

DEVELOPMENT AND EVALUATION OF NOVEL NANOPARTICLE DRUG DELIVERY SYSTEMS FOR TARGETED THERAPY OF INFLAMMATORY BOWEL DISEASE AND COLORECTAL CANCER

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1. Abstract

Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, and colorectal cancer (CRC) are chronic gastrointestinal disorders associated with significant morbidity and mortality worldwide. Conventional therapeutic approaches for these diseases are often limited by poor drug bioavailability, systemic toxicity, non-specific drug distribution, rapid drug degradation, and inadequate therapeutic efficacy at the target site. In recent years, nanotechnology-based drug delivery systems have emerged as promising strategies for improving the therapeutic management of IBD and CRC. Nanoparticles possess unique physicochemical properties such as nanoscale size, enhanced surface area, controlled drug release behavior, and the ability to selectively target inflamed or cancerous tissues, thereby improving treatment outcomes while minimizing adverse effects. The present review aims to comprehensively discuss the development and evaluation of novel nanoparticle drug delivery systems for targeted therapy of inflammatory bowel disease and colorectal cancer. The review focuses on different types of nanoparticles, formulation approaches, targeting mechanisms, characterization techniques, therapeutic applications, recent advancements, and current challenges associated with nanoparticle-mediated drug delivery systems. A detailed literature survey was conducted using scientific databases including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Relevant research articles, review papers, clinical studies, and recent advancements published in peer-reviewed journals were critically analyzed. Keywords such as "nanoparticles," "targeted drug delivery," "inflammatory bowel disease," "colorectal cancer," "nanomedicine," "colon-targeted therapy," and "polymeric nanoparticles" were used for data collection. The selected studies were evaluated based on formulation strategies, therapeutic efficacy, targeting approaches, and safety profiles. Various nanoparticle systems including polymeric nanoparticles, liposomes, solid lipid nanoparticles, dendrimers, metallic nanoparticles, and nanostructured lipid carriers have demonstrated significant potential in the targeted treatment of IBD and CRC. These systems enhance drug stability, improve mucosal penetration, prolong drug retention time, and facilitate site-specific delivery of therapeutic agents. Stimuli-responsive nanoparticles, ligand-mediated targeting systems, and pH-sensitive formulations have shown improved therapeutic efficacy and reduced systemic toxicity. Furthermore, nanoparticle-based delivery of biologics, genes, siRNA, and chemotherapeutic agents has opened new avenues for precision medicine in gastrointestinal disorders. Despite encouraging preclinical and clinical outcomes, challenges related to large-scale manufacturing, long-term safety, regulatory approval, and clinical translation remain major concerns. Novel nanoparticle drug delivery systems represent a promising and rapidly advancing approach for the targeted therapy

of inflammatory bowel disease and colorectal cancer. Their ability to improve drug bioavailability, achieve controlled release, and selectively target diseased tissues offers substantial advantages over conventional therapeutic methods. Continued research focusing on formulation optimization, toxicity evaluation, translational studies, and regulatory standardization is essential to facilitate the successful clinical application of nanoparticle-based therapies in gastrointestinal diseases.

2. Keywords: Inflammatory Bowel Disease, Colorectal Cancer, Nanoparticle Drug Delivery, Targeted Therapy, Nanomedicine

3. Introduction

Inflammatory bowel disease (IBD) and colorectal cancer (CRC) are among the most prevalent and clinically challenging gastrointestinal disorders affecting millions of individuals worldwide. Both diseases are associated with chronic inflammation, altered immune responses, genetic predisposition, and environmental influences that collectively contribute to disease progression and severe complications[1]. Despite remarkable advances in therapeutic strategies, conventional treatment approaches often fail to achieve optimal clinical outcomes because of poor site-specific drug delivery, systemic toxicity, limited bioavailability, and frequent disease relapse. Consequently, there is a growing need for advanced therapeutic systems capable of delivering drugs selectively to diseased tissues while minimizing adverse effects[2]. Nanotechnology-based drug delivery systems have emerged as promising tools for overcoming the limitations of conventional therapies. Nanoparticles possess unique physicochemical characteristics including nanoscale size, high surface-to-volume ratio, tunable surface properties, and controlled drug release capabilities, which enable efficient targeting of inflamed intestinal tissues and tumor microenvironments. Recent developments in nanomedicine have significantly improved the delivery of anti-inflammatory agents, chemotherapeutics, biologics, nucleic acids, and imaging agents for the management of IBD and CRC[3]. Targeted nanoparticle systems not only enhance therapeutic efficacy but also reduce systemic toxicity and improve patient compliance. This review comprehensively discusses the development and evaluation of novel nanoparticle drug delivery systems for targeted therapy of inflammatory bowel disease and colorectal cancer. The review highlights recent advancements in nanoparticle formulation strategies, targeting approaches, characterization techniques, therapeutic applications, clinical perspectives, and future opportunities in this rapidly evolving field[4].

3.1 Overview of Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease is a chronic relapsing inflammatory disorder of the gastrointestinal tract primarily comprising two major conditions: Crohn's disease (CD) and ulcerative colitis (UC). Crohn's disease can affect any part of the gastrointestinal tract from the mouth to the anus and is characterized by transmural inflammation, whereas ulcerative colitis is generally restricted to the colon and rectum with inflammation limited to the mucosal layer. The incidence and prevalence of IBD have increased significantly over recent decades, particularly in industrialized and developing countries, making it a major global healthcare concern. The exact etiology of IBD remains incompletely understood; however, it is believed to result from a complex interaction among genetic susceptibility, environmental factors, intestinal microbiota imbalance, epithelial barrier dysfunction, and dysregulated immune responses[5]. Excessive production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β) contributes significantly to chronic intestinal inflammation and tissue damage. Clinical manifestations commonly include abdominal pain, diarrhea, rectal bleeding, weight loss, fatigue, and malnutrition, which substantially reduce the quality of life of affected individuals[6]. Current therapeutic interventions for IBD include corticosteroids, aminosalicylates, immunosuppressants, antibiotics, and biologic therapies. Although these treatments help control inflammation

and maintain remission, they are often associated with serious adverse effects, poor patient compliance, and limited long-term efficacy. Furthermore, conventional formulations frequently fail to achieve adequate drug concentration at the inflamed intestinal site, necessitating the development of targeted and controlled drug delivery systems[7].

3.2 Overview of Colorectal Cancer (CRC)

Colorectal cancer is one of the leading causes of cancer-related morbidity and mortality worldwide. It develops through a multistep process involving the transformation of normal colonic epithelium into adenomatous polyps and eventually malignant carcinoma[8]. The development of CRC is strongly associated with genetic mutations, chronic inflammation, dietary habits, lifestyle factors, obesity, smoking, alcohol consumption, and inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Molecular mechanisms underlying CRC involve mutations in several oncogenes and tumor suppressor genes including APC, KRAS, TP53, and mismatch repair genes. Chronic inflammation plays a crucial role in promoting tumor initiation, progression, angiogenesis, and metastasis through persistent oxidative stress and cytokine-mediated signaling pathways. Patients with CRC may present with symptoms such as rectal bleeding, abdominal discomfort, altered bowel habits, anemia, and unexplained weight loss[9]. Early-stage CRC is often asymptomatic, which contributes to delayed diagnosis and poor prognosis. Conventional treatment strategies for CRC include surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy. Common chemotherapeutic agents such as 5-fluorouracil, oxaliplatin, and irinotecan are associated with severe systemic toxicity, multidrug resistance, and non-specific tissue distribution. These limitations significantly compromise therapeutic efficacy and patient quality of life[10]. Therefore, advanced drug delivery systems capable of selectively targeting tumor tissues while reducing systemic exposure have gained increasing attention in colorectal cancer management[11].

3.3 Limitations of Conventional Drug Delivery

Conventional drug delivery systems used for the treatment of IBD and CRC are associated with numerous pharmacokinetic and pharmacodynamic limitations that reduce therapeutic effectiveness. Oral and systemic administration of drugs often result in non-specific distribution throughout the body, leading to inadequate drug concentration at the target site and increased systemic toxicity[12]. Many therapeutic agents exhibit poor aqueous solubility, low bioavailability, rapid enzymatic degradation, and short biological half-life, thereby requiring frequent dosing and higher drug concentrations. In the treatment of IBD, conventional formulations are often unable to overcome physiological barriers such as mucus layers, intestinal pH variations, enzymatic degradation, and rapid gastrointestinal transit[13]. As a result, only a limited amount of the administered drug reaches the inflamed intestinal tissues. Long-term use of corticosteroids and immunosuppressive agents may also cause severe adverse effects including osteoporosis, hypertension, hepatotoxicity, nephrotoxicity, and increased susceptibility to infections. Similarly, conventional chemotherapy for CRC suffers from poor selectivity toward cancer cells, resulting in damage to healthy tissues and severe side effects such as myelosuppression, gastrointestinal toxicity, neuropathy, and immunosuppression[14]. Multidrug resistance and limited intracellular uptake of anticancer drugs further reduce treatment efficacy. In addition, many chemotherapeutic agents exhibit poor pharmacokinetic profiles and rapid clearance from systemic circulation. These challenges highlight the urgent need for innovative drug delivery approaches that can enhance therapeutic efficacy, improve drug stability, provide controlled release, and achieve site-specific targeting with minimal systemic toxicity[15].

3.4 Need for Targeted Nanoparticle Drug Delivery Systems

Targeted nanoparticle drug delivery systems have emerged as highly effective approaches for overcoming the limitations associated with conventional therapies. Nanoparticles typically range from 1 to 1000 nm in size and

can be engineered using various materials such as polymers, lipids, metals, proteins, and inorganic compounds. Their unique physicochemical properties enable enhanced drug loading, controlled release, prolonged circulation time, and improved interaction with biological membranes[16]. In IBD therapy, nanoparticles can selectively accumulate in inflamed intestinal tissues due to increased epithelial permeability and altered mucosal environments. Surface-functionalized nanoparticles can further improve site-specific targeting by interacting with overexpressed receptors or inflammatory mediators present in diseased tissues[17]. pH-sensitive and enzyme-responsive nanoparticles have shown particular promise in colon-targeted drug delivery by protecting drugs from premature degradation in the upper gastrointestinal tract and releasing them specifically in the colon. In colorectal cancer therapy, nanoparticles can exploit the enhanced permeability and retention (EPR) effect to preferentially accumulate within tumor tissues. Active targeting strategies involving ligands, antibodies, peptides, and aptamers further improve selective uptake by cancer cells. Nanoparticle-mediated delivery of chemotherapeutic agents enhances intracellular drug accumulation, overcomes multidrug resistance, and reduces systemic toxicity[18]. Moreover, nanoparticles can be utilized for the delivery of genes, siRNA, proteins, and immunotherapeutic agents, thereby expanding their therapeutic potential. The ability of nanoparticles to provide sustained and controlled drug release, improve pharmacokinetic profiles, and facilitate multifunctional therapeutic approaches makes them highly promising platforms for targeted management of gastrointestinal diseases[19].

3.5 Scope and Objectives of the Review

The present review focuses on the recent advancements in the development and evaluation of novel nanoparticle drug delivery systems for targeted therapy of inflammatory bowel disease and colorectal cancer[3]. The review aims to provide a comprehensive understanding of the pathophysiology of these disorders and the role of nanotechnology in overcoming the limitations of conventional treatment strategies. The major objectives of this review include[20]:

- (i) discussing various types of nanoparticles employed in IBD and CRC therapy;
- (ii) describing formulation methods and physicochemical characterization techniques;
- (iii) explaining passive and active targeting strategies for site-specific drug delivery;
- (iv) evaluating recent preclinical and clinical studies related to nanoparticle-mediated therapy;
- (v) highlighting current challenges associated with toxicity, large-scale manufacturing, and regulatory approval; and
- (vi) exploring future perspectives and emerging trends in nanomedicine for gastrointestinal diseases. This review is intended to serve as a valuable scientific resource for researchers, academicians, pharmaceutical scientists, and healthcare professionals involved in the development of advanced targeted drug delivery systems for inflammatory and cancerous gastrointestinal disorders[21].

4. Pathophysiology of Inflammatory Bowel Disease and Colorectal Cancer

Inflammatory bowel disease (IBD) and colorectal cancer (CRC) are multifactorial disorders characterized by complex interactions among genetic, immunological, microbial, and environmental factors. Chronic intestinal inflammation plays a pivotal role in the initiation and progression of both diseases[22]. Persistent activation of inflammatory pathways disrupts intestinal homeostasis, damages epithelial barriers, and promotes cellular proliferation, oxidative stress, angiogenesis, and genomic instability. Although ulcerative colitis and Crohn's disease differ in their pathological manifestations, both conditions are associated with dysregulated immune responses and altered gut microbiota composition[23]. Long-standing inflammatory bowel disease significantly increases the risk of developing colorectal cancer due to continuous inflammatory insult and repeated epithelial regeneration. Understanding the molecular and cellular mechanisms involved in the pathogenesis of IBD and

CRC is essential for identifying novel therapeutic targets and designing advanced nanoparticle-based drug delivery systems for targeted therapy[3].

4.1 Pathogenesis of Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory disorder primarily affecting the mucosal layer of the colon and rectum. The disease usually begins in the rectum and extends proximally in a continuous manner through the colon. The exact etiology of ulcerative colitis remains unclear; however, it is believed to result from a combination of genetic predisposition, epithelial barrier dysfunction, environmental triggers, gut microbiota imbalance, and abnormal immune responses[24]. One of the major pathological features of UC is disruption of the intestinal epithelial barrier, which increases mucosal permeability and facilitates the entry of luminal antigens, bacteria, and toxins into the intestinal tissue. This process activates immune cells such as macrophages, dendritic cells, neutrophils, and T lymphocytes, leading to excessive production of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and interleukin-13 (IL-13). These cytokines further amplify inflammation and contribute to mucosal ulceration and tissue injury[25]. Oxidative stress also plays a significant role in UC pathogenesis. Activated immune cells generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), which damage cellular proteins, lipids, and DNA. Continuous inflammatory insult results in epithelial erosion, crypt abscess formation, edema, and ulceration of the colonic mucosa. Additionally, alterations in gut microbiota composition, commonly referred to as dysbiosis, contribute to disease progression by disturbing immune tolerance and promoting chronic inflammation[26]. Genetic susceptibility factors such as variations in HLA genes, cytokine-related genes, and epithelial barrier-associated proteins have also been implicated in ulcerative colitis. Environmental factors including dietary habits, stress, smoking cessation, and antibiotic exposure may further influence disease severity and progression[27].

4.2 Pathogenesis of Crohn's Disease

Crohn's disease (CD) is a chronic relapsing inflammatory disorder that can affect any part of the gastrointestinal tract, most commonly the terminal ileum and colon. Unlike ulcerative colitis, Crohn's disease is characterized by transmural inflammation that extends through all layers of the intestinal wall, often leading to complications such as fistulas, strictures, abscesses, and fibrosis[28]. The pathogenesis of Crohn's disease involves an exaggerated immune response against intestinal microbiota in genetically susceptible individuals. Defects in innate immunity and impaired mucosal defense mechanisms contribute significantly to disease development. Genetic mutations in nucleotide-binding oligomerization domain-containing protein 2 (NOD2), autophagy-related genes (ATG16L1), and immunity-related GTPase family M protein (IRGM) have been strongly associated with Crohn's disease susceptibility[29]. Disruption of epithelial barrier integrity allows microbial antigens to penetrate intestinal tissues, triggering activation of macrophages, dendritic cells, and T helper (Th1 and Th17) lymphocytes. These immune cells release pro-inflammatory mediators such as TNF- α , interferon-gamma (IFN- γ), IL-12, IL-17, and IL-23, which sustain chronic intestinal inflammation. The activation of nuclear factor-kappa B (NF- κ B) signaling pathways further promotes cytokine production and inflammatory cell recruitment. Granuloma formation is considered a characteristic histopathological feature of Crohn's disease[30]. Persistent inflammation stimulates fibroblast activation and extracellular matrix deposition, resulting in fibrosis and intestinal obstruction. Oxidative stress and mitochondrial dysfunction also contribute to tissue damage and impaired mucosal healing. Microbial dysbiosis is another important factor in Crohn's disease pathogenesis. Reduced populations of beneficial bacteria such as *Faecalibacterium prausnitzii* and increased abundance of pathogenic bacteria contribute to immune dysregulation and intestinal inflammation. Environmental factors including smoking, high-fat diets, stress, and infections may exacerbate disease progression[31].

4.3 Molecular Mechanisms of Colorectal Cancer

Colorectal cancer develops through a multistep process involving genetic mutations, epigenetic alterations, chronic inflammation, and dysregulation of cellular signaling pathways. The transformation of normal colonic epithelium into adenomatous polyps and eventually invasive carcinoma occurs due to the accumulation of molecular abnormalities affecting oncogenes, tumor suppressor genes, and DNA repair mechanisms[32].

One of the most important molecular pathways involved in CRC development is the adenoma-carcinoma sequence. Mutation of the adenomatous polyposis coli (APC) gene is considered an early event in colorectal carcinogenesis. APC mutations result in abnormal activation of the Wnt/ β -catenin signaling pathway, leading to uncontrolled cellular proliferation and impaired apoptosis. Subsequent mutations in KRAS oncogenes further promote tumor growth and progression[33].

Loss of tumor suppressor genes such as TP53 contributes to genomic instability and malignant transformation. Defects in DNA mismatch repair genes including MLH1, MSH2, MSH6, and PMS2 result in microsatellite instability (MSI), which is commonly observed in hereditary and sporadic colorectal cancers. Epigenetic modifications such as DNA methylation and histone alterations also contribute to gene silencing and tumor progression. Inflammatory mediators play a critical role in colorectal carcinogenesis[34]. Persistent activation of NF- κ B, cyclooxygenase-2 (COX-2), signal transducer and activator of transcription 3 (STAT3), and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathways promotes cell survival, angiogenesis, metastasis, and resistance to apoptosis. Increased production of reactive oxygen species and inflammatory cytokines induces oxidative DNA damage and mutation accumulation[35]. Tumor angiogenesis mediated by vascular endothelial growth factor (VEGF) facilitates tumor growth and metastasis by enhancing blood supply to cancerous tissues. Additionally, epithelial-mesenchymal transition (EMT) enables cancer cells to acquire invasive and metastatic properties. These molecular mechanisms collectively contribute to CRC initiation, progression, and therapeutic resistance[36].

4.4 Relationship Between Chronic Inflammation and CRC

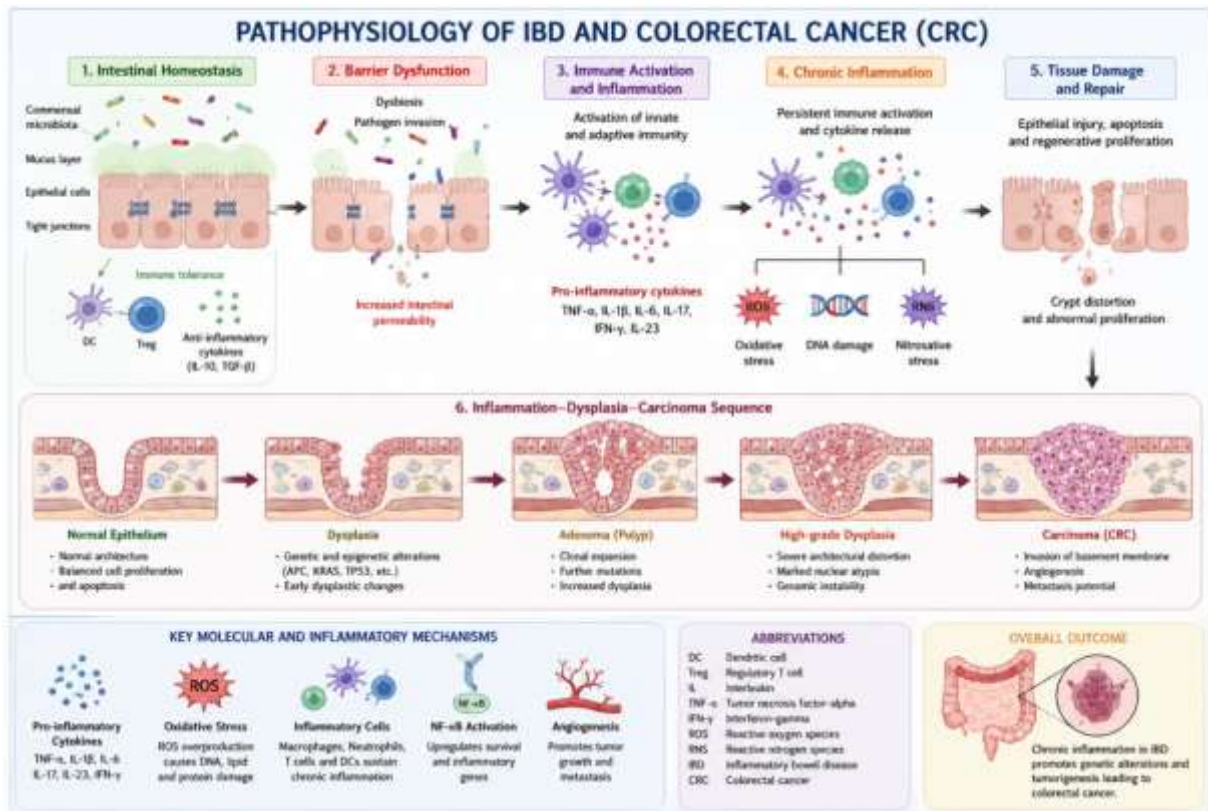
Chronic inflammation is recognized as a major risk factor for colorectal cancer development, particularly in patients with long-standing inflammatory bowel disease. Persistent inflammatory conditions such as ulcerative colitis and Crohn's disease increase the likelihood of dysplasia and colorectal malignancy due to repeated cycles of epithelial injury and regeneration[37].

Continuous inflammation leads to infiltration of immune cells including macrophages, neutrophils, and lymphocytes into intestinal tissues. These cells release pro-inflammatory cytokines, chemokines, growth factors, and reactive oxygen species that create a pro-tumorigenic microenvironment. Oxidative stress induced by chronic inflammation causes DNA mutations, chromosomal instability, and epigenetic alterations that promote malignant transformation[38].

Activation of inflammatory signaling pathways such as NF- κ B, STAT3, and COX-2 contributes to increased cellular proliferation, inhibition of apoptosis, angiogenesis, and tumor invasion. Cytokines including TNF- α , IL-6, and IL-17 play crucial roles in linking chronic inflammation to colorectal carcinogenesis. Persistent activation of these mediators stimulates oncogenic pathways and enhances tumor progression[39].

Inflammation-associated dysbiosis also contributes to CRC development by altering microbial metabolites and increasing production of carcinogenic compounds. Certain pathogenic bacteria such as *Fusobacterium nucleatum* and *Escherichia coli* have been implicated in promoting colorectal tumorigenesis through activation of inflammatory and oncogenic pathways[40].

Patients with extensive colonic involvement, severe inflammation, and prolonged disease duration exhibit a significantly higher risk of developing colorectal cancer. Therefore, controlling chronic inflammation is considered an essential strategy for reducing CRC incidence in IBD patients[41].



4.5 Therapeutic Targets in IBD and CRC

Advances in molecular biology and immunology have led to the identification of several therapeutic targets involved in the pathogenesis of inflammatory bowel disease and colorectal cancer. Targeted therapies aim to selectively inhibit inflammatory mediators, signaling pathways, or tumor-associated molecules while minimizing damage to healthy tissues[42].

In IBD, major therapeutic targets include pro-inflammatory cytokines such as TNF-α, IL-6, IL-12, IL-23, and Janus kinase (JAK)-mediated signaling pathways. Anti-TNF biologics including infliximab and adalimumab have shown significant clinical efficacy in reducing inflammation and inducing remission. Inhibition of integrins and adhesion molecules involved in leukocyte trafficking has also emerged as an effective therapeutic approach[43].

Nuclear factor-kappa B (NF-κB) signaling is considered an important target due to its central role in inflammatory cytokine production and immune activation. Antioxidant therapies targeting oxidative stress and reactive oxygen species are also being investigated for mucosal protection and tissue healing[44].

In colorectal cancer, therapeutic targets include epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), Wnt/β-catenin signaling pathways, PI3K/Akt/mTOR pathways, immune checkpoints, and apoptosis-regulating proteins. Monoclonal antibodies targeting EGFR and VEGF have demonstrated clinical benefits in metastatic CRC treatment[9].

Nanoparticle-based drug delivery systems offer significant advantages in targeting these molecular pathways. Functionalized nanoparticles can selectively deliver drugs, genes, siRNA, or biologics to inflamed tissues or tumor cells, thereby enhancing therapeutic efficacy and reducing systemic toxicity. Stimuli-responsive

nanoparticles capable of releasing drugs in response to pH, enzymes, or inflammatory mediators further improve site-specific therapy[45].

The identification of novel biomarkers and molecular targets continues to drive the development of personalized nanomedicine approaches for effective management of IBD and colorectal cancer[3].

5. Nanoparticle Drug Delivery Systems

Nanoparticle drug delivery systems have emerged as highly advanced therapeutic platforms capable of improving the efficacy and safety of conventional pharmaceutical treatments. Nanotechnology has revolutionized the field of medicine by enabling the design of nanoscale carriers that can selectively transport therapeutic agents to diseased tissues. These systems have shown remarkable potential in the treatment of inflammatory bowel disease (IBD) and colorectal cancer (CRC), where site-specific drug delivery is essential for achieving optimal therapeutic outcomes while minimizing systemic toxicity.

Nanoparticles are colloidal carriers generally ranging from 1 to 1000 nm in size and can be fabricated from polymers, lipids, proteins, metals, ceramics, or hybrid materials. Their unique physicochemical properties, including large surface area, tunable size, surface functionality, and controlled release behavior, allow enhanced interaction with biological systems. Nanoparticle-based formulations can encapsulate a wide variety of therapeutic agents such as anti-inflammatory drugs, chemotherapeutics, peptides, proteins, genes, and nucleic acids, thereby improving drug stability, bioavailability, and therapeutic index.

In gastrointestinal disorders such as IBD and CRC, nanoparticles provide several advantages including protection of drugs from enzymatic degradation, prolonged circulation time, improved mucosal penetration, enhanced accumulation at inflamed or tumor sites, and reduction of off-target effects. Advances in nanotechnology have led to the development of smart and stimuli-responsive nanoparticles capable of releasing drugs in response to pH, enzymes, reactive oxygen species, or inflammatory mediators present within diseased tissues.

5.1 Introduction to Nanotechnology in Drug Delivery

Nanotechnology refers to the manipulation and application of materials at the nanoscale level to develop systems with unique structural, chemical, and biological properties. In drug delivery, nanotechnology involves the design of nanosized carriers that can efficiently transport therapeutic agents to specific target sites within the body. The application of nanotechnology in medicine, commonly known as nanomedicine, has significantly transformed pharmaceutical research by enabling precise and controlled delivery of drugs[46].

Traditional drug delivery systems often suffer from limitations such as poor solubility, rapid degradation, non-specific distribution, and inadequate therapeutic concentration at the disease site. Nanotechnology-based drug delivery systems overcome these limitations by improving the pharmacokinetic and pharmacodynamic properties of drugs. Due to their small size, nanoparticles can penetrate biological barriers, interact with cellular membranes, and accumulate preferentially in diseased tissues[47].

Several nanoparticle systems have been developed for biomedical applications, including polymeric nanoparticles, liposomes, dendrimers, micelles, solid lipid nanoparticles, metallic nanoparticles, and nanostructured lipid carriers. These systems can be engineered to provide controlled drug release, prolonged systemic circulation, enhanced cellular uptake, and selective targeting of pathological tissues[48].

In the treatment of IBD and CRC, nanotechnology enables targeted delivery of anti-inflammatory agents and anticancer drugs directly to the colon, thereby improving therapeutic efficacy while reducing systemic adverse effects. Functionalization of nanoparticles with targeting ligands, antibodies, peptides, or polymers further

enhances their specificity toward inflamed intestinal tissues and tumor cells. Recent advances in nanomedicine have also facilitated the development of multifunctional nanoparticles capable of simultaneous diagnosis, imaging, and therapy, commonly referred to as theranostic nanoparticles[49].

5.2 Characteristics of Ideal Nanoparticles

An ideal nanoparticle drug delivery system should possess several physicochemical and biological characteristics to ensure effective therapeutic performance and clinical applicability. Particle size is one of the most critical parameters influencing biodistribution, cellular uptake, drug release, and tissue penetration. Nanoparticles with sizes ranging between 10 and 200 nm are generally considered optimal for enhanced accumulation in inflamed tissues and tumor microenvironments[50].

Surface charge, commonly expressed as zeta potential, plays an important role in nanoparticle stability and interaction with biological membranes. Positively charged nanoparticles exhibit enhanced cellular uptake due to electrostatic interactions with negatively charged cell membranes, whereas neutral or slightly negative nanoparticles demonstrate prolonged systemic circulation and reduced nonspecific interactions[51].

Biocompatibility and biodegradability are essential characteristics for minimizing toxicity and ensuring safe elimination from the body. Materials used in nanoparticle fabrication should be non-toxic, non-immunogenic, and capable of degrading into biologically acceptable byproducts. Commonly used biodegradable polymers include poly(lactic-co-glycolic acid) (PLGA), chitosan, alginate, and polylactic acid (PLA)[52].

An ideal nanoparticle should also exhibit high drug loading capacity and encapsulation efficiency to deliver adequate therapeutic doses while minimizing carrier-related toxicity. Controlled and sustained drug release behavior is important for maintaining therapeutic drug concentrations over extended periods and reducing dosing frequency[53].

Targeting capability is another crucial feature of ideal nanoparticles. Surface modification with ligands, antibodies, aptamers, or receptor-specific molecules enhances selective accumulation in diseased tissues and improves therapeutic specificity. Additionally, nanoparticles should demonstrate physical and chemical stability during storage and administration to preserve their structural integrity and therapeutic efficacy[47].

5.3 Advantages of Nanoparticle-Based Therapy

Nanoparticle-based therapy offers numerous advantages over conventional drug delivery systems, making it a highly promising approach for the treatment of inflammatory and cancerous diseases. One of the major advantages is enhanced drug bioavailability. Nanoparticles improve the solubility and dissolution rate of poorly water-soluble drugs, thereby increasing their absorption and therapeutic effectiveness[54].

Targeted drug delivery is another significant benefit of nanoparticle systems. Nanoparticles can selectively accumulate in inflamed tissues and tumor microenvironments through passive or active targeting mechanisms. Passive targeting occurs through the enhanced permeability and retention (EPR) effect, whereas active targeting involves ligand-mediated interactions with specific cellular receptors. This selective accumulation minimizes drug exposure to healthy tissues and reduces systemic toxicity[55].

Nanoparticles also provide controlled and sustained drug release, allowing prolonged therapeutic action and reduced dosing frequency. This improves patient compliance and decreases fluctuations in plasma drug concentrations. In addition, nanoparticles protect encapsulated drugs from enzymatic degradation, acidic pH conditions, and premature metabolism, thereby enhancing drug stability and circulation time[56].

In IBD therapy, nanoparticle systems improve mucosal adhesion and penetration, enabling efficient drug delivery to inflamed intestinal tissues. In colorectal cancer treatment, nanoparticles enhance intracellular uptake of chemotherapeutic agents, overcome multidrug resistance, and facilitate targeted destruction of cancer cells[57].

Another important advantage is the versatility of nanoparticles in delivering multiple therapeutic agents simultaneously. Combination therapy using nanoparticles allows co-delivery of anti-inflammatory drugs, chemotherapeutics, genes, proteins, or siRNA for synergistic therapeutic effects. Furthermore, nanoparticles can be engineered as stimuli-responsive systems that release drugs in response to environmental triggers such as pH changes, enzymes, temperature, or oxidative stress[58].

The integration of diagnostic and therapeutic functions within a single nanoparticle platform has also led to the development of theranostic systems capable of disease imaging, monitoring, and treatment simultaneously[59].

5.4 Mechanism of Targeted Drug Delivery

Targeted drug delivery using nanoparticles involves selective transport and controlled release of therapeutic agents at specific pathological sites while minimizing exposure to healthy tissues. Targeting mechanisms are generally classified into passive targeting and active targeting[60].

Passive targeting primarily relies on the enhanced permeability and retention (EPR) effect observed in inflamed and tumor tissues. In pathological conditions such as IBD and CRC, vascular permeability increases due to inflammation and abnormal angiogenesis, allowing nanoparticles to extravasate and accumulate preferentially at diseased sites. Impaired lymphatic drainage further enhances nanoparticle retention within these tissues[61].

Active targeting involves surface modification of nanoparticles with targeting ligands such as antibodies, peptides, folic acid, aptamers, carbohydrates, or receptor-specific molecules. These ligands recognize and bind selectively to receptors or biomarkers overexpressed on inflamed cells or tumor cells, thereby facilitating receptor-mediated endocytosis and enhanced cellular uptake[62].

Stimuli-responsive nanoparticles represent another advanced targeting strategy. These systems are designed to release therapeutic agents in response to specific physiological or pathological stimuli including pH changes, enzymatic activity, temperature, redox potential, and reactive oxygen species. For example, pH-sensitive nanoparticles remain stable in the acidic environment of the stomach but release drugs selectively in the colon where the pH is relatively higher[63].

In colon-targeted drug delivery, nanoparticles may utilize mucoadhesion, microbial enzyme-triggered degradation, or surface charge interactions to enhance localization within intestinal tissues. Surface-coated nanoparticles can also evade immune recognition and prolong systemic circulation through polyethylene glycol (PEG) modification, a process known as PEGylation[64].

Following accumulation at the target site, nanoparticles release encapsulated drugs through diffusion, polymer degradation, swelling, or environmental stimuli, resulting in improved therapeutic efficacy and reduced systemic adverse effects[65].

5.5 Challenges Associated with Nanoparticles

Despite the significant therapeutic advantages of nanoparticle drug delivery systems, several challenges limit their widespread clinical application. One of the major concerns is nanoparticle-associated toxicity. The small size and high surface reactivity of nanoparticles may induce oxidative stress, inflammation, cytotoxicity, and

unintended interactions with biological systems. Long-term accumulation of non-biodegradable nanoparticles in tissues may also lead to chronic toxicity and organ damage[66].

Another important challenge is instability during formulation, storage, and systemic circulation. Nanoparticles may undergo aggregation, premature drug leakage, or structural degradation, which can compromise therapeutic efficacy and reproducibility. Achieving consistent particle size distribution and maintaining physicochemical stability remain critical formulation challenges[67].

Large-scale manufacturing and reproducibility are major obstacles in translating nanoparticle systems from laboratory research to industrial production. Variations in preparation methods, raw materials, and process parameters can affect nanoparticle characteristics and therapeutic performance. Additionally, high production costs and complex fabrication techniques limit commercial feasibility[68].

Biological barriers such as mucus layers, immune clearance mechanisms, protein corona formation, and rapid uptake by the reticuloendothelial system reduce nanoparticle bioavailability and targeting efficiency. Nanoparticles administered systemically may be rapidly recognized and eliminated by macrophages, thereby limiting circulation time and therapeutic accumulation at target sites[69].

Regulatory and safety concerns also present substantial challenges. The lack of standardized guidelines for nanoparticle characterization, toxicity assessment, and quality control complicates regulatory approval processes. Comprehensive evaluation of long-term safety, immunogenicity, pharmacokinetics, and environmental impact is essential before clinical translation[70].

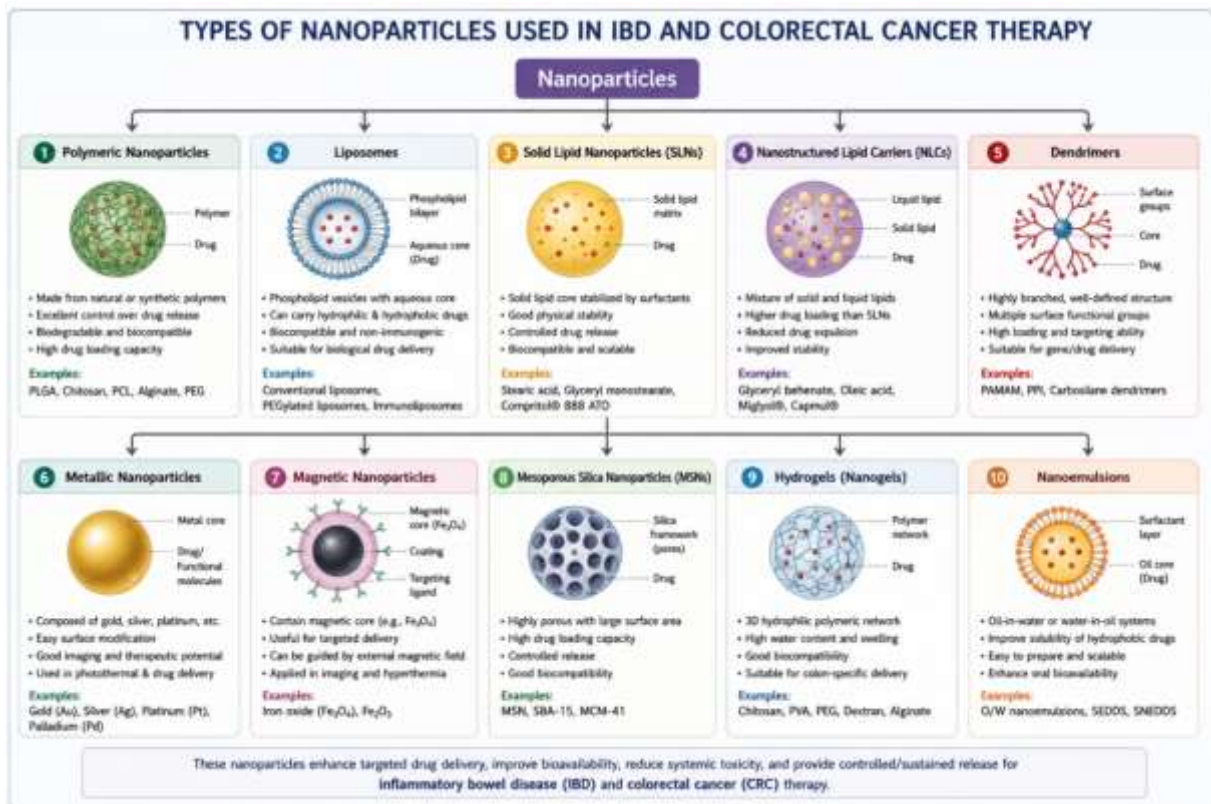
Furthermore, tumor heterogeneity and variable inflammatory microenvironments may affect nanoparticle targeting efficiency and therapeutic response. Personalized nanoparticle-based therapies may therefore be necessary to achieve optimal clinical outcomes in different patient populations[71].

Although significant progress has been achieved in nanomedicine research, continued advancements in formulation design, safety evaluation, manufacturing technologies, and regulatory frameworks are required to fully realize the clinical potential of nanoparticle drug delivery systems for inflammatory bowel disease and colorectal cancer[3].

6. Types of Nanoparticles Used in IBD and CRC Therapy

Nanoparticle-based drug delivery systems have gained considerable attention in the treatment of inflammatory bowel disease (IBD) and colorectal cancer (CRC) due to their ability to improve drug targeting, enhance therapeutic efficacy, and reduce systemic toxicity. Various types of nanoparticles have been developed using organic, inorganic, and hybrid materials to overcome physiological barriers associated with gastrointestinal diseases. The selection of an appropriate nanoparticle system depends on several factors including drug properties, targeting requirements, release characteristics, biocompatibility, and therapeutic objectives[20].

Different nanoparticle systems exhibit unique structural and functional properties that influence drug encapsulation, stability, biodistribution, cellular uptake, and therapeutic performance. Recent advancements in nanotechnology have enabled the development of multifunctional nanoparticles capable of targeted delivery, controlled release, imaging, and combined therapeutic applications in IBD and CRC management[3].



6.1 Polymeric Nanoparticles

Polymeric nanoparticles are among the most extensively investigated nanocarriers for targeted drug delivery in inflammatory bowel disease and colorectal cancer. These nanoparticles are generally fabricated using biodegradable and biocompatible natural or synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), chitosan, alginate, gelatin, and polycaprolactone (PCL). Depending on their structural organization, polymeric nanoparticles may exist as nanospheres or nanocapsules[72].

Polymeric nanoparticles offer several advantages including high drug loading capacity, controlled and sustained drug release, improved stability, and enhanced protection of encapsulated drugs from enzymatic degradation. Surface modification of polymeric nanoparticles with targeting ligands, polyethylene glycol (PEG), antibodies, or peptides further improves their targeting efficiency and circulation time[73].

In IBD therapy, chitosan-based nanoparticles have shown significant potential due to their mucoadhesive properties and ability to enhance intestinal permeation. These nanoparticles effectively deliver anti-inflammatory agents such as corticosteroids, mesalamine, and biologics directly to inflamed intestinal tissues. Similarly, PLGA nanoparticles have demonstrated prolonged drug release and improved therapeutic efficacy in experimental colitis models[74].

In colorectal cancer treatment, polymeric nanoparticles facilitate targeted delivery of chemotherapeutic agents including 5-fluorouracil, doxorubicin, irinotecan, and paclitaxel. Functionalized polymeric nanoparticles improve intracellular uptake by tumor cells and overcome multidrug resistance mechanisms. Moreover, polymeric nanoparticles are widely utilized for gene delivery, siRNA transport, and immunotherapeutic applications due to their tunable physicochemical properties and favorable safety profiles[75].

6.2 Lipid-Based Nanoparticles

Lipid-based nanoparticles are versatile nanocarriers composed of physiological lipids that provide enhanced biocompatibility, low toxicity, and efficient drug encapsulation. These systems include liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid nanoemulsions, and lipid-polymer hybrid nanoparticles[76].

Lipid-based nanoparticles improve the solubility and bioavailability of poorly water-soluble drugs while protecting them from degradation within the gastrointestinal tract. Due to their lipid composition, these nanoparticles exhibit excellent membrane compatibility and enhanced cellular uptake[77].

In IBD therapy, lipid-based nanoparticles have demonstrated increased mucosal penetration and prolonged retention within inflamed intestinal tissues. Encapsulation of anti-inflammatory drugs within lipid carriers improves therapeutic efficacy while minimizing systemic exposure and gastrointestinal irritation[7].

In colorectal cancer, lipid-based nanoparticles enable targeted delivery of anticancer agents and facilitate passive accumulation within tumor tissues through the enhanced permeability and retention (EPR) effect. Surface-functionalized lipid nanoparticles can further improve tumor-specific targeting and reduce off-target toxicity. Additionally, lipid-based systems have emerged as promising carriers for nucleic acid delivery including mRNA, siRNA, and CRISPR-based therapeutics[78].

6.3 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles are submicron colloidal carriers composed of solid lipids stabilized by surfactants. These nanoparticles combine the advantages of polymeric nanoparticles and traditional lipid emulsions while overcoming many limitations associated with other colloidal systems. The lipid core remains solid at both room and body temperature, enabling controlled drug release and enhanced drug stability[79].

SLNs exhibit several favorable properties including biocompatibility, biodegradability, protection of encapsulated drugs from chemical degradation, and ease of large-scale production. They are particularly useful for delivering lipophilic drugs with poor aqueous solubility[80].

In inflammatory bowel disease, SLNs enhance colon-specific delivery of anti-inflammatory agents and improve mucosal adhesion. Their small particle size facilitates penetration through inflamed intestinal tissues, resulting in improved local drug accumulation and reduced systemic adverse effects[81].

In colorectal cancer therapy, SLNs have been investigated for the delivery of chemotherapeutic drugs such as curcumin, doxorubicin, and paclitaxel. These nanoparticles improve drug stability, prolong circulation time, and enhance intracellular uptake by cancer cells. Furthermore, SLNs can be modified with targeting ligands to achieve active targeting toward tumor-specific receptors.

Despite their advantages, SLNs may exhibit limitations such as limited drug loading capacity and drug expulsion during storage due to lipid crystallization. These challenges have led to the development of advanced lipid systems such as nanostructured lipid carriers[82].

6.4 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers are second-generation lipid nanoparticles developed to overcome the limitations associated with solid lipid nanoparticles. NLCs are composed of a mixture of solid and liquid lipids, resulting in an imperfect lipid matrix that enhances drug loading capacity and reduces drug expulsion during storage[83].

The disordered internal structure of NLCs provides improved encapsulation efficiency, controlled release behavior, and enhanced physical stability. These nanoparticles exhibit excellent biocompatibility and are suitable for oral, parenteral, and topical drug delivery applications[84].

In IBD treatment, NLCs have shown improved delivery of anti-inflammatory drugs to inflamed colonic tissues. Their lipid composition enhances mucosal penetration and retention, resulting in sustained therapeutic action. NLCs can also be engineered as pH-sensitive or enzyme-responsive systems for colon-specific drug release[85].

In colorectal cancer therapy, NLCs facilitate efficient delivery of chemotherapeutic agents and improve tumor targeting. Surface-modified NLCs can selectively bind to tumor cells, enhancing drug uptake and reducing systemic toxicity. Co-delivery of multiple drugs using NLCs has also been explored for combination therapy in CRC management.

Due to their superior drug loading capacity, stability, and controlled release properties, NLCs are considered highly promising nanocarriers for gastrointestinal drug delivery[86].

6.5 Liposomes

Liposomes are spherical vesicular structures composed of phospholipid bilayers surrounding an aqueous core. They are among the earliest and most extensively studied nanoparticle systems for drug delivery applications. Liposomes can encapsulate both hydrophilic and lipophilic drugs, making them highly versatile therapeutic carriers[87].

The biocompatible and biodegradable nature of phospholipids contributes to the low toxicity profile of liposomes. Surface modification with polyethylene glycol (PEGylation) prolongs systemic circulation and reduces immune recognition. Functionalization with antibodies or ligands further enables active targeting of diseased tissues.

In IBD therapy, liposomes improve local delivery of corticosteroids, anti-inflammatory drugs, and biologics to inflamed intestinal regions. Liposomal formulations protect therapeutic agents from degradation and enhance mucosal penetration[88].

In colorectal cancer treatment, liposomes facilitate targeted delivery of chemotherapeutic drugs while reducing systemic side effects. Liposomal formulations of doxorubicin and irinotecan have demonstrated improved therapeutic efficacy and reduced cardiotoxicity. Thermosensitive and pH-sensitive liposomes have also been developed for stimuli-responsive drug release within tumor microenvironments[89].

Although liposomes offer several therapeutic advantages, their clinical application may be limited by instability, drug leakage, and high production costs.

6.6 Dendrimers

Dendrimers are highly branched, monodisperse, three-dimensional macromolecules with well-defined architectures and multiple surface functional groups. Their unique structural characteristics enable precise control over size, shape, and surface chemistry, making them attractive nanocarriers for targeted drug delivery[90].

Dendrimers possess internal cavities capable of encapsulating therapeutic agents, while surface functional groups allow conjugation with drugs, targeting ligands, or imaging agents. Polyamidoamine (PAMAM) dendrimers are among the most widely studied dendritic systems in biomedical applications[91].

In inflammatory bowel disease, dendrimers enhance targeted delivery of anti-inflammatory drugs and nucleic acids to inflamed intestinal tissues. Surface-modified dendrimers improve mucosal penetration and cellular uptake, leading to enhanced therapeutic outcomes.

In colorectal cancer therapy, dendrimers facilitate efficient intracellular delivery of anticancer drugs, genes, and siRNA. Their multivalent surface architecture enables simultaneous targeting and therapeutic functions. Dendrimer-based systems have shown potential in overcoming multidrug resistance and improving tumor selectivity[92].

However, positively charged dendrimers may induce cytotoxicity and hemolysis due to strong interactions with cellular membranes. Surface modification and PEGylation are commonly employed to improve their biocompatibility and reduce toxicity.

6.7 Metallic Nanoparticles

Metallic nanoparticles are inorganic nanocarriers synthesized using metals such as gold, silver, platinum, zinc oxide, and titanium dioxide. These nanoparticles possess unique optical, electronic, magnetic, and catalytic properties that make them valuable for biomedical applications including imaging, diagnosis, and targeted therapy[93].

Gold nanoparticles are particularly attractive due to their excellent biocompatibility, surface functionalization capability, and photothermal properties. In colorectal cancer therapy, gold nanoparticles have been extensively investigated for targeted drug delivery, photothermal therapy, and imaging applications. Their ability to convert light into heat enables selective destruction of tumor cells[94].

Silver nanoparticles exhibit potent antimicrobial and anti-inflammatory activities, making them useful in IBD treatment. However, concerns regarding long-term toxicity and accumulation remain significant challenges.

Metallic nanoparticles can also serve as carriers for chemotherapeutic agents, proteins, and nucleic acids. Surface modification with polymers or targeting ligands improves their stability and targeting specificity. Despite their promising therapeutic potential, careful evaluation of toxicity, biodistribution, and environmental impact is essential for clinical translation[95].

6.8 Magnetic Nanoparticles

Magnetic nanoparticles are generally composed of iron oxide materials such as magnetite (Fe_3O_4) or maghemite ($\gamma\text{-Fe}_2\text{O}_3$). These nanoparticles possess superparamagnetic properties that enable external magnetic field-guided targeting and imaging applications.

Magnetic nanoparticles can be directed toward specific disease sites using external magnetic fields, thereby enhancing localized drug accumulation and reducing systemic toxicity. In addition to drug delivery, these nanoparticles are widely used in magnetic resonance imaging (MRI), hyperthermia therapy, and biosensing applications[96].

In colorectal cancer treatment, magnetic nanoparticles have demonstrated significant potential in targeted chemotherapy and magnetic hyperthermia. Under alternating magnetic fields, these nanoparticles generate localized heat capable of inducing tumor cell death. Magnetic nanoparticles also facilitate targeted delivery of anticancer drugs and genes to tumor tissues[97].

In inflammatory bowel disease, magnetic nanoparticles have been explored for site-specific delivery of anti-inflammatory agents and diagnostic imaging. Surface coating with biocompatible polymers improves their stability, circulation time, and safety profile.

Although magnetic nanoparticles offer multifunctional therapeutic capabilities, challenges related to aggregation, long-term toxicity, and precise magnetic targeting require further investigation[98].

6.9 Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are porous inorganic nanocarriers characterized by large surface area, tunable pore size, high drug loading capacity, and excellent structural stability. Their porous architecture enables efficient encapsulation of a wide range of therapeutic agents including small molecules, proteins, and nucleic acids[99].

MSNs provide controlled and stimuli-responsive drug release through surface functionalization and pore modification. These nanoparticles can be engineered to respond to pH, enzymes, redox conditions, or temperature changes within pathological environments.

In IBD therapy, MSNs facilitate targeted delivery of anti-inflammatory drugs to inflamed intestinal tissues while protecting drugs from premature degradation. Their large surface area enhances drug loading efficiency and sustained release behavior[100].

In colorectal cancer treatment, mesoporous silica nanoparticles have shown promising applications in chemotherapy, photodynamic therapy, gene delivery, and combination therapy. Surface-functionalized MSNs improve tumor targeting and intracellular drug delivery. Multifunctional MSNs capable of simultaneous imaging and therapy have also been developed for theranostic applications[101].

However, concerns regarding biodegradability, long-term accumulation, and silica-associated toxicity remain important considerations for clinical applications.

6.10 Hydrogels and Nanoemulsions

Hydrogels are three-dimensional hydrophilic polymer networks capable of absorbing large amounts of water while maintaining structural integrity. These systems exhibit excellent biocompatibility, mucoadhesive properties, and controlled drug release behavior, making them highly suitable for gastrointestinal drug delivery applications[102].

In IBD treatment, hydrogels provide localized and sustained release of anti-inflammatory drugs directly to inflamed intestinal tissues. Stimuli-responsive hydrogels capable of responding to pH, temperature, or inflammatory mediators further enhance site-specific drug delivery.

Nanoemulsions are thermodynamically or kinetically stable colloidal dispersions consisting of oil, water, surfactants, and co-surfactants with droplet sizes typically ranging from 20 to 200 nm. Nanoemulsions improve the solubility and bioavailability of hydrophobic drugs while enhancing intestinal absorption and tissue penetration[103].

In colorectal cancer therapy, nanoemulsions facilitate efficient delivery of chemotherapeutic agents and improve intracellular drug uptake. Surface-functionalized nanoemulsions can also achieve targeted delivery to tumor tissues. Due to their ease of preparation, high stability, and excellent drug solubilization properties, nanoemulsions have emerged as promising carriers for oral and parenteral drug delivery[104].

The combination of hydrogels with nanoparticles or nanoemulsions has further expanded opportunities for developing advanced multifunctional drug delivery platforms for IBD and CRC therapy.

Table 1. Comparison of nanoparticle systems used in inflammatory bowel disease and colorectal cancer therapy.

Nanoparticle Type	Major Advantages	Limitations	Therapeutic Applications
Polymeric Nanoparticles	Controlled release, biodegradable	Possible polymer toxicity	Drug and gene delivery
Liposomes	Biocompatible, high drug loading	Stability issues	Chemotherapy and biologics
SLNs	Improved drug stability	Limited drug loading	Oral drug delivery
NLCs	Enhanced encapsulation efficiency	Complex formulation	Controlled release
Dendrimers	Precise structure, surface modification	Cytotoxicity concerns	Targeted therapy
Metallic Nanoparticles	Imaging and photothermal effects	Long-term toxicity	Cancer therapy
Magnetic Nanoparticles	Magnetic targeting	Aggregation tendency	Imaging and hyperthermia
Mesoporous Silica Nanoparticles	Large surface area	Slow biodegradation	Controlled drug delivery
Hydrogels	Mucoadhesion and localized delivery	Poor mechanical strength	Colon-targeted therapy

7. Targeting Strategies in Nanoparticle Drug Delivery

Targeted drug delivery is a fundamental objective in nanomedicine aimed at improving therapeutic efficacy while minimizing systemic toxicity and adverse effects. In inflammatory bowel disease (IBD) and colorectal cancer (CRC), conventional drug delivery systems often fail to achieve adequate drug concentration at diseased tissues because of physiological barriers, rapid drug degradation, and nonspecific distribution. Nanoparticle-based drug delivery systems have emerged as highly efficient platforms for overcoming these limitations through selective targeting of inflamed intestinal tissues and tumor microenvironments[4].

Targeting strategies in nanoparticle drug delivery are designed to enhance localization, retention, cellular uptake, and controlled release of therapeutic agents at specific pathological sites. These strategies may involve passive accumulation, receptor-mediated targeting, stimuli-responsive release mechanisms, or colon-specific delivery approaches. Advances in surface engineering and functionalization techniques have further improved the specificity and therapeutic performance of nanoparticles in gastrointestinal disorders[19].

7.1 Passive Targeting

Passive targeting is one of the most widely utilized strategies in nanoparticle-mediated drug delivery and primarily depends on the enhanced permeability and retention (EPR) effect. The EPR effect results from abnormal vascular architecture and impaired lymphatic drainage commonly observed in inflamed tissues and solid tumors. Increased vascular permeability allows nanoparticles to extravasate from blood vessels and accumulate preferentially within diseased tissues[61].

In inflammatory bowel disease, chronic inflammation disrupts intestinal epithelial integrity and increases vascular permeability within inflamed mucosal tissues. These pathological changes facilitate enhanced penetration and retention of nanoparticles at the inflammation site. Nanoparticles can therefore selectively deliver anti-inflammatory agents directly to affected intestinal regions while reducing systemic exposure[100].

Similarly, in colorectal cancer, rapidly growing tumor tissues exhibit defective and leaky vasculature with poor lymphatic drainage. Nanoparticles circulating within the bloodstream preferentially accumulate within tumor tissues due to these abnormalities. Passive targeting improves local drug concentration, prolongs drug retention time, and enhances therapeutic efficacy[105].

Particle size, surface charge, hydrophobicity, and circulation time significantly influence passive targeting efficiency. Nanoparticles within the size range of approximately 10–200 nm are generally considered optimal for enhanced accumulation in tumor and inflamed tissues. Surface modification with hydrophilic polymers such as polyethylene glycol (PEG) further prolongs systemic circulation by reducing recognition and clearance by the reticuloendothelial system[106].

Although passive targeting provides improved localization compared to conventional drug delivery, its specificity may be limited due to heterogeneity in vascular permeability among patients and disease conditions. Therefore, passive targeting is often combined with active targeting strategies to achieve greater therapeutic precision[107].

7.2 Active Targeting

Active targeting involves the surface modification of nanoparticles with specific ligands capable of recognizing and binding to receptors or biomarkers overexpressed on diseased cells. This strategy enhances selective uptake of nanoparticles through receptor-mediated endocytosis and improves intracellular drug delivery[108].

Various targeting ligands including antibodies, peptides, aptamers, carbohydrates, vitamins, and small molecules have been employed for active targeting applications. In IBD and CRC, several receptors such as folate receptors, transferrin receptors, integrins, CD44 receptors, epidermal growth factor receptors (EGFR), and inflammatory cell markers are overexpressed and serve as potential targets for nanoparticle-mediated therapy[67].

In inflammatory bowel disease, nanoparticles functionalized with antibodies or adhesion molecule-targeting ligands can selectively bind to activated immune cells and inflamed intestinal tissues. This targeted approach improves local drug accumulation and reduces systemic immunosuppression. Active targeting also enhances penetration through mucus layers and improves cellular uptake within inflamed mucosal regions[109].

In colorectal cancer therapy, actively targeted nanoparticles selectively recognize tumor cells and deliver chemotherapeutic agents directly to malignant tissues. Folate receptor-targeted nanoparticles, for example, exhibit enhanced uptake by cancer cells due to overexpression of folate receptors in many colorectal tumors. Similarly, antibody-conjugated nanoparticles targeting EGFR improve tumor specificity and therapeutic efficacy.

Active targeting offers several advantages including enhanced cellular internalization, reduced off-target toxicity, lower therapeutic doses, and improved treatment outcomes. However, challenges such as ligand instability, immunogenicity, receptor heterogeneity, and complex manufacturing processes may limit clinical translation[110].

7.3 pH-Sensitive Drug Delivery

pH-sensitive drug delivery systems are stimuli-responsive nanoparticles designed to release therapeutic agents selectively in response to variations in pH within different regions of the gastrointestinal tract or pathological tissues. This strategy is particularly useful in IBD and CRC because significant pH differences exist between healthy tissues, inflamed intestinal regions, and tumor microenvironments[100].

The gastrointestinal tract exhibits distinct pH gradients, with acidic conditions in the stomach and near-neutral to slightly alkaline conditions in the intestine and colon. pH-sensitive nanoparticles remain stable in the acidic gastric environment and release drugs selectively upon reaching the colon where the pH is relatively higher. This approach protects therapeutic agents from premature degradation and enhances colon-specific drug delivery[111].

In inflammatory bowel disease, pH-sensitive nanoparticles improve localized delivery of anti-inflammatory drugs such as mesalamine, corticosteroids, and biologics directly to inflamed colonic tissues. Polymers commonly used in pH-sensitive systems include Eudragit®, chitosan derivatives, alginate, and cellulose acetate phthalate.

In colorectal cancer therapy, tumor tissues often exhibit slightly acidic microenvironments due to increased glycolytic metabolism and hypoxia. pH-responsive nanoparticles exploit these acidic conditions to trigger drug release selectively within tumor tissues. This targeted release minimizes systemic toxicity and enhances anticancer efficacy[112].

Advanced pH-sensitive systems may also incorporate dual-responsive mechanisms involving pH and redox sensitivity or enzyme responsiveness to further improve therapeutic precision and controlled drug release.

7.4 Enzyme-Responsive Nanoparticles

Enzyme-responsive nanoparticles are intelligent drug delivery systems designed to release therapeutic agents in response to specific enzymes present within pathological environments. These systems exploit abnormal enzyme expression associated with inflammation, tumor progression, or intestinal microbiota activity[113].

In inflammatory bowel disease and colorectal cancer, several enzymes including matrix metalloproteinases (MMPs), phospholipases, azoreductases, glycosidases, and proteases are overexpressed within diseased tissues. Enzyme-responsive nanoparticles contain biodegradable linkers or coatings that undergo degradation upon exposure to these enzymes, thereby triggering localized drug release.

In IBD therapy, nanoparticles responsive to colonic bacterial enzymes provide selective drug release within the colon. Polysaccharide-based carriers such as dextran, pectin, guar gum, and chitosan are degraded by bacterial enzymes present in the colon, resulting in site-specific release of anti-inflammatory drugs[114].

In colorectal cancer treatment, matrix metalloproteinase-responsive nanoparticles selectively release anticancer drugs within tumor microenvironments where MMP expression is significantly elevated. These nanoparticles enhance tumor specificity and reduce systemic adverse effects associated with conventional chemotherapy.

Enzyme-responsive systems offer several advantages including precise site-specific drug release, improved therapeutic efficiency, and reduced premature drug leakage. However, variations in enzyme expression among patients and disease stages may influence therapeutic performance and require further optimization[115].

7.5 Colon-Specific Targeting Approaches

Colon-specific targeting aims to deliver therapeutic agents directly to the colon while minimizing drug release in the upper gastrointestinal tract. This approach is particularly important in the treatment of inflammatory bowel disease and colorectal cancer, where localized therapy can significantly improve therapeutic outcomes and reduce systemic toxicity.

Several strategies have been developed for colon-targeted drug delivery, including pH-dependent systems, time-dependent systems, microbiota-triggered systems, pressure-controlled systems, and mucoadhesive formulations[116].

pH-dependent systems utilize enteric polymers that dissolve selectively at the higher pH of the distal intestine and colon. Time-dependent systems rely on delayed drug release based on gastrointestinal transit time. Microbiota-triggered systems employ polysaccharides degraded specifically by colonic bacterial enzymes, ensuring localized drug release.

Mucoadhesive nanoparticles enhance retention within the colonic mucosa by interacting with mucus glycoproteins and epithelial surfaces. Chitosan-based nanoparticles are particularly effective due to their positive surface charge and strong mucoadhesive properties[117].

In colorectal cancer therapy, colon-targeted nanoparticles improve local accumulation of chemotherapeutic agents and reduce systemic exposure. Combining colon-targeting approaches with active targeting strategies further enhances tumor specificity and therapeutic efficacy.

The development of multifunctional colon-specific nanoparticles capable of responding to pH, enzymes, inflammatory mediators, or oxidative stress has significantly advanced targeted therapy for gastrointestinal disorders[109].

7.6 Ligand-Mediated Targeting

Ligand-mediated targeting is a highly specialized form of active targeting in which nanoparticles are functionalized with ligands capable of selectively binding to receptors expressed on diseased cells. This strategy enhances nanoparticle specificity, cellular uptake, and therapeutic efficiency[118].

Various ligands including antibodies, peptides, aptamers, carbohydrates, folic acid, transferrin, hyaluronic acid, and mannose have been employed for targeted drug delivery applications. The selection of appropriate ligands depends on receptor expression patterns and disease-specific biomarkers[119].

In inflammatory bowel disease, ligand-mediated nanoparticles target activated macrophages, dendritic cells, and inflamed epithelial cells. Mannose-modified nanoparticles, for example, selectively bind to macrophage mannose receptors and enhance intracellular delivery of anti-inflammatory agents. Hyaluronic acid-coated nanoparticles target CD44 receptors overexpressed in inflamed intestinal tissues.

In colorectal cancer therapy, folic acid-functionalized nanoparticles target folate receptors frequently overexpressed in tumor cells. Similarly, transferrin-conjugated nanoparticles exploit increased transferrin receptor expression associated with rapidly proliferating cancer cells. Antibody-mediated targeting against EGFR and HER2 receptors has also demonstrated promising therapeutic outcomes[120].

Ligand-mediated targeting significantly improves drug accumulation within diseased tissues while reducing nonspecific interactions with healthy cells. Additionally, receptor-mediated endocytosis enhances intracellular drug delivery and therapeutic effectiveness.

Despite its promising potential, ligand-mediated targeting faces challenges including ligand instability, receptor heterogeneity, immune responses, and large-scale manufacturing complexity. Continued advancements in ligand engineering and nanoparticle surface modification are expected to improve the clinical applicability of targeted nanomedicine in IBD and colorectal cancer therapy[3].

8. Development of Nanoparticle Formulations

The development of nanoparticle formulations is a critical step in designing efficient targeted drug delivery systems for inflammatory bowel disease (IBD) and colorectal cancer (CRC). Formulation development involves careful selection of therapeutic agents, carrier materials, preparation methods, and surface engineering approaches to achieve optimal physicochemical characteristics and therapeutic performance. The properties of nanoparticles such as particle size, surface charge, morphology, drug loading capacity, release profile, and targeting efficiency are strongly influenced by formulation variables and fabrication techniques[121].

An ideal nanoparticle formulation should provide high drug encapsulation efficiency, controlled and site-specific drug release, stability during storage and administration, minimal toxicity, and enhanced therapeutic efficacy. Recent advancements in formulation technologies have enabled the development of multifunctional nanoparticles capable of overcoming biological barriers and improving targeted delivery to inflamed intestinal tissues and tumor microenvironments[4].

8.1 Selection of Drug Candidate

Selection of an appropriate drug candidate is a crucial factor in the successful development of nanoparticle drug delivery systems. The physicochemical and pharmacological properties of the drug significantly influence formulation design, encapsulation efficiency, release kinetics, and therapeutic outcomes[122].

Drugs selected for nanoparticle formulation in IBD and CRC therapy generally include anti-inflammatory agents, corticosteroids, immunosuppressants, chemotherapeutic agents, biologics, peptides, proteins, nucleic acids, and gene therapeutics. The suitability of a drug candidate depends on factors such as solubility, stability, molecular weight, half-life, permeability, and therapeutic index.

Hydrophobic drugs are particularly suitable for nanoparticle encapsulation because nanocarriers improve their aqueous solubility and bioavailability. Many anticancer drugs used in CRC therapy, including paclitaxel, curcumin, and doxorubicin, exhibit poor water solubility and benefit significantly from nanoparticle-mediated delivery. Similarly, biologics and nucleic acid-based therapeutics require protection from enzymatic degradation and improved intracellular delivery, which can be achieved through nanoparticle encapsulation[123].

The drug's mechanism of action and target site must also be considered during formulation development. Drugs intended for colon-specific therapy should remain stable in the upper gastrointestinal tract and release selectively at inflamed or tumor tissues. Additionally, compatibility between the drug and carrier material is essential to prevent drug degradation, leakage, or reduced therapeutic activity[124].

Pharmacokinetic properties such as absorption, distribution, metabolism, and elimination further influence drug selection. Nanoparticle systems are especially advantageous for drugs with short biological half-lives, poor tissue penetration, or high systemic toxicity because they improve drug stability and site-specific accumulation[125].

8.2 Selection of Polymers and Excipients

Polymers and excipients play a fundamental role in determining the structural integrity, drug release behavior, stability, and targeting efficiency of nanoparticle formulations. The selection of suitable materials depends on formulation objectives, route of administration, drug properties, and desired therapeutic outcomes[121].

An ideal polymer for nanoparticle fabrication should be biocompatible, biodegradable, non-toxic, non-immunogenic, and capable of providing controlled drug release. Both natural and synthetic polymers are widely employed in nanoparticle development.

Natural polymers such as chitosan, alginate, gelatin, dextran, pectin, and hyaluronic acid are preferred due to their biodegradability, mucoadhesive properties, and favorable safety profiles. Chitosan is particularly useful in colon-targeted drug delivery because of its positive charge and strong interaction with mucosal tissues. Polysaccharide-based polymers are also advantageous in microbiota-responsive drug delivery systems for IBD and CRC[111].

Synthetic polymers including poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polycaprolactone (PCL), and polyethylene glycol (PEG) are extensively used because of their controlled degradation rates, mechanical strength, and reproducibility. PEGylation enhances nanoparticle circulation time by reducing immune recognition and protein adsorption.

Excipients such as surfactants, stabilizers, cryoprotectants, and solvents are also important formulation components. Surfactants like polyvinyl alcohol (PVA), Tween 80, and poloxamers stabilize nanoparticles and prevent aggregation during preparation. Lipids, co-polymers, and targeting ligands may also be incorporated to improve drug loading and targeting efficiency[126].

The physicochemical compatibility between drugs, polymers, and excipients is critical for achieving stable and reproducible formulations with optimal therapeutic performance.

8.3 Methods of Nanoparticle Preparation

Several techniques have been developed for the preparation of nanoparticle formulations depending on the nature of the drug, carrier material, and intended application. The choice of preparation method significantly influences particle size, morphology, encapsulation efficiency, drug release behavior, and stability[127].

8.3.1 Solvent Evaporation Method

The solvent evaporation method is one of the most commonly used techniques for preparing polymeric nanoparticles. In this method, the drug and polymer are dissolved in a volatile organic solvent such as dichloromethane, chloroform, or ethyl acetate to form the organic phase. This organic solution is then emulsified into an aqueous phase containing a stabilizer or surfactant under continuous stirring or homogenization[128].

Following emulsification, the organic solvent is evaporated either by continuous stirring, reduced pressure, or heating, resulting in precipitation of nanoparticles. The formed nanoparticles are subsequently collected by centrifugation, filtration, or lyophilization.

The solvent evaporation method offers several advantages including simplicity, reproducibility, controlled particle size, and suitability for both hydrophilic and hydrophobic drugs. It is widely employed for the preparation of PLGA and PLA nanoparticles used in IBD and CRC therapy[11].

However, limitations such as residual solvent toxicity, low encapsulation efficiency for water-soluble drugs, and potential drug degradation during solvent exposure may affect formulation quality.

8.3.2 Nanoprecipitation Method

Nanoprecipitation, also known as the solvent displacement method, is a simple and rapid technique for preparing nanoparticles, particularly suitable for hydrophobic drugs and polymers. In this method, the drug and polymer are dissolved in a water-miscible organic solvent such as acetone or ethanol. The organic phase is then added dropwise into an aqueous phase containing stabilizers under moderate stirring[60].

Rapid diffusion of the organic solvent into the aqueous medium causes supersaturation and precipitation of nanoparticles. The organic solvent is subsequently removed by evaporation or dialysis.

Nanoprecipitation offers several advantages including ease of preparation, low energy requirements, narrow particle size distribution, and minimal use of surfactants. This method is widely utilized for preparing polymeric nanoparticles and lipid-polymer hybrid systems for targeted gastrointestinal drug delivery[129].

Despite its simplicity, nanoprecipitation may not be suitable for highly water-soluble drugs because of potential drug leakage into the aqueous phase.

8.3.3 Emulsification Technique

The emulsification technique is commonly employed for preparing nanoparticles and nanoemulsions using oil-in-water (O/W), water-in-oil (W/O), or double emulsion systems. In this method, the drug-containing phase is emulsified into another immiscible phase using high-speed homogenization, ultrasonication, or mechanical stirring[130].

Double emulsion techniques such as water-in-oil-in-water (W/O/W) emulsions are particularly useful for encapsulating hydrophilic drugs, proteins, and nucleic acids. After emulsification, solvent removal or polymer solidification leads to nanoparticle formation.

The emulsification technique provides high encapsulation efficiency and is suitable for a wide range of therapeutic agents. It is frequently employed in the preparation of liposomes, polymeric nanoparticles, and lipid-based nanocarriers used in IBD and CRC therapy[131].

However, challenges such as emulsion instability, particle aggregation, and batch-to-batch variability may affect formulation reproducibility.

8.3.4 Ionic Gelation Method

The ionic gelation method is primarily used for preparing nanoparticles from naturally occurring polyelectrolytes such as chitosan and alginate. This method involves electrostatic interaction between oppositely charged polymers and crosslinking agents, resulting in spontaneous nanoparticle formation under mild conditions[132].

For example, chitosan nanoparticles are commonly prepared using sodium tripolyphosphate (TPP) as a crosslinking agent. Upon mixing the polymer and crosslinker solutions, ionic interactions induce gelation and nanoparticle formation.

The ionic gelation method offers several advantages including mild preparation conditions, absence of toxic organic solvents, high biocompatibility, and suitability for sensitive biomolecules such as proteins and nucleic acids. Chitosan nanoparticles prepared by ionic gelation have shown excellent mucoadhesive properties and enhanced colon-targeting capabilities in IBD therapy[133].

Limitations include relatively broad particle size distribution and lower mechanical stability compared to synthetic polymer-based nanoparticles.

8.3.5 Spray Drying Method

Spray drying is a scalable and industrially applicable technique widely used for producing dry nanoparticle powders. In this method, a drug-polymer solution or suspension is atomized into fine droplets using a spray nozzle and introduced into a chamber containing heated air. Rapid solvent evaporation results in the formation of dry nanoparticles or microparticles[134].

Spray drying offers several advantages including large-scale production capability, improved product stability, and ease of handling. The method is particularly useful for preparing inhalable formulations, colon-targeted systems, and solid oral dosage forms.

In IBD and CRC therapy, spray-dried nanoparticles improve drug stability and facilitate controlled release within the gastrointestinal tract. The technique also enables incorporation of heat-sensitive drugs by optimizing drying conditions[135].

However, high processing temperatures may cause degradation of thermolabile compounds, and optimization of process parameters is essential to achieve desired particle characteristics[136].

8.4 Drug Loading and Encapsulation Efficiency

Drug loading and encapsulation efficiency are important parameters that determine the therapeutic effectiveness and economic feasibility of nanoparticle formulations. Drug loading refers to the amount of drug incorporated within nanoparticles relative to the total weight of the formulation, whereas encapsulation efficiency represents the percentage of the initial drug successfully entrapped within the nanoparticles[137].

High drug loading is desirable to minimize the amount of carrier material required and reduce potential carrier-related toxicity. Encapsulation efficiency depends on several factors including drug solubility, polymer-drug compatibility, preparation method, surfactant concentration, and formulation conditions[138].

Hydrophobic drugs generally exhibit higher encapsulation efficiency in polymeric and lipid-based nanoparticles due to favorable interactions with hydrophobic carrier matrices. In contrast, hydrophilic drugs may exhibit drug leakage during formulation preparation, reducing encapsulation efficiency.

Optimization of formulation parameters such as polymer concentration, solvent selection, stirring speed, pH, and crosslinking conditions is essential for achieving high encapsulation efficiency and controlled drug release profiles[139].

Efficient drug loading improves therapeutic efficacy, prolongs drug release, and enhances targeted delivery to inflamed intestinal tissues and tumor sites.

8.5 Surface Modification Techniques

Surface modification is an important strategy used to improve nanoparticle stability, targeting efficiency, circulation time, and biological interactions. Functionalization of nanoparticle surfaces enables selective targeting of inflamed tissues, tumor cells, or specific cellular receptors[140].

Polyethylene glycol (PEG) coating, commonly known as PEGylation, is widely used to enhance nanoparticle stability and prolong systemic circulation by reducing protein adsorption and immune recognition. PEGylated

nanoparticles exhibit improved pharmacokinetic profiles and enhanced passive targeting through the enhanced permeability and retention effect.

Ligand conjugation is another important surface modification approach. Nanoparticles can be functionalized with antibodies, peptides, folic acid, hyaluronic acid, aptamers, or carbohydrates to achieve active targeting toward receptors overexpressed in IBD and CRC tissues[141].

Mucoadhesive surface modifications using chitosan or lectins improve intestinal retention and mucosal penetration in colon-targeted drug delivery. Additionally, stimuli-responsive coatings enable controlled drug release in response to pH, enzymes, temperature, or oxidative stress.

Surface engineering also plays a crucial role in reducing nanoparticle toxicity and improving biocompatibility. Modification of surface charge and hydrophilicity influences cellular uptake, biodistribution, and interaction with biological barriers[142].

Advanced multifunctional nanoparticles combining targeting ligands, imaging agents, and stimuli-responsive components have shown significant promise in improving the diagnosis and treatment of inflammatory bowel disease and colorectal cancer[3].

9. Evaluation and Characterization of Nanoparticles

Evaluation and characterization of nanoparticle formulations are essential steps in the development of efficient and reproducible drug delivery systems for inflammatory bowel disease (IBD) and colorectal cancer (CRC). Comprehensive characterization helps determine the physicochemical, biological, and therapeutic properties of nanoparticles, which directly influence their stability, targeting ability, drug release behavior, biodistribution, and clinical performance[4].

Critical parameters such as particle size, surface charge, morphology, encapsulation efficiency, release kinetics, and biological interactions must be carefully analyzed to ensure formulation quality and therapeutic efficacy. Various analytical and imaging techniques are employed to characterize nanoparticles and evaluate their suitability for targeted drug delivery applications. Proper evaluation also facilitates optimization of formulation variables, quality control, regulatory compliance, and successful clinical translation[143].

9.1 Particle Size Analysis

Particle size is one of the most important physicochemical parameters influencing nanoparticle performance, including drug release, cellular uptake, biodistribution, stability, and targeting efficiency. Nanoparticles intended for drug delivery applications generally range from 1 to 1000 nm in diameter, although particles within the range of 10–200 nm are considered optimal for passive targeting through the enhanced permeability and retention (EPR) effect[144].

Smaller nanoparticles exhibit enhanced tissue penetration, improved cellular internalization, and prolonged systemic circulation, whereas larger particles may undergo rapid clearance by the reticuloendothelial system. In gastrointestinal drug delivery, particle size also affects mucosal penetration and intestinal retention[145].

Particle size analysis is commonly performed using dynamic light scattering (DLS), photon correlation spectroscopy (PCS), nanoparticle tracking analysis (NTA), and laser diffraction techniques. Dynamic light scattering is the most widely employed method due to its rapid and non-destructive nature. DLS measures fluctuations in scattered light intensity caused by Brownian motion of nanoparticles suspended in a liquid medium[146].

In addition to average particle size, polydispersity index (PDI) is also determined to assess particle size distribution and formulation uniformity. A low PDI value indicates homogeneous particle distribution and better formulation stability[147].

9.2 Zeta Potential Measurement

Zeta potential is a measure of the electrical charge present on the surface of nanoparticles and is an important indicator of colloidal stability. Surface charge significantly influences nanoparticle aggregation, cellular interactions, biodistribution, and mucoadhesive properties[148].

Nanoparticles with high positive or negative zeta potential values generally exhibit better physical stability due to electrostatic repulsion between particles, which prevents aggregation. Formulations with zeta potential values greater than ± 30 mV are generally considered stable.

Positively charged nanoparticles demonstrate enhanced interaction with negatively charged biological membranes and mucus layers, thereby improving cellular uptake and mucoadhesion. However, highly cationic nanoparticles may also induce cytotoxicity and nonspecific interactions. Neutral or slightly negative nanoparticles often exhibit prolonged circulation time and reduced immune recognition[149].

Zeta potential is typically measured using electrophoretic light scattering techniques based on the movement of nanoparticles under an applied electric field. Surface charge analysis is essential for predicting nanoparticle behavior in biological systems and optimizing targeting efficiency[150].

9.3 Morphological Characterization (SEM/TEM)

Morphological characterization provides detailed information regarding the shape, surface structure, size distribution, and physical integrity of nanoparticles. Morphology significantly influences drug loading, release kinetics, cellular uptake, and biological interactions[143].

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are widely employed for nanoparticle imaging and structural analysis. SEM provides high-resolution surface images and allows examination of particle shape, surface texture, aggregation behavior, and topography. TEM offers detailed internal structural information and enables visualization of nanoparticle size and morphology at the nanometer scale.

Spherical nanoparticles generally exhibit superior cellular uptake and uniform drug release characteristics compared to irregularly shaped particles. TEM analysis is particularly useful for confirming particle size obtained from dynamic light scattering studies and evaluating core-shell structures in complex nanoparticle systems[151].

Additional imaging techniques such as atomic force microscopy (AFM) and confocal laser scanning microscopy (CLSM) may also be utilized for surface characterization and visualization of nanoparticle interactions with biological tissues[152].

9.4 Drug Entrapment Efficiency

Drug entrapment efficiency represents the percentage of the initial drug successfully encapsulated within the nanoparticle system relative to the total amount of drug used during formulation preparation. High entrapment efficiency is essential for achieving effective therapeutic drug concentrations and minimizing drug wastage[153].

Entrapment efficiency is influenced by several factors including drug solubility, polymer-drug compatibility, preparation method, surfactant concentration, and formulation conditions. Hydrophobic drugs generally exhibit

higher encapsulation efficiency in lipid and polymeric nanoparticles due to stronger hydrophobic interactions[154].

Drug entrapment efficiency is commonly determined by separating free drug from nanoparticle-associated drug using centrifugation, ultrafiltration, dialysis, or chromatography techniques. The amount of entrapped drug is subsequently quantified using analytical methods such as ultraviolet-visible spectroscopy (UV-Vis), high-performance liquid chromatography (HPLC), or spectrofluorimetry[155].

High entrapment efficiency improves therapeutic efficacy, prolongs drug release, and reduces the frequency of drug administration. Therefore, optimization of formulation variables is critical for maximizing drug encapsulation within nanoparticle systems.

9.5 In-vitro Drug Release Studies

In-vitro drug release studies are performed to evaluate the release behavior of therapeutic agents from nanoparticle formulations under simulated physiological conditions. These studies provide important information regarding release kinetics, drug diffusion mechanisms, and formulation stability[156].

Controlled and sustained drug release is highly desirable in nanoparticle-mediated therapy because it maintains therapeutic drug concentrations over extended periods while reducing dosing frequency and systemic toxicity. In colon-targeted drug delivery, nanoparticles are often designed to release drugs selectively in response to pH changes, enzymes, or inflammatory conditions[111].

Drug release studies are commonly conducted using dialysis bag diffusion methods, Franz diffusion cells, sample-and-separate techniques, or dissolution apparatus under simulated gastric and intestinal conditions. Release media are selected based on physiological relevance and may include phosphate buffer solutions of varying pH.

Drug release profiles are analyzed using mathematical kinetic models such as zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models to determine the mechanism of drug release. Controlled release behavior indicates effective encapsulation and stable nanoparticle structure[157].

9.6 Stability Studies

Stability studies are essential for evaluating the physical, chemical, and biological stability of nanoparticle formulations during storage and administration. Stability directly influences therapeutic efficacy, shelf life, reproducibility, and clinical applicability[70].

Nanoparticles may undergo aggregation, drug leakage, hydrolysis, oxidation, or structural degradation during storage. Therefore, parameters such as particle size, zeta potential, drug content, morphology, and release profile are periodically evaluated under different storage conditions.

Stability studies are generally conducted according to International Council for Harmonisation (ICH) guidelines using varying temperature, humidity, and light exposure conditions. Freeze-thaw stability and lyophilization studies may also be performed to assess formulation robustness[158].

Cryoprotectants such as trehalose, mannitol, and sucrose are commonly employed during freeze-drying to prevent nanoparticle aggregation and preserve structural integrity. Stable nanoparticle formulations ensure reproducible therapeutic performance and successful clinical translation[159].

7 Mucoadhesion Studies

Mucoadhesion studies evaluate the ability of nanoparticles to adhere to mucus layers and intestinal mucosal surfaces. Mucoadhesive properties are particularly important in inflammatory bowel disease and colon-targeted drug delivery because prolonged retention at the disease site enhances local drug concentration and therapeutic efficacy[17].

Mucoadhesive nanoparticles interact with mucus glycoproteins through electrostatic interactions, hydrogen bonding, hydrophobic interactions, or polymer chain interpenetration. Polymers such as chitosan, carbopol, alginate, and hyaluronic acid exhibit strong mucoadhesive characteristics.

Several methods are employed to assess mucoadhesion, including mucin-binding assays, wash-off tests, rheological measurements, tensile strength analysis, and ex-vivo intestinal adhesion studies. Enhanced mucoadhesion improves nanoparticle residence time, drug absorption, and localized therapeutic action within inflamed intestinal tissues[160].

In colon-targeted therapy, mucoadhesive nanoparticles also facilitate penetration through mucus barriers and improve interaction with epithelial cells, thereby enhancing drug uptake and retention[161].

9.8 Cytotoxicity and Cell Viability Assays

Cytotoxicity and cell viability assays are performed to evaluate the safety, biocompatibility, and therapeutic efficacy of nanoparticle formulations in vitro. These studies help determine the effects of nanoparticles on cellular metabolism, membrane integrity, proliferation, and apoptosis[162].

Commonly used cell lines for evaluating IBD and CRC formulations include Caco-2, HT-29, HCT-116, RAW 264.7 macrophages, and intestinal epithelial cell lines. Cytotoxicity assessment is essential for identifying potential nanoparticle-induced toxicity and optimizing formulation safety.

Several assays are employed for cell viability analysis, including MTT assay, XTT assay, WST-1 assay, neutral red uptake assay, lactate dehydrogenase (LDH) release assay, and trypan blue exclusion tests. These assays measure mitochondrial activity, membrane damage, or cellular metabolic function following nanoparticle exposure[163].

In colorectal cancer therapy, cytotoxicity assays evaluate the anticancer efficacy of drug-loaded nanoparticles against tumor cells. Apoptosis studies, cell cycle analysis, and reactive oxygen species measurements are also commonly performed to investigate therapeutic mechanisms[164].

Biocompatible nanoparticles should exhibit minimal toxicity toward healthy cells while selectively inducing cytotoxicity in cancerous or inflamed tissues.

9.9 In-vivo Evaluation Studies

In-vivo studies are essential for assessing the therapeutic efficacy, safety, biodistribution, targeting ability, and pharmacological performance of nanoparticle formulations under physiological conditions. Animal models provide valuable information regarding nanoparticle interactions with biological systems and their translational potential[123].

Experimental models of inflammatory bowel disease commonly include dextran sulfate sodium (DSS)-induced colitis, trinitrobenzene sulfonic acid (TNBS)-induced colitis, and acetic acid-induced colitis models. These

models are used to evaluate anti-inflammatory efficacy, colon targeting, mucosal healing, and reduction of inflammatory cytokines.

In colorectal cancer research, xenograft tumor models, orthotopic tumor models, and chemically induced colorectal carcinogenesis models are widely employed to evaluate tumor inhibition, survival rate, and therapeutic response[165].

Parameters assessed during in-vivo studies include body weight changes, histopathological examination, inflammatory markers, tumor size, drug accumulation, immune response, and systemic toxicity. Imaging techniques such as fluorescence imaging, magnetic resonance imaging (MRI), and positron emission tomography (PET) are also used to monitor nanoparticle distribution and targeting efficiency[166].

Successful in-vivo evaluation is critical for advancing nanoparticle formulations toward clinical studies and regulatory approval.

9.10 Pharmacokinetic and Biodistribution Studies

Pharmacokinetic and biodistribution studies are performed to evaluate the absorption, distribution, metabolism, elimination, and tissue accumulation of nanoparticle formulations. These studies provide important information regarding drug release behavior, circulation time, targeting efficiency, and therapeutic exposure[167].

Nanoparticle systems are designed to improve pharmacokinetic properties by prolonging systemic circulation, reducing premature drug degradation, and enhancing site-specific accumulation. Pharmacokinetic parameters commonly evaluated include maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), area under the curve (AUC), half-life ($t_{1/2}$), clearance, and volume of distribution.

Biodistribution studies determine nanoparticle accumulation in various organs and tissues including the colon, liver, spleen, kidneys, lungs, and tumors. Radiolabeling, fluorescence labeling, and imaging techniques are commonly used to track nanoparticle localization and targeting behavior[168].

In IBD therapy, successful formulations should demonstrate increased accumulation within inflamed intestinal tissues while minimizing systemic distribution. In colorectal cancer treatment, targeted nanoparticles should preferentially accumulate within tumor tissues through passive or active targeting mechanisms[141].

Pharmacokinetic and biodistribution analysis is essential for optimizing therapeutic efficacy, minimizing toxicity, and ensuring safe clinical application of nanoparticle drug delivery systems.

10. Applications of Nanoparticles in IBD Therapy

Nanoparticle-based drug delivery systems have emerged as highly promising therapeutic platforms for the management of inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease. Conventional therapeutic approaches for IBD are often associated with poor drug bioavailability, systemic toxicity, frequent dosing, and inadequate accumulation of drugs at inflamed intestinal tissues. Nanotechnology offers innovative solutions to these challenges by enabling targeted, controlled, and sustained drug delivery directly to diseased regions of the gastrointestinal tract[169].

Nanoparticles improve therapeutic efficacy through enhanced mucosal penetration, prolonged intestinal retention, protection of drugs from enzymatic degradation, and selective accumulation within inflamed tissues. Various nanoparticle systems including polymeric nanoparticles, lipid-based carriers, liposomes, hydrogels, and stimuli-responsive nanocarriers have demonstrated significant potential in improving IBD treatment outcomes.

Furthermore, advances in nanomedicine have enabled the delivery of biologics, genes, and nucleic acid therapeutics for precise modulation of inflammatory pathways involved in disease progression[4].

10.1 Delivery of Anti-inflammatory Drugs

Anti-inflammatory drugs are among the most commonly used therapeutic agents for the treatment of inflammatory bowel disease. However, conventional oral and systemic administration of these drugs often results in limited drug concentration at inflamed intestinal sites and increased systemic adverse effects. Nanoparticle-based delivery systems significantly improve the therapeutic performance of anti-inflammatory agents by enabling colon-specific targeting and controlled drug release[20].

Mesalamine (5-aminosalicylic acid), one of the primary drugs used in IBD management, has been extensively incorporated into nanoparticle formulations to improve its stability and intestinal retention. Polymeric nanoparticles prepared using chitosan, PLGA, and alginate have demonstrated enhanced accumulation of mesalamine in inflamed colonic tissues and prolonged therapeutic activity[170].

Nanoparticles also improve the delivery of nonsteroidal anti-inflammatory drugs and natural anti-inflammatory compounds such as curcumin, resveratrol, and quercetin. Curcumin-loaded nanoparticles, for example, exhibit enhanced bioavailability, improved intestinal permeability, and stronger anti-inflammatory effects compared to free curcumin due to improved protection from degradation and sustained drug release.

Stimuli-responsive nanoparticles capable of releasing anti-inflammatory drugs in response to pH changes, reactive oxygen species, or inflammatory enzymes have shown promising results in reducing intestinal inflammation. These systems minimize premature drug release in the upper gastrointestinal tract and enhance selective delivery to inflamed regions[19].

Additionally, mucoadhesive nanoparticles improve local drug retention by interacting with intestinal mucus layers and epithelial tissues, thereby enhancing therapeutic efficacy and reducing dosing frequency[4].

10.2 Delivery of Corticosteroids

Corticosteroids are highly effective anti-inflammatory agents widely used in moderate to severe inflammatory bowel disease. Drugs such as budesonide, dexamethasone, and prednisolone suppress inflammatory cytokine production and immune cell activation. However, prolonged systemic administration of corticosteroids is associated with significant adverse effects including immunosuppression, osteoporosis, hypertension, hyperglycemia, and adrenal suppression[171].

Nanoparticle-mediated corticosteroid delivery aims to enhance local drug concentration within inflamed intestinal tissues while minimizing systemic exposure and toxicity. Encapsulation of corticosteroids within polymeric nanoparticles, liposomes, and lipid-based carriers provides controlled and sustained drug release directly at the site of inflammation[172].

Budesonide-loaded nanoparticles have demonstrated improved colon-specific delivery and enhanced therapeutic efficacy in experimental colitis models. Chitosan-coated nanoparticles enhance mucoadhesion and prolong drug retention within inflamed mucosal tissues, resulting in better inflammation control and reduced systemic absorption.

Dexamethasone-loaded liposomes and solid lipid nanoparticles have shown enhanced uptake by activated macrophages and immune cells present within inflamed intestinal regions. Targeted delivery of corticosteroids

through nanoparticle systems significantly reduces inflammatory cytokine production and tissue damage while lowering systemic corticosteroid-related complications[172].

Stimuli-responsive corticosteroid nanoparticles have also been developed to release drugs selectively in response to inflammatory conditions or pH variations within the colon. These advanced systems improve therapeutic precision and reduce unwanted drug exposure to healthy tissues[20].

10.3 Delivery of Biologics

Biologic therapies have revolutionized the treatment of inflammatory bowel disease by specifically targeting immune mediators involved in chronic intestinal inflammation. Biologics such as monoclonal antibodies against tumor necrosis factor-alpha (TNF- α), interleukins, and integrins are highly effective in inducing and maintaining remission in IBD patients[173].

Despite their therapeutic benefits, biologics face several limitations including poor oral bioavailability, enzymatic degradation, high molecular weight, systemic immunogenicity, and the need for frequent parenteral administration. Nanoparticle-based delivery systems offer promising strategies for improving the stability, targeting efficiency, and controlled release of biologic therapeutics.

Polymeric nanoparticles, liposomes, and hydrogel-based carriers have been employed for the encapsulation and delivery of biologics such as infliximab, adalimumab, and vedolizumab. These nanocarriers protect biologics from gastrointestinal degradation and facilitate targeted delivery to inflamed intestinal tissues[100].

Nanoparticles can also enhance intracellular delivery of biologic agents to immune cells involved in inflammatory responses. Surface modification with targeting ligands improves selective accumulation within inflamed mucosal tissues and activated macrophages.

Oral nanoparticle formulations for biologic delivery are currently being investigated to improve patient compliance and reduce dependence on injectable therapies. Additionally, nanocarriers capable of co-delivering biologics and anti-inflammatory drugs have demonstrated synergistic therapeutic effects in experimental IBD models[100].

Although biologic-loaded nanoparticles show significant therapeutic promise, challenges related to protein stability, large-scale manufacturing, and long-term immunogenicity require further investigation before widespread clinical application[19].

10.4 Gene and siRNA Delivery

Gene therapy and small interfering RNA (siRNA)-based therapeutics represent advanced approaches for modulating molecular pathways involved in inflammatory bowel disease. These therapies target specific genes and signaling molecules responsible for inflammatory responses, cytokine production, and immune dysregulation[174].

However, naked nucleic acids are highly susceptible to enzymatic degradation, poor cellular uptake, and rapid systemic clearance. Nanoparticle-based delivery systems protect genetic materials from degradation and facilitate efficient intracellular transport and gene silencing.

Polymeric nanoparticles, lipid nanoparticles, dendrimers, and liposomes are widely utilized for gene and siRNA delivery in IBD therapy. Chitosan-based nanoparticles have demonstrated excellent potential due to their positive surface charge, biocompatibility, and ability to form stable complexes with negatively charged nucleic acids[175].

siRNA-loaded nanoparticles targeting TNF- α , NF- κ B, IL-6, and other inflammatory mediators have shown significant anti-inflammatory effects in experimental colitis models. These nanoparticles selectively suppress pro-inflammatory gene expression and reduce intestinal tissue damage.

Gene delivery systems have also been investigated for enhancing epithelial barrier repair and promoting mucosal healing through delivery of anti-inflammatory cytokine genes and growth factors. Surface-functionalized nanoparticles improve cellular uptake and targeting specificity toward inflamed intestinal tissues and immune cells[100].

Recent advances in lipid nanoparticle technology and CRISPR/Cas-based gene editing systems have further expanded opportunities for precise molecular therapy in inflammatory bowel disease.

10.5 Recent Advances in IBD Nanotherapy

Recent advances in nanotechnology have significantly transformed the therapeutic landscape of inflammatory bowel disease. Development of multifunctional and stimuli-responsive nanoparticles has improved drug targeting, therapeutic precision, and disease monitoring[4].

Stimuli-responsive nanoparticles capable of responding to pH, reactive oxygen species, enzymes, and inflammatory mediators have demonstrated highly selective drug release within inflamed intestinal tissues. Reactive oxygen species-responsive nanoparticles are particularly attractive because oxidative stress is significantly elevated in IBD-associated inflammation[176].

Biomimetic nanoparticles coated with cell membranes derived from macrophages, neutrophils, or stem cells have shown enhanced immune evasion and targeting efficiency. These biomimetic systems mimic natural cellular interactions and improve accumulation within inflamed tissues.

Nanoparticle-mediated microbiome modulation has also emerged as a novel therapeutic approach in IBD management. Probiotic-loaded nanoparticles and microbiota-targeting systems aim to restore intestinal microbial balance and reduce inflammation.

Advanced hydrogel-nanoparticle hybrid systems have been developed for prolonged mucosal retention and localized drug delivery. These systems combine the mucoadhesive properties of hydrogels with the targeting efficiency of nanoparticles to improve therapeutic outcomes[177].

Theranostic nanoparticles integrating diagnostic imaging and therapeutic functions have enabled simultaneous disease monitoring and treatment. Fluorescent, magnetic, and radiolabeled nanoparticles facilitate visualization of inflammation sites and evaluation of therapeutic response.

Artificial intelligence and machine learning are increasingly being utilized in nanoparticle design and optimization for personalized IBD therapy. Precision nanomedicine approaches tailored to patient-specific inflammatory profiles are expected to play a crucial role in future IBD management[4].

Although substantial progress has been achieved in IBD nanotherapy, challenges related to clinical translation, long-term safety, regulatory approval, and large-scale manufacturing remain important areas for future research and development.

11. Applications of Nanoparticles in Colorectal Cancer Therapy

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality worldwide. Conventional treatment approaches such as surgery, chemotherapy, radiotherapy, and targeted therapy have

significantly improved patient survival; however, these strategies are often associated with severe systemic toxicity, multidrug resistance, poor tumor selectivity, and limited therapeutic efficacy. Nanoparticle-based drug delivery systems have emerged as advanced therapeutic platforms capable of overcoming many limitations associated with conventional colorectal cancer treatment[67].

Nanoparticles enhance the delivery of anticancer agents through improved drug solubility, prolonged circulation time, controlled drug release, and selective accumulation within tumor tissues. Their small size and modifiable surface characteristics allow efficient penetration into tumor microenvironments and facilitate targeted intracellular drug delivery. In addition to improving chemotherapy, nanoparticles have shown promising applications in targeted therapy, combination therapy, immunotherapy, and theranostic approaches for colorectal cancer management[178].

Recent advancements in nanomedicine have enabled the development of multifunctional nanoparticles capable of simultaneous drug delivery, imaging, and molecular targeting, thereby improving treatment precision and therapeutic outcomes in colorectal cancer[67].

Table 2. Therapeutic applications of nanoparticle-based drug delivery systems in inflammatory bowel disease and colorectal cancer.

Therapeutic Agent	Nanoparticle System	Disease Target	Major Therapeutic Outcome
Mesalamine	Polymeric nanoparticles	IBD	Enhanced colon targeting
Budesonide	Chitosan nanoparticles	IBD	Reduced systemic toxicity
Curcumin	Liposomes/NLCs	IBD & CRC	Improved bioavailability
Infliximab	Liposomal carriers	IBD	Enhanced biologic stability
siRNA	Polymeric nanoparticles	IBD	Gene silencing of inflammatory cytokines
5-Fluorouracil	Liposomes	CRC	Sustained drug release
Oxaliplatin	Polymeric nanoparticles	CRC	Enhanced tumor targeting
Paclitaxel	Solid lipid nanoparticles	CRC	Improved anticancer activity
Doxorubicin	Magnetic nanoparticles	CRC	Targeted chemotherapy
Gold nanoparticles	Theranostic nanoparticles	CRC	Imaging and photothermal therapy

11.1 Chemotherapeutic Drug Delivery

Chemotherapy remains one of the primary treatment modalities for colorectal cancer, particularly in advanced and metastatic stages. Commonly used chemotherapeutic agents include 5-fluorouracil, oxaliplatin, irinotecan, capecitabine, doxorubicin, and paclitaxel. Although these drugs exhibit potent anticancer activity, their clinical utility is often limited by poor bioavailability, nonspecific distribution, rapid metabolism, systemic toxicity, and multidrug resistance[179].

Nanoparticle-based chemotherapeutic delivery systems significantly improve the pharmacokinetic and pharmacodynamic profiles of anticancer drugs. Encapsulation of chemotherapeutic agents within nanoparticles enhances drug solubility, protects drugs from premature degradation, prolongs systemic circulation, and facilitates controlled release at tumor sites.

Polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and mesoporous silica nanoparticles have been extensively investigated for colorectal cancer chemotherapy. These systems preferentially accumulate within tumor tissues through the enhanced permeability and retention (EPR) effect, thereby increasing local drug concentration while reducing systemic toxicity[67].

5-fluorouracil-loaded nanoparticles have demonstrated enhanced tumor targeting and prolonged drug release compared to conventional formulations. Similarly, irinotecan-loaded liposomes improve drug stability and reduce gastrointestinal toxicity. Curcumin and paclitaxel nanoparticles have also shown enhanced cellular uptake and anticancer efficacy against colorectal tumor cells[180].

Nanoparticle-mediated delivery improves intracellular drug accumulation and may overcome multidrug resistance mechanisms by bypassing efflux transporters such as P-glycoprotein. Controlled release behavior further maintains sustained therapeutic drug concentrations within tumor tissues, enhancing anticancer efficacy while minimizing adverse effects.

11.2 Targeted Therapy Using Nanoparticles

Targeted therapy aims to selectively inhibit molecular pathways and receptors involved in tumor growth, angiogenesis, metastasis, and cancer cell survival. Nanoparticles play an important role in improving the specificity and efficacy of targeted therapeutic agents in colorectal cancer[181].

Surface-functionalized nanoparticles can selectively bind to receptors overexpressed on colorectal cancer cells, including folate receptors, epidermal growth factor receptors (EGFR), CD44 receptors, transferrin receptors, and vascular endothelial growth factor (VEGF) receptors. Ligand-mediated targeting enhances receptor-specific cellular uptake and reduces off-target toxicity.

Folate-conjugated nanoparticles have demonstrated enhanced uptake by colorectal tumor cells due to increased folate receptor expression. Similarly, antibody-functionalized nanoparticles targeting EGFR improve tumor selectivity and intracellular delivery of anticancer drugs[67].

Nanoparticles are also utilized for the targeted delivery of tyrosine kinase inhibitors, monoclonal antibodies, gene therapeutics, and small interfering RNA (siRNA). These systems improve therapeutic stability and facilitate selective inhibition of oncogenic signaling pathways involved in colorectal cancer progression.

Stimuli-responsive nanoparticles capable of releasing drugs in response to tumor-specific conditions such as acidic pH, elevated enzyme activity, reactive oxygen species, or hypoxia further enhance therapeutic precision. These smart nanoparticles minimize premature drug release and maximize drug accumulation within tumor tissues[182].

Targeted nanoparticle systems reduce systemic toxicity, improve therapeutic index, and offer significant potential for personalized colorectal cancer treatment.

11.3 Combination Therapy Approaches

Combination therapy involves the simultaneous administration of multiple therapeutic agents or treatment modalities to achieve synergistic anticancer effects and overcome drug resistance. Nanoparticle-based platforms are highly suitable for combination therapy because they can co-deliver multiple drugs with different physicochemical properties in a controlled and targeted manner[183].

In colorectal cancer, nanoparticles have been developed for the co-delivery of chemotherapeutic agents such as 5-fluorouracil, irinotecan, oxaliplatin, and paclitaxel. Co-encapsulation of drugs within a single nanocarrier

improves synchronized drug delivery, enhances synergistic effects, and reduces the likelihood of multidrug resistance.

Nanoparticles are also employed for combining chemotherapy with gene therapy, immunotherapy, photothermal therapy, photodynamic therapy, and radiotherapy. For example, nanoparticles carrying both chemotherapeutic agents and siRNA can simultaneously inhibit tumor growth and suppress resistance-associated genes[184].

Photothermal therapy using gold nanoparticles or magnetic nanoparticles combined with chemotherapy has demonstrated enhanced tumor destruction through localized heat generation and improved drug penetration. Similarly, photodynamic therapy involving photosensitizer-loaded nanoparticles induces reactive oxygen species-mediated tumor cell death upon light activation[124].

Combination therapy nanoparticles improve therapeutic efficacy while reducing individual drug dosages and associated toxicity. Multifunctional nanocarriers capable of sequential or stimuli-responsive release of multiple therapeutic agents have shown particularly promising results in preclinical colorectal cancer models.

11.4 Immunotherapy and Nanoparticles

Immunotherapy has emerged as a highly promising strategy for colorectal cancer treatment by enhancing the body's immune response against tumor cells. However, conventional immunotherapeutic approaches face challenges including limited tumor penetration, systemic immune-related adverse effects, and poor therapeutic response in certain patient populations.

Nanoparticles offer significant advantages in improving the delivery and efficacy of immunotherapeutic agents. These systems facilitate targeted delivery of immune modulators, cytokines, tumor antigens, checkpoint inhibitors, and nucleic acid therapeutics directly to tumor tissues and immune cells[185].

Nanoparticles can enhance antigen presentation and activation of dendritic cells, T lymphocytes, and macrophages involved in antitumor immunity. Lipid nanoparticles and polymeric nanoparticles have been widely investigated for cancer vaccine delivery and immune activation.

Immune checkpoint inhibitors targeting programmed death receptor-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have demonstrated improved therapeutic efficacy when delivered using nanoparticle systems. Targeted nanoparticle delivery enhances tumor accumulation of checkpoint inhibitors while minimizing systemic immune toxicity[186].

Nanoparticles are also used for delivering cytokines, adjuvants, and gene-editing systems that modulate the tumor immune microenvironment. Combination of nanoparticle-mediated immunotherapy with chemotherapy or photothermal therapy has shown synergistic antitumor effects in colorectal cancer models.

Biomimetic nanoparticles coated with immune cell membranes have further improved immune evasion and tumor targeting capabilities. These advanced systems represent an important step toward personalized cancer immunotherapy[187].

11.5 Theranostic Nanoparticles in CRC

Theranostic nanoparticles are multifunctional nanocarriers that integrate diagnostic imaging and therapeutic functions within a single platform. These advanced systems enable simultaneous tumor detection, targeted therapy, treatment monitoring, and evaluation of therapeutic response in colorectal cancer[188].

Theranostic nanoparticles are generally composed of imaging agents combined with therapeutic drugs or targeting ligands. Various imaging modalities including magnetic resonance imaging (MRI), fluorescence imaging, computed tomography (CT), positron emission tomography (PET), and photoacoustic imaging have been incorporated into nanoparticle systems.

Gold nanoparticles, magnetic nanoparticles, quantum dots, mesoporous silica nanoparticles, and upconversion nanoparticles are widely investigated for theranostic applications in colorectal cancer. Magnetic nanoparticles containing iron oxide enable simultaneous drug delivery and MRI visualization of tumor tissues[189].

Fluorescent nanoparticles facilitate real-time imaging of tumor localization and nanoparticle biodistribution, while gold nanoparticles exhibit both imaging and photothermal therapeutic capabilities. Mesoporous silica nanoparticles can simultaneously encapsulate imaging agents and chemotherapeutic drugs for combined diagnostic and therapeutic applications.

Theranostic nanoparticles improve early tumor detection, enhance therapeutic precision, and allow real-time monitoring of drug delivery and treatment response. These systems support personalized medicine by enabling patient-specific optimization of therapy based on imaging feedback.

Recent advances in smart theranostic nanoparticles include stimuli-responsive systems capable of controlled drug release in response to tumor microenvironment conditions. Artificial intelligence-assisted imaging analysis and multifunctional nanoplatforms are further expanding the potential of theranostic nanomedicine in colorectal cancer management[190].

Despite significant progress, challenges related to long-term safety, imaging sensitivity, large-scale production, and regulatory approval must be addressed before widespread clinical implementation of theranostic nanoparticles[191].

13. Current Challenges and Future Perspectives

Nanoparticle-based drug delivery systems have demonstrated remarkable potential in improving the treatment of inflammatory bowel disease (IBD) and colorectal cancer (CRC). Despite extensive progress in nanomedicine research, only a limited number of nanoparticle formulations have successfully reached clinical application. Several scientific, technical, regulatory, and economic challenges continue to hinder the large-scale translation of nanoparticle therapeutics from laboratory research to commercial and clinical use[68].

Issues related to large-scale manufacturing, formulation stability, toxicity, reproducibility, and regulatory approval remain major obstacles in the development of safe and effective nanomedicines. Furthermore, the complex biological behavior of nanoparticles within the human body and variability among patient populations present additional challenges for achieving consistent therapeutic outcomes[192].

Future advancements in nanotechnology, materials science, biotechnology, artificial intelligence, and precision medicine are expected to overcome many of these limitations and expand the clinical applicability of nanoparticle-based therapies. Continued interdisciplinary research and standardized regulatory frameworks will be essential for the successful integration of nanomedicine into routine clinical practice for IBD and colorectal cancer management[3].

13.1 Scale-Up and Manufacturing Issues

One of the major challenges associated with nanoparticle drug delivery systems is the difficulty in scaling up laboratory formulations for industrial production. Many nanoparticle preparation methods that are effective at the research level become difficult to reproduce consistently during large-scale manufacturing[193].

Parameters such as particle size, zeta potential, encapsulation efficiency, morphology, and drug release behavior are highly sensitive to formulation conditions including temperature, mixing speed, solvent composition, and polymer concentration. Minor variations in these parameters during scale-up may significantly affect nanoparticle quality and therapeutic performance.

Techniques such as solvent evaporation, nanoprecipitation, emulsification, and ionic gelation often face limitations related to batch-to-batch variability, solvent removal efficiency, energy consumption, and production cost. Industrial-scale manufacturing also requires highly specialized equipment and stringent process control systems to ensure reproducibility and product uniformity[194].

Sterilization of nanoparticle formulations presents another important challenge. Conventional sterilization methods such as autoclaving or gamma irradiation may alter nanoparticle structure, drug stability, or release characteristics. Therefore, optimization of sterilization techniques compatible with nanoparticle systems is necessary[195].

Regulatory agencies require strict quality control and characterization standards for nanomedicine products. However, the absence of universally accepted manufacturing guidelines and standardization protocols complicates commercial production and regulatory approval.

Emerging technologies such as microfluidics, continuous manufacturing systems, automated synthesis platforms, and artificial intelligence-assisted process optimization may improve scalability and reproducibility of nanoparticle formulations in the future[162].

13.2 Stability and Storage Challenges

Stability is a critical factor influencing the shelf life, therapeutic efficacy, and clinical applicability of nanoparticle formulations. Nanoparticles are highly dynamic systems that may undergo physical and chemical instability during storage and transportation[67].

Common stability-related issues include particle aggregation, sedimentation, drug leakage, hydrolysis, oxidation, crystallization, and degradation of carrier materials. Changes in particle size distribution and surface charge may significantly alter biodistribution, targeting efficiency, and drug release behavior.

Lipid-based nanoparticles such as liposomes and solid lipid nanoparticles are particularly susceptible to oxidation and lipid polymorphic transitions during storage. Similarly, polymeric nanoparticles may undergo hydrolytic degradation or structural collapse under unfavorable environmental conditions[196].

Environmental factors including temperature, humidity, pH, light exposure, and ionic strength strongly influence nanoparticle stability. Therefore, careful optimization of storage conditions and formulation composition is essential to preserve nanoparticle integrity.

Freeze-drying (lyophilization) is widely employed to improve long-term stability of nanoparticle formulations. Cryoprotectants such as trehalose, sucrose, and mannitol help prevent aggregation and structural damage during freeze-drying and reconstitution[197].

Development of stable oral nanoparticle formulations for IBD and CRC therapy remains particularly challenging because nanoparticles must withstand harsh gastrointestinal conditions including acidic pH, digestive enzymes, mucus barriers, and variable intestinal transit times.

Future research should focus on designing more robust and environmentally stable nanoparticle systems with improved shelf life and simplified storage requirements[198].

13.3 Toxicity and Biocompatibility Issues

Toxicity and biocompatibility remain among the most critical concerns limiting the clinical translation of nanoparticle-based therapies. Although many nanoparticle systems are designed using biocompatible materials, their nanoscale size and unique physicochemical properties may lead to unexpected biological interactions and adverse effects[199].

Nanoparticles may induce oxidative stress, inflammation, mitochondrial dysfunction, DNA damage, membrane disruption, and immune activation depending on their size, shape, composition, surface charge, and concentration. Long-term accumulation of non-biodegradable nanoparticles in organs such as the liver, spleen, kidneys, and lungs may result in chronic toxicity.

Positively charged nanoparticles often exhibit enhanced cellular uptake but may also cause increased cytotoxicity due to strong electrostatic interactions with cell membranes. Metallic nanoparticles such as silver, gold, and quantum dots may generate reactive oxygen species and exhibit dose-dependent toxicity[200].

In inflammatory bowel disease, excessive immune activation or disruption of intestinal microbiota by nanoparticles may aggravate intestinal inflammation. Similarly, nonspecific distribution of anticancer nanoparticles in colorectal cancer therapy may damage healthy tissues and cause systemic side effects.

Protein corona formation following nanoparticle exposure to biological fluids can alter nanoparticle behavior, biodistribution, and immune recognition. This phenomenon complicates prediction of nanoparticle performance under physiological conditions[201].

Comprehensive evaluation of acute and chronic toxicity, immunogenicity, genotoxicity, reproductive toxicity, and environmental impact is essential before clinical application. Standardized toxicity assessment protocols and long-term safety studies are required to ensure safe clinical translation of nanomedicines.

Biodegradable and biomimetic nanoparticles, green synthesis approaches, and surface engineering strategies are being explored to improve nanoparticle safety and biocompatibility[202].

13.4 Future Research Directions

Future research in nanoparticle drug delivery systems is expected to focus on developing more precise, multifunctional, safe, and patient-specific therapeutic platforms for inflammatory bowel disease and colorectal cancer[4].

Stimuli-responsive nanoparticles capable of responding to pH, enzymes, temperature, reactive oxygen species, inflammatory mediators, or hypoxic conditions are likely to play an increasingly important role in targeted therapy. These smart systems provide highly controlled drug release and improve therapeutic precision.

Biomimetic nanoparticles coated with cell membranes derived from immune cells, stem cells, or bacteria are emerging as advanced strategies for improving immune evasion and tissue-specific targeting. These systems mimic natural biological interactions and enhance nanoparticle accumulation within diseased tissues[203].

Nanoparticle-mediated gene editing using CRISPR/Cas systems represents another promising research area for precise modulation of inflammatory and oncogenic pathways. Combined delivery of drugs, genes, proteins, and imaging agents through multifunctional nanocarriers may further improve therapeutic outcomes.

Artificial intelligence (AI) and machine learning technologies are increasingly being integrated into nanoparticle design, formulation optimization, and predictive modeling. AI-assisted approaches may accelerate the development of personalized nanomedicine by identifying optimal formulations based on patient-specific characteristics[204].

Microbiome-targeted nanotherapy is another rapidly growing field in IBD research. Nanoparticles designed to modulate intestinal microbiota composition and function may offer novel therapeutic opportunities for controlling chronic intestinal inflammation.

Future clinical translation will require interdisciplinary collaboration among pharmaceutical scientists, clinicians, material scientists, engineers, toxicologists, and regulatory agencies to address current limitations and establish standardized evaluation protocols[4].

13.5 Personalized Nanomedicine

Personalized nanomedicine represents a transformative approach in which nanoparticle-based therapies are tailored according to the genetic, molecular, immunological, and physiological characteristics of individual patients. This strategy aims to maximize therapeutic efficacy while minimizing adverse effects and treatment variability[205].

In inflammatory bowel disease and colorectal cancer, significant heterogeneity exists in disease pathogenesis, inflammatory profiles, genetic mutations, immune responses, and treatment outcomes among patients. Personalized nanomedicine utilizes biomarkers, genomic analysis, molecular diagnostics, and advanced imaging technologies to design individualized therapeutic strategies.

Targeted nanoparticles can be engineered to recognize patient-specific receptors, tumor markers, inflammatory mediators, or genetic abnormalities. Customized drug combinations and controlled release systems may improve therapeutic response and reduce resistance development[206].

Nanoparticle-assisted companion diagnostics enable real-time monitoring of disease progression, treatment response, and drug biodistribution. Theranostic nanoparticles integrating diagnostic and therapeutic functions support precision medicine by facilitating individualized treatment optimization.

Advances in artificial intelligence, bioinformatics, nanotechnology, and molecular biology are expected to accelerate the development of patient-specific nanotherapeutics. Personalized nanomedicine may also improve treatment outcomes in patients with refractory or treatment-resistant IBD and CRC[3].

Despite its enormous potential, personalized nanomedicine faces challenges related to high development costs, complex manufacturing requirements, regulatory considerations, and accessibility. Ethical and data privacy concerns associated with genomic and personalized health information must also be carefully addressed[207].

Nevertheless, continued technological advancements and improved understanding of disease biology are likely to make personalized nanomedicine an integral component of future gastrointestinal disease management[208].

14. Conclusion

Nanoparticle-based drug delivery systems have emerged as highly promising and innovative therapeutic platforms for the management of inflammatory bowel disease (IBD) and colorectal cancer (CRC). Conventional therapeutic approaches for these disorders are often limited by poor site specificity, systemic toxicity, rapid drug degradation, inadequate bioavailability, and frequent dosing requirements. Nanotechnology has provided effective solutions to many of these challenges by enabling targeted, controlled, and sustained delivery of therapeutic agents directly to diseased tissues.

A wide variety of nanoparticle systems including polymeric nanoparticles, lipid-based nanoparticles, liposomes, dendrimers, metallic nanoparticles, mesoporous silica nanoparticles, hydrogels, and nanoemulsions have demonstrated significant potential in improving therapeutic outcomes. These nanocarriers enhance drug stability, prolong systemic circulation, improve mucosal penetration, and facilitate selective accumulation within inflamed intestinal tissues and tumor microenvironments. Advanced targeting strategies such as passive targeting, active targeting, ligand-mediated delivery, pH-sensitive systems, and enzyme-responsive nanoparticles have further improved therapeutic precision and reduced off-target adverse effects.

In inflammatory bowel disease, nanoparticle-mediated delivery of anti-inflammatory drugs, corticosteroids, biologics, genes, and siRNA has shown enhanced efficacy in controlling intestinal inflammation while minimizing systemic toxicity. Similarly, in colorectal cancer therapy, nanoparticles have improved the delivery of chemotherapeutic agents, targeted therapeutics, immunotherapeutic agents, and combination therapies. Theranostic nanoparticles integrating diagnostic and therapeutic functions have also opened new possibilities for real-time disease monitoring and personalized treatment.

Despite these advancements, several challenges continue to limit the clinical translation of nanoparticle-based therapies. Issues related to large-scale manufacturing, reproducibility, long-term stability, toxicity, biodistribution, regulatory approval, and cost-effectiveness require further investigation and optimization. Comprehensive evaluation of nanoparticle safety and establishment of standardized regulatory guidelines remain essential for successful commercialization and clinical application.

Future research should focus on the development of multifunctional, stimuli-responsive, biomimetic, and personalized nanoparticle systems capable of addressing the complex pathophysiology of IBD and CRC. Integration of nanotechnology with artificial intelligence, molecular diagnostics, microbiome research, and precision medicine is expected to significantly enhance therapeutic efficiency and patient outcomes.

Overall, nanoparticle drug delivery systems represent a rapidly evolving field with enormous potential to transform the diagnosis, treatment, and management of inflammatory bowel disease and colorectal cancer. Continued interdisciplinary research and technological advancements are likely to accelerate the clinical translation of nanomedicine and establish nanoparticle-based therapies as integral components of future gastrointestinal healthcare.

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