Advancements in nanotechnology for drug delivery: A review of recent innovations in Pharmacy-GIT as a model

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Abstract---Background: Nanoparticles (NPs) have emerged as a transformative technology in drug delivery, offering advancements in precision medicine, especially in managing chronic diseases and gastrointestinal (GIT) disorders. Due to their unique properties and the ability to be engineered at the nanoscale, NPs provide enhanced targeting, controlled release, and reduced side effects compared to traditional drug delivery systems. Aim: This review aims to summarize recent innovations in nanoparticle technology and their applications in drug delivery systems, with a focus on gastrointestinal diseases. Methods: The review synthesizes current literature on NP technologies and their applications in treating GIT disorders. It covers a range of nanocarriers, including metal and polymeric NPs, liposomes, hydrogels, and lipid nanoparticles. The review evaluates their effectiveness, challenges, and advancements in GIT drug delivery. Results: Recent advancements in NP technology have demonstrated significant potential in improving drug delivery to the GIT. Innovations include pH-sensitive NPs, enzyme-responsive NPs, and targeted formulations for diseases such as inflammatory bowel disease (IBD) and colorectal cancer. Lipid nanoparticles, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have shown promise in enhancing stability, targeting, and drug release profiles. Conclusion: Nanoparticles represent a major advancement in drug delivery systems, particularly for GIT applications. Their ability to be tailored for specific therapeutic needs and their improved targeting capabilities make them a valuable tool in treating GIT disorders. Future research should focus on overcoming current limitations, such as variability in individual responses and optimizing NP characteristics for enhanced efficacy.

Keywords---nanoparticles, drug delivery, gastrointestinal tract, inflammatory bowel disease, colorectal cancer, lipid nanoparticles.

Introduction

Nanoparticles (NPs) represent a novel advancement in medical technology, offering potential applications in managing chronic diseases, oncology, surgical procedures, and the evolution of personalized medicine due to their specificity achieved through synthetic design [1-4]. Typically, NPs are inorganic entities ranging from 1 to 1000 nanometers in size. Their distinctive properties make them advantageous for therapeutic interventions. Unlike organic materials, NPs are less influenced by biological factors and can be externally controlled, enhancing drug delivery targeting, marker binding sensitivity for advanced imaging, and the detection of disease biomarkers [5].

In the context of the gastrointestinal tract (GIT), these features are crucial for treating various ailments. Traditional drug delivery methods within the GIT have been constrained by the need for pH, microbial, or receptor-sensitive approaches. NPs offer a promising alternative, enabling precise control over drug release without relying on these conventional regulators. Additionally, NPs can deliver localized radiation and heat to targeted areas after binding to specific locations. This capability allows for the selective imaging of bound structures and measurement of binding levels for diagnostic purposes, facilitating better planning of radiative and surgical interventions [7].

For gastrointestinal diseases, NPs present a valuable therapeutic option for drug delivery, enhancing cell surface interaction and tissue-specific deposition [8-22]. Although current research predominantly focuses on NP-based drug delivery to the colon, advancements in technology are expected to extend these capabilities to the stomach, esophagus, small intestine, gallbladder, liver, and pancreas. NPs with adjustable chemical properties enable higher drug encapsulation and targeted therapeutic delivery [23, 24]. An ideal system would precisely target inflamed areas within the gut, ensuring prolonged drug release at the intended site with minimal side effects. Consequently, factors such as NP shape, size, surface chemistry, and other physicochemical characteristics are critical in developing effective nanocarriers for biopharmaceutical applications [25]. This review will explore recent progress in NP technology and its application in treating gastrointestinal diseases.

In conclusion, nanoparticles represent a transformative development in medical technology with significant potential in the treatment and prevention of gastrointestinal diseases. Their unique properties, including enhanced targeting and control over drug delivery, imaging, and therapeutic interventions, make them a valuable tool in advancing personalized medicine. While current research has primarily focused on colon-targeted delivery, future technological advancements are poised to expand NP applications to other regions of the gastrointestinal tract. The ability to modify NP properties to achieve precise drug delivery and minimal side effects underscores their promise as effective therapeutic agents. Continued exploration and refinement of NP technology will be crucial in optimizing its benefits for diverse medical applications, ultimately leading to improved patient outcomes and more effective management of gastrointestinal disorders.

Nanosystems for GIT

A diverse array of nanocarriers has been employed for drug delivery within the gastrointestinal (GI) tract, including metal and polymeric nanoparticles (NPs), liposomes, and nano-micro drug delivery systems such as hydrogels [23-37]. Additionally, nanocarriers have been developed to address infectious diseases in the gut. Despite the demonstrated antimicrobial effects of many nanosystems, specific targeting of particular bacteria or microbes remains unachieved. Contemporary research indicates that antibiotic-based nanoformulations might offer improved targeting of bacteria; however, these formulations face limitations such as reduced efficacy against resistant bacteria and poor affinity for altered cell wall structures.

The primary benefits of NP-based formulations for GI diseases include enhanced specificity, increased efficiency in terms of therapeutic timing and effects, targeted activity, and reduced cytotoxicity to the host [38]. However, several challenges must be resolved before nanoparticles can be effectively utilized for drug delivery in the GI tract. Critical factors such as NP size, shape, surface charge, and bioconjugation need to be carefully considered to optimize their performance for GI drug delivery. The utilization of nanocarriers for drug delivery in the GI tract offers considerable promise due to their ability to enhance specificity, efficiency, and targeted therapeutic effects. While various nanocarriers, including metal and polymeric NPs, liposomes, and hydrogels, have shown potential, challenges remain in achieving precise targeting of specific bacterial strains and overcoming limitations related to bacterial resistance and altered cell wall structures. Addressing these challenges will require careful consideration of NP properties, including size, shape, surface charge, and bioconjugation. Advances in these areas could significantly improve the effectiveness of NP-based therapies, leading to more efficient and targeted treatment options for gastrointestinal diseases and infections.

Challenges of GIT Drug Delivery

In treating gastrointestinal (GI) diseases, the delivery of drugs via nanoparticles (NPs) presents several notable challenges. The timing of drug release is particularly crucial, given the complexities of oral bioavailability, dosing regimens, and the goal of maximizing drug accumulation at targeted inflammatory sites. Furthermore, localization and internalization into gut tissue pose difficulties due to the inherent physiology of the GI tract. However, recent advancements in NP technology have begun to address these issues effectively.

3.1 Timing of Drug Release

Premature release of therapeutic agents can lead to adverse effects and reduced therapeutic efficiency. Although drug encapsulation is a common method for controlled delivery, issues such as erosion of the polymer or diffusion through aqueous environments can cause premature release, especially for hydrophilic drugs [39]. This premature release diminishes the drug's efficacy in targeting inflammation. To counteract this problem, research has shown that covalent binding of the anti-inflammatory agent 5-amino salicylic acid (5ASA) to the NP

matrix can significantly delay drug release in vitro, resulting in extended drug release. In a study, NP formulations with a 5ASA dose of 0.5 mg/kg demonstrated comparable efficacy to a 30 mg/kg dose of 5ASA administered as a solution, as measured by myeloperoxidase (MPO) activity in a TNBS-induced colitis model [13]. Diarrhea, a common symptom in gut diseases, also poses a challenge by reducing drug release time and accelerating NP elimination [40]. Larger micrometer-sized carriers are particularly susceptible to these effects, highlighting the advantages of NPs due to their smaller size and design characteristics.

3.2 Targeting Specificity

The use of NPs for targeted delivery in GI diseases is a relatively recent development, with substantial potential for improvement. Various targeting strategies, including pH-dependent release NPs, enzyme-sensitive NPs, siRNA-loaded NPs, and antibody-conjugated NPs, enhance therapeutic specificity [14, 15, 24, 40-42]. For instance, budesonide-loaded pH/enzyme-dependent NPs have been shown to effectively target colitis by releasing the drug selectively at the colon's pH, facilitated by azo-reductase, an enzyme abundant in inflamed colonic tissues [14]. Similarly, a study utilizing nanostructured lipid carriers (NLCs) with budesonide demonstrated reduced neutrophil infiltration and lower levels of pro-inflammatory cytokines in a mouse model of inflammatory bowel disease (IBD) [43]. A pH-dependent NP release system has also been developed for Tacrolimus, showing effective drug retention and release at appropriate pH levels within the GI tract [40]. Despite these advances, variability in pH among individuals and disease states remains a limitation.

The specificity of small interfering RNA (siRNA) provides another avenue for enhanced targeting. siRNAs, which modulate gene expression without requiring genome integration, are incorporated into RNA-induced silencing complexes (RISC) that selectively bind to complementary mRNA, inducing gene silencing. In a study, siRNA-loaded NPs targeting CD98, a glycoprotein upregulated in inflammatory conditions, effectively reduced colitis in a mouse model [41]. Additionally, bioconjugation of NPs with specific proteins or antibodies can further enhance targeting. For example, NPs bioconjugated with anti-M-cell-specific antibodies demonstrated improved targeting and sustained release in gut-associated lymphoid tissue (GALT), significantly outperforming free drugs [42]. Nanoparticle-based drug delivery systems offer significant potential for treating gastrointestinal diseases by addressing key challenges such as timing of drug release and targeting specificity. While advancements in NP technology have made strides in overcoming these obstacles, including enhanced drug release control and targeted delivery mechanisms, challenges remain. Addressing issues like variability in individual responses and optimizing NP characteristics will be crucial for maximizing therapeutic efficacy. Continued innovation in NP design and targeting strategies promises to improve drug delivery systems, offering more effective treatments for GI diseases and potentially transforming current therapeutic approaches.

3.3 Transmission and Accumulation into Gut Tissue

The gastrointestinal (GI) tract presents unique challenges for drug delivery due to its distinct physiological properties compared to other tissues. Delivering drugs past digestive enzymatic degradation and systemic absorption to target sites of colonic inflammation remains challenging. However, recent advancements in nanotechnology have enabled the design of nanoparticles (NPs) that address these challenges by overcoming enzymatic degradation and preventing premature drug release. Research indicates that the increased adhesion and accumulation of NPs at inflamed sites are largely attributed to elevated mucus production in these areas and the uptake of NPs by macrophages [13, 16, 17]. Muco-adhesive drug delivery systems utilizing NPs can be developed to enhance drug delivery within the GI tract. These systems utilize hydrogen bonding between polymeric chains on the NP and mucin chains in the mucus layer, facilitating NP adhesion and subsequent diffusion into the intestinal epithelial cell lining. Ulcerations in inflamed regions may further enhance NP adhesion to specific gut tissues [13].

In diseases such as inflammatory bowel disease (IBD), there is an increased presence of immune cells, including macrophages, neutrophils, and natural killer cells, which can uptake NPs of various sizes and morphologies [13, 25]. NPs can be internalized into the gut through several mechanisms, including phagocytosis, receptor-mediated recognition, chemically-enhanced adhesion, clathrin-mediated endocytosis, and caveolae-mediated endocytosis [17, 24]. The size of NPs plays a crucial role in determining the efficacy and mechanism of drug delivery to the gut [21-25, 43, 45, 46]. Smaller NPs tend to enter the bloodstream more readily, evade detection as foreign agents, and penetrate the GI barrier more effectively [24, 25]. An experimental study using a rat colitis model demonstrated that NPs with sizes ranging from 100 nm to 1000 nm exhibited 5-6.5 times greater accumulation in inflamed tissues compared to healthy controls [39]. Furthermore, clathrin-mediated endocytosis is the predominant mechanism for NPs smaller than 200 nm, whereas caveolae-mediated endocytosis is more common for NPs with diameters under 500 nm [18]. The delivery of nanoparticles to target inflamed gut tissues presents a unique set of challenges due to the GI tract's complex physiological environment. Recent advancements in NP technology have improved the ability to overcome these challenges, such as enzymatic degradation and inefficient drug release. By enhancing NP adhesion through muco-adhesive properties and optimizing NP size for better accumulation and internalization, these technologies offer promising solutions for targeted drug delivery in inflammatory gut diseases. Continued research into the mechanisms of NP uptake and their interactions with gut tissues will be essential in refining these strategies, ultimately leading to more effective treatments for GI disorders.

Common GIT Disorders and Nanosystems

Inflammatory Bowel Disease (IBD)

Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract with an unclear etiology, influenced by genetic, bacterial, and environmental factors. The pathophysiology of IBD involves immune

dysregulation against gut commensal bacteria. IBD is classified into two main types: Ulcerative Colitis (UC) and Crohn's Disease (CD).

- Ulcerative Colitis (UC): Characterized by continuous mucosal inflammation primarily in the distal colon, predominantly involving TH2 cells and neutrophils.
- Crohn's Disease (CD): Features patchy transmural inflammation that can affect any part of the GI tract. CD is marked by lymphocytic infiltrates, non-caseating granulomas, and involves TH1 and TH17 cells.
  Current treatment approaches for IBD aim to reduce inflammation, suppress the immune response, and manage symptoms. First-line treatments include aminosalicylates, which act directly at the site of inflammation. Oral medications are convenient, while suppositories target the lower GI tract, mainly for UC. Systemic immunosuppression, although effective, carries risks of infections and systemic side effects. Surgical options are curative for UC but only provide temporary relief for CD, where inflammation often recurs at excision sites. Nanoparticle (NP) technology offers a promising alternative to address these treatment challenges, potentially enhancing drug delivery and reducing systemic side effects. Here are several studies demonstrating the application of NPs in treating IBD:
- Silk Fibroin NPs (SFNs): Functionalized with the RGD peptide (arginine–glycine–aspartic acid) to improve interaction with injured intestinal tissue. SFNs have shown to ameliorate colonic damage, reduce neutrophil infiltration, and improve oxidative status in rat models of colitis [47].
- KPV-Loaded NPs: KPV, a naturally occurring tripeptide, was loaded into hyaluronic acid (HA)-functionalized polymeric NPs. These NPs successfully targeted colonic epithelial cells and macrophages, accelerating mucosal healing and alleviating inflammation in UC models. Encapsulation in chitosan/alginate hydrogel further enhanced therapeutic efficacy [20].
- Superoxide Dismutase/Catalase Mimetic Nanomedicine: This nanotherapy includes a β-cyclodextrin-based matrix and Tempol (Tpl), a free radical scavenger. It provides a functional, safe nanocarrier for ROS-responsive delivery of therapeutics, with potential applications in IBD and other intestinal diseases [48].
- Silver Nanoparticles (NanoAg1 and NanoAg2): Administered intracoelomically, these nanoparticles effectively alleviated colitis in mouse models of UC and CD by suppressing neutrophil recruitment and modifying colonic microbiota [49].
- PEGylated Bilirubin NPs (BRNPs): Bilirubin, a potent antioxidant, was conjugated with polyethylene glycol to form nanoscale particles. BRNPs showed high efficiency in scavenging hydrogen peroxide and significantly inhibited inflammation in a murine model of UC [50].
- RNA Interference (RNAi)-Based NPs: Nanovectors loaded with siRNA or miRNA provide targeted regulation of pro-inflammatory cytokines, reducing IBD progression and promoting mucosal recovery. Development of effective delivery systems and minimization of off-target effects remain critical challenges [51].
- Ginger-Derived NPs (GDNPs-2): Derived from edible ginger, these NPs demonstrated efficient colon targeting and reduced inflammation, enhanced

intestinal repair, and prevented chronic colitis and associated cancer in mouse models [52].

- Gold Nanoparticles (GNPs) for Diagnostics: Modified GNPs were used to develop an assay for differentiating between IBS and IBD based on breath chemical analysis. The assay achieved 88% accuracy, offering a cost-effective and specific diagnostic tool [53].

Nanoparticle technology holds significant promise for advancing the treatment of IBD. By improving drug delivery, targeting specific sites of inflammation, and reducing systemic side effects, NPs offer a more effective approach compared to traditional treatments. Continued research and development in NP design, including functionalization and targeting strategies, will be crucial in addressing the complexities of IBD and enhancing therapeutic outcomes.

Colorectal Cancer

Colorectal cancer is the third most common cancer in the United States and has the third highest mortality rate among cancers. Current treatments focus on surgical resection and adjuvant chemotherapy, which have improved prognosis and survival rates for locally advanced and metastatic cancers. For stage I, IIA, and IIIA colorectal cancer, the five-year survival rate is above 85%. However, challenges such as multidrug resistance and adverse effects limit the efficiency of these treatments. The increasing incidence of colorectal cancer in younger individuals highlights the need for improved screening methods. Nanoparticle (NP) technologies offer promising solutions for both treatment and early detection of colorectal cancer.

NP-Based Imaging and Screening

NP-based imaging modalities can enhance visualization of tumors and aid in more precise surgical and radiation treatments. Additionally, NP-based screening techniques might facilitate earlier detection and routine screening, particularly beneficial given the rising incidence in younger populations.

Targeted NP Treatments

NPs offer improved targeting for local and metastatic colorectal cancer, enhancing the efficacy of radiation and chemotherapy. Several novel approaches utilizing NPs for colorectal cancer treatment include:

1. Gold Nanoparticles (Au@CB):
   o Derived from brown macroalgae Cystoseira baccata (CB) extracts, Au@CB demonstrated strong cytotoxic activity against colorectal cancer cell lines HT-29 and Caco-2 while maintaining biocompatibility with healthy cells. Au@CB induced apoptosis through both extrinsic and mitochondrial pathways, showing potential for colon cancer treatment [55].
2. Silver Nanoparticles (AgNPs):
   o Biogenic AgNPs from Balanites aegyptiaca fruit extract were tested against colon and liver cancer cells, altering gene expression related to cancer cell apoptosis and multidrug resistance [9].

3. Non-Apoptotic Cell Death Pathways:
   o Research on lysosomal-mediated programmed cell death (LM-PCD), necroptosis, and autophagy has identified new pathways for cancer therapy. Chloroquine (CQ) combined with mRIP3 enhanced tumor inhibition by increasing autophagic flux and inducing RIP3-dependent necroptosis [56].

4. Resveratrol-Loaded Lipid-Core-Nanocapsules (RSV-LNC):
   o RSV-LNC showed potential to target colon cancer cells effectively in vitro. Further studies on animal models are needed to confirm the efficacy of these nanoformulations [21].

5. Self-Immolative Polymer Prodrug NPs:
   o These NPs simultaneously regulate polyamine metabolism and deliver miRNA, enhancing therapeutic effects and tumor growth inhibition in preclinical models [22].

6. Cerium Oxide Nanoparticles (Nanoceria):
   o Nanoceria modulates intracellular reactive oxygen species (ROS) and is effective in scavenging ROS in cancer cells. The size of nanoceria affects its cellular uptake and ROS scavenging efficiency [57].

7. Hyaluronic Acid (HA) Conjugates:
   o BSA-HA conjugates self-assemble into NPs that deliver hydrophobic cytotoxic drugs like paclitaxel, targeting cancer cells with overexpressed CD44 receptors [58].

8. Intraperitoneal Nanoparticle Delivery:
   o NPs administered intraperitoneally can better target peritoneal tumors, leveraging the tendency of phagocytes to transport NPs to tumors and stimulate antitumor immune responses [59].

9. Bladder Cancer Treatment:
   o HA-IR-780 NPs with targeting and photothermal ablation properties offer a promising strategy for treating bladder cancer, potentially preserving bladder function [60].

10. Silica Nanoparticles (SNPs):
    o SNPs induce autophagy by accumulating in the endoplasmic reticulum, offering insights into ER autophagy and potential for developing safer silica-based NPs [61].

11. Ultrasound-Induced Hyperthermia:
    o NP-enhanced ultrasound hyperthermia allows for more precise heating of malignant tissues, reducing exposure time and power requirements compared to conventional methods [62].

Future Directions

While NP technologies present numerous advancements for colorectal cancer treatment, challenges such as scaling-up and regulatory approval remain significant barriers. Continued research and development are necessary to transition these promising NP-based therapies from the bench to clinical practice.

Lipid Nanoparticles (Lipid NPs)

Lipid nanoparticles (Lipid NPs) are increasingly utilized in the treatment of inflammatory bowel disease (IBD) and various gastrointestinal (GI) tract cancers.

These NPs include a diverse range of non-polar particles such as liposomes, colloids, emulsions, solid lipid NPs (SLNs), and nanostructured lipid carriers (NLCs). Among these, SLNs and NLCs are particularly prominent in drug delivery due to their stability and effective targeting capabilities.

Types of Lipid NPs

1. Traditional Lipid NPs:
o Liposomes: These are lipid bilayers encasing an aqueous core designed to deliver pharmaceuticals. Despite their promise for targeted delivery with minimal side effects, they suffer from low stability, rapid degradation, and leakage.
o Colloids and Emulsions: These involve lipids suspending pharmaceuticals. While they offer targeted delivery, they face similar stability issues as liposomes.
2. Solid Lipid NPs (SLNs):
o Structure and Composition: SLNs are composed of solid lipids and surfactants, making them suitable for delivering both hydrophobic and hydrophilic drugs. They are solid at body temperature and can be designed with various models, such as core-shell models with drug-enriched cores or shells, and solid-solution models.
o Advantages: SLNs provide improved stability, lower production costs, increased diversity of payloads, and reduced toxicity compared to traditional lipid NPs.
o Challenges: SLNs can have issues with payload volume due to their stable crystalline structure, which may affect delivery efficiency and cause coagulation.
3. Nanostructured Lipid Carriers (NLCs):
   o Structure and Types: NLCs combine solid and liquid lipids to enhance drug retention and stability. The three main types are:
     ▪ Class I NLCs: Solid lipid structures combined with fatty acids where drugs are sequestered within fatty acid chains.
     ▪ Class II NLCs: Use formless lipids for drug sequestration.
     ▪ Class III NLCs: Multiple types combining various lipid structures for diverse drug delivery.
   o Advantages: NLCs improve drug retention and stability compared to SLNs but may be limited to lipophilic drugs.

Applications and Recent Studies

1. Cancer Treatment:
   o Etoposide and Curcumin Delivery: Mixed-type NLCs were used to deliver etoposide and curcumin to gastric cancers, showing high levels of selective delivery in mouse models [12].
   o Colorectal Cancer: SLNs have been employed to deliver doxorubicin, 5-fluorouracil, and docetaxel, demonstrating improved efficacy in vitro compared to free drugs [8-10].
   o Hepatocellular Carcinoma: SLNs showed increased accumulation and efficacy of docetaxel in treating liver cancer cells.

2. Inflammatory Bowel Disease (IBD) Treatment:
   o Embelin Lipid Nanospheres: These showed a modest decrease in inflammation markers (MPO, LDH, LPO, and GSH) [44].
   o Cyclosporine-loaded NLCs: Used to treat dextran sulfate sodium-induced colitis in mice. Despite high toxicity of commercial cyclosporine, NLCs did not significantly reduce colon inflammation in acute stages [64].
   o Dexamethasone and Budesonide-loaded SLNs/NLCs: These showed promise in reducing inflammatory markers (TNF-α, IL-1β, IL-6, IL-12) and improving histological scores in mouse models [11, 43, 63].

Conclusion

Lipid NPs, particularly SLNs and NLCs, offer significant advantages for drug delivery in treating GI tract cancers and IBD. They provide stability, targeted delivery, and reduced toxicity compared to traditional NP models. Although many studies are still in preliminary phases, they highlight the potential of lipid NPs to revolutionize treatment strategies for these challenging conditions. Future research should address existing limitations to fully realize the clinical potential of lipid NPs in drug delivery.

Challenges with Nanoparticle Delivery and the Gut Microbiota

Delivering nanoparticles (NPs) effectively to the site of inflammation in inflammatory bowel disease (IBD) presents several challenges. Optimal drug delivery in IBD should target the inflamed areas with high drug concentrations while minimizing systemic absorption. However, achieving this is complicated by the altered conditions in the gut during inflammation.

Key Challenges in NP Delivery

1. Inflammation and Intestinal Environment:
   o Altered pH and Microbiota: Inflammation in IBD leads to a more acidic pH and changes in the gut microbiota from its normal composition. These changes can affect NP behavior and efficacy [45, 67].
   o Intestinal Epithelium Damage: Inflammation damages the gut lining, leading to increased permeability and enhanced NP uptake at the site of inflammation [68].
2. Size and Adhesion:
   o Particle Size Effects: Studies have shown that smaller NPs (e.g., 100 nm) exhibit higher adhesion to inflamed areas of the colon compared to larger particles (e.g., 10 μm). Smaller particles can penetrate deeper into the intestinal wall [70].
   o Macrophage and Dendritic Cell Uptake: NPs are taken up by immune cells like macrophages and dendritic cells, which can facilitate their accumulation at inflamed sites. Increased mucosal secretion during inflammation further aids NP adhesion [71, 72].
3. Drug Release and Retention:
   o Rapid Drug Release: NPs can have a high surface area leading to rapid release of the drug. This can limit the effectiveness of the treatment as the drug may be released before reaching the targeted site [17].

o Controlled Release Strategies: Efforts are being made to develop NPs with slower or delayed drug release. For instance, indomethacin-loaded NPs with nitroxide radicals showed improved drug retention and reduced inflammatory effects [74].

Interaction with Gut Microbiota

1. Microbiota Alterations:
   o Impact of Inflammation: Inflammation disrupts the intestinal barrier, increases mucus production, and affects the composition of the gut microbiota. IBD patients often show reduced microbiome diversity and an increase in specific bacterial species such as Bacteroides and Eubacteria [75, 76].
   o Transit Time and Microbiota Changes: Increased or decreased gut motility and diarrhea in IBD patients can alter the microbiome by affecting nutrient availability and bacterial exposure. Patients with small intestinal bacterial overgrowth (SIBO) exhibit longer orocecal transit times compared to those without SIBO [79, 80].
2. Effects on NP Therapy:
   o Microbiota Interaction: The altered microbiota in IBD patients can influence the efficacy of NP-based therapies. Changes in the gut environment and microbiome may impact NP behavior and drug delivery efficiency [77, 81-83].
   o Potential Adverse Effects: The interaction between NP systems and the host microbiota may lead to unintended health effects, potentially impacting treatment outcomes for gut diseases like IBD [75].

Conclusion

Nanoparticles (NPs) have significantly advanced the field of drug delivery, particularly within the gastrointestinal tract (GIT), where they offer transformative potential for treating various disorders. Their unique properties, such as their nanoscale size, surface chemistry, and ability to be engineered for specific functions, enable precise drug targeting and controlled release that surpass traditional methods. Recent innovations have highlighted the effectiveness of NPs in addressing the challenges of GIT drug delivery. For instance, advancements in pH-sensitive and enzyme-responsive NPs have improved the targeting and efficacy of treatments for conditions like inflammatory bowel disease (IBD) and colorectal cancer. These technologies allow for more effective localization of drugs to inflamed areas and the reduction of systemic side effects. Additionally, lipid-based NPs, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have demonstrated enhanced stability and drug retention, further optimizing therapeutic outcomes. Despite these advancements, several challenges remain. Issues such as premature drug release, variability in patient responses, and difficulties in targeting specific bacterial strains or microbes need to be addressed. Moreover, the interaction of NPs with the gut microbiota and the physiological conditions of the GIT can impact their efficacy. Future research should focus on refining NP design to enhance targeting specificity, control drug release more effectively, and better navigate the complexities of the GIT environment. In conclusion, while nanoparticle technology has made substantial

progress in improving drug delivery for GIT disorders, continued innovation and research are crucial. By addressing existing challenges and leveraging the full potential of NP technology, significant advancements in personalized medicine and therapeutic efficacy are anticipated, leading to improved management of gastrointestinal diseases and overall patient outcomes.

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