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REVIEW

Nanoparticle-Based Drug Delivery Systems for Inflammatory Bowel Disease Treatment

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Abstract: Inflammatory bowel disease (IBD) is a chronic, non-specific inflammatory condition characterized by recurring inflammation of the intestinal mucosa. However, the existing IBD treatments are ineffective and have serious side effects. The etiology of IBD is multifactorial and encompasses immune, genetic, environmental, dietary, and microbial factors. The nanoparticles (NPs) developed based on specific targeting methodologies exhibit great potential as nanotechnology advances. Nanoparticles are defined as particles between 1 and 100 nm in size. Depending on their size and surface functionality, NPs exhibit different properties. A variety of nanoparticle types have been employed as drug carriers for the treatment of inflammatory bowel disease (IBD), with encouraging outcomes observed in experimental models. They increase the bioavailability of drugs and enable targeted drug delivery, promoting localized treatment and thus enhancing efficacy. Nevertheless, numerous challenges persist in the translation from nanomedicine to clinical application, including enhanced formulations and preparation techniques, enhanced drug safety profiles, and so forth. In the future, it will be necessary for scientists and clinicians to collaborate in order to study disease mechanisms, develop new drug delivery strategies, and screen new nanomedicines. Nevertheless, numerous challenges persist in the translation from nanomedicine to clinical application, including enhanced formulations and preparation techniques, enhanced drug safety profiles, and so forth. In the future, it will be necessary for scientists and clinicians to collaborate in order to study disease mechanisms, develop new drug delivery strategies, and screen new nanomedicines.

Keywords: nanoparticles, inflammatory bowel diseases, targeted delivery, passive targeting, active targeting, drug delivery system

Introduction

Inflammatory bowel disease (IBD) is a chronic, non-specific inflammatory disease that affects the intestinal tract.[1] The prevalence of IBD is highest in North America and Europe, where it is estimated that 6.9 million people globally have it.[2,3] The prevalence of inflammatory bowel disease (IBD) has been on the rise in newly industrialised countries over the past two decades, reaching a point of accelerated growth.[2,3] In contrast, the Western world is currently experiencing a phase of stabilisation in terms of incidence, with prevalence expected to remain at approximately one percent by 2030.[4] This presents a significant challenge to global public health.

The two main types of IBD are Crohn's disease,[1] which typically affects the gastrointestinal tract in a segmented structure, and ulcerative colitis, where lesions primarily affect the colonic mucosa and submucosa in a continuous pattern.[5] Abdominal pain, diarrhea, bloody stools, and weight loss are only a few of the primary clinical symptoms. Additionally, the most typical extra-intestinal problems primarily affect the joints, skin, eyes, and bile ducts, significantly impacting the quality of life.[6,7]

Although the exact cause of IBD is still unknown,[8] several factors, including immunological, gastrointestinal, environmental, nutritional, and microbial infections, may be linked to IBD.[9,10] The pathophysiology of IBD is characterised by a loss of function of the mucosal epithelial cell system, local immune cell responses, dysbiosis of the gut microbiota, and changes in the local environment of the tissues. Despite the lack of curative treatment for the eradication of IBD,[11] these physiological and pathological changes provide new targets for the development of targeted drug delivery

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systems for IBD. Inducing an initial remission and preventing relapse during remission are the general principles of pharmacological treatment of IBD.[12] Aminosalicylates, antibiotics, glucocorticoids, immunomodulators, and biologics are commonly used in conventional drug therapy for IBD. These drugs aim to improve the mucosal lining of the colon and repair, induce and maintain inflammatory remission.

A significant obstacle to effective treatment is drug delivery to the diseased site. Parenteral, transoral, and rectal enema are traditional delivery methods for IBD.[13] Because of its low cost of production, convenience of handling, and good compliance, the oral dose form is regarded as the most desirable and acceptable form of daily administration for treating IBD.[14,15] However, the active ingredient is absorbed by the mucosal membrane of the alimentary tract and distributed throughout the body following oral formulation. The development of systemic adverse drug reactions can impact treatment outcomes, as they are influenced by notable variations in the gastrointestinal environment and between healthy and inflamed intestinal regions. Intrarectal administration can potentially deliver tissue concentrations even higher than oral administration and provide local treatment for IBD in the distal colon.[16] However, conventional enemas are ineffective in patient compliance because of their short retention time in the colorectal lumen and the need for frequent administration.[17,18] Therefore, it is imperative to design effective drug delivery systems (DDSs) to deliver more drugs to the site of inflammation precisely.

Medical nanomaterials have come a long way in the last few years. Its goal is to design and manufacture materials with novel properties and functions on the scale of 1 to 1000 nm, namely nanoparticles (NPs).[19] NPs are small, have a large surface area, and have a unique shape. As a novel bioactive carrier, NPs increase the local drug concentration at the disease site to maximize drug efficacy. They have been significant in gastrointestinal diseases.[20] Significant advancements have been made in nanoparticle-based strategies for the treatment of inflammation and tumours. Several chronic diseases, such as osteoarthritis,[21] rheumatoid arthritis[22] and skin conditions,[23] have been treated with NSAIDs (non-steroidal anti-inflammatory drugs) or Glucocorticoids as either a primary or adjunctive treatment option. These diseases often require prolonged anti-inflammatory therapy. The developments in nanotechnology have markedly enhanced the accumulation of anti-inflammatory agents. Targeting is the key to treating IBD. Targeted delivery of IBD reduces systemic drug exposure and related side effects by releasing the drug directly into the inflamed tissue, lowering the frequency of administration to obtain the required dosage, and minimizing the non-specific distribution of the drug throughout the body. Currently, various NPs, including polymeric NPs, lipid-based NPs, liposomes, silica NPs, nanogels, shell-core NPs, and particle NPs, are used as drug carriers for treating IBD.[24]

Several targeting strategies have been investigated so far, and they are often predicted by different physiological factors between the colonic and proximal sections of the gastrointestinal tract.[25] Its three primary divisions are passive, active, and hybrid targeting. This paper has reviewed and discussed the targeting and functional roles of nanopharmaceutical agents in treating IBD (Tables 1–3). We have summarised the effectiveness and limitations of different types of delivery systems for the treatment of IBD (Table 4). Additionally, we have summarized the challenges and possible avenues for further study in this area.

Passive Targeting

The primary determinants of passive targeting are the physicochemical characteristics of the particle carrier itself (size, charge, etc). and the local microenvironment.[101] Thus, passive targeting methods for IBD may be achieved by altering the nanosize of the NPs and exploring the local microenvironmental characteristics of the intestine (pH, reactive oxygen species [ROS] levels, and overexpression of the digestive enzymes).

Targeting Based on Enhanced Permeability and Retention (EPR) Effect

In normal tissues, microvascular gaps seem to be densified and structurally intact. In contrast, to enable particle adherence, the inflammatory intestine produces more mucus than normal tissue, and the small size of NPs increases their capacity to penetrate the mucus.[102] Furthermore, increased endothelial barrier permeability has been linked to epithelial injury and loss of intercellular tight junction chains produced by various factors (inflammatory mediators, cytokines, etc).[103,104] NPs are taken up and retained in the inflammatory site by the infiltrating immune and inflammatory cells, such as macrophages, dendritic cells, and neutrophils.[105] This is known as the epithelial increased permeability and retention effect (EPR) (Figure 1A).[106] As a result, NPs can prolong their stay at the inflammation site by passively targeting it.

Table 1 The Passive Targeting and Functional Effects of Nanoformulations for IBD Treatment

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/Cargo	NPs Delivery System	Model	Main Results	Ref
UC	Passive	EPR effect	Oral delivery	Bud	NLCs	DSS mice model, J774 cells line model	High encapsulation rate; lower level of inflammatory factors; longer drug residence duration in the colon.	[26]
UC	Passive	EPR effect	Oral delivery	Cyclosporin A	Protamine nanocapsules	Jurkat cells line model	High encapsulation efficiency and good drug loading capacity decrease IL-2 secretion.	[27]
UC	Passive	EPR effect	Oral delivery	Celecoxib	Nanomixed micelles	Acetic acid rabbit model	The nanomixed micelles have good anti-inflammatory and antioxidant properties that help alleviate colitis.	[28]
UC	Passive	EPR effect	Oral delivery	Bud	PLGA	Oxazolone mice model	The NPs target the colonic inflammatory site to release drugs.	[29]
UC	Passive	EPR effect	Oral delivery	5-ASA	Hemoglobin NPs	Caco-2 and HT-29 cell line models	High rate of drug release combined with excellent biocompatibility and biodegradability.	[30]
UC	Passive	EPR effect	Oral delivery	Rifaximin	Tamarind gum NPs	TNBS rats model	The NPs exhibit positive therapeutic effects on colitis and function as antioxidants.	[31]
UC	Passive	EPR effect	Intravenous delivery	H2S donors	ST-H2S liposomes	DSS mice model, Caco-2 model, and RAW 264.7 cell line model	ST-H2S liposomes have an excellent immunomodulatory potential.	[32]
UC	Passive	EPR effect	Oral delivery	Oleuropein	NLCs	DSS mice model, J774 cells line model	Anti-inflammatory and antioxidant effects via lowering TNF-α and ROS production and secretion.	[33]
UC	Passive	EPR effect	Oral delivery	IFX	EAC-IFX-L and AC-IFX-L	DSS mice model	AC-IFX-L and EAC-IFX-L showed better symptom relief than the DSS treatment group.	[34]
UC	Passive	Lysozyme-triggered	Oral delivery	Vancomycin	Chitosan-polyaniline microgels	Caco-2 cell line model	Specific inflammatory colonization, inhibition of *Staphylococcus aureus*, superior biosafety.	[35]
UC	Passive	Azoreductase enzymes	Oral delivery	Hydrocortisone	MSs	DSS mice model	Excellent stability, drug release rate, and capacity to regulate intestinal flora.	[36]
UC	Passive	Esterases	Oral delivery	5-ASA	SiNP	TNBS mice model	High adhesion and low toxicity.	[37]
UC	Passive	Esterases	Oral delivery	Dex	PPNP	DSS mice model	Biosafety, specific targeting ability, and antioxidant activity.	[38]

(*Continued*)

Table 1 (Continued).

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/Cargo	NPs Delivery System	Model	Main Results	Ref
UC	Passive	Acid sphingomyelinase	Vein injection	Fluorescent agent ICG	Sphingomyelin liposomes	DSS mice model and Caco-2 cell line model	Target-specific liposomes facilitate macrophage uptake.	[39]
UC	Passive	Azoreductase enzymes	–	Ornidazole and sulfasalazine	Sulfasalazine-polyethylene glycol micelles	HEK 293 cell line model	The excellent stability nanomicelles release the loaded drug by being activated by azo reductase.	[40]
UC	Passive	Azoreductase triggered	Oral delivery	M-Saf M-Bud	MSMs	Mice model	Capable of delivering drugs to targeted colonic sites	[41]
UC	Passive	α-amylase responsive	Oral delivery	Dex	HES-CUR NPs	DSS mice model	The excellent anti-inflammatory and antioxidant properties of NPs enable multi-drug combination therapy.	[42]
UC	Passive	ROS-responsive	Oral delivery	Bud and Tpl	Bud-ATK-Tpl	DSS mice model and RAW264.7 cell line model	High drug release to minimize adverse effects; colitis treatment that combines anti-inflammatory and antioxidant treatment.	[43]
UC	Passive	ROS-responsive	Oral delivery	Tpl	OxbCD	DSS mice and TNBS mice model	Excellent biosafety and antioxidant function are achieved via drug molecule release from multiple components that eliminate ROS.	[44]
UC	Passive	ROS responsive	Oral delivery	Silymarin	SiRNP	DSS mice model and RAW 264.7 cells model	Effective elimination of ROS, biodegradable, and improved bioavailability of the drug.	[45]
UC	Passive	ROS-responsive	Oral delivery	SeM	SeM@EM	DSS mice model and HT29 cell line model	SeM@EM improves drug adherence, alleviates inflammation, and promotes the growth of beneficial intestinal microbiota.	[46]
UC	Passive	ROS-responsive	Intravenous and subcutaneous injection	–	OxbCD NPs	Guinea pigs model B16F10 cells and MDA-MB-231 cells lines model	Superior ROS sensitivity and biocompatibility.	[47]
UC	Passive	pH-sensitive	Oral delivery	OVA	PLGA NPs	DSS mice model and Caco-2 cell line model	Superior stability and specificity in targeting the colon.	[14]
UC	Passive	pH-sensitive	Oral delivery	Bud	Eudragit S 100/ Capryol 90 nanocapsules	Acetic acid rat model	Favorable drug release rate and effective targeting for colonic drug delivery.	[48]
UC	Passive	pH-sensitive	Oral delivery	BBR	PLGA NPs	DSS mice model	Dual drug release properties to reduce the frequency of drug administration.	[49]

(*Continued*)

Table 1 (Continued).

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/Cargo	NPs Delivery System	Model	Main Results	Ref
UC	Passive	pH-sensitive	Oral delivery	Cur	Polyacrylamide-grafted -xanthan gum NPs	Acetic acid rat model	NPs have a high degree of colonic targeting and alleviate myeloperoxidase and nitrite levels to relieve colitis symptoms.	[50]
UC	Passive	pH-sensitive	Oral delivery	IL-1Ra	Alginate/chitosan microcapsules	DSS mice model	Microcapsules can release the drug in situ in the colon, reducing systemic adverse effects.	[51]
UC	Passive	pH-sensitive	Oral delivery	Tacrolimus	P-4135F NP	DSS mice model	High drug loading and release rates.	[52]
UC	Passive	pH-sensitive	Oral delivery	Cur and Dex	HPMCAS-HF microencapsulated PLGA NPs	RAW 264.7, HT29-MTX, and T84 cell line model	Microcapsules have burst and sustained drug release with excellent anti-inflammatory properties.	[53]
UC	Passive	pH-sensitive	Oral delivery	Bud	PLGA NPs	DSS mice model	Relieves colitis and has pH-dependent drug-releasing properties.	[54]
UC	Passive	pH-sensitive	–	5-ASA	Ginger-derived nanocarriers	In vitro	High encapsulation rate, outstanding stability, and excellent target specificity.	[55]
UC	Passive	pH-sensitive	–	5-ASA	Polyvinyl alcohol/ sodium alginate/ polylactic acid blend carrier	–	Controlled release of therapeutic drugs through good pH sensitivity.	[56]
UC	Passive	pH-sensitive	In vitro	GAR	PLGA NPs	Caco-2 cell line model	NPs can alleviate the response to inflammation by decreasing MPO activity.	[57]
UC	Passive	pH-sensitive	Oral delivery	5-ASA and Cur	Sulfated chitosan/ alginate composite microparticles	TNBS rats model	Releases two drugs into the target area; its therapeutic effect is better than a single-dose treatment.	[58]
UC	Passive	pH-sensitive	Oral delivery	Bud and prednisolone	MSNs	DSS mice model	The particles resulted in lower levels of pro-inflammatory cytokines than uncoated particles.	[59]
UC	Passive	pH-sensitive	Oral delivery	Cur	Curcumin coupled with Eudragit® S100	DSS mice model, HCT116, and HT-29 cell line model	Great stability and loading rates; inhibits inflammatory response.	[60]
UC	Passive	pH-sensitive	Oral delivery	Prednisolone	Prednisolone wrapped by Eudragit S100	In vitro	The nanocapsules specifically release the drug into the colon.	[61]

(*Continued*)

Table 1 (Continued).

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/Cargo	NPs Delivery System	Model	Main Results	Ref
UC	Passive	pH-responsive	Oral delivery	Prednisolone	Encapsulated by succinylated ε-polylysine 3-aminopropyl-functionalized mesoporous silica NPs	RAW 264.7, LS 174T, and Caco-2 cell line model	MCM-NH2 is pH sensitive, allowing for targeted colonic delivery.	[62]
UC	Passive	pH-sensitive azo-reductase	Oral delivery	Bud	ES-Azo. Pu NPs	TNBS mice model	NPs are sensitive to enzymes and pH, allowing for sustained targeted drug release.	[63]
UC	Passive	pH-sensitive amylase enzyme	Oral delivery	Safranin O dye	MSNs	Rat model and, Caco-2 cell line model	Dual targeting improves the inflammatory colonic tissue specificity of the drug.	[64]
UC	Passive	pH-sensitive, H2O2-responsive	–	Rifaximin	OxiDEX NPs encapsulated in HPMCAS	Caco-2 and HT29-MTX cell line model	Highly adhesive, sensitive to H_2O_2 and pH; capable of reducing the systemic adverse effect of drugs.	[65]
UC	Passive	pH-sensitive, Positive charges, and ROS-responsive	Oral delivery	Infliximab	Polyphenol-PEG-containing polymers NPs	DSS mice model	Higher adhesion, excellent target specificity, and biosafety	[66]
UC	Passive	pH-sensitive and azo-reductase enzymes	Oral delivery	Safranin O and hydrocortisone	Magnetic mesoporous silica microparticles functionalized by azo derivatives	TNBS rats model	The NPS increases the delivery efficiency of loaded drugs and improves therapeutic efficacy.	[67]
UC	Passive	Positive charges	Intrarectally administered	Betamethasone	Ethylcellulose nanospheres coated with polysorbate 20	TNBS mice model, C2BBe1, and RAW 264.7 cell line model	Negatively charged: the ability to target areas of inflammation with favorable adhesion.	[68]
UC	Passive	Positive charges	Intrarectally administered	Bud and colony-stimulating	HEP-HSA NPs	DSS mice model and RAW 264.7 cells line model	Simultaneous loading of drugs and biologics. Better anti-inflammatory effect than a single drug-loaded NP.	[69]
UC	Passive	Positive charges	Oral delivery	CeO2 NPs	CeO2@MMT	DSS mice model and RAW 264.7 cells line model	CeO2@MMT treats inflammation via target specificity and antioxidant action.	[70]
UC	Passive	Positive charges	Oral delivery	TNF-α	Polymeric NPs coupled by two different chain lengths (2 kDa and 5 kDa) of PEG and PLEG	DSS mice model, Caco-2 cells, and J774 cells lines model	PLGA-PEG2K NPs are more protective of drugs and more effective in treatment than the PLGA-PEG5K NPs.	[71]
UC	Passive	Positive charges	Oral delivery	Infliximab	IFX NM	TNBS mice model and HT29 cell model	Sustained release function and anti-inflammatory properties promote mucosal healing.	[72]

(*Continued*)

Table 1 (Continued).

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/Cargo	NPs Delivery System	Model	Main Results	Ref
UC	Passive	Positive charges	–	Zingerone	Zin-SLNPs	RAW 264.7 cell line model	Negative surface charge for better adhesion; superior biosafety.	[73]
UC	Passive	Positive charges and esterase	Intrarectally administered	Dex	Inflammation targeting hydrogel	DSS mice and TRUC mice model, Caco2, and HT-29 cell line model	IT-hydrogel reduces systemic drug exposure, prolongs local drug release, and improves efficacy more than free Dex enemas.	[74]

Abbreviations: ST, Spleen targeting; H_2S, H_2S donor; NLCs, nanostructured lipid carriers; SiNP, silica nanoparticles; PPNP, polymers self-assembled nano-particle; IFX, infliximab; PLGA, poly(lactic-co-glycolic acid); 5-ASA, 5-Amino salicylic acid; siRNP, silica-containing redox nanoparticles; SeM, diselenide-bridged mesoporous silica nanoparticles; AC, aminoclay-liposome-coated; EAC, Eudragit S100-liposome-coated; MSMs, mesoporous silica materials; MSs, multilayer-coated mesoporous silica; Cur, curcumin; EM, *Escherichia coli* strain Nissle 1917-(EcN) membrane; Bud, budesonide; Azo.pu, azo-polyurethane; HES, hydroxyethyl starch; Tpl, tempol; OxbCD, Oxidation-responsive b-cyclodextrin; OVA, oval-bumin; BBR, berberine; HPMCAS, hydroxypropyl methylcellulose acetate succinate; GAR, garcinol; MSNs, mesoporous silica nanoparticles; OxiDEX, oxidation-sensitive dextran; TNF- α, tumor necrosis factor-α; PEG, polyethylene glycol; HEP, heparin; HAS, human serum albumin; NP, nanopolyplexe; SLNPs, solid lipid nanoparticles; MMT, montmorillonite.

Table 2 The Active Targeting and Functional Effects of Nanoformulations for IBD Treatment

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/ Cargo	Nps Delivery System	Model	Main Results	Ref
UC	Active	Mannose receptors	Oral delivery	Cur	Cur–AceKGM NPs	RAW264.7 cells lines model	Cur-AceKGM NPs are more targeted and have superior therapeutic efficacy compared to oral doses of free Cur.	[75]
UC	Active	SRA1	Oral delivery	SOD	ARC-SOD	J774 A.1 cells and Caco-2 cells lines model	Potent antioxidant and anti-inflammatory properties promote macrophage endocytosis of drug loading.	[76]
UC	Active	Folate receptors	Intrarectally administered	SOD	SNP-FA	TNBS mice model and RAW264.7 cells line model	Good stability and biological activity; capable of targeted colonic delivery to reduce drug side effects	[77]
UC	Active	CD44 receptors	–	Bud	HANPs	Caco-2 and NIH3T3 cells lines model	Excellent biosafety; better ability to inhibit inflammatory factors than free drugs	[78]
UC	Active	CCR5 receptor	Oral delivery	Piceatannol	Piceatannol–PLGA–CCL4	UC patients, DSS mice model and Caco-2 cells line model	Excellent biocompatibility; inhibits the expression of pro-inflammatory genes; regulates the balance of intestinal flora	[79]

(*Continued*)

Table 2 (Continued).

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/ Cargo	Nps Delivery System	Model	Main Results	Ref
UC	Active	Cytoplasmic/ membrane proteins of the intestinal mucosa	Oral delivery	–	GDNPs 2	DSS mice model and RAW264.7 cells lines model	GDNPs 2 are natural NPs that reduce the production of pro-inflammatory factors and improve the treatment of colitis	[80]
UC	Active	Mannose receptors	Oral delivery	Apremilast	CDs.EP/Man/Meth.Cs NPs	Caco-2 and RAW 264.7 cells line model	CDs.EP/Man/Meth.Cs NPs enable specific accumulation of drugs at the site of inflammation allowing uptake by macrophages	[81]
UC	Active	Mannose receptors	Oral delivery	Anti-TNF -a nucleotides	cKGM and ASO	DSS mice, CT-26 cells and RAW 264.7 cells lines model	cKGM and ASO can transfer ASO to colonic macrophages and reduce the symptoms of colitis by decreasing TNF-a levels	[82]
UC	Active	Mannose receptors	–	Bud	Mn-NLCs	Oxazolone rat model and J774A.1 cells line model	Excellent encapsulation rate; great biocompatibility; capable of reducing the level of inflammatory factors	[83]
UC	Active	CAR1	Oral delivery	Inf	INF/LMSN@GE	DSS mice model	Transmission stability; colonic targeting specificity; anti-inflammatory effects	[84]
UC	Active	SRA1	Oral delivery	Dex	NAC-Dex	THP-1 cells and Caco-2 cells lines model	NAC-Dex reduces the release of inflammatory factors and the production of reactive oxygen species; repairs the intestinal barrier	[85]
UC	Active	SRA1	–	Dex	SAN-Dex	J774A.1 cells and Caco-2 cells lines model	Compared to free Dex, SAN-Dex is more effective in reducing inflammatory factors	[86]
UC	Active	Scavenger receptors (SRs)	Oral delivery	Bud	hMnO2 NPs.	DSS mice model and RAW 264.7 cells line model	NPs carriers with antioxidant function synergize with loaded drugs for the treatment of colitis	[87]

(*Continued*)

Table 2 (Continued).

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/ Cargo	Nps Delivery System	Model	Main Results	Ref
UC	Active	Adhesion molecule receptors and proinflammatory cytokine receptors	Oral delivery	PDA	PDA@mCRAMP@MM	DSS mice model and RAW264.7 cells line model	Inflammatory targeting; anti-inflammatory effect through regulation of immune function; regulation of intestinal flora	[88]
UC	Active	Folate-targeted	Oral delivery	Resveratro	PLGA-FA-RSV	TNBS rats model and Caco-2 cells line model	PLGA-FA-RSV enhances the targeted transport of the drug with excellent therapeutic efficacy	[89]
UC	Active	Galactose receptors	Oral delivery	TNF-α siRNA	PLA-PEG	DSS mice model, RAW264.7 cells and Caco-2 cells lines model	Improved drug utilization and delivery efficiency; biodegradability; anti-inflammatory effects through inhibition of inflammatory factor production	[90]
UC	Active	CD44 receptors	Oral delivery	OPN	BSA/OPN-NPs	DSS mice model	Exerts anti-inflammatory effects by inhibiting MPO and inflammatory factor levels	[91]
UC	Active	CD44 receptors	Oral delivery	Bilirubin	HABN	DSS mice model and J774A.1 cells line model	Greater target specificity of HABN compared to NPs without HA function painting	[92]
UC	Active	CD44 receptors	Oral delivery	Cur	Cur-HA NPs	DSS mice model and HT-29 cells line model	Improve intestinal mucosal barrier; regulate intestinal flora diversity	[93]
UC	Active	Integrin αv	Oral delivery	PA	cRGD–PA-SF NPs	DSS mice, Caco-2 and RAW 264.7 cell line	cRGD-PASFNs can alleviate inflammation and improve the colonic barrier with good therapeutic effects.	[94]

Abbreviations: AceKGM, acetylated konjac glucomannan; CDs.EP, carbon dots functionalized Enteromorpha polysaccharide; Man, mannose; Meth.Cs, methionine functionalized Chitosan; cKGM, cationic konjac glucomannan; ASO, antisense nucleotide; Mn, mannosylated nanostructured; LMSN, large mesoporous silicon nanoparticle; GE, ginger-derived exosome; ARC, archaeolipids; SOD, superoxide dismutase; NAC, nanostructured archaeolipid carriers; Dex, dexamethasone; SAN, solid archaeolipid nanoparticles; hMnO2, hollow mesoporous manganese dioxide; PDA, polydopamine; mCRAMP, mouse cathelicidin-related antimicrobial peptide; SNP, lipid–polymer hybrid nanoparticles; FA, folic acid; RSV, resveratrol; mCRAMP, mouse cathelicidin-related antimicrobial peptide; MM, macrophage membrane; PLA, poly (lactic acid); PEG, poly (ethylene glycol); OPN, osteopontin; BSA, bovine serum albumin; HA, hyaluronic acid; HABN, hyaluronic acid–bilirubin nanomedicine; CCL4, chemokine C–C motif ligand 4.

Lamprecht et al[107] showed the advantageous impacts of nanoscale particle size for UC treatment by comparing the bioadhesive capabilities of fluorescent polystyrene particles measuring 10 µm, 1 µm, and 100 nm. When compared to a healthy colon, it was discovered that 100 nm particles adhered to an inflammatory colon in rats under oral

Table 3 The Hybrid Targeting and Functional Effects of Nanoformulations for IBD Treatment

IBD	Type of Targeting	Targeting Mechanism	Delivery route	Loaded Agents/ Cargo	NSPs delivery system	Model	Main results	Ref
UC	Passive, active	pH-sensitive, mannose receptor	Oral delivery	cKGM and ASO	GelMA	DSS mice model, CT-26 cells, and RAW 264.7 cells lines model	The microspheres can target macrophages, thereby reducing inflammation and drug toxicity.	[95]
UC	Passive, active	ROS-responsive CD44 receptor	Oral delivery	Thioketa	Ra@TH	DSS mice model, RAW 264.7 and HT-29 cells	The Ra@TH system enables the delivery of rapamycin to sites of colitis-specific inflammation through the active targeting of the CD44 receptor. This allows for the controlled release of rapamycin at ROS-sensitive lesions.	[96]
UC	Passive, active	ROS-responsive CD44 receptor	Oral delivery	Infliximab	IFXSS@HA or IFXTK@HA	TNBS mice model and HT 29 cell line model	The nanocomposite has a high drug-loading capacity and high specificity, which reduces systemic exposure and provides better therapeutic results than intravenous drugs.	[97]
UC	Passive active	Positive charges, mannose receptor	–	Man-NPs	CDs/Man-NPs	DSS mice model, RAW 264.7, and Caco-2 cell line model	CDs/Man-NPs target macrophages and are internalized by absorption, reduce adverse effects of drugs, and improve drug utilization.	[98]
UC	Passive active	pH-sensitive CD44 receptor	Oral delivery	SK	ES100/HA/ CS NPs	TNBS mice model and RAW 264.7 cell line model	ES100/HA/CS NPs exert therapeutic effects by reducing ROS production and inhibiting the release of inflammatory factors.	[99]
UC	Passive active	pH-sensitive CD44 receptor	Oral delivery	Methotrexate	HA-CS /ES100/ PLGA NPs	TNBS mice model RAW 264.7 cell line model	HA-CS/ES100/PLGA NPs are specific; they alleviate intestinal inflammation by reducing inflammatory cell infiltration and decreasing intestinal mucosal damage.	[100]

Abbreviations: GelMA, gelatin methacryloyl; SK, shikonin; CS, chitosan; ES100, Eudragits S100; MTX, methotrexate; CDs, carbon dots; Man, mannosylated; PA, patchouli alcohol; cRGD, cyclo RGD peptide; and SF, silk fibroin.

administration compared to a healthy colon. Furthermore, the faster the drug was absorbed and the greater the therapeutic effect, the smaller the particle size.

Solid lipid NPs (SLNs) have become an appealing drug delivery mechanism among the available nanocarriers.[108] Compared to other lipid NPs (liposomes, etc)., SLNs have superior stability, biocompatibility, and degradability in the gastrointestinal tract, along with the capacity to influence immune responses and anti-inflammatory properties.[109,110] Beloqui et al developed nanostructured lipid carriers (BDS-NLC) containing budesonide (BDS) with an average diameter of approximately 200 nm.[26] Research conducted in vitro showed that BDS-NLC could encapsulate up to 95% of the drug and prolong its half-life in the colon. Similarly, it produced therapeutic benefits comparable to those of healthy control

Table 4 The Effectiveness and Limitations of Different Types of Drug Delivery Systems for the Treatment of IBD

Type of Targeting	Targeting Mechanism	Effectiveness	Limitations
Passive targeting	EPR effect	The NPs developed based on the EPR effect accumulate at the site of inflammation, prolonging the residence time in the inflamed intestinal area and avoiding the rapid clearance of the carrier. It could reduce the adverse effects of the loaded drug and improve the utilisation of the drug compared to the free drug.	The EPR effect only promotes the accumulation of DDSs in colitis tissues, whereas inefficient target cell uptake and insufficient intracellular drug release limit the therapeutic efficacy of anti-inflammatory drugs. Moreover, the instability of NPs drugs may increase during the preparation process or when the formulation is changed.
	Enzymes	Enzyme-targeted NPs with a favourable biosafety profile can selectively accumulate in inflamed tissues and achieve therapeutic efficacy through delayed release. Some NPs drugs protect the integrity of the intestinal barrier and enhance intestinal homeostasis.	Shorter gastrointestinal transit times may reduce drug release under disease conditions.
	ROS-responsive	The drug release of ROS-dependent NPs is efficient and less toxic, while its synergy of anti-inflammatory and antioxidant effects can attenuate the inflammatory damage in the colonic mucosa.	Oxidative stress may not be the main causative agent of the disease. If the loaded drug was released in bursts, its excessively rapid release rate may make the duration of the drug quite short.
	pH-sensitive	The pH-dependent delivery system protects the drug from gastrointestinal disorders, resists unfavourable gastrointestinal conditions and reduces premature drug release.	The design of drug delivery systems based solely on the pH of the gastrointestinal tract is unreliable due to differences of pH between individuals and the variation of pH in the intestinal lumen caused by disease states. It can result in incomplete or premature drug release from the colonic target site.
	Positive charge	The positive charge-targeted NPs promote cellular uptake and drug release, allowing better drug contact with mucosal surfaces and increasing targeting and retention of the drug delivery system.	The charge-dependent nanoparticles have the potential to bind to other charge-modified substances during gastrointestinal transport. There are fewer studies on charge-dependent delivery system loading and further experimental exploration is needed.
Active targeting	/	Actively targeted drugs are highly specific and selective for the site of targeting, reducing drug redistribution in healthy tissues, improving therapeutic efficacy and reducing systemic adverse events of the drug.	Further in vivo studies are needed to assess the efficacy and stability of different targeting ligands and formulations in animal models of colitis.
Hybrid targeting	/	Integrated systems with different release triggering mechanisms help overcome pathophysiological variability more than single systems. Passive targeting reduces the non-specific uptake of drug carriers at non-target sites and improves the targeting of active targeting systems. Active targeting promotes specificity of the drug system. Thus hybrid targeting systems enable precise targeting of drug-carrying nanoparticles and further reduce their side effects.	The release triggering mechanisms of different hybrid-targeted nanoparticles still need to be further refined. And the differences between animal models and human patients should be fully recognised, which requires more experimental data models to validate the biosafety and efficacy of the newly developed NPs.

colon tissue by lowering the levels of myeloperoxidase (MPO), interleukin (IL) IL-1β, and tumor necrosis factor (TNF) TNF-α (Figure 2).

Furthermore, protamine has been used to develop stable nanocapsules.[111] Jakubiak et al encapsulated cyclosporine A in protamine-coated nanocapsules.[27] The average particle size of these NPs was 160–180 nm. Although this nanocapsule showed

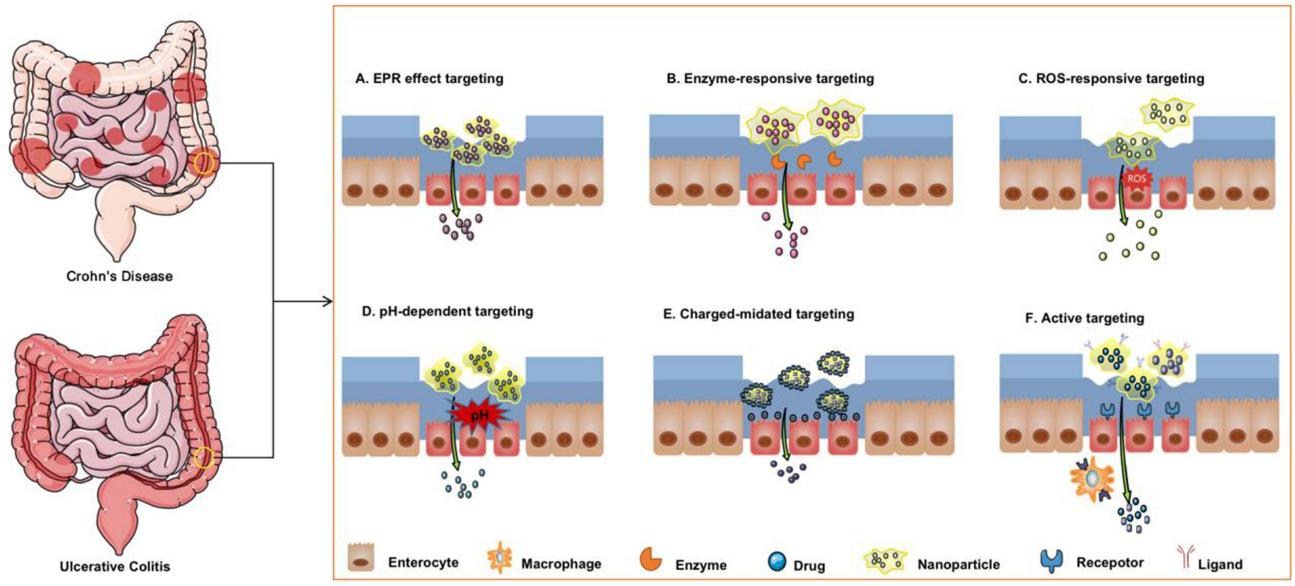

Figure 1 Strategies for inflammatory bowel disease treatment using nanoparticle-based drug delivery systems. Nanoparticles specifically target inflammatory colonic epithelial cells based on enhanced permeability and retention effects (**A**), specific enzyme levels (**B**), reactive oxygen species (ROS) levels (**C**), specific pH levels (**D**), electrostatic interactions (**E**), and ligand-receptor interactions (**F**).

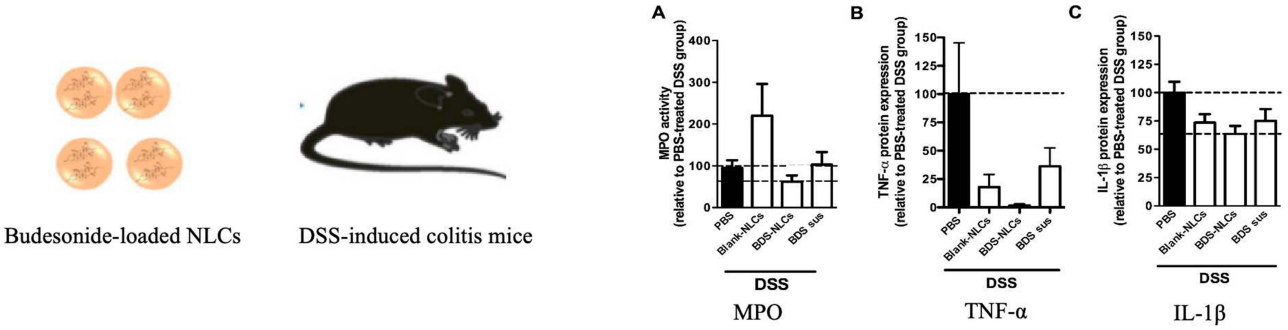

Figure 2 The expression of myeloperoxidase activity (**A**), TNF-α (**B**), and IL-1β (**C**) was significantly decreased in the colon of mice treated with budesonide-nanostructured lipid carriers compared to the control group. Reprinted from *Int J Pharm*, volume 454(2), Beloqui A, Coco R, Alhouayek M, et al. Budesonide-loaded nanostructured lipid carriers reduce inflammation in murine DSS-induced colitis. 775–783, Copyright 2013, with permission from Elsevier.[26]

good stability against trypsin in simulated trials, predicting its stability and drug release in vivo is challenging. In vitro experiments demonstrated that these NPs were superior to commercial agents in their ability to decrease IL-2 levels.

The treatment of experimental colitis with celecoxib (CXB) has demonstrated significant efficacy.[112,113] A formulation of CXB nanomixed micelles (NMMs) was developed to investigate the adverse effects of colon-targeted agents to reduce CXB. The NMMs were then integrated into a novel pulsatile capsule with an average particle size <290 nm.[28] The capsule could be released in vitro in 88.35% of cases if the capsule is designed to target the colonic site. Furthermore, it demonstrates superior defense against acetic acid-induced experimental colitis models compared to regular capsules.

Ali et al designed NPs that target inflammatory colonic mucosa by inserting budesonide into poly(l-propylene-glycoside lactone) (PLGA) NPs with an average particle size of 200 nm.[29] Fluorescence analysis showed that while the NPs could be dispersed throughout the digestive tract in the colonic tissues of healthy mice, the particles appeared more at the inflamed site in inflamed mice. It is also important to note that the drug displayed a biphasic release pattern in vitro, releasing rapid at first, then slowly and continuously after that. They suggest that the initial rapid release could be because the drug molecules are just attached to the surface of the NPs rather than fully encapsulated.

Protein NPs have gathered attention recently because of their excellent biocompatibility and advantages in biodegradability.[114,115] Covalently binding 5-aminosalicylic acid to hemoglobin produced the NPs with a diameter of

about 220 nm.[30] Only 8% of the drug was absorbed and released within 4 h following the vitro simulation test. Data from their vivo trials also showed that 85% of the NPs could reach the colon and release the drug. This suggests that the system has outstanding stability and is able to slow drug release in the stomach.

The lack of polysaccharide-degrading enzymes in the human body may prevent the natural polysaccharide found in sawdust gum from being degraded in the upper gastrointestinal tract.[116] However, the microflora enzymes present in the colorectum can degrade it to produce fatty acids.[117,118] A regimen with a mean particle size of 228 nm was shown to be optimized by Amaldoss et al after developing tamarind gum NPs loaded with rifaximin.[31] Compared to the control group, the NPs effectively lowered colonic inflammation. Furthermore, studies conducted on patients with IBD have demonstrated a significant increase in platelet counts in the literature.[119] However, they performed testing studies and discovered that neither the treatment group nor the blood fractions had significantly higher platelet levels.

Additionally, passive targeting based on the EPR effect has been observed by others. This could lead to some passive accumulation of NPs at the inflammation site and decrease the loaded drug's adverse effects.[32–34] However, this single effect-based approach to drug delivery is not ideal. Furthermore, during the synthesis of NPs, the drug encapsulation rate may be satisfactory. However, variations in the preparation processes or formulations may cause NPs to have unstable properties, making it challenging to achieve acceptable outcomes. Furthermore, it is unlikely that the interactions of NPs with the tissues or cells in the inflamed colon will be the primary means of targeting the colon.[34]

Targeting Based on Enzymes

The gastrointestinal tract contains various enzymes, including lysozyme, azo reductase, esterases, sphingomyelinase, etc.[11,120] Furthermore, the enzyme secretion of patients with IBD significantly differed from that of healthy individuals. These digestive enzymes quickly degrade drugs, which reduces their therapeutic efficacy. The enzyme reaction pattern depends on certain enzymes to catalyze chemical reactions. The drug is released at the lesion site by surface-modified DDSs, which use the enzymes as stimuli to cause their degradation or morphological transformation (Figure 1B).[35–41]

Intestinal pathogens cause aberrant lysozyme secretion in the colon by interfering with cellular function.[121,122] Li et al developed a lysozyme-triggered chitosan polyaniline microgels loaded with vancomycin (VM).[35] The biodegradation of the microgel was triggered by lysozyme, which also cleaved the glycosidic bond and released VM (Figure 3). According to an in vitro test, the drug was released in the inflammatory colon within 30 min, up to 76.9%. The microgel system inhibited *S. aureus* at the same concentration as the control without lysozyme. The Caco-2 cell line had an excellent biosafety profile with a cell survival rate of >86.1% in experiments.

Moreover, azo reductase is the most widely used enzyme for azo polymer adhesion, hydrogels, coatings, etc.[123] Additionally, the researchers developed multilayer-coated mesoporous silica (MSs), which activates azo reductase generated by intestinal microorganisms to release loaded drugs.[36] According to the test findings, mice in the oral-free drug group had a drug concentration 35 times lower at the colonic site than the mice. Notably, aryl hydrocarbon receptor activation by tryptophan-functionalized chitosan can protect the integrity of the intestinal barrier and enhance intestinal homeostasis when it is transformed into metabolites by intestinal flora.

Silica as a drug carrier NP in biomedical applications has advanced significantly. Researchers have developed a pre-drug system to treat colitis by loading 5-aminosalicylic acid onto silica NPs (SiNP).[37] Studies revealed that mice in the SiNP group accumulated six times as much drug in the inflamed tissue as in the control group, significantly decreasing the drug dosage needed for treatment. Experiments conducted on mice have demonstrated that the nanodrug selectively accumulates in inflamed tissues and prolongs the presentation duration to achieve a therapeutic impact with a delayed release. Although esterases can gradually initiate the catabolic conversion of precursor drugs, as demonstrated by drug release experiments, further in vivo research is required to understand this phenomenon fully.

Furthermore, natural polyphenols have drawn much attention as safe compounds with free radical scavenging and antioxidant properties.[124,125] Consequently, researchers designed a DDSs encapsulated with dexamethasone (DEX) by self-assembling polyphenols (tannins) and polymers.[38] When esterase is present at a concentration of 30 U/mL, up to 62% of DEX is released. According to pharmacofluorescence imaging, the fluorescence intensity of the inflamed mouse colon was shown to be four times higher than that of the healthy colon. Furthermore, PPNP-DEX had a better therapeutic impact on colitis-affected mice than PPNP and free DEX. Research has shown that non-degradable polyethylene glycol

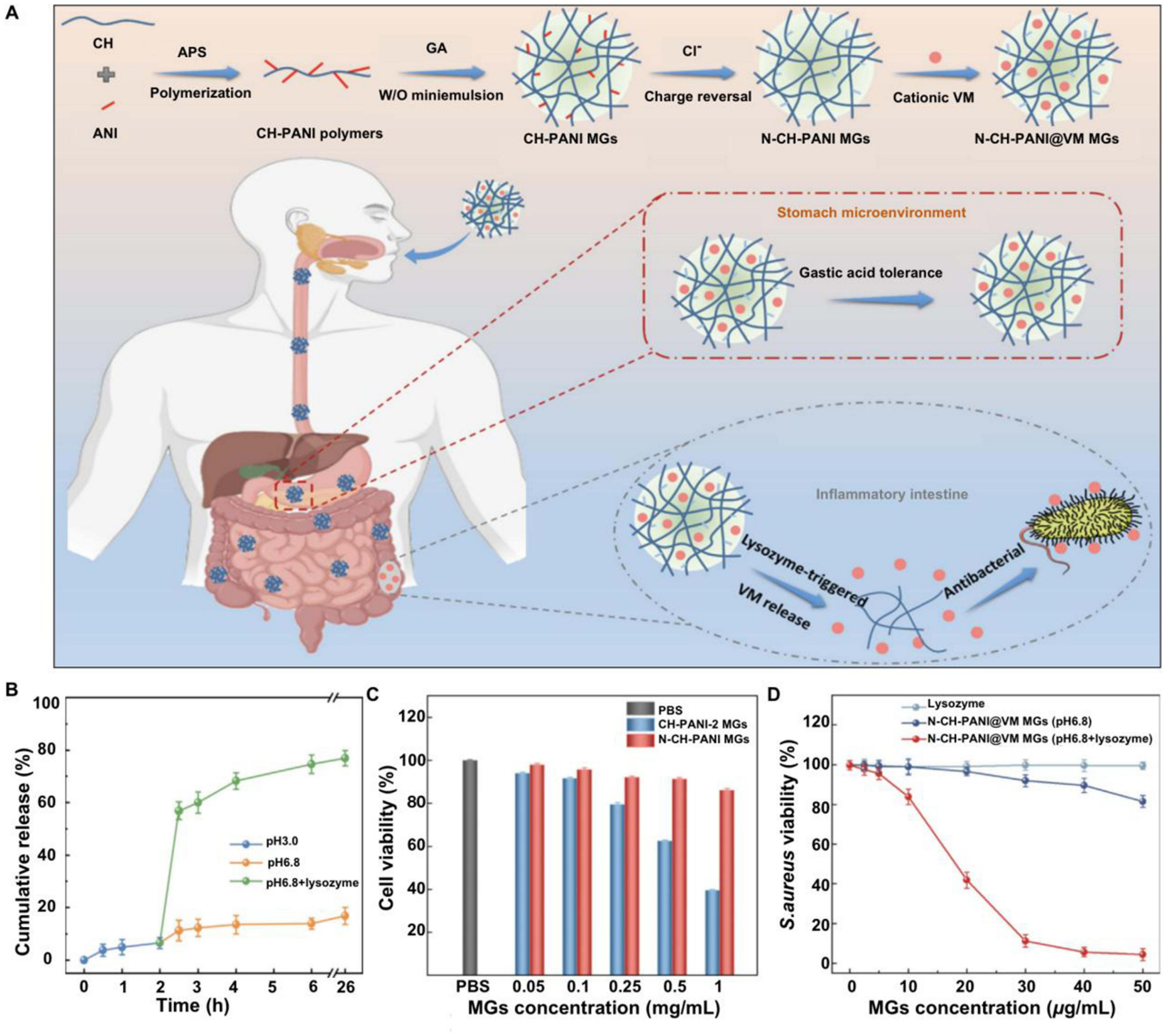

Figure 3 Lysozyme-triggered release of vancomycin from chitosan microgels for treating inflammatory bowel disease. (**A**) Schematic representation and mechanism of action of lysozyme-triggered nanoparticles. (**B**) Determination of Caco-2 cell activity in various treatment groups. (**C**) Inhibitory effect of N-CH-PANI@VM MGs on *Staphylococcus aureus* in various environments. (**D**) Cumulative release of lysozyme-induced VM in various simulated environments. Adapted from *J Adv Res*, volume 43, Li X, Hetjens L, Wolter N, et al. Charge-reversible and biodegradable chitosan-based microgels for lysozyme-triggered release of vancomycin. 87–96, Copyright 2023, with permission from Elsevier.[35]

(PEG) compounds can produce anti-polyethylene glycol antibodies in vivo, making PEG drugs biologically inactive.[126] However, they discovered little impact of anti-PEG antibodies on oral PEG drugs by fluorescence imaging, contrary to the report.

Sphingolipid liposomes were also used to develop the NPs,[39] and ICG was fluorescently labeled because sphingomyelinase is present outside of cells during cellular stress.[127] The results of the experiment showed that liposomes could be taken up by both epithelial cells and macrophages, thus accomplishing drug delivery. In the inflammatory colon, macrophages produced higher sphingomyelinase activity and greater drug phagocytosis than epithelial cells.

Furthermore, materials made of naturally occurring chemicals offer good biosafety and biocompatibility. Xu et al produced NP formulations with anti-inflammatory and antioxidant properties by packing DEX within curcumin and hydroxyethyl starch micelles.[42] In vitro release assays demonstrated that the negatively charged outer surface of NPs aided in their binding to inflammatory colon cells, and the α-amylase increased the drug release rate. NPs decreased the severity of inflammatory lesions and improved the effectiveness of free DEX compared to the untreated group.

Targeting Based on ROS

Free radicals, such as superoxide (O_2) and ^{-}OH, and non-free radicals, like singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2), make up the majority of ROS.[128,129] Bowel inflammation is caused by pro-inflammatory mediators, including TNF-α and IL-1, produced when ROS triggers the NF-κB signaling cascade.[130] Oxidative damage in the colon is caused by an excess of ROS and an imbalance of antioxidants in the intestinal mucosa of patients with IBD.[129,131,132] Activated phagocytes and leukocytes at the site of colitis are the primary source of the increased production of ROS.[133] According to a study, patients with IBD had 10- to 100-fold higher ROS concentrations in intestinal inflammation than healthy individuals.[134,135] Redox-responsive DDSs have gained attention from researchers to improve targeted drug delivery in inflamed intestinal areas (Figure 1C).[43–47]

Drug-drug coupling systems, with their high drug loading and minimal side effects, have been suggested as a novel approach. Li et al developed spherical nanostructures by self-assembling ROS-sensitive aromatized thione linkers with the anti-inflammatory drug budesonide and the antioxidant tempol (Figure 4).[43] Interestingly, the drug loading of the NPs was more significant (41% and 16%) than the loading of the two drugs in the PLGA NPs (6% and 3%). In the simulated environment experiment, the ROS-dependent release pattern led to nearly full release (99% and 98%) of these NPs for both drugs. Conversely, only 44% and 18% of the drug was released from PLGA NPs. The concurrent release of the two drugs allowed for the synergistic anti-inflammatory and antioxidant effects.

Additionally, superoxide dismutase (SOD) breaks down superoxide to form hydrogen peroxide, which catalase then breaks down into water. Zhang et al produced NPs (Tpl/OxbCD NP) by encapsulating the free radical scavenger Tempol (Tpl) in oxidation-responsive b-cyclodextrin, which releases cargo molecules by scavenging ROS components. According to drug imaging, OxbCD NPs had a higher targeting effectiveness than control PLGA NPs and accumulated 2.5 times more fluorescence intensity in mouse colon tissue than in normal mice. The oral Tpl/OxbCD NPs group showed a significant reduction in symptoms in three mice colitis models, with more efficacy than the free radical scavenger Tpl and -based control nanomedicine.[44]

In addition, IBD makes it easier for pathogens, such as intestinal bacteria, to enter the bloodstream and invade other organs. The goal of the design was a drug delivery system that scavenges ROS from the inflamed colon while also delivering antioxidant drugs to the bloodstream to reduce systemic inflammation. Researchers have developed silica-containing redox NPs that can scavenge ROS when loaded with silymarin.[45] According to the findings of in vivo experiments conducted on mice, the blood uptake of silymarin was significantly increased by the antioxidant carrier (siRNP). Additionally, the damage to the inflamed colonic mucosa was decreased considerably by the synergistic antioxidant effect of the drug and carrier.

Targeting Based on pH Levels

In contrast to the colon and rectum, which have pH values between 7.1 and 7.5, the stomach has an acidic pH.[136] Drug protection from gastrointestinal conditions and delayed drug release in acidic pH conditions can be achieved by NPs with a pH-sensitive design (Figure 1D). Scientists have developed drugs that are unique to the colon due to variations in the pH of the various gastrointestinal tract organs. Several pH-sensitive nanostructures, such as nanospheres, nanocapsules, and nano-polymers encapsulating other materials, have been developed. Additionally, colon-targeted drug delivery systems were designed using pH-dependent polymers, including methacrylic acid and methyl methacrylate (Eudragit® S 100, Eudragit® L, Eudragit® FS and Eudragit® P4135 F),[137] hydroxypropyl methyl phthalate cellulose, and few other polymers.[14,48–62] Eudragit® polymer is one of the most widely used synthetic copolymers for colonic drug delivery.[138]

The ionization of carboxyl functional groups makes the Eudragit® s100 resistant to invasion of the upper gastrointestinal tract, and it becomes soluble at pH >7.[139,140] Qelliny et al[48] synthesized NPs were loaded with budesonide, and their surface was coated with pH-sensitive Eudragit® s100. Studies conducted in vitro show that up to 72% of its maximum short-term cumulative release occurs at pH 7.4. Additionally, studies conducted on animals suggested that it had a more significant therapeutic effect on UC than the drug suspension in its free form.

Furthermore, Zhang et al developed hybrid drug delivery systems by encapsulating PLGA NPs loaded with berberine within an Eudragit® FS 30D matrix that has already been pre-encapsulated with berberine (Figure 5).[49] This pH-sensitive system immediately releases the drug-loaded NPs and berberine upon reaching the colon for lysis. The PLGA NPs are then absorbed by the colonic mucosa and gradually breakdown to maintain the sustained release of the drug. This pH-

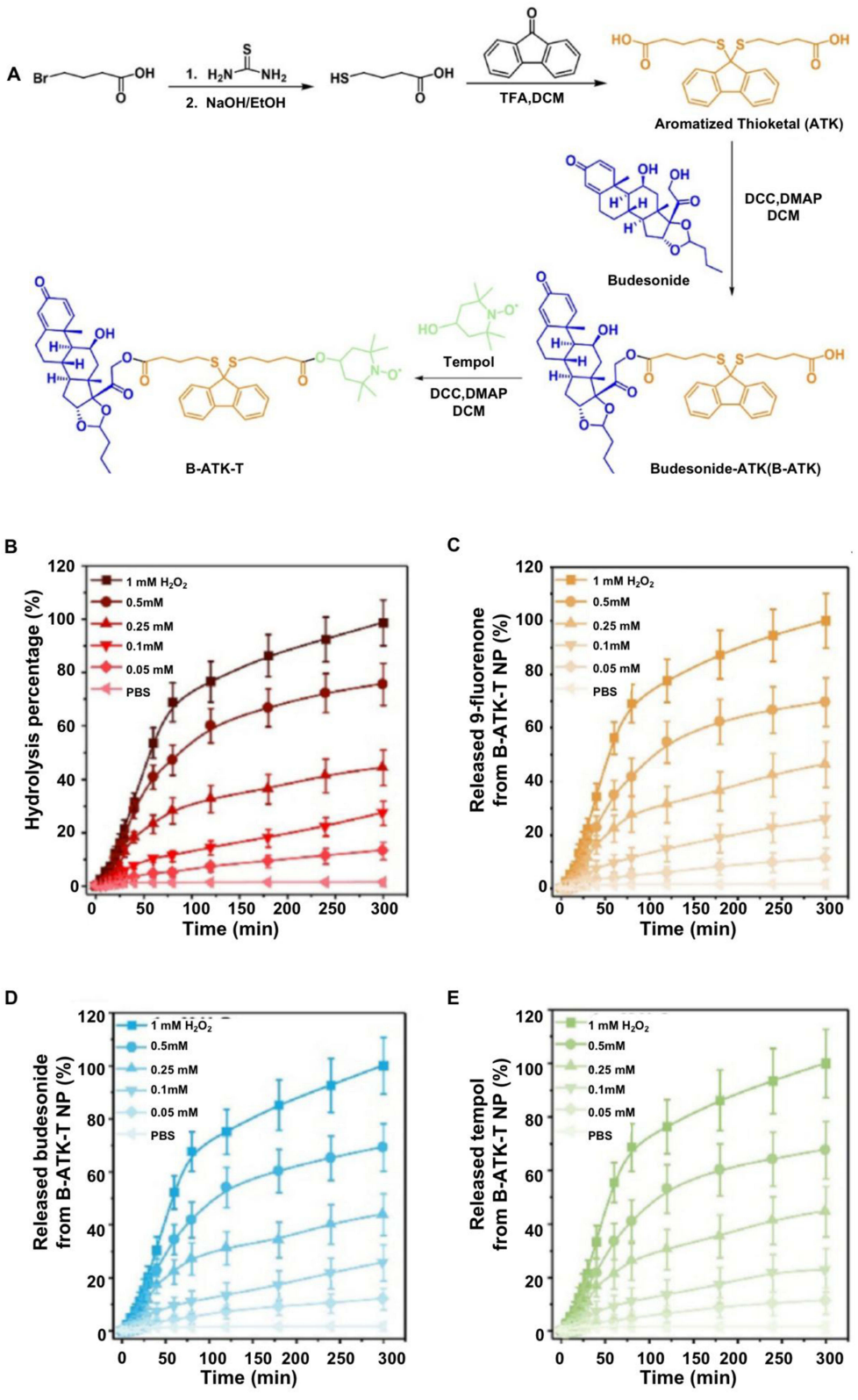

Figure 4 Sensitive reactive oxygen species-responsive B-ATK-T nanoparticles (NP) for treating irritable bowel disease. (**A**) The synthetic process of B-ATK-T. (**B**) Hydrolysis rate of B-ATK-T NP at various concentrations of hydrogen peroxide (H_2O_2). The release profiles of 9-fluorenone (**C**), budesonide (**D**), and tempol (**E**) from B-ATK-T NP at varying concentrations of H_2O_2 concentrations. Reprinted from *J Control Release*, volume 316, Li S, Xie A, Li H, et al. A self-assembled, ROS-responsive Janus-prodrug for targeted therapy of inflammatory bowel disease. 66–78, copyright 2019, with permission from Elsevier.[43]

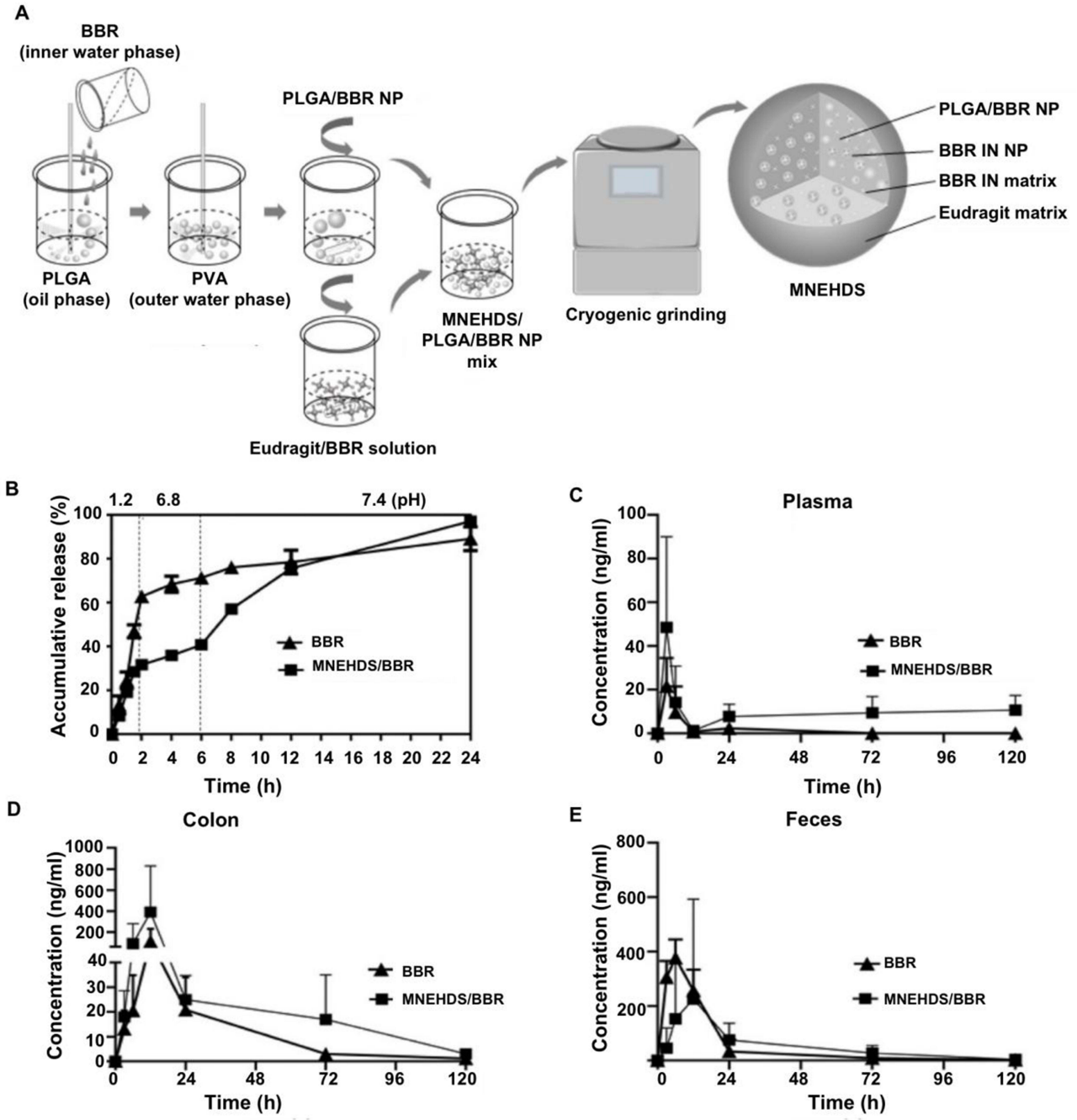

Figure 5 The novel nano-delivery system MNEHDS for treating irritable bowel disease. (**A**) The manufacturing process of MNEHDS. (**B**) Berberine (BBR) drug release rates in various simulated environments. The changes in BBR concentrations were investigated at various intervals in the plasma (**C**), colon (**D**), and feces (**E**). Reprinted from Zhang L, Li M, Zhang G, et al. Micro- and nanoencapsulated hybrid delivery system (MNEHDS): a novel approach for colon-targeted oral delivery of berberine. *Mol Pharmaceut.* 2021;18(4):1573–1581. Copyright © 2021 American Chemical Society.[49]

sensitive nanosystem accomplishes drug release into the tissue instantly and continuously. It promotes better therapeutic efficacy and patient compliance by lowering the amount of drug required and the frequency of administration.

The process of creating polymer NPs involves grafting polyacrylamide (PAAm) onto the backbone of xanthan gum (XG).[50] Upon additional NP hydrolysis, the PAAm amide functional group is transformed into a carboxylic acid (-COOH) group, creating a pH-sensitive copolymer.[141] Moreover, coliform bacteria can activate XG. Therefore, the NPs are very selective for colonic targeting. At a pH of 6.8, 3 h were needed to release approximately 65% of the drug. In vitro tests on rats

have revealed that the drug release rate is <15% with an acidic pH. However, within 8 h, the drug release rate may reach 100% if the pH of the solution is increased to 6.8 and intestinal contents are added.

Additionally, IL-1 receptor antagonist (IL-1Ra)-containing alginate/chitosan microcapsules were prepared.[51] Chitosan is a cationic polysaccharide.[142] The electrostatic interaction between the two is diminished in weak alkaline solutions because chitosan has a lower positive charge than alginate. This lets alginate absorb water and swell in an inflammatory colon environment, releasing the drug.[143] Furthermore, the microcapsules acquired an ultimate cumulative release rate of 86.2% in vitro. The microcapsules decreased the dose-induced colitis in mice, partially allowing the drug to accumulate in the colon.

Meissner et al developed a pH-sensitive Eudragit P-4135F polymer for colonic delivery of drug-loaded NPs to increase drug delivery efficiency and tolerability.[52] The polymer can break down and release the drug at pH >7.2. In vitro tests demonstrated that after 30 min, 100% of the loaded drug release at pH 7.4 could be achieved. Moreover, the oral NP formulation outperformed the free oral drug, although it was less effective in alleviating experimental colitis than subcutaneous administration.

The pH-dependent delivery mechanism may keep the drugs from dispersing before they reach the colon site. However, patients with IBD have a more acidic pH range in their colons,[136] which leads to partial drug release from the target site.[144] Researchers have created pH-dependent systems with alternative drug delivery systems, such as ROS-dependent or enzyme-triggered systems, to overcome the limitations of single pH-dependent DDSs.[63–67]

Naeem et al developed a pH- and azo reductase-sensitive azo polyurethane and Eudragit® S100 NPs.[63] Compared to single-trigger ES NPs, the NPs provide superior therapeutic efficacy by preventing a sudden release of the drug in the ileum and delivering an adequate amount to the inflamed colon. Budesonide is then sustained and released by an enzymatic reaction compared to single-trigger ES NPs. Pilot tests have demonstrated that the NPs are more stable than the pH-dependent type alone, preventing early drug release and enabling targeted colonic drug delivery.

The researchers developed mesoporous silica NPs, coated them with hydrolyzed starch, and placed them inside capsules containing Eudragit® FS 30D.[64] The nanosystem made it possible to alleviate the adverse effects of the drug and increase drug concentration at the colonic inflammatory site. Mesoporous silica NPs are released from the nanocapsules at colonic pH and are endocytically transported into colon cells after amylase stimulation.

The researchers developed an antioxidant-responsive dextrose (OxiDEX) NPs loaded with rifaximin.[65] The pH-responsive polymer hydroxypropyl methylcellulose acetate succinate was then used to encapsulate the NPs in chitosan surfaces. A pH- and ROS-responsive nanodelivery system was formed. Upon entering the colon and passing the acidic environment of the stomach, the NPs will release RIF in response to a trigger that increases ROS levels. In vitro experiments have demonstrated that the system can initiate the release mechanism at intestinal pH (6.8) and that, in the presence of H_2O_2, NPs can release >60% of the drug.

In addition, Wang et al developed infliximab-loaded polyphenol-containing PEG polymer self-assembled NPs.[66] In the stomach, the NPs aggregated into large-sized NPs. Then, at neutral pH in the colon, they reversibly transformed into small-sized negatively charged NPs (~100 nm). The antibody drug is then released from the NPs when they bind to the inflammatory colonic site through charge interactions and are impacted by high ROS concentrations in the mucosa. The favorable colonic targeting specificity and excellent therapeutic efficacy of the NPs were demonstrated in vivo in mice with colitis.

Targeting Based on Positive Charge

Surface-negatively charged DDSs has a high molecular target in the form of the positively charged protein (transferrin), which is overexpressed on the inflamed epithelial surface of IBD.[145] Negatively charged particles exhibit preferential adherence to injured sections of the colon through electrostatic interactions with these proteins (Figure 1E).[68–73]

Surfactants can impact the targeting efficiency of NPs. The NPs with negatively charged surfaces were created using polysorbate 20 as a surfactant.[68] In 30 min, the colonic site may release 80% of the loaded drug. The same NPs interacted two to three times more with macrophages (RAW 264.7 cells) than with enterocytes (C2BBe1 cells), which is an interesting aspect that implies a simple cell line is not a sufficient model of inflamed tissue in vivo.

Furthermore, heparin has a significant negative charge on the outer surface. Zhang et al developed NPs targeting inflammatory colon (HEP-HSA NPs) that use the electrostatic interactions at the region of intestinal inflammation to load both biological agents and small molecule drugs.[69] In vitro assays revealed that the NPs had a more potent anti-

inflammatory impact than NPs loaded with a single drug. Notably, it was discovered that there was a negative correlation between the diameter of HEP-HSA NPs and mucosal binding, with larger NPs preferentially binding to inflamed mucosa. And the investigation indicates that the smaller particle-size NPs enter the submucosa deeper.

Active Targeting

Drug distribution was improved in the inflamed areas of the colon by the EPR effect, which was facilitated by the particle size and surface physicochemical properties of NPs. However, this only promoted the accumulation of DDSs in colitis tissues. Insufficient target cell absorption efficiency and low intracellular drug release restrict anti-inflammatory drug therapeutic efficacy. Therefore, developing nanocarriers capable of actively targeting inflammatory cells may enable more precise targeting of colonic disease and minimize adverse side effects more effectively.

Specific antigens or receptors, such as the mannose, scavenger, folate, CD44, and chemokine receptors, are significantly overexpressed by epithelial cells and activated macrophages during the development of IBD. The interaction between particular receptors expressed at the diseased site and targeting ligands on the surface of the vector has increased targeting specificity. It also increases the degree of endocytosis and the bioadhesion of drug agents to particular cells (Figure 1F).[75–94]

The mannose receptor is overexpressed explicitly on the surface of macrophages at the site of inflammation.[146] Upon contact with this receptor system, NPs are rapidly internalized through receptor-mediated endocytosis, resulting in targeted drug delivery. Wang et al developed a naturally occurring polysaccharide-based NP that targets binding to macrophage mannose receptors.[75] According to the experimental results, NPs exhibited 81% drug release within 48 h, and the MPO levels of the mice were decreased. The NPs offer sustained release of curcumin and effective therapeutic outcomes compared to oral free curcumin administration (Figure 6).

Phosphatidylglycerophosphate methyl ester (PGP-Me) is a ligand for the scavenger receptor, which is highly expressed in macrophages and dendritic cells.[147] SOD was delivered via nanovesicles containing PGP-Me, which also could promote endocytosis of the drug carried by macrophages.[76] The study showed that mouse macrophages took up the nanosystem 6.4 times more than liposomal NPs. The activity of the enzymes it contains remained unchanged when exposed to conditions similar to oral administration, compared to the control group.

Furthermore, Le et al developed NPs functionalized on folic acid surfaces that were loaded with antioxidant enzymes.[77] They next evaluated a mechanism dependent on cellular endocytosis mediated by the folic acid receptor. Its PEG coating keeps antioxidant enzymes from breaking down. In vitro, cellular uptake tests demonstrated that the NPs could be absorbed by macrophages and epithelial cells and displayed a powerful solid fluorescent signal compared to controls. Moreover, the results of in vivo tests showed that intrarectal administration significantly decreased colitis symptoms in mice models by downregulating the production of pro-inflammatory cytokines.

Moreover, hyaluronic acid is a primary gastrointestinal mucosal epithelial extracellular matrix component, enabling interaction with overexpressed CD44 receptors.[148,149] Budesonide-loaded hyaluronic acid nanosystems (HANPs) were designed.[78] Compared to uncoated nanocomplexes, the HANPs enhanced cell adhesion and uptake in vitro experiments. Moreover, when HANPs and the exact dosage of free drugs were used in inflammatory cell models, HANPs showed higher anti-inflammatory effects on the secretion of inflammatory factors.

Chemokine receptor (CCR5) can be expressed on the macrophage surface.[150] Gong et al combined the chemokine ligand CCL4 with PLGA NPs to allow it to bind to the macrophage surface receptor CCR5, significantly improving the targeting ability of the drug.[79] Fluorescence staining showed that colonic macrophages could take up the NPs. The NPs not only improved the dysbiosis of the intestinal flora, but also promoted the repair of the intestinal barrier function by loading spleen tyrosine kinase inhibitors and decreasing the production of cytokines and chemokines.

Overall, the active targeting of ligands attached to the surface of nanodelivery systems is a promising strategy for treating IBD. Targeted ligands and targeted receptors expressed at inflammatory areas may improve the bioadhesion of drug formulations to particular cells and increase the degree of drug endocytosis. However, further in vivo research is required to evaluate the effectiveness of different strategies.

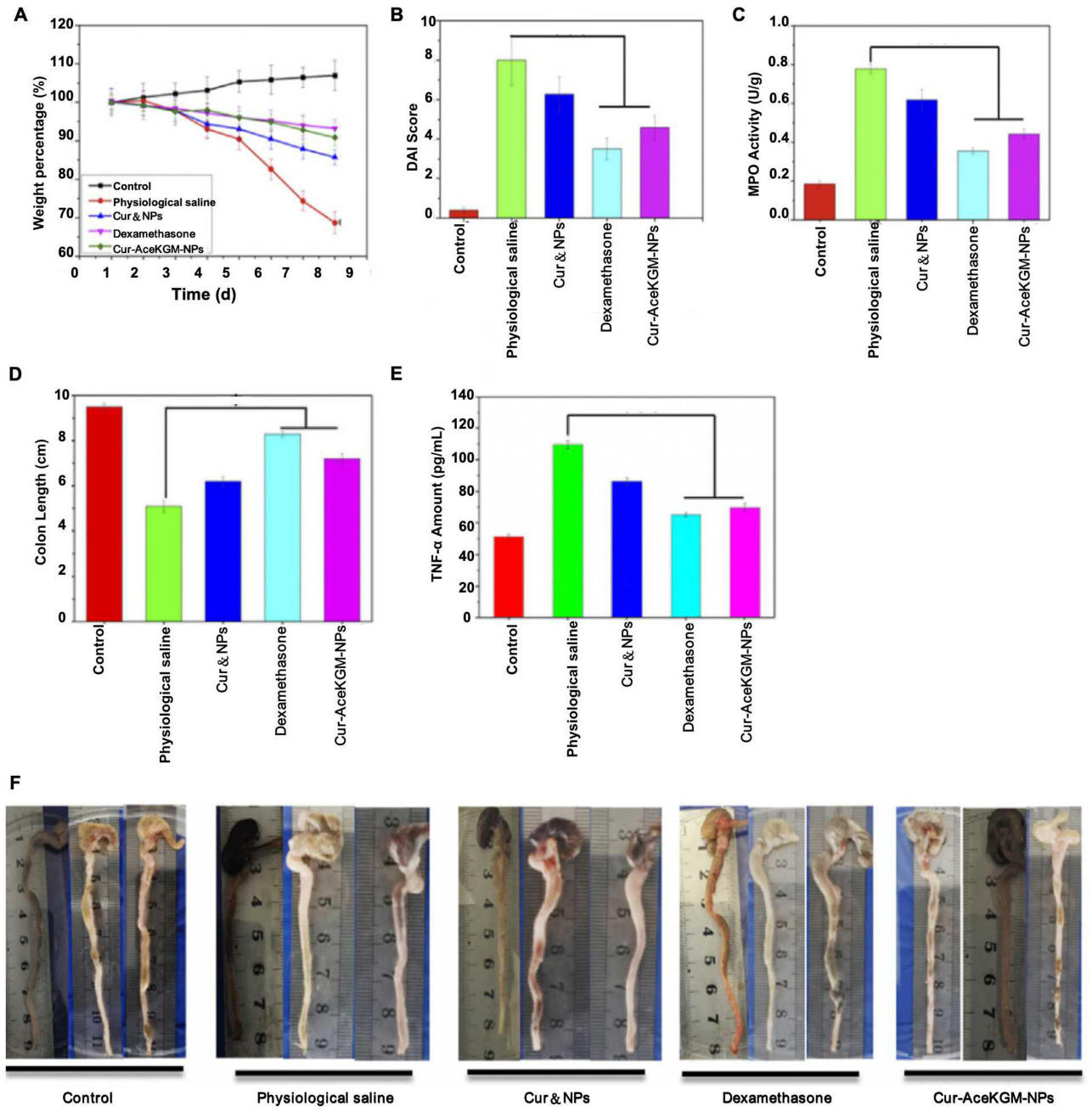

Figure 6 AceKGM nanoparticles for the treatment of irritable bowel disease. The percentage change in mice from various treatment groups body weight (**A**), Disease Activity Index score (**B**), myeloperoxidase activity (**C**), colon length (**D**), and TNF-α content (**E**). (**F**) Mice colonic tissues from various treatment groups. Reprinted from Wang C, Guo Z, Liang J, et al. An oral delivery vehicle based on konjac glucomannan acetate targeting the colon for inflammatory bowel disease therapy. Front Bioeng Biotechnol. 2022;10:1025155. Creative Commons.[75]

Hybrid Targeting

Apart from the above mentioned passive or active targeting strategies that rely on single factors (pH, enzymes, ROS, receptors, etc)., researchers have attempted to design targeting strategies that rely on multiple factors to overcome the multiple biological challenges encountered with orally delivered nanoparticle systems.[95,97–100] These targeting strategies, which combine different NP triggers, take advantage of the benefits of a single form while potentially mitigating its disadvantages to attain maximum effectiveness.

Mannose was abundant in cationic konjac glucomannan (cKGM) and selectively identified mannose receptors on the membranes of macrophages.[151,152] The researchers used methacrylate-based gelatin (GelMA) loaded with cKGM and

ASO nanocomposite and embedded in pH-sensitive Eudragit FS30D to create pH and mannose receptor-responsive nanocomposites.[95] The alkaline environment of the colon promotes the release of nanocomplexes, and colonic macrophages can absorb ASO through mannose receptor-mediated endocytosis. According to the experimental data, colitis mice may benefit from the targeted release of nanonucleic acids into their colons, which may help reduce inflammation and mitigate damage. This could have an impact on how IBD is treated.

Additionally, infliximab was loaded into the oral NP delivery system by combining it with ROS-reactive cross-linkers and altering it with hyaluronic acid.[97] Two synthetic ROS-responsive cross-linkers, SS and TK linkers, are highly sensitive to ROS to protect the integrity of NPs and allow the release of antibodies in the inflamed intestinal mucosa. Hyaluronic acid-modified NPs target CD44 receptors and improve NP uptake by macrophages and colonic epithelial cells. In vivo experiments revealed that the NPs were more effective in terms of therapeutic efficacy than in the intravenous administration of infliximab (Figure 7).

Furthermore, carbon dots (CDs) have become essential nanomaterials due to their excellent stability and biocompatibility.[153] Researchers have prepared mannosylated nanocomposites by covalent polymerization of mannosylated NPs (Man-NPs) with CDs, and the glycosylation process is negatively charged due to the carboxyl group possessed on the main chain of inulin.[98] Man-NPs can bind selectively to the mannose receptor on the macrophage surface, leading to preferential cellular absorption.

Other Functional Effects

Other methods based on nano-delivery systems can be used to treat and diagnose IBD, in addition to using passive and active targeting strategies to target inflammatory colon tissue for drug action.

Immune regulation has a role in the pathogenesis of IBD. The spleen is the largest lymphoid organ and can regulate the immune system. A splenic-targeted PEG liposome (ST-H_2S lipo) loaded with H_2S donors was developed to treat UC by immunomodulation.[32] According to a fluorescence assay against drug release, the fluorescence intensity of liposomes loaded with H_2S donors was higher than that of controls. ST-H_2S lipo exhibited significant absorption in the spleen following the intravenous drug administration. On the other hand, both conventional long-circulating liposomes (LC-H_2S lipo) and ST-H_2S lipo accumulated in the colon, with LC-H_2S lipo demonstrating a higher absorption rate. Compared to LC-H_2S liposomes, ST-H_2S liposomes had a more substantial immunomodulatory effect and a better therapeutic effect.

Restoring colon homeostasis using a microbiota-based strategy may be an effective IBD treatment. Nanomedicines containing components of cell membranes show promise as a therapeutic approach for managing a range of inflammatory diseases.[46] Scientists have recently developed a nanosystem with both antioxidant and anti-inflammatory functions (SeM@EM) by coating the surface of mesoporous silica NPs with a natural *E. coli* membrane that acted as a ROS scavenger. It was demonstrated that the NPs reduced inflammation and improved the adhesion of the drug. It is also remarkable how the NPs regulated the intestinal homeostatic balance and the growth of good intestinal microbiota.

Imaging IBD can be complex because the routinely used contrast agents (iodine-based and barium-based) are usually non-specific for the site of inflammation in IBD. Nahaet al developed a cerium oxide NP (Dex-CeNP) coated with dextrose anhydride as a contrast agent for IBD diagnostic imaging.[154] The presence of dextran provides good NP stability, biocompatibility, and specificity. Cerium oxide is also an antioxidant, neutralizing free radicals and reducing inflammation. Dex-CeNPs provide significant computed tomography contrast in the colon and accumulate in colitis-affected tissues. Notably, oral doses can nearly completely leave the body in 24 h.

Cerium dioxide NPs exhibit diverse enzymatic properties, such as superoxide dismutase and catalase activities, in addition to their capacity to scavenge hydroxyl radicals. Zhao et al combined cerium dioxide NPs and negatively charged montmorillonite to create the nanoenzyme complex.[70] When administered orally, the nanosystem targets the positively charged, inflamed colon and, in addition to its antioxidant properties, acts as montmorillonite to reduce bleeding.

Challenges and Future Perspectives

Despite substantial advancements in treating IBD based on nanodelivery techniques, there are still some issues and inefficiencies in the development process.

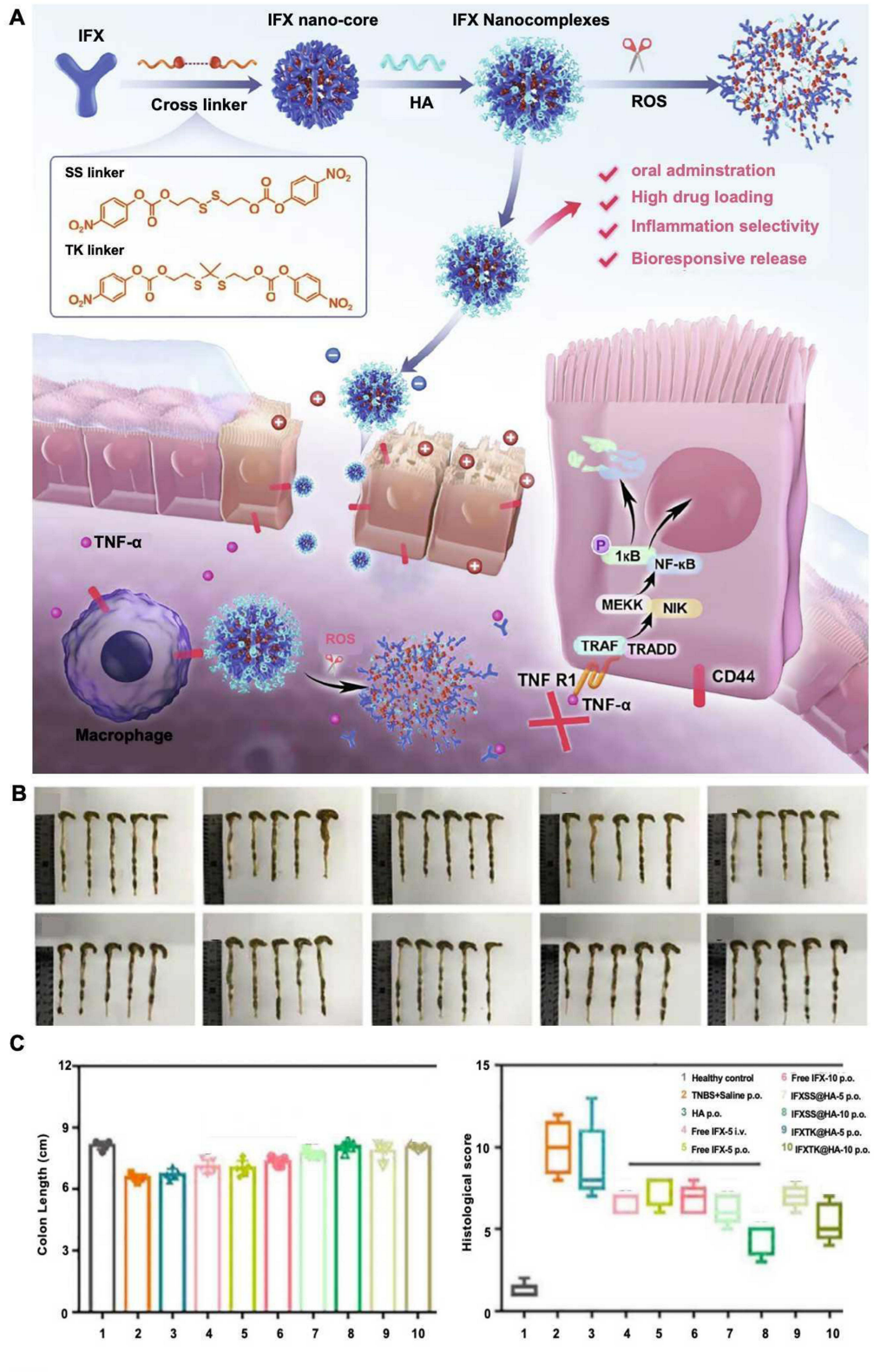

Figure 7 (**A**) IFXSS@HA/IFXTK@HA drug synthesis process and irritable bowel disease treatment mechanism. Colonic tissues (**B**), colonic length, and histopathologic histologic scores (**C**) of mice post-treatment in each group. Adapted from *Chem Eng J*, volume 445, Li X, Fang S, Yu Y, et al. Oral administration of inflammatory microenvironment-responsive carrier-free infliximab nanocomplex for the targeted treatment of inflammatory bowel disease. 136438, Copyright 2022, with permission from Elsevier.[97]

Formulation improvement of drug preparation. Increased drug release from the colonic site and improved therapeutic efficacy can arise from formulation optimization of the product. For instance, multiple NPs were developed using various formulation ratios, and it was ultimately discovered that capryol 90 may be used as the carrier to enable complete drug release.[48]

Improvement of the preparation process. Some preparation methods require a time-consuming, multi-step process with production scale restrictions, making the prepared NPs less stable The drugs made partially by self-assembly have inadequate drug loading and low encapsulation rates. Problems regarding drug stability, loading discrepancies, and dimensional variations in the nano-delivery platform may also occur in large-scale production, whereas they do not occur in small batch production. Therefore, additional research on nano/micro-targeted drug delivery and developing new preparation processes is required to obtain a straightforward and dependable medication production.

Different results may stem from different experimental models. In vitro simulation experiments using NPs can produce positive findings regarding anti-inflammatory and antioxidant results. However, there are differences between experimental models (rodents) and human patient species. In vivo modeling of drug release and predicting stability of the gastrointestinal tract is challenging due to the complexity and individual heterogeneity of the gastrointestinal tract. For instance, the relevant targeting and therapeutic effect will be lessened if inflammation exists in other sites. Further research should be done to find an animal model that can accurately represent human IBD disease and imitate the pathophysiological environment of human IBD.

Optimal drug properties. Despite the excellent performance of the prepared NPs in trials, new designs must still be found to increase the precise release rate of the drug. The intended clinical outcome cannot be achieved by focusing on just one factor; instead, multiple combinations of strategies must be used. IBD treatment should include improving intestinal flora and re-establishing intestinal balance. Drug biocompatibility and biosafety should also be considered because nanocarriers may be toxic to the liver, kidneys, or other organs during their breakdown, metabolism, and excretion. Further experimental design and validation are required for some experimental results that did not investigate and understand the origins of the occurrence.

There are a number of potential issues to be addressed from the translation of nanomedicines to the clinic, including insufficient understanding of the mechanisms and chemical structure materials of NPs, safety profiles, regulatory and legal challenges. Therefore, the absorption and binding mechanisms during gastrointestinal transit still need to be studied in depth for the development of more advanced DDSs with more rational use of the pathological and physiological microenvironment. It is also essential to assess the long-term toxicity of DDSs and to develop relevant regulatory programmes. For drugs, more extensive multi-centre clinical studies are also needed to validate their efficacy. Concerted efforts by scientists and clinicians are needed in the development of nanomaterial drug delivery systems for the treatment of inflammatory diseases. The regulatory situation and ethical considerations pertaining to the development and application of nanoparticle-based therapeutics are also important factors to be taken into account in the context of translational research and clinical applications.

We are glad to note the innovative theories and strategies that nanotechnology has contributed to treating IBD and the diagnostic advancements it has brought about. The following qualities should be included in a perfect nanomedicine: A) it should be simple to make and can be mass-produced; B) it should be stable, with high drug loading and excellent drug release rates; C) it should have high target specificity, acting directly on the inflammatory colon site and releasing the drug continuously; and D) it should be easy to breakdown and absorb by the human body and should have good biosafety.

Conclusions

There is no complete treatment plan for IBD because it is a chronic idiopathic inflammatory disease with an unknown etiology. Every traditional therapeutic drug and treatment has disadvantages and causes more adverse effects and causes more adverse effects. Nano-agents, which can target and have various functional effects through both passive and active targeting, have been produced with the advancement of nanotechnology. Nanomedicines have demonstrated superior experimental therapeutic results. Currently, research on the clinical application of drug preparation, experimental design, and clinical application of drugs is still unsatisfactory. But these will be the areas of focus for future research. Future research will tend to the following aspects. Investigate the pathophysiological mechanism of the disease in more detail; develop novel drug delivery strategies by combining the research features of active and passive targeting; examine novel

experimental animal models to provide adequate pathological information for experiments; and screen optimal targeting drugs for early release into clinical practice.

Author Contributions

JG: Writing-reviewing and editing. JL: Conceptualization and methodology. ZL: Software. HW: Visualization and supervision. ZM: Funding acquisition. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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