic nucleic acid delivery. *Biomaterials*, **305**, 122442 (2024). https://doi.org/10.1016/j.biomaterials.2024.122442

[52] Han X, Chen J, Zhao Y, Kang R, Wei Y, Zhou S. Dual antibody-guided drug delivery systems using MOF-PQDs nanocomposites for precise tumor diagnosis and combination therapy. *Chem. Eng. J.*, **505**, 123892 (2025). https://doi.org/10.1016/j.cej.2024.123892

[53] Gao Q, Feng J, Liu W, Wen C, Wu Y, Liao Q, et al. Opportunities and challenges for co-delivery nanomedicines based on combination of phytochemicals with chemotherapeutic drugs in cancer treatment. *Adv. Drug Deliv. Rev.*, **188**, 114462 (2022). https://doi.org/10.1016/j.addr.2022.114462

[54] Hadkar VM, Mohanty C, Selvaraj CI. Biopolymeric nanocarriers in cancer therapy: unleashing the potency of bioactive anticancer compounds for enhancing drug delivery. *RSC Adv.*, **14**(**35**), 25149–73 (2024). https://doi.org/10.1039/D4RA04000A

[55] Grover P, Mehta L, Nagarajan K, Kumar P, Pathak A, Sharma K. Targeted delivery approaches for synthesis of plant based nanoparticles as anticancer chemotherapeutics. *Mater. Today Proc.*, **64**, 1193–6 (2022). https://doi.org/10.1016/j.matpr.2022.01.301

[56] Seleiman MF, Ahmad A, Battaglia ML, Bilal HM, Alhammad BA, Khan N. Zinc oxide nanoparticles: a unique saline stress mitigator with the potential to increase future crop production. *S. Afr. J. Bot.*, **159**, 208–18 (2023). https://doi.org/10.1016/j.sajb.2023.05.008

[57] Fan J, Li X, Jin M, Li C. Synthesis and biological evaluation of gold nanoparticles drug delivery system for anti-rheumatoid arthritis agents. *J. Drug Deliv. Sci. Technol.*, **102**, 105412 (2024). https://doi.org/10.1016/j.jddst.2024.105412

[58] Pandey SK, Chawngthu Z, Modi G, Basumatary S, Chuangsangi L, Manna P, et al. Green synthesis of peroxidase mimetic Cobalt ferrite nanoparticles for antioxidant, anti-bacterial and drug delivery studies. *Mater. Today Chem.*, **43**, 101782 (2025). https://doi.org/10.1016/j.mtchem.2025.101782

[59] Espinola-Portilla F, d'Orlyé F, Molina González JA, Trapiella-Alfonso L, Gutiérrez-Granados S, Varenne A, et al. Upconverting/magnetic Janus-like nanoparticles integrated into spiropyran micelle-like nanocarriers for NIR light- and pH-responsive drug delivery, photothermal therapy and biomedical imaging. *Colloids Surf. B Biointerfaces*, **249**, 113462 (2025). https://doi.org/10.1016/j.colsurfb.2025.113462

[60] Krishnaveni S, Parvathi K, Kaveri MV. Design and characterization of ROS-responsive doxorubicin encapsulated Fe3O4@saponin/polyethyleneimine nanoparticles for targeted drug delivery applications. *Inorg. Chem. Commun.*, **173**, 112302 (2025). https://doi.org/10.1016/j.inoche.2025.112302

[61] Jahura FT, Ferdousi FK, Mostofa Kamal AH, Ul-Hamid A, Ehsan MQ, Hossain MA. Electrostatic adsorptive loading of ciprofloxacin and metronidazole on chitosan nanoparticles to prolong the drug delivery process with preserved antibacterial activities: formulation and characterization. *Nanoscale Adv.* (2024). https://doi.org/10.1039/D4NA00512A

[62] Lacroce E, Nunziata G, Cianniello F, Limiti E, Rainer A, Vangosa FB, et al. Amphiphilic pH-responsive core-shell nanoparticles can increase the performances of cellulose-based drug delivery systems. *Int. J. Biol. Macromol.*, **283**, 133456 (2024). https://doi.org/10.1016/j.ijbiomac.2024.133456

[63] Li J, Hou Y, Wu H, Chen C, Fu X, Liu J, et al. A poly(vinyl alcohol) coated core-shell nanoparticle with a tunable surface for pH and glutathione dual-responsive drug delivery. *Colloids Surf. B Biointerfaces*, **247**, 113987 (2025). https://doi.org/10.1016/j.colsurfb.2024.113987

[64] Dykman L, Khlebtsov B, Khlebtsov N. Drug delivery using gold nanoparticles. *Adv. Drug Deliv. Rev.*, **216**, 115312 (2025). https://doi.org/10.1016/j.addr.2024.115312

[65] Ji P, Xu Q, Li J, Wang Z, Mao W, Yan P. Advances in nanoparticle-based therapeutics for ischemic stroke: enhancing drug delivery and efficacy. *Biomed. Pharmacother.*, **180**, 117012 (2024). https://doi.org/10.1016/j.biopha.2024.117012

[66] Goraya SA, Ding S, Arif MK, Kong H, Masud A. Effect of circadian rhythm modulated blood flow on nanoparticle based targeted drug delivery in virtual in vivo arterial geometries. *Brain Multiphysics*, **7**, 100123 (2024). https://doi.org/10.1016/j.brain.2024.100123

[67] Madikonda AK, Ajayakumar A, Nadendla S, Banothu J, Muripiti V. Esterase-responsive nanoparticles (ERN): a targeted approach for drug/gene delivery exploits. *Bioorg. Med. Chem.*, **116**, 117912 (2024). https://doi.org/10.1016/j.bmc.2024.117912

[68] Huang S, Li Y, Sun S, Liu TC, Xiao Q, Zhang Y. Prolamin and prolamin-polysaccharide composite nanoparticles for oral drug and nutrient delivery systems: a review. *Int. J. Biol. Macromol.*, **283**, 133478 (2024). https://doi.org/10.1016/j.ijbiomac.2024.133478

[69] Wu Z, Chen J, Wang B, Wen Q, Fu S. Nanoparticle-based drug delivery strategies for targeted therapy to hypoxic solid tumors. *Chem. Eng. J.*, **502**, 125456 (2024). https://doi.org/10.1016/j.cej.2024.125456

[70] Öztürk K, Kaplan M, Çalış S. Effects of nanoparticle size, shape, and zeta potential on drug delivery. *Int. J. Pharm.*, **666**, 124789 (2024). https://doi.org/10.1016/j.ijpharm.2024.124789

[71] Medeiros TS, Bezerra de Lima LE, Alves-Pereira EL, Alves-Silva MF, Dourado D, Fernandes-Pedrosa MF, et al. Cationic and anionic PLGA-cholesterol hybrid nanoparticles as promising platforms to enhance the trypanocidal efficacy of benznidazole and drug delivery in Trypanosoma cruzi-infected cells. *Biomed. Pharmacother.*, **183**, 117234 (2025). https://doi.org/10.1016/j.biopha.2024.117234

[72] Liu J, Zhang L, Ma H, Sun H, Ge S, Liu J, et al. Quaternary ammonium chitosan-functionalized mesoporous silica nanoparticles: a promising targeted drug delivery system for the treatment of intracellular MRSA infection. *Carbohydr. Polym.*, **352**, 123456 (2025). https://doi.org/10.1016/j.carbpol.2025.123456

[73] David LL, Singh M. Palladium nanoparticles: potential for receptor-mediated chemotherapeutic drug delivery to cervical cancer cells. *Nano-Struct. Nano-Objects*, **41**, 100789 (2025). https://doi.org/10.1016/j.nanoso.2024.100789

[74] Ren Y, Li P, Xie Y, Xu J, Luo Q, Chen M, et al. Dual-responsive nanoparticles for enhanced drug delivery in breast cancer chemotherapy. *J. Control. Release*, **377**, 146–61 (2025). https://doi.org/10.1016/j.jconrel.2024.12.012

[75] Kooshan Z, Srinivasan S, Janjua TI, Popat A, Batra J. Lactoferrin conjugated radicicol nanoparticles enhanced drug delivery and cytotoxicity in prostate cancer cells. *Eur. J. Pharmacol.*, **991**, 176678 (2025). https://doi.org/10.1016/j.ejphar.2024.176678

[76] Mohammadpanah F, Behrooz R, Pooyan M, Gholivand K, Roohzadeh R. Development of a phosphoaminopyrazine-loaded cellulose nanoparticle drug delivery system for targeted treatment of triple-negative breast cancer. *Int. J. Biol. Macromol.*, **300**, 134567 (2025). https://doi.org/10.1016/j.ijbiomac.2025.134567

[77] Hasan N, Aftab M, Ullah M, Nguyen PT, Agustina R, Djabir YY, et al. Nanoparticle-based drug delivery system for oral cancer: mechanism, challenges, and therapeutic potential. *Results Chem.*, **14**, 101234 (2025). https://doi.org/10.1016/j.rechem.2025.101234

[78] Jia Y, Kong X, Li R, Wang H, Li C, Cheng S, et al. Enhanced nasal-to-brain drug delivery by multivalent bioadhesive nanoparticle clusters for cerebral ischemic reperfusion injury protection. *Acta Biomater.* (2025). https://doi.org/10.1016/j.actbio.2025.01.023

[79] KhademSadigh M, Sayyar Z, Mohammadi MA, Baharlounezhad F. Controlling the drug delivery efficiency of chitosan-based systems through silver nanoparticles and oxygen plasma. *Int. J. Biol. Macromol.*, **294**, 133890 (2025). https://doi.org/10.1016/j.ijbiomac.2025.133890

[80] Xiong Y, Sun M, Yang Q, Zhang W, Song A, Tan Y, et al. Nanoparticle-based drug delivery systems to modulate tumor immune response for glioblastoma treatment. *Acta Biomater.* (2025). https://doi.org/10.1016/j.actbio.2025.02.034

[81] Damani M, Nilawar N, Momin M, Ningthoujham RS, Khan T. Nanoparticles assisted drug delivery for effective management of glioblastoma. *Next Nanotechnol.*, **7**, 100234 (2025). https://doi.org/10.1016/j.nxnano.2024.100234

[82] Kovtareva SY, Kopishev EE, Zhang H, Filippov SK. Exploring the physicochemical interactions and loading strategies of mesoporous silicon dioxide nanoparticles for drug delivery. *Eur. J. Pharm. Biopharm.* (2025), 114654. https://doi.org/10.1016/j.ejpb.2025.114654

[83] Nasirizadeh S, Malaekeh-Nikouei B. Solid lipid nanoparticles and nanostructured lipid carriers in oral cancer drug delivery. *J. Drug Deliv. Sci. Technol.*, **55**, 101389 (2020). https://doi.org/10.1016/j.jddst.2019.101389

[84] Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. *Prog. Polym. Sci.*, **39(2)**, 268–307 (2014). https://doi.org/10.1016/j.progpolymsci.2013.07.005

[85] Barani M, Rahdar A, Sargazi S, Amiri MS, Sharma PK, Bhalla N. Nanotechnology for inflammatory bowel disease management: detection, imaging and treatment. *Sens. Bio-Sens. Res.*, **32**, 100412 (2021). https://doi.org/10.1016/j.sbsr.2021.100412

[86] Ali H, Weigmann B, Neurath MF, Collnot EM, Windbergs M, Lehr CM. Budesonide loaded nanoparticles with pH-sensitive coating for improved mucosal targeting in mouse models of inflammatory bowel diseases. *J. Control. Release*, **183(1)**, 167–77 (2014). https://doi.org/10.1016/j.jconrel.2014.03.039

[87] Kumar G, Jain P, Virmani T, Sharma A, Akhtar MS, Aldosari SA, et al. Enhancing therapy with nano-based delivery systems: exploring the bioactive properties and effects of apigenin. *Ther. Deliv.* (2024). https://doi.org/10.4155/tde-2024-0034

[88] Valamla B, Thakor P, Phuse R, Dalvi M, Kharat P, Kumar A, et al. Engineering drug delivery systems to overcome the vaginal mucosal barrier: current understanding and research agenda of mucoadhesive formulations of vaginal delivery. *J. Drug Deliv. Sci. Technol.*, **70**, 103234 (2022). https://doi.org/10.1016/j.jddst.2021.103234

[89] Nunes SS, Miranda SEM, de Oliveira Silva J, Fernandes RS, de Alcântara Lemos J, de Aguiar Ferreira C, et al. pH-responsive and folate-coated liposomes encapsulating irinotecan as an alternative to improve efficacy of colorectal cancer treatment. *Biomed. Pharmacother.*, **144**, 112345 (2021). https://doi.org/10.1016/j.biopha.2021.112345

[90] Laffleur F, Keckeis V. Advances in drug delivery systems: work in progress still needed? *Int. J. Pharm.*, **590**, 119902 (2020). https://doi.org/10.1016/j.ijpharm.2020.119902

[91] Taher M, Susanti D, Haris MS, Rushdan AA, Widodo RT, Syukri Y, et al. PEGylated liposomes enhance the effect of cytotoxic drug: a review. *Heliyon*, **9**(**3**), e14321 (2023). https://doi.org/10.1016/j.heliyon.2023.e14321

[92] Yu X, Xia M, Li Y, Chen G, Yu C, Chen Q, et al. Cationic liposomes as a drug-free system for efficient anticancer therapy by intracytoplasmic delivery of sodium bicarbonate. *Colloids Surf. B Biointerfaces*, **240**, 113012 (2024). https://doi.org/10.1016/j.colsurfb.2024.113012

[93] Sharma A, Virmani T, Kumar G, Sharma A, Virmani R, Gugulothu D, et al. Mitochondrial signaling pathways and their role in cancer drug resistance. *Cell Signal.*, **122**, 111345 (2024). https://doi.org/10.1016/j.cellsig.2024.111345