

Pathophysiology of IBD as a Key Strategy for Polymeric Nanoparticle Development

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Inflammatory bowel disease (IBD) is a complex chronic inflammatory disorder of the gastrointestinal (GI) tract with an uncertain etiology. Currently, IBD therapy relies on the induction of clinical remission followed by maintenance therapy using anti-inflammatory drugs and immunosuppressants; however, a definite cure of the disease is still out of scope. Established approaches are characterized by adverse drug-related side effects that can even be potentially life-threatening. In contrast, increased interest and remarkable scientific progress in targeted drug delivery systems offer a promising approach to reduce systemic adverse events, delivering the therapeutic substances only to inflamed tissue. All alteration in gastrointestinal barrier integrity, especially a disturbed epithelial barrier, a unique pattern of the receptors on cell surface and/or an oxidative stress milieu in inflamed areas can be used as effective approaches for targeted and controlled drug delivery. Hence, this review focuses on the pathophysiology of the inflamed GI tract as a potential strategy for targeted polymeric nanoparticles for IBD treatment. Interdisciplinary efforts between the polymeric chemistry and gastroenterology/immunology promise to create novel synergies that improve the development of effective nanoparticle systems with significant clinical impact. In this regard, the current challenges in the clinical translation of promising nanomedicine are also discussed.

1. Introduction

1.1. Established Strategies in IBD Treatment

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders that dramatically change the lives of millions of patients.^[1,2] CD is characterized by a transmural inflammation from the mouth to the anus, while UC is a chronic inflammation of the colorectal mucosa.^[3,4] While the etiology of IBD is still unknown, genetic predispositions, microbiome–host interactions, or the environment play an important role in its multifunctional pathogenesis.^[5,6] There are a number of treatment strategies currently available for IBD patients. These depend on several factors, including the severity of CD or UC, associated diseases, previous treatment, age, and treatment aim.^[3] The focus of IBD treatment is to inhibit the immune-inflammatory cascade and to induce and maintain clinical remission.

Management of IBD treatment includes

aminosalicylates (mesalamine, balsalazide, sulfasalazine), orally or parenterally applied corticosteroids, immunosuppressants (azathioprine, mercaptopurine, methotrexate, and/or calcineurin inhibitors), intravenous biologic drugs (antibodies against TNF- α , $\alpha 4\beta 7$ integrins, IL-12/23 and/or IL-23), and small molecules (JAK inhibitors and/or sphingosine-1-phosphate receptor modulators).^[3,7–10] While there is a huge list of possible treatment regimes, nowadays there is no cure for the disease, which can control the clinical remission and improve the life conditions of IBD patients.

1.2. Limitations of Conventional Drug Delivery System in IBD Treatment

Conventional drug delivery systems, such as suppositories, foams, enemas, tablets and injectables, have several limitations. They often lack specificity, have high toxicity and require high drug dosages. Additionally, while biologics demonstrated very promising clinical results, 30–50% of patients do not respond to biologics or may develop neutralizing antibodies that lead to a secondary loss of response.^[7,11] Moreover, patients with IBD face an extensive list of mild to moderate drug related side effects, including cancer, infections including opportunistic infections,

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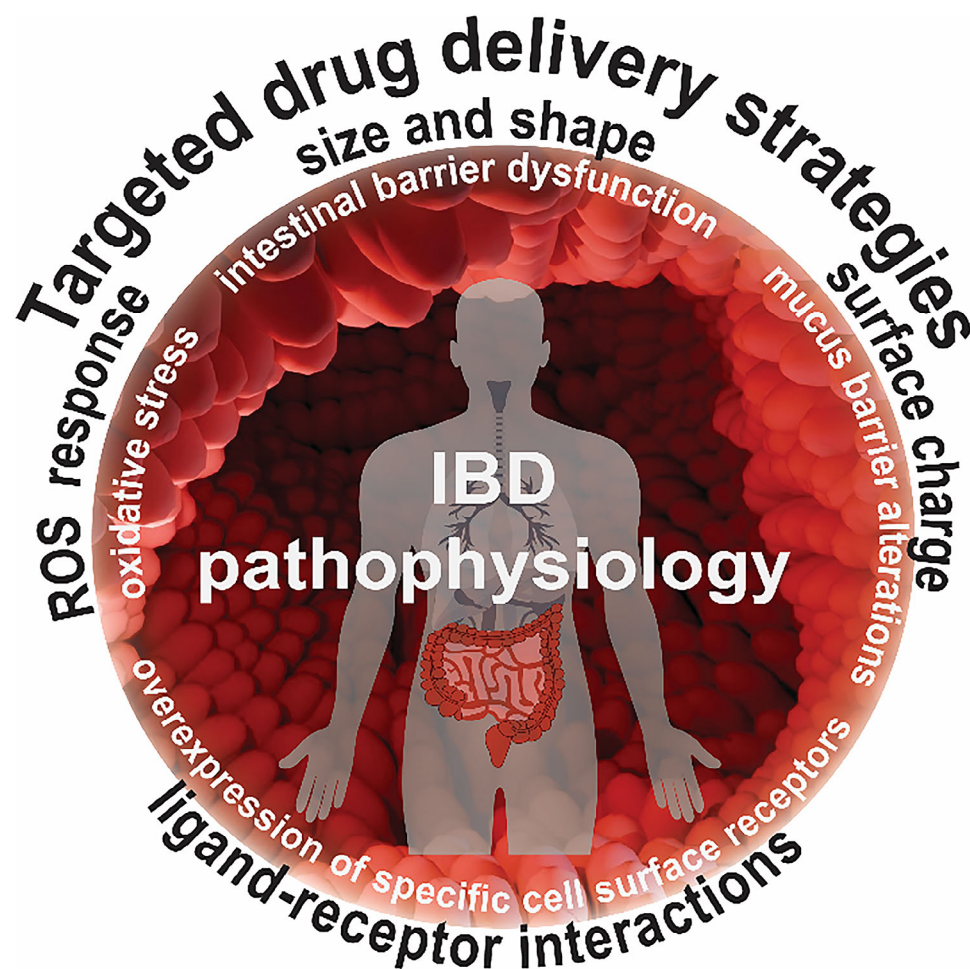


Figure 1. Correlations between pathophysiological changes during IBD and targeted drug delivery strategies.

glaucoma, cataracts, tremor, osteoporosis, osteonecrosis, hepatic fibrosis, hypersensitivity pneumonitis or hepatitis, myopathy, gingival hyperplasia, seizures, hypertension, hyperglycemia, emotional disturbances, weight gain, etc.^[7,11–13] This extensive list of adverse reactions, together with repeated surgery, highlights the urgent need for novel treatment approaches and therapeutic options, as well as new drug delivery systems.^[4,14,15] In contrast to conventional drug delivery systems, nanoparticles can be fabricated for high specific gastrointestinal targeting and controlled drug release. In principle, nanoparticles could potentially cover the drawbacks of conventional therapeutic options.

Here, in this review we focused on polymeric nanoparticles as drug delivery systems in the context of the pathophysiology of IBD. Polymeric nanoparticles offer several advantages as they can be fine-tuned and tailored in their design, shape, and size, or adapted by sophisticated modification.^[16] At the same time, alterations in the GI tract during IBD can provide the opportunity for such nanoparticles to target the inflamed areas of the intestine, releasing the encapsulated drug selectively at the targeted cells. Since the immune-inflammatory cascade alters the structural and functional characteristics of the GI tract, it is critical to consider these changes during the fabrication and modification of nanoparticles. Ligand-modified nanoparticles can ac-

tively target cells with increased expression of specific surface receptors. In addition, stimuli-responsive nanoparticles can be exploited due to oxidative stress and the abnormal release of reactive oxygen species (ROS) in the inflamed intestine. Thus, a thorough understanding of the pathophysiology of IBD is essential for the development of highly effective polymeric nanoparticles for drug delivery (**Figure 1**).

It is noteworthy that there are currently no approved medications for patients with IBD that incorporate nanoparticles. However, numerous smart delivery systems have demonstrated promising results in vivo experiments. The aim of this review is to provide a summary of the current progress in the field of nanomedicine for potential IBD therapy, with a particular focus on polymeric nanoparticles and the pathophysiological changes observed in patients.

2. Polymeric Nanoparticles as a Nanomedicine Strategy for IBD Therapy

Nanoparticles as drug delivery systems can open the opportunity for insoluble hydrophobic drugs to reach the inflamed tissue, reduce its cytotoxicity, and optimize drug pharmacokinetics. Additionally, nanoparticles can safeguard the drug disintegration

Table 1. Comparison of nanoparticles.

Nanoparticles	Advantages	Challenges	Ref.
Polymeric (polymersomes; polymeric micelles; dendrimers, etc.)	<ul style="list-style-type: none"> ✓ Smart drug delivery ✓ Spatial and temporal controlled drug release ✓ Sustained drug release ✓ Diverse and highly sophisticated functionality and design ✓ Controllable size, shape, and surface charge ✓ Easy surface modification ✓ Suitable for hydrophobic and hydrophilic drugs ✓ High loading efficiency ✓ Stimuli response 	<ul style="list-style-type: none"> • Safety issues • Complexity • High cost • Scalability issues 	[16,17,23]
Inorganic (quantum dots; silica, iron oxide, gold nanoparticles, etc.)	<ul style="list-style-type: none"> ✓ Unique electrical properties ✓ Size and geometry ✓ Good drug loading capacity 	<ul style="list-style-type: none"> • Toxicity risks • Limited solubility 	[17,24,25]
Lipid-based (liposome, lipid nanoparticles, etc.)	<ul style="list-style-type: none"> ✓ High bioavailability ✓ Suitable for hydrophobic and hydrophilic drugs ✓ Simple formulation 	<ul style="list-style-type: none"> • Low encapsulation efficacy • Stability • Easily clearance by the lymphatic system 	[17,26]

in the harsh environment of the GI tract. Thus, nanoparticles improve the bioavailability of the drug while simultaneously reducing the non-specific distribution of the drug within the body. The variable localization of inflammation in ulcerative colitis and Crohn's disease represents a significant challenge for the development of targeted therapeutic strategies. There is a clear requirement for selective targeting and drug release within the inflamed tissue, with minimal interaction with the healthy intestine.^[17,18] The successful targeting of inflamed sites in IBD is depending on several factors, including physiological functions and the extent of inflammation, as well as the physicochemical parameters of nanoparticles.^[19] The shape of nanoparticles, hydrophilicity, their surface charge and the reactive moieties, play an important role in determining the efficacy of the nanoparticles as drug delivery vehicles. It is essential that nanoparticle-based drug delivery systems for the IBD treatment are biodegradable, are able to target specific cells, and release the drug exclusively within the region of the intestine affected by inflammation. The inflamed mucosa of patients with IBD exhibits notable differences from healthy tissue. These differences can be leveraged in a range of strategies for nanoparticle fabrication.^[17,20,21]

Nanoparticles are typically composed of polymers, lipids, metals, etc. It is essential to consider both the advantages and limitations of these materials when developing new nanoparticles (Table 1). Currently polymeric nanoparticles represent the biggest part of approved nanoparticle medications in the global market (35%) compared to lipid-based (29%), nanocrystals (26%), and nonpolymeric nanoparticles (10%).^[22]

The polymeric nanoparticles could protect the loaded proteins,^[27] bioactive molecules^[28–32] from the degradation in the harsh environment of GI tract, thereby maintaining the effective bioavailability and targeted delivery in the inflamed tissue. The self-assembly of polymers with polyphenols enhances the bioavailability and absorption of polyphenols. Polyphenols, including catechin, tannic acid, quercetin, curcumin, rosmarinic acid, and others, reduce inflammation and scavenge ROS. Polyphenol polymer assemblies show promising results in recent studies on the treatment of IBD. Furthermore, the physicochemical properties of polyphenols enhance the loading

efficacy of mRNA and proteins, thus providing a potential therapeutic strategy for the treatment of colitis.^[33–35]

The most used nanoparticles for possible IBD treatment based on natural polymers are chitosan, alginate, hyaluronic acid, and pectin.^[36–39] Polysaccharides have high bioavailability, biocompatibility, low toxicity, biodegradability in the colon, that is crucial for IBD therapy.^[37,39,40] Chitosan and its derivatives as a pH-sensitive *N*-succinyl chitosan demonstrated their ability to improve the therapeutic efficacy of water-insoluble drugs.^[31,36,41,42] Thus, natural polymers offer an attractive source for the development of drug-delivery systems. However, several challenges remain, including the issue of batch-to-batch variation, the possibility of an immune response and the limited tunability of the properties of natural polymers.^[16,43] Synthetic polymers, in contrast, offer a vast array of options for the manipulation of their chemical composition, molecular weight, and the alteration of end groups through the integration of functional ligands via diverse polymerization techniques.^[21,40,44–46] Moreover, the diverse range of polymer architectures provides the ability to regulate the morphology of assembled nanoparticles. Additionally, reactive groups can be integrated into the polymer side or main chain, which react upon a stimulus and enable the local release of encapsulated drugs from corresponding nanoparticles in a targeted manner within the colonic mucosa. For instance, polymer disintegration and degradation can be initiated in a particular microenvironment (pH, ROS, enzymes). The diverse design and tunability of polymeric nanoparticles improve the targeting of inflamed tissue, thereby representing a promising material for pharmacological applications. At the same time, the pathophysiology of IBD must be considered during the design of nanoparticles.^[47–49]

3. pH in the GI Tract and Transit time as Approach for pH-Dependent Nanoparticles

The physiological microenvironment of the GI tract represents a significant challenge for the effective oral drug administration. The pH value differs between the stomach (pH 1.5–3.5), the small intestine (pH 5.5–6.8) and the colon (pH 7.0–8.0).^[50,51] Thus, pH-dependent alterations of drug bioavailability, absorption,

stability, and intestinal permeability may occur. To eliminate the harsh microenvironment of the GI tract, pH-sensitive polymers can be used for enteric coating, effectively covering the drug and enhancing its bioavailability.^[52,53] Nowadays, solid oral dosage forms coated with poly(methacrylic acid-co-methyl methacrylate) resins (Eudragit L, S, and F) are successfully translated into clinical practice. Eudragit polymers represent the most widely used coating materials with pH-responsive properties for the targeted release of drugs at colonic pH.^[40,48,52,54,55] pH- and time-dependent Eudragits are frequently applied as polymers to reduce the initial drug release and absorption in the upper sections of the GI tract, thereby enhancing the drug delivery to the inflamed colon.^[42] Y. Turanlı and F. Acartürk, for example, employed anionic polymethacrylate Eudragit S100 (ES100) as a pH-dependent polymer and cationic polymethacrylate Eudragit RS100 as a time-dependent polymer in the fabrication of budesonide-loaded nanoparticles.^[56]

Additionally, a number of other polymers exhibit comparable pH-responsive properties. For example, polymers as pectin, hydroxypropyl-methylcellulose phthalate, hydroxypropyl-methylcellulose acetate succinate, cellulose acetate phthalate, acetate trimellitate, and polyvinyl acetate phthalate, o-phenylene dimethyl acetate cellulose, chitosan, PLGA, etc. might degrade when pH changes or under other specific conditions.^[36,57–61] A recent study has demonstrated that pH-soluble PLGA nanoparticles loaded with sorting nexin 10-shRNA plasmid have the potential to reduce intestinal mucosal damage and inflammation in both acute and chronic IBD mice models following oral administration.^[62] Tollemeto et al. fabricated polymerosomes from poly(ethylene glycol)-poly(caprolactone-gradient-trimethylene carbonate) (PEG-p(CL-g-TMC)) amphiphilic block copolymers for the intestinal delivery of immunosuppressants. The polymeric vesicles displayed stability at low gastric pH, undergoing disintegration at the pH of the small intestine.^[63]

The physical crosslinking of the natural polysaccharide polymers, such as sodium alginate and chitosan, forms a biodegradable and pH-sensitive 3D hydrogel structure.^[64] The gel protects the drug from degradation, thereby increasing its bioavailability and enhancing its ability to achieve colon-specific targeting.^[36] The hydrogel-encapsulated nanoemulsions represent an innovative strategy for colon-specific targeting and controlled drug release.

Despite the current dominance of Eudragit and analogous polymers in pH-sensitive encapsulation, these formulations are limited in their capability to facilitate targeted drug release within the GI tract. These polymers only protect the drug in the stomach and release it in specific intestinal segments. However, the released drug affects all areas of the intestine, so targeting only inflamed areas is not possible with these polymers. Therefore, there is an unmet need for the development of smart nanoparticles with enhanced selectivity for inflamed colon tissue.

4. Mucus Barrier Alterations as Target for Surface Modified Polymeric Nanoparticles

The intestinal barrier functions as the first line of defense, playing a pivotal role in maintaining homeostasis and protect the

body from microbial and toxic agents. Furthermore, secretory immunoglobulin A, antimicrobial proteins and commensal bacterial flora maintain immunological defense mechanisms.^[65] The transportation of antigens from the lumen to the lymphoid tissue is a key function of microfold (M) cells, and thus represents a vital aspect of mucosal immunity. These properties of M cells are especially relevant in the context of oral mucosal vaccination.^[66–68] Furthermore, the elevated number of M cells in CD and enhanced expression of IBD-susceptible genes in patients with UC may indicate a significant contribution of M cells to the pathogenesis of IBD.^[69]

A mucus layer that coats the epithelium in the GI tract creates an additional barrier that helps maintain optimal physiological conditions. The mucus layer contains water, mucins, globular proteins, salts, DNA, lipids, cells and cellular debris. Even minor alterations in the composition of these components can result in significant changes in the physicochemical properties, which may ultimately lead to the development of a disease state.^[70] Goblet cells produce secretory and membrane-associated mucins, predominantly MUC2, on the luminal surface of the epithelium. Mucins are glycoproteins with a high molecular weight and a carbohydrate density of over 70%. They form a brush-like structure with O-linked oligosaccharides and N-glycan chains, coupled with a protein backbone. Glycoproteins of mucins are responsible for the cohesive and adhesive properties (Figure 2).^[70–72] The physicochemical properties of the mucus layer, including pore size (50–1800 nm), viscoelasticity (87 mEq L⁻¹ for colon), pH, ionic strength (1.1–25.816 mPa s for small intestine), and charge, determine the penetration of drug delivery systems. The high density of sulfate and sialic acid groups in glycoproteins of mucin contributes to a negative surface charge. Additionally, mucus contains hydrophobic and hydrophilic domains. Therefore, the rigidity, the size and the surface charge of nanoparticles regulate the possibility to cross this barrier.^[16,70,73–75]

The concept of mucoadhesion and mucopenetration is a fundamental aspect of enteral drug delivery. It has been widely discussed, implemented and some approaches are currently in clinical use.^[76,77] A number of mucus-interacting systems have already received FDA approval for use in the treatment of various conditions. These include mucoadhesive Carbomer (MuGard, ProctiGard) for the treatment of mucositis, cellulose (diphenoxylate hydrochloride) for the treatment of diarrhea, and mucus-penetrative Pluronic (SP1049C) for the treatment of gastric carcinomas.^[78]

During IBD, the number of goblet cells undergoes a marked decline, resulting in alterations to mucin production. At the same time, the number of immature goblet cells, which secrete incomplete mucus, increases. This consequently results in the disruption of the mucus layer that provokes the penetration of pathogens and bacteria, which induce inflammation and therefore ulcerative colitis.^[80–86] The alterations during IBD lead to a reduction in the electrostatic negative charge of this layer. Additionally, the pH level in the colon of patients with active UC is reduced in comparison to a healthy state. The reduction in pH level results in alterations to the physicochemical properties of the mucus layer.^[87] Furthermore, it was demonstrated that an elevated number of sulfate-reducing bacteria within the colonic mucosa of patients with UC can influence the disruption of disulfide bonds

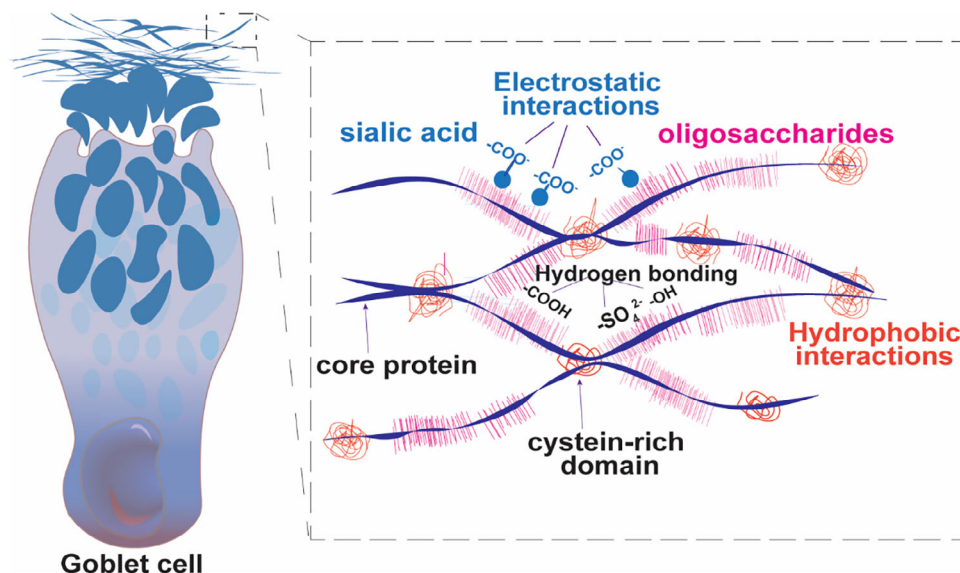


Figure 2. Schematic illustration of potentially mucoadhesive elements of mucin glycoproteins. Adapted from.^[79]

between mucin 2 (MUC2), which results in enhanced mucosal permeability.^[88,89]

It is noteworthy that the amount of mucus layer differs between patients with CD and UC. UC is characterized by decreased mucus layer (due to goblet cell depletion) and reduced mucin glycosylation and sulphation. In contrast, Crohn's disease is characterized by increased mucin production (most probably due to goblet cell hyperplasia) and its abnormal glycosylation.^[71,83,84] At the same time, oligosaccharide chain length of mucin is 50% shorter in patients with CD compared to healthy individuals which results in a reduction in the viscoelasticity of mucin. Moreover, the expression of mucins in patients with Crohn's disease is dependent on the state of disease activity, with a correlation between increased activity scores and elevated mucin expression. This is in contrast to patients with UC, where mucin expression is not associated with disease activity.^[90]

Having this aspect in mind, it is essential to evaluate the design of nanoparticles that can interact with mucus components, as this interaction may alter the targeting efficacy (**Figure 3**).

4.1. Electrically Neutral Nanoparticles

The physicochemical properties of mucus permit the effortless penetration of nanoparticles that are nearly electrically neutral, hydrophilic, and mucus inert. These nanoparticles can thus reach epithelial cells that are located beneath the mucus layer.^[16] It has been shown, that the polyethylene glycol (PEG) modification of nanoparticles (PEGylation) creates almost an electrically neutral surface, which diminishes the interaction with mucin and thus enhances permeability of the mucosal barrier.^[16] Consequently, if the rapid penetration of the mucosal barrier is necessary, the use of nanoparticles with a high density of PEGylation can lead to more favorable outcomes.^[91–93] In particular, a high density of low-molecular-weight PEG (2kDa) demonstrated a rapid mucus penetration.^[94,95] In contrast, surface modification of nanoparti-

cles with 5 kDa PEG resulted in increased hydrophilicity and consequently decreased interaction with inflamed tissue.^[92] By eliminating any unfavorable interactions with mucus, PLGA-PEG nanoparticles are capable of locally delivering an encapsulated monoclonal antibody against TNF- α into inflamed gastrointestinal tissue.^[92]

An alternative option to PEGylation could be electrically neutral and hydrophilic zwitterionic polymers, such as poly(carboxybetaine) and poly[2-(*N*-oxide-*N*,*N*-diethylamino)ethyl methacrylate], which also demonstrate mucus-penetrating properties.^[96–99] Thus, it was shown that laminarin zwitterionic carboxylate and sulfonate improved gut dysbiosis and intestinal barrier function in DSS-induced colitis.^[100]

Furthermore, the coating of nanoparticles with FDA-approved Pluronic (copolymers of poly(ethylene glycol)-poly(propylene oxide)-poly(ethylene glycol) (PEG-PPO-PEG)) may markedly diminish the physicochemical interaction between nanoparticles and mucin glycoproteins, consequently enhancing permeability through the mucus.^[94,101,102] Thus, the functionalization of PLGA nanoparticles with Pluronic F127 (a polyoxyethylene-polyoxypropylene triblock copolymer) significantly enhanced their mucus-penetrating capacity and nanoparticle accumulation in inflamed colon tissue.^[103,102]

4.2. Negatively Charged Nanoparticles

In contrast to electrically neutral nanoparticles, particles with a surface charge demonstrate electrostatic interactions with the mucosal barrier. The use of charged nanoparticles may be advantageous in applications where the distribution and retention of drugs within mucus layer is desired. The damaged epithelium with a reduced mucus layer and an accumulation of neutrophils in this area is characterized by a cationic surface. Moreover, in the inflamed mucosa of colitis patients, there is an increased

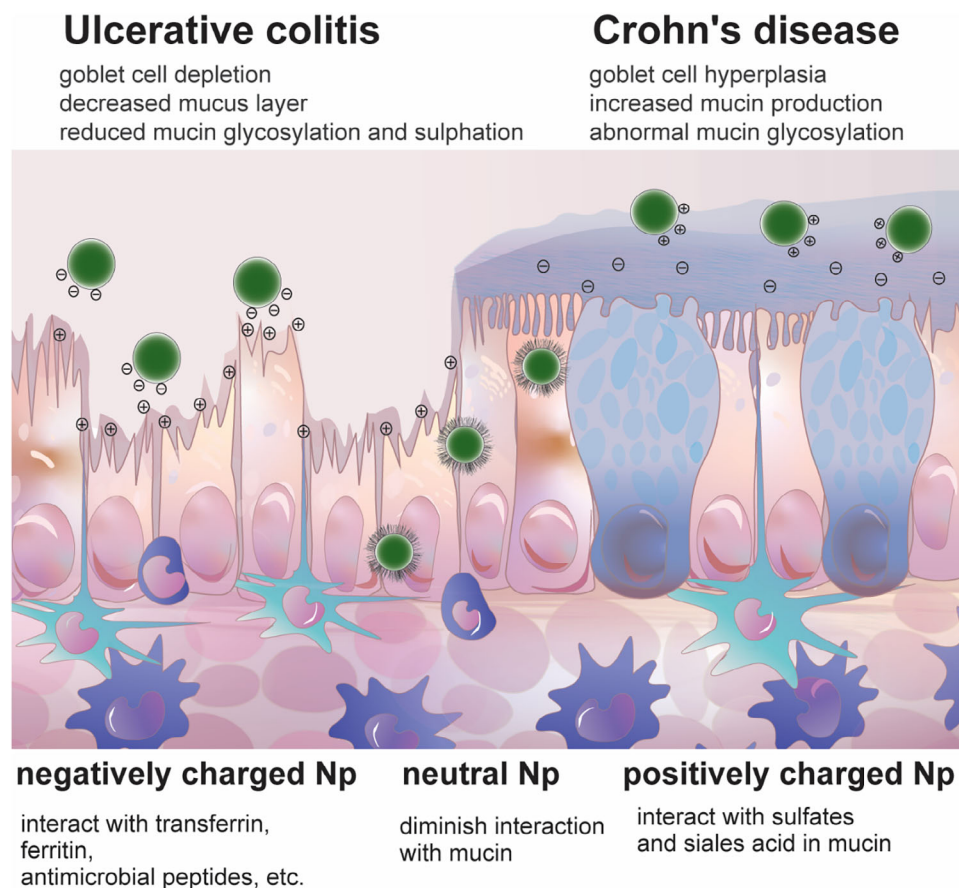


Figure 3. Schematic illustration of electrostatic interactions of nanoparticles with mucus and epithelial cells.

expression of the transferrin receptor on the surface of epithelial cells. Together with the exposed positively charged proteins (transferrin and eosinophil cationic proteins), these can be targeted by the negatively charged particles (Figure 3).^[104–106] The cationic surface accumulates negatively charged nanoparticles via biophysical electrostatic interactions.^[92,106–110] Furthermore, the anionic charge on the surface of the nanoemulsion prevented the aggregation of nanoparticles, thereby stabilizing the system.^[111]

Sato et al. fabricated cyclosporine A (CsA) loaded polymeric nanoparticles based on polystyrene-block-polyacrylic acid (PAA-CsA). PAA has mucoadhesive properties due to electrostatic interaction with mucus, which improves CsA bioavailability.^[112] Thus, CsA loaded polymeric improved pharmacokinetics of orally dosed CsA in vivo experiments.^[112]

Complexation between cationic and anionic polymers can also be used to produce polymeric nanoparticles. The anionic polymers are often used for the final coating on the surface to create a negative surface charge on the final nanoparticles. For example, to increase the interaction with the inflamed mucosa the cationic polyethyleneimine (PEI) nanoparticles were self-assembled with the natural polyanionic polysaccharide sodium alginate.^[113] Dong et al. used PEI polymer to achieve high dexamethasone loading rates, while sodium alginate enhanced the effective interaction of these nanoparticles with the inflamed mucosa after rectal administration.^[113] Sodium alginate was also

used in the formation of a multilayer polyelectrolyte coating structure with chitosan to improve the interaction of the nanoparticles in mucus. Effective targeted delivery of 5-aminosalicylic acid to the inflamed colon was demonstrated using these negatively charged nanoparticles.^[114] Most likely, the carboxyl groups of alginate could theoretically form a hydrogen bond with the sialic acid in mucin.^[77] High targeting to inflamed mucosa was also observed with the negatively charged pectin-based nanoparticles.^[38]

Nanoparticles based on the self-assembly of polymers with polyphenols demonstrated clear colon targeting due to the tissue adhesion properties of the polyphenols.^[115] For example, the phenolic hydroxyl groups of tannic acid facilitate the bioadhesion of polyphenol polymer nanoparticles in an inflamed colon.^[116] Wang et al. used tannic acid and PEG-containing polymers for self-assembling supramolecular nanoparticles to load the proteins (as anti-TNF antibodies).^[117] These negatively charged polymeric nanoparticles showed a higher interaction with the transferrin-coated surface compared to the mucin-coated surface, which is important for targeting inflamed mucosa. Interestingly, in contrast to intravenous administration with accumulation in the liver, spleen and kidney, only orally administered nanoparticles showed anti-TNF antibody accumulation in the colon.^[117] Biologics are a promising option for IBD treatment. However, up to 50% of patients do not respond to antibodies and there is a risk of serious side effects.^[4] Administration of antibodies orally

can improve their bioavailability and reduce severe side effects following systemic administration of antibodies.

4.3. Positively Charged Nanoparticles

Since diarrhea is very common in IBD, significant accumulation of nanoparticles on the surface of the mucus layer of inflamed sites may be a useful approach.^[118] This gives the nanoparticles a better chance of releasing their drug in the inflamed area before they are cleared. The positively charged nanoparticles demonstrate their mucoadhesive properties by interacting with the sulphates and sialic acid in the carbohydrates on the surface of the mucins (Figure 3). The spatial charge distribution and presence of hydrophobic moieties are also key factors.^[86,119–121]

Chitosan is often used to produce positively charged polymeric nanoparticles. These nanoparticles exhibit strong mucoadhesive properties through electrostatic interactions with mucus.^[42,122,123] However, to increase the permeability of chitosan nanoparticles through mucus and to enhance the internalization of nanoparticles into epithelial cells, N-2-Hydroxypropyl trimethyl ammonium chloride chitosan can be functionalized with hydrophobic palmitic acid and cysteine.^[124] In order to reduce the toxicity of high molecular weight chitosan nanoparticles, low molecular weight, water-soluble chitosan nanoparticles can be used. The mucoadhesive properties of these positively charged nanoparticles may prolong the interaction time with the inflamed mucosa, and bilirubin attached to these nanoparticles could regenerate the disrupted epithelial barrier.^[125]

It is important to note that cationic polymers can be used for successful oral or rectal delivery of siRNA.^[44,126] Although the etiology of IBD is unknown, the genetic predisposition plays an important role.^[5] From this perspective, gene delivery to inflamed tissue may improve the condition of IBD patients. Cationic nanoparticles fabricated by direct copolymerization of catechol and amine monomers via radical and ring opening metathesis polymerization demonstrated siRNA delivery after rectal administration.^[44]

The concept of mucoadhesive and mucopenetrative nanoparticles is surrounded by intense discussions, challenges and unanswered questions. The principal advantage of mucoadhesive nanoparticles is their capacity to exert a prolonged effect. However, mucoadhesive nanoparticles adhere to all areas, including healthy intestine, which limits their targeted properties. Nevertheless, there is debate as to whether their adhesion is stronger to inflamed tissue compared to healthy tissue. Additionally, it is important to note the difference between UC and CD and the relatively fast (1 h for the inner layer) spontaneous turnover of mucus, with the estimated range of mucus growth around 240 $\mu\text{m h}^{-1}$.^[78,112,89]

5. Intestinal Barrier Dysfunction for Size and Shape dependent Penetration of Nanoparticles

To target cells in the lamina propria, nanoparticles have to overcome not only the mucus barrier but also the epithelial barrier. The structure of the epithelial layer determines its defense function. Paracellular transport, tissue integrity and barrier func-

tion are regulated by the apical junction complex (AJC) that connects epithelial cells to each other. Tight junctions (zonula occludens (ZO)), adherens junctions and desmosomes form the AJC.^[127,128] Tight junctions (TJ) consist of transmembrane proteins – claudins, occludins and tricellulin that form the selectively permeable paracellular barrier.^[129,130] However, during IBD, the structural changes and reduction in AJC increase the transcytosis of antigens, pathogens or microbial products from the lumen. This triggers the cascade of immune responses that further damage the intestinal barrier.^[131,132] Together with apoptosis of epithelial cells, disruption of the inner mucus layer alters the intestinal barrier functions in patients with IBD.^[132–134] Permeability dysfunction of the intestinal barrier provokes inappropriate immune response in the lamina propria that continuously destroys the mucosal tissue.

At the same time, alterations and damage of the intestinal barrier can be a crucial strategy for selective drug delivery into inflamed areas of the intestine and therefore a valuable reduction in drug-related severe complications.^[135–137] For example, patients with UC have a disturbed epithelial barrier, epithelial gaps and permeability dysfunction in the inflamed site of the colon, providing an opportunity for nanoparticles to accumulate in this area due to the epithelial Enhanced Permeability and Retention (epEPR) effect (Figure 4).^[20,138–143] Thus, size-dependent accumulation of nanoparticles in the inflamed colon was often demonstrated in *in vivo* and *ex vivo* experiments.^[19,144,145] The most commonly used nanoparticles are spherical in shape. However, recent research has focused on nanoparticles with different shapes, including elongated structures.^[21,146] Compared to spherical nanoparticles, rod-shaped polystyrene nanoparticles have a higher uptake rate by intestinal cells.^[147] We also demonstrated that wormlike polymeric nanoparticles (20.5 nm diameter, 1 μm length) assembled from the amphiphilic block copolymer poly(butyl acrylate)-block-poly(ethylene oxide) are selectively taken up into inflamed colonic mucosa from IBD patients, whereas vesicles and spherical nanoparticles are non-selective for inflamed tissue.^[21] Similar results have been demonstrated in a nude mouse model of colorectal cancer using poly(1,4-butadiene)-block-poly(ethylene oxide) polymeric wormlike nanoparticles with an improved rate of diffusion through the intestinal mucosal barrier.^[148] In addition, elongated nanoparticles have a high drug loading capacity, high surface area and the reptation behavior of flexible structures allows them to penetrate deeper into the tissue.^[149,150]

6. Oxidative Stress in IBD as Target for ROS-Sensitive Nanoparticles

Sites of inflammation in IBD are characterized by abnormal production of free radicals created by electron reduction of O_2 . In principle, reactive oxygen species (ROS) – superoxide anion, hydrogen peroxide, hydroxyl ion, hydroxyl radical etc., – play a crucial role in homeostasis. Cells are able to catabolize ROS enzymatically (superoxide dismutases, catalases, glutathione peroxidases and reductases, etc.) and non-enzymatically (ascorbate, pyruvate, etc.). However, an imbalance and overproduction of ROS in epithelial and immune cells has been implicated in the pathogenesis of IBD. Inappropriately high levels of ROS can be cytotoxic and induce oxidative stress.^[151–153] ROS escalate

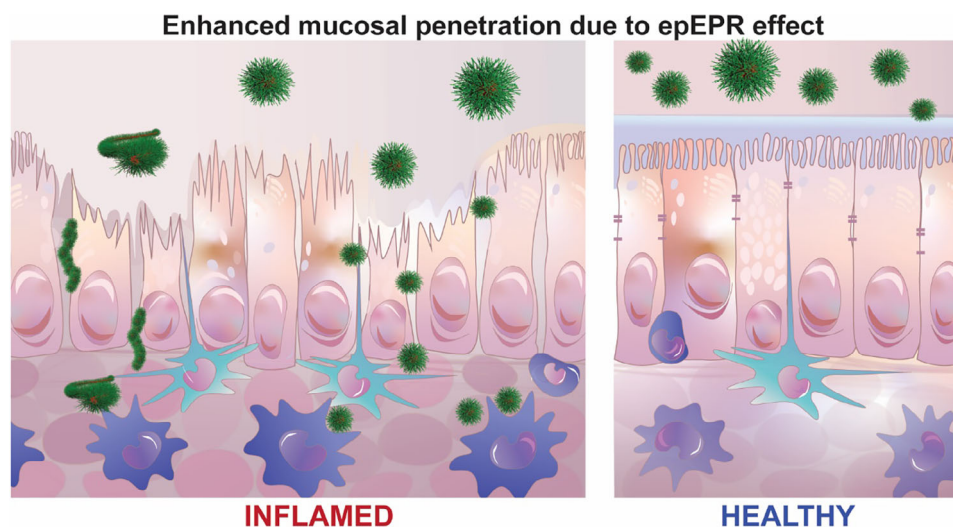


Figure 4. Schematic illustration of intestinal barrier dysfunction and the epithelial enhanced permeability and retention (epEPR) effect that provide the opportunity for small spherical nanoparticles and nanoparticles with elongated shape accumulate in the inflamed colon.

intestinal mucosal damage by inducing epithelial permeability via altered TJs and microbial dysbiosis. These dramatically undermine the function of the epithelial barrier.^[154–156] Thus, scavenging free radicals in the inflamed part of the GI tract is one of the strategies in IBD therapy.^[157,158] For example, antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) can be encapsulated into nanoparticles formed from amphiphilic modified cyclodextrins and delivered to the inflamed part of the GI tract.^[159] Zeng et al. demonstrated the high bioavailability and therapeutic efficacy of these nanoparticles in induced animal colitis. They significantly inhibited inflammation by reducing ROS levels.^[159] Significant amelioration of DSS-induced colitis via rectal administration was demonstrated by SOD-loaded supra-amphiphilic nanoparticles based on boronated polylysine with a lipidated catechol.^[158] An alternative approach was used by Liang and coworkers. They encapsulated SOD and CAT in polymer shells by using a surface-initiated *in situ* polymerization reaction to obtain capsules that were suitable for oral administration.^[27] Nanoparticles made from ROS-scavenging hydroxyethyl starch-curcumin conjugates demonstrated their ability to degrade in response to α -amylase overexpressed in the inflamed colon.^[160] Moreover, their negative charge and ability to accumulate in the inflamed colon via the epEPR effect demonstrated their colon targeting function.^[160] ROS scavenging was also demonstrated by phenolic groups in natural polyphenols.^[161] ROS scavenging was shown in colitis-induced mice by pro-cyanidin and free iron, encapsulated in polyvinylpyrrolidone nanoparticles.^[162]

Oxidative stress in IBD also provides an opportunity to use ROS-sensitive nanoparticles. Thus, disulfide, diselenide, thioether, phenylboronic ester, thioketal are common examples of ROS-responsive linkers for drug-polymer conjugation or as the backbone of polymer.^[16] ROS-responsive polymeric nanoparticles disintegrate and change their morphology in a controlled manner in the presence of ROS, releasing their cargo at targeted sites and in targeted cells. (Figure 5). For example, we have shown that there is a significant correlation between excessive

ROS in monocytes isolated from patients with active IBD and the degradation of oxidation-sensitive polymeric nanoparticles formed from a biocompatible amphiphilic block copolymer with thioether moieties.^[163] Using similar thioether groups in a D- α -tocopherol-modified polyethylene glycol succinate-*b*-poly(β -thioester) copolymer, Tan et al. fabricated ROS-responsive nanoparticles that can change their size and release the drug at the site of oxidative stress.^[164] While PEGylation could improve nanoparticle penetration through mucus, it could also inhibit further cell internalization. To improve cell internalization of nanoparticles, de-PEGylation via a thioketal linker between PEG and PLGA in the presence of a high concentration of ROS may enhance further targeted drug release. Oral delivery of ROS-cleavable PEG-PLGA nanoparticles demonstrated targeted delivery of teduglutide, a glucagon-like peptide-2 analogue, in IBD model.^[165] In a recent study, ROS-responsive thioketal nanoparticles were used for the targeted delivery of tubastatin A to the inflamed colon of mice.^[166] A novel ROS-responsive nanoparticles fabricated from a phenylboronic esters modified carboxymethyl chitosan also demonstrated its degradation in the presence of ROS and amelioration of colitis in DSS mice by loading berberine into the nanoparticles.^[167] The utilization of a ROS-sensitive hydrogel, formulated from a diselenide-bridged arctigenin and chitosan conjugate, enabled the selective targeting of an inflamed colon and the restoration of the intestinal mucosal barrier.^[168] The oral administration of ROS-sensitive dopamine-coated berberine demonstrated notable adhesive properties and therapeutic efficacy in a DSS-induced colitis model.^[169]

Another approach is the scavenging of ROS and proinflammatory cell-free DNA (cfDNA) using polyethyleneimine (PEI) conjugated to antioxidant diselenide-bridged mesoporous organosilica nanoparticles. These nanoparticles demonstrated high cfDNA binding affinity and ROS-responsive degradation in murine colitis models (DSS and TNBS induced).^[170] Recently, novel ROS-sensitive polymeric nanoparticles were developed to deliver cinnamaldehyde prodrug intravenously and accumulate it in the in-

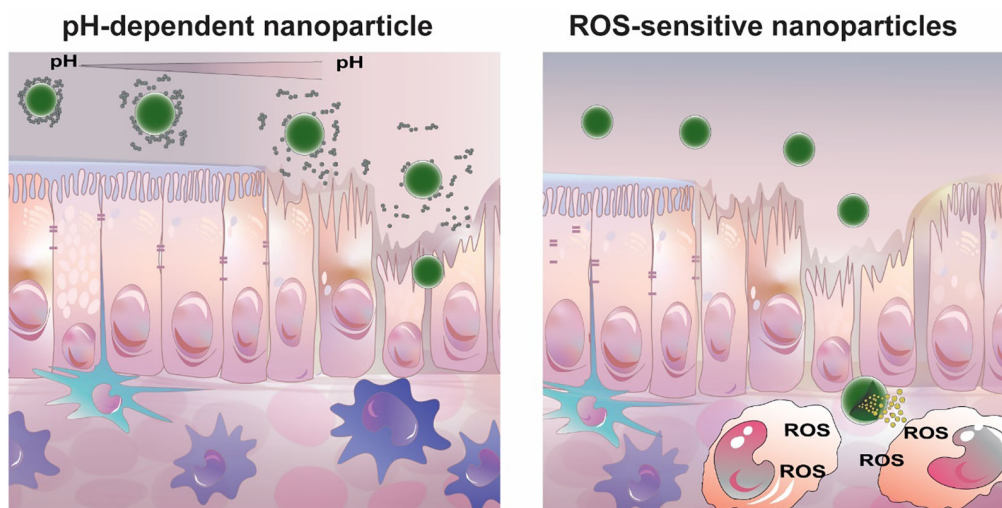


Figure 5. Schematic illustration of altered microenvironment of inflamed colon as an approach for nanomedicine strategies.

flamed colon. Cinnamaldehyde was conjugated to the polymer chain via a thioacetal linker to protect the cargo from uncontrolled release.^[171] The silica-containing redox copolymer poly[4-(2,2,6,6-tetramethylpiperidine-1-oxyl)aminomethylstyrene (PEG-b-siPMNT)] was used to prepare nanoparticles for effective retention of a hydrophobic drug (silymarin) in the colonic mucosa.^[30]

The use of the multiresponsive nanoparticles can be advantageous in the harsh environment of the GI tract. Thus, the pH- and redox-responsive natural-based polymeric nanoparticles were prepared based on angelica sinensis polysaccharide with urocanic acid and α -lipoic acid. Due to imidazole groups in urocanic acid, the nanoparticles are pH-responsive, while redox-responsive properties are obtained by disulfide bond breakage in α -lipoic acid.^[141] Moreover, these pH/redox responsive polymeric nanoparticles demonstrated colonic targeting and drug release after intravenous injection in DSS-induced colitis. By modifying glycogen with urocanic acid and α -lipoic acid, Xu et al. obtained pH- and redox-sensitive polymeric nanoparticles due to the presence of imidazole group in urocanic acid and disulfide bond in α -lipoic acid.^[28] These redox- and pH-sensitive nanoparticles demonstrated effective delivery of the natural bioactive component (ginsenoside Rh2) to the inflamed colon of DSS-induced colitis model.^[28] Another example of colonic pH/redox sensitive butyrate-rich nanoparticles were prepared from PEG block and Eudragit mimicking polymers for colonic targeting and selective release of magnolol in DSS-induced colitis mice.^[172]

ROS-sensitive polymers are an exciting area of research and a good example of the potential of nanoparticle-based delivery systems for selective and targeted drug release. Further interesting developments are certainly expected in the future. However, it is important to note that the effect of ROS-responsive polymers should not be demonstrated simply by adding *in vitro* H₂O₂ to cell lines, as is unfortunately often the case. Clear correlations between the physiological microenvironment at the site of inflammation and degradation of the ROS-sensitive nanoparticles must be demonstrated.

7. Overexpression of Specific Cell Surface Receptors as an Approach for Active Targeting

Nanoparticles can target inflamed tissue actively and passively. Passive targeting of the inflamed intestine could be achieved via the effect of increased permeability and retention of the epithelium and endothelium, and even passive targeting of immune cells has been demonstrated in inflamed human mucosa. By modifying the surface of well-tailored polymeric nanoparticles, it could be possible to actively target specific cells in the inflamed area of the intestine. Active targeting can improve selective drug delivery and the overall treatment approach.^[21,49,173]

Specific cell surface receptors and adhesion molecules are overexpressed on the surface of colonic epithelial, endothelial and immune cells in IBD. These include the mannose receptor, macrophage galactose lectin, transferrin receptor, folate receptor, CD98, CD44, dectin-1, peptide transporter 1 (PepT1) and F4/80. Nanoparticles modified with specific ligands which bind to these receptors and cell adhesion molecules can improve targeted drug delivery to inflamed tissue by reducing non-specific interactions with healthy tissues and cells. Ligand-modified nanoparticles trigger receptor-mediated endocytosis upon binding to specific receptors overexpressed on target cells.^[29,47,52,173–176]

7.1. Polysaccharides

Drug-loaded nanoparticles that can actively target inflamed tissue represent a potentially effective approach for the treatment of IBD. A number of different targeted cells have been identified for IBD treatment. The direct treatment of epithelial cells remains a challenging area of research. Currently, only a limited number of research groups are actively investigating this field.^[177,178] In contrast, the targeting of immune cells and the subsequent modulation of the immune response has emerged as a dominant approach within the field of nanomedicine.^[175,179–181]

For example, the CD44 is a known receptor that is overexpressed in inflammatory cells in colon tissue. Polymeric nanoparticles with hyaluronic acid (HA) can be applied for active targeting and nanoparticle endocytosis, as HA has a high affinity for CD44 receptors.^[29,52,182,183] Therefore, following oral administration of ES100-coated chitosan nanoparticles, ES100 is dissolved in the colon due to increased pH, resulting in the display of HA on the surface of the nanoparticles. The increased intestinal permeability at the sites of inflammation (eEPR effect) allows nanoparticles to penetrate through the disturbed epithelial barrier and reach the immune cells that have infiltrated the lamina propria of the inflamed tissue. Active targeting of macrophages is achieved due to the high affinity of HA for CD44, resulting in controlled drug delivery and improvement of experimental colitis.^[29,52,182] Chitosan-PLGA nanoparticles modified with HA ligands demonstrated active targeting of CD44 receptors and delivery of anti-miR-301a to the colon of DSS-induced colitis mice.^[182] The targeted properties and therapeutic effect of hyaluronan-functionalized PLGA-chitosan nanoparticles loaded with the immunosuppressant cyclosporine A were demonstrated in animal colitis and human colonic biopsies.^[107] A recent study by Uthaman et al. illustrates the potential of targeting CD44 receptors.^[184] They fabricated programmable micelles based on a self-assembling HA and stearic acid conjugates, with drug release properties via a ROS-responsive thioether linker. The micelles demonstrated effective targeting of the inflamed colon and drug release in DSS colitis mice upon oral administration.^[184]

The bilirubin-loaded HA-PLGA nanoparticles effectively targeted the colon in a UC mouse model, modulating epithelial cell proliferation and stem cell regeneration. The administration of these nanoparticles resulted in an increase in the number of Lgr5+ intestinal epithelial stem cells, which play a pivotal role in the modulation of intestinal epithelial regeneration during IBD.^[185,186]

7.2. Monosaccharides

While macrophages overexpress galactose and mannose receptors during the inflammatory process, nanoparticles with ligand-mediated targeting can be an effective strategy for targeting the inflamed intestine.^[187] Thus, galactosylated polymeric nanoparticles active target macrophage via galactose type-lectin-C (MGL-2) surface receptors. These stimuli-sensitive, biofunctionalized ES100/Pullulan coated d-galactose-PLGA nanoparticles were fabricated for dexamethasone delivery.^[188] Galactose-bound PLGA nanoparticles^[189] or galactosylated carboxymethyl chitosan polymeric micelles,^[190] can be utilized to achieve enhanced targeting of intestinal macrophages in inflamed regions.

An alteration in the intestinal barrier in IBD provides an opportunity to use glycocalyx-mimicking nanoparticles that can target inflamed sites of the colon due to glycocalyx-mediated interactions. It was demonstrated that the glycocalyx-mimicking nanoparticles target macrophages in the inflamed colon. The glycopolymers were synthesized through a random copolymerization process involving the methacrylamide forms of glucose, galactose, mannose, *N*-acetylglucosamine and *N*-acetylgalactosamine.^[191]

7.3. Peptide/Protein Ligands

During inflammation, the endothelial cells overexpress the cell adhesion molecules such as selectins, immunoglobulins, vascular cell adhesion molecule 1 (VCAM1) and intercellular adhesion molecule 1 (ICAM1).^[49] Thus, by modifying the surface of polymeric nanoparticles with a peptide that has a high binding affinity to a VCAM1, the effective targeting of inflamed tissue could be achieved. The example of peptide ligand modification is the recent work on the selective delivery of interleukin-1 receptor-associated kinase 4 inhibitor into inflamed tissue using modified by a peptide (VHPKQHRGGSKGC) poly(ethylene glycol)-block-poly(-caprolactone) nanoparticles.^[192] The intravenous administration of PLGA nanoparticles decorated with P-selectin-binding peptides effectively targets the inflamed colon.^[193] The expression of P-selectin is increased in vascular endothelial cells at the site of inflammation, which allows for the targeted delivery of nanoparticles to the affected area.^[194]

Macrophage targeting was also achieved after intravenous administration of peptide-functionalized polymersomes. TNF- α siRNA and dexamethasone sodium phosphate were co-encapsulated into a peptide-functionalized, reversibly cross-linked polymersomes made of an asymmetric triblock copolymer, poly(ethylene glycol)-*b*-poly(trimethylene carbonate-dithiolane trimethylene carbonate)-*b*-polyethylenimine (PEG-P(TMC-DTC)-PEI). The terminal PEG was modified with Thr-Lys-Pro-Arg. The pendant dithiolane rings in the P(TMC-DTC) block form a redox-sensitive disulfide bond, which is crucial for stimulus-responsive drug/siRNA release. Peptide-functionalized polymersomes targeted macrophages followed by GSH-triggered cytoplasmic drug/siRNA release. These polymersomes significantly prevented inflammation in DSS-induced colitis animals.^[195] Another example of ligand-modified polymeric nanoparticles is transferrin (Tf)-modified PEG-PLGA nanoparticles. These nanoparticles showed increased uptake by Caco-2 cells and colon targeting in colitis-induced rats, compared to unmodified nanoparticles.^[196]

The protein coating of nanoparticles plays a crucial role in their uptake by the epithelial mucosa, either reducing or improving active targeting. To enhance the transcytosis of Tf-PLGA nanoparticles, their surface can be precoated with mucin. As demonstrated by Yang et al., Tf-PLGA nanoparticles absorb proteins from the mucus layer, thereby reducing the efficiency of penetration through the mucosal epithelial barrier. However, precoating these nanoparticles with mucin improves transcytosis and the formation of a protein corona on the surface of the nanoparticles.^[197]

8. Characterization of Nanoparticle–Tissue Interactions

Due to the complex pathogenesis of IBD and the localization of inflammation in the GI tract, it is essential to investigate the nanoparticle-tissue interaction. It is crucial to consider that not all parts of GI tract in IBD patients are affected. Therefore, interactions between nanoparticles and healthy tissue, as well as the release of drugs in these areas, must be avoided. The targeted properties of polymeric nanoparticles play a pivotal role in the management of IBD, particularly in the context of transmural

Table 2. Comparison of main methods for characterizing nanoparticle-tissue interactions.

Method	Advantages	Limitations
IVIS	<ul style="list-style-type: none"> ✓ Real time biodistribution of nanoparticles in GI tract and in each organ ✓ Noninvasive 	<ul style="list-style-type: none"> • No cell uptake information • Semiquantitative analysis • Qualitative analysis
NIR-II fluorescence imaging and 3D MSOT images	<ul style="list-style-type: none"> ✓ Biodistribution of nanoparticles in GI tract and in each organ ✓ Noninvasive approach ✓ Deep-tissue imaging ✓ High resolution ✓ Improved contrast 	<ul style="list-style-type: none"> • Qualitative analysis • Photoluminescent contrast agents • High cost of high sensitive InGaAs camera • Technical limitations (thermal background noise from animals)
Fluorescent microscopy with image analysis	<ul style="list-style-type: none"> ✓ Localization of nanoparticles ✓ Translocation of nanoparticles across epithelial barrier ✓ High resolution (CLSM, SRM) 	<ul style="list-style-type: none"> • Semi-quantitative analyze • Invasive
Flow cytometry	<ul style="list-style-type: none"> ✓ Quantitative analyze ✓ Most precise approach for nanoparticle uptake 	<ul style="list-style-type: none"> • Time consuming • Invasive

inflammation from the mouth to the anus during CD and colo-rectal mucosal inflammation during UC. A number of techniques may be employed to characterize the interactions between nanoparticles and intestinal tissue (Table 2). The *in vivo* imaging system (IVIS) is the standard method of determining the biodistribution of nanoparticles *in vivo*.^[198–200] The IVIS is a valuable tool for demonstrating the localization of nanoparticles in specific sections of the GI tract and their subsequent distribution in other organs. Furthermore, the IVIS system is frequently used in *ex vivo* adhesion experiments, wherein nanoparticles are incubated with animal or human colon samples.^[201,202] As an alternative, near-infrared second window (NIR-II) fluorescence and multispectral optoacoustic tomography (MSOT) imaging can be employed to achieve a deep-tissue imaging with high resolution and improved contrast.^[54,203,204] Immunofluorescence analysis of thin cryosections of mucosal tissue represents the predominant approach for the determination of target properties of nanoparticles at the cellular level. Confocal laser scanning microscopy (CSLM) and super-resolution microscopy (SRM) provide enhanced resolution and details regarding the localization and uptake of fluorescent-labelled nanoparticles within tissue.^[205,206] In order to obtain more quantitative results, an image analysis can be conducted.^[21] A novel automated multicolor mesoscopic light- and fluorescence imaging system has recently been presented, which enables the tracing of nanoparticles in large tissue samples.^[207] The most accurate method for evaluating the characterization of nanoparticle-tissue interactions is flow cytometry. Flow cytometry analysis is a quantitative method of analyzing the uptake of nanoparticles by colonic lamina propria cells.^[208–210]

In order to achieve an accurate representation of the targeted properties of nanoparticles, it is necessary to employ a combination of several analytical methods. Currently, there is still a limited amount of information available concerning the mechanisms of nanoparticle translocation across gastrointestinal barriers, the processes of nanoparticle adhesion, and the mechanisms of nanoparticle absorption. In order to correctly interpret the results and successfully translate nanomedicine into clinical practice, it is essential to gain a comprehensive understanding of the interaction between nanoparticles and both healthy and inflamed colon tissue.

9. Challenges of Translation into Clinical Practice

The majority of commercially available (53%) or *in-clinical* trial nanomedicines are designed for cancer therapy. In contrast, only 5% of nanomedicines are intended for use in the treatment of immunological diseases.^[211,212] Certolizumab pegol (Cimzia) is one of the few examples of a humanized antigen-binding fragment (Fab') of a PEG-conjugated monoclonal antibody approved for the treatment of Crohn's disease.^[17,213] Given the advantages of polymeric systems, there was a slight increase in the number of clinical trials utilizing polymers in drug delivery between the periods 2016–2021 and 2002–2016, respectively.^[214]

It is important to note that the recent outbreak of the SARS-CoV-2 virus and development of a nanoparticle-based vaccine had a considerable impact on the global nanomedicine industry. Despite the visible achievements and progress toward the development of new drug delivery systems, a number of issues persist within the field of nanomedicine. The absence of uniform nomenclature for nanoparticles, the absence of agreed regulatory guidelines, the absence of adequate characterization, nanoparticle stability, their scale-up for manufacturing, investigation of nanoparticle interactions not under real physiological conditions, and systemic biodistribution are the principal challenges associated with nanomedicine regulation. These challenges result in a low level of clinical translation.^[215,216]

Furthermore, limitations of existing animal models of IBD explain the challenges in clinical translation. For example, the DSS colitis model mimics acute inflammation, which is not representative of the chronic inflammation observed in patients with UC. Consequently, the acute colitis model restricts the understanding of nanomedicine efficacy and the interpretation of the results.^[168] It is crucial to accurately interpret the results from animal experiments, understand the differences between animal and human physiology and predict the effect of drug-loaded nanoparticles during real chronic inflammation. This will lead to the successful clinical translation of promising nanomedicines. It must be acknowledged that IBD is a complex disorder, and it is extremely challenging to create an appropriately representative IBD model in laboratory settings. To overcome the clinical translation issue, a reliable model must be established that more closely

represents the pathophysiology of IBD. Therefore, the establishment and implementation of a novel alternative model, a combination of different and alternative approaches, will undoubtedly lead to improved results interpretation and further successful clinical translation. The most useful alternative models are gut organoids developed from patients or animal biopsies,^[217–220] ex vivo techniques with utilization of patients' tissue Ussing chambers^[19,21,145] or precision-cut intestinal slices.^[221,222] Confirmation of drug-loaded nanoparticles' efficacy in pathophysiological models that more closely resemble human diseases may facilitate the introduction of promising nanomedicine into clinical practice.

As nanomedicine is an interdisciplinary field, there are methodological reliability and reproducibility issues that need to be addressed.^[223] The utilization of unsuitable analytical methodologies for nanoparticle characterization is a significant factor contributing to the low rates of clinical translation. It is a common assumption that the implementation of quality system regulations, such as those set forth by the European Medicines Agency (EMA) and FDA, as well as good manufacturing practice (GMP) and good laboratory practice (GLP) regulations, is an unnecessary investment of resources in the academic setting. However, the benefits of developing reliable and reproducible nanomaterials with high clinical translation rates are indisputable.^[223–227] A "minimum information standard" has been proposed for experimental bio-nano interactions, encompassing material characterization, biological characterization and details of experimental protocols. This could facilitate improved reproducibility, quantitative comparisons of nanoparticles and further support in silico modeling.^[228] Recently, Joyce and colleagues proposed the translational DELIVER framework to promote nanomedicines to the clinic.^[229] During the development of nanomedicine, it is essential to define the nanoparticle properties and functionality for the IBD treatment. This should include consideration of the compatibility of the drug and polymer, toxicity, and biocompatibility. Additionally, a final formulation must be defined in accordance with the route of administration.^[229] The application of machine learning and artificial intelligence has the potential to enhance the prediction of risks associated with the formulation of nanoparticles, thereby facilitating their clinical translation in the future.^[230,231]

Furthermore, in order to ensure the successful clinical translation of promising nanomaterials, a comprehensive investigation of adsorption, distribution, metabolism, and elimination (ADME) must be undertaken. The biocompatible nanoparticles can easily penetrate cell membranes, placental and blood-brain barriers. Therefore, it is critical to understand the fate of nanoparticles and their ADME in order to ensure the safety of nanomedicine. Additionally, it is essential to examine the first-pass effect of the released drug in the targeted inflamed colon.^[23,36,117,232,233] Moreover, the safety and immunogenicity of nanoparticles must be considered at an early stage of the development process. The recent widespread use of PEGylated mRNA vaccines resulted in the development of PEG immunogenicity, characterized by an increase in anti-PEG IgM formation.^[234–236] The example of interspecies differences in PEG immunogenicity illustrates the significant challenges associated with the prediction of the safety of novel polymers.^[234] Furthermore, the size, morphology, surface charge, and surface modification of

nanoparticles influence their pharmacokinetic and toxicological profiles.^[237,238] An additional factor that must be taken into consideration with regard to polymeric micelles is the crosslinked density. It has previously been demonstrated that nanoparticles with low crosslinking density in the core or shell are able to trigger an immune response.^[239,240] Therefore, in order to create a more complex system with a hybrid targeted approach, it is essential to consider the balance between the complicity of nanoparticles and their toxicity. Ensuring the safety of nanoparticles is a fundamental aspect of their development and implementation in clinical settings.

The above issues must be resolved to successfully translate nanomedicine from laboratory bench to the clinic. To overcome these issues, a deep and tight collaboration between chemists, biologists, physicians, physicists and computer scientists is essential. Scientists must be aware of the entire process of translating nanomedicine to the clinic to ensure the best possible outcome. With a vast number of new materials emerging almost daily, it is critical to address the key characteristics of nanoparticles in order to achieve sufficient targeted drug delivery to patients with IBD. It is essential to establish open communication between scientists, representatives of GMP manufacturers, preclinical and clinical studies. Open interdisciplinary discussion and analysis of failed clinical trials will undoubtedly benefit the nanomedicine.

10. Conclusion

There is a clear need for the development of new and alternative strategies for the management of IBD treatment. The current medication is unable to adequately treat the inflammation without causing significant adverse effects. Drug delivery systems represent a potential alternative approach for the treatment of IBD. Nanoparticles can be used to deliver therapeutic agents, such as corticosteroids, mRNA, and biological mediators, directly to sites of inflammation. This reduces unspecific interactions with healthy tissue, thereby preventing the drug-related side effects. The fabrication of nanoparticles requires consideration of the pathophysiological alterations of the GI tract that occur during IBD. These alterations include changes in microflora, pH, intraluminal pressure, transit time, ROS production, the disruption of the epithelial barrier, and the emergence of a distinctive pattern of receptors on the surface of cells.

Polymeric nanoparticles represent a promising approach to drug delivery, offering numerous advantages and perspectives. The potential for polymeric nanoparticles is based on their well-tailored size, shape and stimuli responsiveness. Moreover, the surface of these nanoparticles can be modified to increase specific targeting. Furthermore, hydrophilic and hydrophobic drugs could be encapsulated with high loading efficiency into polymeric nanoparticles, including proteins and nucleic acids.^[16] Significant progress has been made in the development of polymeric nanoparticles, characterized by notable variations in their surface ligands, dimensions, shapes, and shell structures. A significant number of recent studies have employed the incorporation of ROS/pH sensitivity (56%). Over the past five years, ≈26% of studies have focused on the implementation of the receptor-mediated targeting and eERP effect. It is likely that the implementation of multiple targeted strategies could facilitate a more successful translation of polymeric nanoparticles to clinical practice. **Table 3**

Table 3. Comparison of targeted strategies of polymeric nanoparticles for IBD treatment.

Mechanism	Advantages	Limitations and issues	Ref.
Electrostatic interactions	<ul style="list-style-type: none"> ✓ Improved drug contact with mucosal surfaces ✓ Increased nanoparticles retention ✓ Improved drug pharmacokinetics 	<ul style="list-style-type: none"> • Passive targeting • Nonspecific interactions with healthy intestine • Limited targeted properties • Not suitable for intracellular delivery 	[241,242]
Receptor-mediated	<ul style="list-style-type: none"> ✓ Active targeting ✓ Enhanced selective drug delivery 	<ul style="list-style-type: none"> • Need for identification, and development of high specific receptors and ligands correlated with IBD • Need to shield the targeting ligands and its de-shielding only at the target site 	[16,26]
ROS-responsive	<ul style="list-style-type: none"> ✓ Efficient site-specific drug release ✓ Drug release in specific intestinal segments regarding pH 	<ul style="list-style-type: none"> • Limited information regarding the real level of ROS in colon tissue during IBD and required concentration of ROS to achieve effective drug release • Passive targeting 	[26]
pH-responsive	<ul style="list-style-type: none"> ✓ Protection of premature drug release ✓ Drug release in specific intestinal segments regarding pH ✓ Efficient site-specific drug release 	<ul style="list-style-type: none"> • Drug release in the whole segment of the GIT with regard to pH change • Non-specific targeting for inflamed tissue • Different pH level in UC and CD, in active and remission stage of IBD 	[26,87]
Epithelial enhanced permeability effect	<ul style="list-style-type: none"> ✓ Primary passive method ✓ Accumulation of nanoparticles in the inflamed part of the GIT 	<ul style="list-style-type: none"> • Limitation due to passive targeting • Uncontrollable drug release 	[241]
Multiresponse	<ul style="list-style-type: none"> ✓ Enhanced selective drug delivery ✓ More accurate and precise approach 	<ul style="list-style-type: none"> • Complex drug release mechanism • Complex nanoparticle design 	[241,243]

provides an overview of the key advantages and limitations associated with each targeted strategy of polymeric nanoparticles for IBD treatment.

The aim of this review is to combine the novel research progress achieved in this topic over the past five years. This review is intended to assist scientists in optimizing their drug delivery systems and ultimately developing a new generation of nanoparticles for the treatment of patients with IBD. The successful fabrication of drug delivery systems for the treatment of IBD requires the consideration of several factors. These include the ability of the system to resist multiple stimulations in an inflamed colon, the size of the nanoparticles, their shape, their surface charge, and ligand modification. Additionally, the pathophysiology of IBD must be taken into account during the research and development process. Despite the existence of a vast number of polymeric materials with various promising characteristics, the development of a drug delivery system that can improve the quality of life of IBD patients remains a significant unmet need. Nevertheless, recent positive results and progress in the targeted delivery of small molecules, biologics, and nucleic acids to the site of inflammation indicate that the development of nanomedicines for IBD patient is likely to be highly rewarding soon. Understanding the challenges faced by polymeric nanoparticles in targeting inflamed tissue in IBD patients could help to develop more effective delivery systems.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

E.G. conceptualized, planned, wrote the manuscript, and made the illustrations. J.C.B. and A.S. supervised and edited the manuscript.

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