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REVIEW

Recent Achievements and Perspectives in Smart Nano-in-Micro Platforms for Ocular Disease Treatment

Yuhan Huang[1,*], Dan Yan[1,*], Weijie Ouyang[1,2,*], Jiaoyue Hu[1,3], Zuguo Liu[1,3,4]

[1]Xiamen University Affiliated Xiamen Eye Center; Fujian Provincial Key Laboratory of Ophthalmology and Visual Science; Fujian Engineering and Research Center of Eye Regenerative Medicine; Eye Institute of Xiamen University; School of Medicine, Xiamen University, Xiamen, Fujian, People's Republic of China; [2]Department of Ophthalmology, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, People's Republic of China; [3]Department of Ophthalmology, Xiang'an Hospital of Xiamen University, Xiamen, Fujian, People's Republic of China; [4]Department of Ophthalmology, The First Affiliated Hospital of University of South China, Hengyang, Hunan, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zuguo Liu; Jiaoyue Hu, Eye Institute of Xiamen University, 168 Daxue Road, Xiamen, Fujian, People's Republic of China, Email zuguoliu@xmu.edu.cn; mydear_22000@163.com

Abstract: Ocular diseases present unique therapeutic challenges due to the complex anatomical and physiological barriers of the eye. Conventional drug delivery systems often suffer from poor bioavailability, rapid clearance, and inadequate targeting, limiting their clinical efficacy. Recent advances in smart nano-in-micro (NIM) platforms have emerged as a transformative strategy, combining the precision of nanoscale drug carriers with the stability and sustained-release capabilities of microscale matrices. These hierarchical systems enable enhanced drug penetration, prolonged retention, and targeted delivery to both anterior and posterior ocular segments. This review highlights the latest developments in NIM platforms, focusing on material innovations that optimize drug loading, release kinetics, and biocompatibility. The shared physicochemical properties of nano-micro particles that influence their performance across different administration routes (topical, intravitreal, subconjunctival), supported by mechanistic insights into their interactions with ocular tissues are discussed. By bridging nanoscale engineering with clinical ophthalmology, NIM platforms represent a paradigm shift in ocular therapeutics, offering the potential to revolutionize treatment for previously intractable eye diseases.

Keywords: nano-in-micro, nanoparticles, ocular diseases, ocular drug delivery

Introduction

The global burden of visual impairment remains a critical public health challenge. According to data from the Global Burden of Disease (GBD) database, disability-adjusted life years (DALYs) attributable to blindness and vision loss have exhibited a progressive increase from 1990 to 2021 (https://vizhub.healthdata.org/gbd-compare/).[1,2] Despite advances in pharmacotherapy, this concerning trend persists, primarily due to the unique anatomical barriers of the eye—including the blood-retinal barrier (BRB) and rapid tear turnover—which severely restrict the bioavailability of topical formulations and the therapeutic half-life of intravitreal injections.[3,4] Conventional nanotechnologies (eg, liposomes, polymeric nanoparticles) have only partially addressed these challenges,[5,6] as their single-scale design necessitates a trade-off between barrier penetration and therapeutic retention.

The nano-in-micro (NIM) platform represents a hierarchically structured drug delivery system that strategically integrates functional nanoscale components (eg, nanoparticles (NPs), nucleic acid nanostructures) into microscale carriers (eg, polymeric microparticles, liposomes)[7–9] (Figure 1). This architecture synergizes the advantages of both scales: nanoscale modules enable precise targeting and controlled release, while microscale carriers provide structural stability and enhanced payload capacity. By leveraging size-dependent interactions (<100 nm for barrier penetration and >1 μm for sustained retention), the NIM system uniquely addresses the dual challenges of ocular bioavailability and

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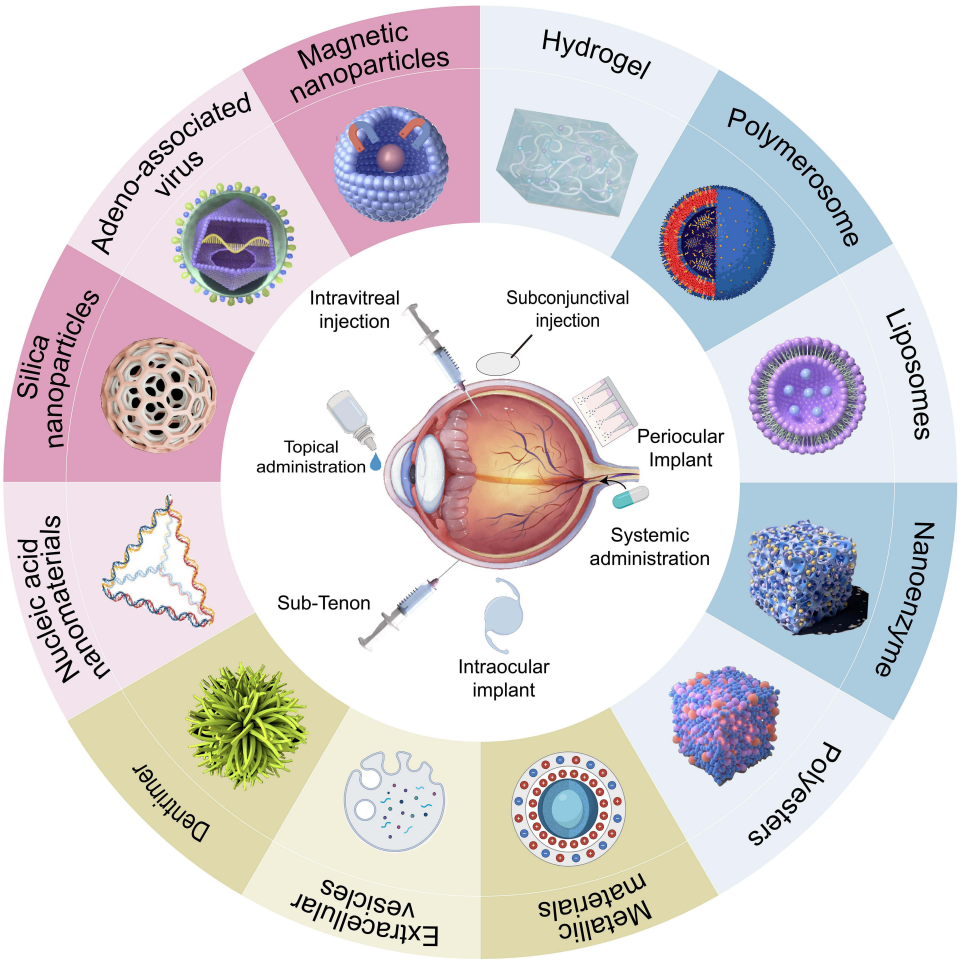

Figure 1 Graphical representation of the various delivery routes for ocular administration. It displays the conventional routes of drug administration for ophthalmic diseases, emphasizing both internal and external methods. Alongside these traditional pathways, the figure also introduces a graphical representation of various nanomaterials with distinct structural characteristics that can be utilized for ocular administration. These nanomaterials, with their unique properties such as enhanced penetration, controlled release, and biocompatibility, offer promising alternatives to conventional drug delivery systems. Created using BioRender.

localized biodistribution.[10,11] Through sophisticated surface functionalization and hierarchical structural design, the NIM platform integrates diverse material properties, thereby synergistically enhancing biointerfacial interactions (eg, improved cellular uptake efficiency) and physicochemical characteristics (eg, hydrophilicity-tuned ζ-potential).[11–13] The resulting hybrid system demonstrates superior performance in overcoming multi-layered ocular barriers, achieving spatiotemporally controlled drug release, and maintaining targeted delivery precision.[14–16] This comprehensive optimization paradigm stands in stark contrast to conventional single-material systems, which rely predominantly on passive diffusion mechanisms (eg, the low corneal bioavailability of standard eye drops).

Traditional NPs face inherent limitations in ocular drug delivery, including rapid clearance, passive diffusion-dependent targeting (resulting in poor retinal bioavailability), and payload instability. The NIM platform innovatively overcomes these barriers through its hierarchical design.[8,17,18] Unlike single-scale systems, NIM exploits a dual-scale synergy: 1 nanoscale precision (for instance, surface-functionalized liposomes enable receptor-mediated BRB delivery;[19] 2 microscale stability (for instance, encapsulation within poly(lactic-co-glycolic acid) (PLGA) microspheres prolongs intraocular retention and shields payloads from enzymatic degradation[20]); 3 synergistic control (the microcarrier acts as a reservoir for sustained nanocarrier release, achieving spatiotemporal precision unattainable with conventional NPs).[21,22] This structural innovation resolves the "targeting-retention paradox" in ocular therapy: NPs small enough to penetrate barriers are rapidly cleared, whereas larger particles with better retention lack penetration capacity. NIM addresses this by decoupling penetration (nanoscale) and retention (microscale) functions—a critical advancement supported by extensive

research.[22–24] Compared to standard NPs, the NIM platform exhibits a higher therapeutic index while utilizing lower drug concentrations, thereby mitigating systemic toxicity.[25] Emerging NIM technologies enable efficient delivery of therapeutics or gene-editing systems to specific target cells, demonstrating translational potential through prolonged drug half-life, enhanced bioavailability, and reduced adverse effects.[26,27] However, clinical translation of NIM systems faces regulatory challenges, particularly in addressing the complexity of hybrid NIM constructs.[28] Recent breakthroughs in microfluidic manufacturing and biodegradable matrices have paved the way for scalable production.[29–32]

This review critically evaluates the application potential of cutting-edge technologies—including nucleic acid nanomaterials and stimulus-responsive nano-micelles—in ophthalmic therapy. We aim to elucidate the key determinants and future trajectories of nanotechnology-driven innovation in ophthalmology. By bridging nanoscale innovation with microscale engineering, the NIM platform is redefining the frontier of ocular medicine, offering transformative solutions for previously intractable conditions such as geographic atrophy and diabetic macular edema.

Common Ophthalmology Diseases and Therapy Approaches

A variety of ocular diseases have been explored through extensive research in nanomedicine, with NIM technology demonstrating remarkable efficacy.[18] Research has primarily focused on developing multifunctional nano-systems, which include nucleic acid nanomaterials, inorganic NPs, and other nano-carriers.

Novel drug delivery nano-systems offer new strategies for treating dry eye, showing significant advantages over traditional eye drops.[33] Several ocular nanocarriers are currently in clinical trials or various stages of development, with some already approved by the FDA for market release.[34] However, the treatment of posterior segment diseases still faces challenges due to complex pathophysiological mechanisms and biological barriers, such as the blood-retinal barrier, which are difficult to penetrate. The retinal pigment epithelium serves as a rate-limiting factor for posterior delivery routes.[35,36]

Vascular-related diseases, such as retinopathy of prematurity, diabetic retinopathy, and age-related macular degeneration (AMD), are common conditions affecting the posterior segment of the eye. Anti-VEGF drugs represent a promising approach to treat these diseases, but intravitreal injection therapies have limitations, including short drug half-lives, the need for repeated injections, and potential systemic adverse events.[37] Retinal degeneration, as a complication of AMD and diabetic retinopathy, is also characteristic of various hereditary diseases, presenting limited treatment options due to the complexity of the pathophysiological processes involved.[38] Regarding retinal tumors, although several treatment options exist, there remains a lack of minimally invasive drug delivery alternatives.[39,40]

Challenges in the Current Ocular Drug Delivery Systems

Currently, traditional drug delivery methods for ocular diseases include systemic administration, topical application, periocular delivery, and intravitreal injections. However, due to the delicate structure of the eye, rapid tear drainage, drug metabolism and degradation, and the presence of multiple ocular barriers (Figure 2), challenges such as difficulty in controlling local drug concentrations, low bioavailability, and adverse reactions remain urgent issues to address (Table 1). While extensive research has focused on overcoming the limitations of ocular drug delivery, further efforts are still needed. Although nanotechnology holds promise for overcoming these challenges, it must still navigate multiple physiological barriers, including the tear film, cornea, conjunctiva, sclera, and blood-retinal barrier.[41]

Diverse NIM Platform from Different Materials

The NIM platform leverages its nanoscale dimensions and surface characteristics to effectively overcome ocular barriers and achieve targeted drug delivery (Figure 1). While conventional NPs (eg, liposomes, polymeric NPs) demonstrate some ocular delivery capability, they inherently struggle with the "penetration-retention paradox" - smaller NPs can penetrate ocular barriers but are rapidly cleared, while larger particles with better retention capacity lack penetration ability.[42–45] The NIM platform ingeniously addresses this limitation through hierarchical engineering that decouples these functions into two cooperative scales.[46]

The NIM platform incorporates several groundbreaking innovations that collectively address the challenges of ocular drug delivery. One key advancement is its Dual-Ligand Engineering system, which strategically combines microscale

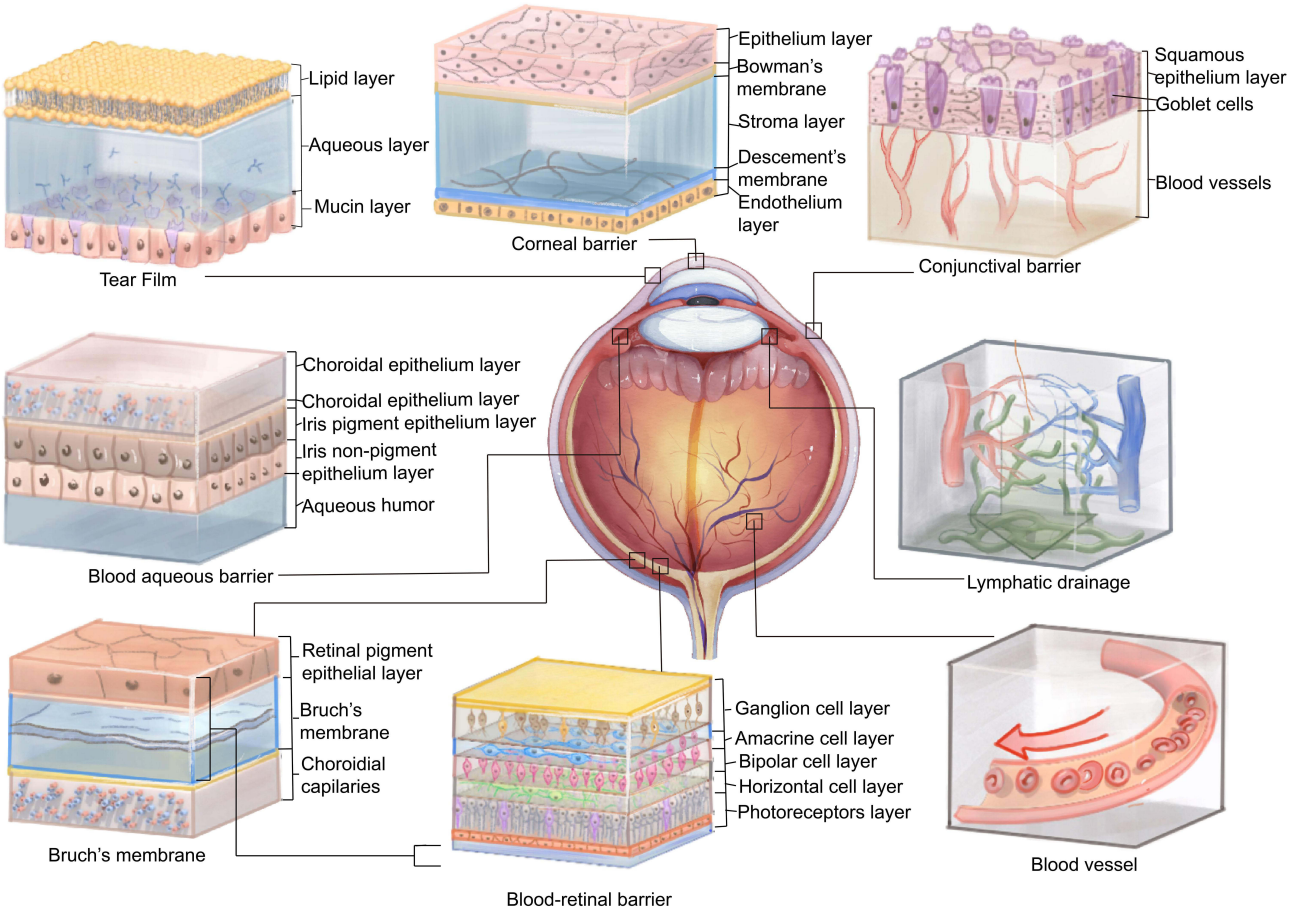

Figure 2 Multiple barriers of the eye. It exhibits various physiological barriers and factors that may influence drug distribution in ophthalmic therapy, encompassing the tear film, the blood-retina barrier, and other critical components. It highlights the complex interplay of these barriers, which can significantly impact the delivery and efficacy of therapeutic agents targeting ocular diseases. Understanding these barriers is crucial for the development of effective drug delivery systems that can navigate these challenges, ensuring optimal treatment outcomes in ophthalmic care. Drawn with Procreate.

carriers enhanced with mucoadhesive polymers (eg, chitosan) for improved precorneal retention[47,48] with nanoscale modules designed for cell-specific targeting, such as the AS1411 aptamer for retinoblastoma therapy.[49–51] Another significant innovation is the platform's Stimuli-Responsive release capability, where drug delivery can be precisely activated by specific biological conditions including pH, ROS levels, or glucose concentrations. This is exemplified by glucose-responsive carboxyphenylboronic acid (CPBA)-functionalized mesoporous silica NPs (MSNs) that enable controlled delivery of 1,25-dihydroxyvitamin D3 for diabetic retinopathy treatment.[52] Furthermore, the platform's Scalable Manufacturing process, utilizing microfluidic production techniques, demonstrates markedly superior batch-to-batch consistency compared to conventional methods, effectively overcoming critical translational challenges in pharmaceutical development.[53,54] These integrated innovations position the NIM platform as a transformative approach in ocular therapeutics.

Inorganic Nanomaterials for Ophthalmic Applications (Table 2)

Inorganic NPs (eg, gold, silver, silica, quantum dots) possess controllable dimensions, structures, and unique optoelectromagnetic properties that make them promising candidates for drug delivery and therapeutic applications. However, they face several challenges including susceptibility to degradation, poor biocompatibility, and insufficient stability/dispersibility, which limit their clinical utility.[55,56] Surface functionalization with organic/inorganic coatings can significantly improve their dispersion and stability in biological systems.[57] These materials have been strategically

Table 1 Overview of Advantages and Limitations of Conventional Drug Delivery Methods for Ophthalmic Disorders[41]

Strategies		Indications	Drawbacks
Systemic administration	Oral administration, intramuscular injections, intravenous injections	Involvement of multiple body systems with severe systemic symptoms	Drug toxicity at high doses; ocular barriers reduce biocompatibility; systemic side effects
Topical administration	Eye drops (solutions, suspensions and emulsions)	Anterior segment diseases	Poor bioavailability due to tear drainage; physicochemical properties affect drugs; uncontrolled drug release; frequent dosing required
	Ointments	Anterior segment diseases	Patients' discomfort, eg, blurred vision; uncontrolled release of drugs
Periocular administration	Scleral route	Posterior segment diseases	Minimally invasive; limited by ocular barriers (RPE, choroid and sclera)
	Sub-conjunctival injection, sub-tenon injection	Anterior and posterior segment diseases	Puncture-related pain, infection, bleeding; high drug concentration; optic nerve damage risk; reduced bioavailability via blood, tears; worsens cataracts, ocular hypertension
	Supra-choroidal injection, sub-retinal injection	Posterior segment diseases	Puncture causes pain, toxicity, infection, bleeding; risks of choroidal detachment, optic nerve damage; invasive, complex
Intraocular administration	Intravitreal injection	Posterior segment and whole eye diseases	Puncture leads to pain, infection, bleeding; heightened risks of retinal detachment, lens damage

incorporated into NIM platforms to overcome the limitations of single-component systems[58,59] (Figure 3), demonstrating unique advantages in ophthalmic therapies.

Nanozymes exhibit enzyme-mimicking catalytic activities with remarkable antioxidant and anti-inflammatory effects. Their nanoscale dimensions and ease of modification enable effective ocular barrier penetration, making them ideal for targeted treatment of multifactorial eye diseases like dry eye syndrome and AMD.[107] A recent study[108] developed a novel nanozyme-incorporated hydrogel coating (NHC) through Schiff base reaction between polyaldehyde oligomers (PAO) and amino-functionalized hyaluronic acid (AHA). This system co-loaded voriconazole and copper procyanidin (CuPC) nanozymes for fungal keratitis treatment, where the combined catalase-like and superoxide dismutase-like activities synergistically promoted corneal wound healing, with enhanced efficacy through prolonged retention and improved corneal permeability.

Quantum dots (QDs), particularly carbon-based quantum dots (CDs), have emerged as attractive nanomaterials due to their exceptional fluorescence properties, ultra-small size for cellular/tissue penetration, facile synthesis and surface modification, low cytotoxicity and superior aqueous dispersibility. These characteristics make CDs excellent candidates for ocular imaging, drug delivery, and disease diagnosis.[109–112] Notably, spermidine-derived carbon QDs (CQDSpds) synthesized via a one-step dry-heat method demonstrated antibacterial properties and enhanced corneal epithelial permeability through their ultrahigh positive charge-induced tight junction opening.[73]

Mesoporous silica NPs (MSNs) offer tremendous potential for drug delivery owing to their high stability, large surface area and pore volume, tunable pore sizes and ease of production and functionalization. Hydrophilic MSNs serve as stable, biocompatible carriers that prolong blood circulation, making them a research hotspot.[113,114] Surface-functionalized MSNs with NH2 and PEG modifications, combined with nanomolding technology for drug conjugation, have shown improved bioavailability and prolonged therapeutic effects in treating retinal pathological neovascularization.[115]

Innovative metal nanomaterial designs have demonstrated significant therapeutic enhancements. PEG-coated nanoceria (P/CeO_2) developed by Haijie Han's team exhibited improved biocompatibility, hydrophilicity, and remarkable ocular tolerance while prolonging precorneal retention.[116] Urchin-like gold nanostructures with optimized branch length showed 150-fold greater corneal retention compared to smooth gold NPs. In dry eye rabbit models, quercetin-loaded nano-urchins (NU-Q(H)) demonstrated: 30-fold increase in tear production, 49-fold suppression of IL-6 expression, 32-fold reduction in pathological angiogenesis, as well as 18-fold enhancement in nerve regeneration.[117] Ion-responsive alginate-capped nanoceria (Ce-ALG) for β-1,3-glucan delivery in corneal abrasion treatment: Alginate coating improved mucoadhesion via hydrogen bonding, Ca^{2+}-mediated "egg-box" structure enhanced drug loading and sustained release,

Table 2 Representative Applications of Inorganic NPs in Drug Delivery Systems

Inorganic nanomaterials	Drug/Modification	Application	Model	Function	Ref.
Iron oxide NPs	Mesenchymal stem cells	Intravenous injection	Rat	Cell delivery to outer retina for macular degeneration and retinitis pigmentosa	[60]
		Magnetic hyperthermia	Cells	Utilizing magnetic hyperthermia for targeted cell ablation in retinoblastoma	[61]
	Avastin	None	None	Minimize the dosage of Avastin administered for AMD to mitigate systemic adverse effects	[62]
	Diclofenac sodium	Transscleral drug delivery	Human cadaver eyes	Utilize magnetic field to enhance drug delivery across the sclera.	[63]
	VEGF	Intravitreal injection	Zebrafish	Specifically target the choroid	[64]
	None	Intravenous injection	Rabbit	Measuring blood volume and contrast agent uptake facilitates tumor diagnosis and viability assessment	[65,66]
	Neurotrophins	Intravitreal injection	Zebrafish	Autonomously localize in the retina, exerting neuroprotective function	[67]
	None	Intravitreal injection	Xenopus embryos	Specific targeting of RPE	[68]
	Guanabenz and valproic acid	Topical	Mice	Invasive drug delivery to the mouse photoreceptors	[69]
Cobalt ferrite NPs as core inside a cubic iron oxide NPs shell	None	None	Bovine cornea endothelial cells	Photothermal therapy agents for eye diseases and could be a target in an ocular system using MRI	[70]
Silica iron-oxide NPs	X-tremeGENE-HP	None	Human corneal epithelial cells and explanted human corneas	Magnetofection with anti-apoptotic P35 gene effectively blocked apoptosis	[71]
	Dexamethasone	Intravitreal injection	Rabbit	Targeted drug delivery to the retina	[72]

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Quantum dots	Biogenic polyamines	Topical	Rabbit	As eye drop formulation for topical treatment of bacterial keratitis	[73]
	Nitrogen doped, Arg-Gly-Asp-Ser (RGDS) peptides modified	Topical	Mice	Neutralize ROS and modulate intracellular antioxidant pathways	[74]
		Inject into the anterior chamber of the eyes; intravitreal injection	Mice; human vitreous	Trace lymphatic drainage; prevent the fibrillation of type I collagen and destroy collagen fibers to treat vitreous opacities	[75,76]
	Nanozyme loaded in hydrogel	Topical	Mice	Enhanced retention time on the ocular surface and increased bioavailability, resulting in a satisfactory therapeutic outcome for dry eye	[77]
	Imidazole-modified, dissolve in microneedle patches	Topical	Rabbit	Antibacterial activity and effective drug delivery to treat bacterial keratitis	[78]
	Carboxylated CuInS/ZnS quantum dots			Generate localized heat and prevent posterior capsule opacification	[79]
	Nitrogen-doped			Electrocatalytic treatment of choroidal melanoma	[80]
	Non-oxidized MXene-Ti(3)C(2)Tx	Intraocular injection	Mice	Inhibits the proliferation, invasion, and migration of uveal melanoma cells and exerts robust antitumor activity in vivo	[81]
	Lipid-NPs-based co-delivery, melphalan	Intravitreal injection	Mice	Inhibit cell proliferation and reduce retinoblastoma	[82]
	Polymeric curcumin to arginine-derived carbon quantum dots	Topical	Rat	Antioxidative, anti-inflammatory, and pro-proliferative to treat ocular infection	[83]
	Graphitic carbon nitride	Topical	Rabbit	Increase the oxygen concentration within the corneal stroma for corneal ectasias and other corneal diseases	[84]
	Anti-VEGF-aptamer modified	Topical	Rat	Inhibit VEGF-stimulated angiogenesis treat AMD and diabetic retinopathy	[85]
	Pyrolysis of lysine hydrochloride	Topical	Mice	Free radical scavenging, anti-inflammatory activity, high biocompatibility, and a remarkable ocular bio-adhesive property to treat dry eye	[86]
	Dextran/aliphatic diamines carbonized nanogels	Intravitreal injection	Rat	Possess efficient suppression of ocular microbial infection and inflammation in endophthalmitis	[87]
	Peptide-functionalized silicon NPs	Intravenous injection	Mice	Antiangiogenic ability	[88]
	Sodium alginate and 1,8-diaminooctane	Intravitreal injection	Chicken embryos and rabbit eyes	To treat various angiogenesis-related ocular diseases	[89]
Mesoporous silica NPs	Bevacizumab with zinc ion	Topical	Rat	Inhibiting corneal neovascularization	[90]
	Pilocarpine	Intracameral administration	Rabbit	Extended drug release profiles in progressively glaucomatous eyes	[91]
AuNPs	Doxorubicin -loaded fucoidan	Intraocular injection	Rabbit	Selective light absorption treating and diagnosing the eye tumors	[92]
	Ascorbic acid onto the exosomal phospholipid membrane of exosomes	Topical	Mice	Improves corneal epithelium recovery and anti-inflammation capacity, decreases corneal reactive oxygen species, and restores tear secretion in dry eye	[93]
	siRNA	None	Human melanoma cell lines	Therapeutic gene regulatory	[94]

(*Continued*)

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Table 2 (Continued).

Inorganic nanomaterials	Drug/Modification	Application	Model	Function	Ref.
AgNPs	Camellia sinensis	Topical	Dunkin-Hartley guinea pigs	Result in allergic conjunctivitis low clinical score	[95]
	Poly(sulfobetaine methacrylate-co-dopamine methacrylamide)	Topical	Rabbit	Antibacterial to treat bacterial keratitis	[96]
	Abelmoschus esculentus	Intraperitoneally injection	Rat	Manages the diabetic retinopathy	[97]
	Ketoconazole and amphotericin B		Fugal	Enhance the activities of ketoconazole and amphotericin B	[98]
	Curcumin		Human Pterygium-Derived Keratinocytes	Representing an alternative and a more sophisticated strategy for the treatment of human pterygium	[99]
			Cosmopolitan amoebae from Acanthamoeba genus	Prevent against Acanthamoeba keratitis infection.	[100]
	Electrospun Poly(lactic Acid) Fibrous Scaffold	Conjunctival repair	Rabbit	Kill the infectious pathogens	[101]
Cerium oxide NPs		Topical	Mice	Antioxidant and neuroprotective treatment for both dry and wet forms of AMD disease.	[102]
	Negative surface charge			Genotoxic effects at higher exposures in the treatment of cataract	[103]
	Curcumin	Intravenous injection	Rat	ROS scavenging activity and also providing anti-glycation for the treatment of diabetic cataract	[104]
	Coated with PEG-PLGA	Subconjunctival administration	Rat	Antioxidant and glycation inhibitor for palliation of diabetic cataracts	[105]
Yttrium oxide NPs		Intravitreal injection	Mice	Prevent photoreceptor death in a light-damage model of retinal degeneration	[106]

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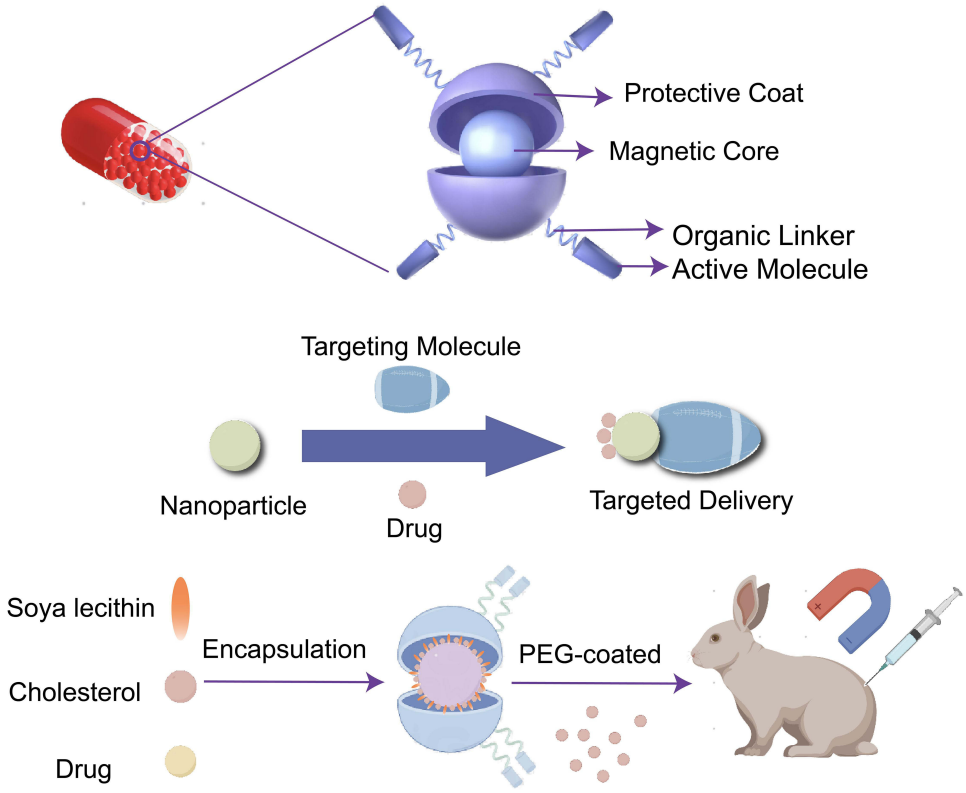

Figure 3 Schematic model of a magnetic nanoparticle for drug delivery. It presents a schematic model of a magnetic nanoparticle specifically designed for drug delivery applications. This illustrative example showcases the intricate structure and functionality of such particles, which leverage magnetic properties to enable precise targeting and controlled release of therapeutic agents. By incorporating magnetic cores encapsulated within biodegradable and biocompatible materials, these nanoparticles facilitate enhanced drug delivery efficacy and reduced side effects, marking a significant advancement in the field of targeted therapies.

single-dose treatment reduced epithelial defects by 99%. It Showed 45–53 times greater efficacy than conventional treatments.[118]

Carbon nanomaterials derive their antioxidant, radical-scavenging, and anti-inflammatory properties from: heteroatom doping, sp2 domains, edge structures, and functional groups Notably, sodium alginate/1,8-diaminooctane-derived carbon nanodots (SA/DAO-CNDs) demonstrated >10-fold stronger binding affinity to VEGF-A165 than clinically used inhibitors (aflibercept and ranibizumab).[89]

Polymeric-Based Materials for the Treatment of Ocular Diseases

Polymers (Table 3) can be categorized into natural and synthetic types, offering high stability and drug-loading capacity. Their mucoadhesive properties make them ideal carriers for ocular drug delivery, prolonging drug retention and reducing clearance.[41,119] Some polymers exhibit stimuli responsiveness, allowing smart polymers to function as in situ gelling systems. Biodegradability is a significant advantage, facilitating sustained drug release.[120,121] Recent advancements in precisely controlling the molecular weight and sequence of synthetic polymers have enabled effective mucoadhesion and physiological barrier penetration. Controlled radical polymerization techniques allow for the preparation of complex polymer ligands, with homogeneous monomer sequence polymers supporting precise delivery.[8,121]

Polysaccharide-based biomaterials have emerged as a highly promising class of ocular drug delivery vehicles, demonstrating superior tissue compatibility and outperforming synthetic materials in both drug retention and ocular permeability. Natural polysaccharides like chitosan and hyaluronic acid have been successfully engineered into nanocarriers that combine excellent biocompatibility with enhanced drug bioavailability and favorable safety profiles. Through strategic chemical modifications, researchers have further optimized these systems to improve ocular residence time and drug solubility.[123] The therapeutic potential of polysaccharide-based nanocarriers has been extensively

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Table 3 Condensed Overview of Polymers in Ophthalmic Applications.[122]

	Polymer Name	Generally Recognized as Safe	Experimental/Clinical/FDA Approved Biomaterial Forms	FDA Approved Indications	Approved For Use In Eye	Characterization	
						Pros	Cons
Synthetic polymers	Poly(amidoamine) (PAMAM)	×	NPs, hydrogels	✓ topicals, drug delivery	×	Easily customizable with numerous reactive groups for functionalization	Lacks FDA approval for ocular applications
	Poly(vinyl alcohol) (PVA)	✓	Implants, hydrogels, NPs	✓ coatings, food additives, food packaging	✓	Offer a slow and controlled degradation rate	Synthesis process involves the use of harsh solvents
	Poly(methacrylates) and derivatives (PMMA)	✓ (mostly)	Hydrogels, contact lenses	✓ coatings, ocular lens, dental fillers, bone cement	✓	Well established ocular polymer, inexpensive	Non-biodegradable nature
	Poly(lactic acid) (PLA)	✓	All types	✓ absorbable sutures, medical devices, food packaging	✓	Derived from natural sources, facilitating straightforward processing	Characterized by a slow degradation rate
	Poly(caprolactone) (PCL)	×	Hydrogels, films, NPs	✓ implants, delivery devices	×	Versatile and cost-effective, allowing for easy modification	Not FDA-approved for use in ocular applications
	Poly(ethylene glycol) (PEG)	✓	Implants, hydrogels, NPs	✓ injectables, topicals, rectal and nasal	✓	Demonstrates water solubility and excellent biocompatibility	Experiences faster degradation compared to other synthetic polymers
	Poly(acrylic acid) PAA	×	Hydrogels, eye drops,	✓ topicals	✓	Excellent water solubility and mucoadhesive propertiesCons:	Biodegradation may result in acidic byproducts
	Poly(glycolic acid-co-lactic acid) (PLGA)	✓	All types	✓ implants, drug delivery, medical devices	✓	Versatile with adjustable degradation rate, water solubility, and prevalent in ocular drug delivery	Degradation may lead to acidic byproducts
Biopolymers	Cellulose	✓	Hydrogels, films, NPs, inserts	✓ food additive, topicals	×	Biocompatible, non-toxic, with high molecular loading capacity, enabling feasible nanomaterial fabrication	Low solubility
	Hyaluronic acid	×(classified as medical device currently)	Hydrogels, NPs, films, tissue scaffolds	✓ cosmetic fillers, injectable for osteoarthritis, topicals	✓	Biocompatible, mucoadhesive, excellent viscoelasticity, naturally sourced	Complex functionalization, challenging drug conjugation, unclear molecular weight impact
	Gelatin	✓	Hydrogels, NPs, films, tissue engineering	✓ medical devices, food additive	×	Easily sourced, biocompatible, abundant ECM protein, low immunogenicity, transparent, cost-effective	Variable strength based on source and processing, residual immunogenicity, crosslinking safety concerns
	Carboxymethyl cellulose	✓	Hydrogels, eye drops, NPs	✓ disintegrant, dental devices	✓	Biodegradable, biocompatible, featuring sustained release and pH-sensitivity	Difficulty in formulating suitable viscous solutions
	Dextran	✓	Hydrogels, films, NPs	✓ shock and other blood related indications, inhalant	✓	Unparalleled biocompatibility	Functionalization challenges persist
	Polydopamine	Not evaluated	NPs, Intraocular Lenses	× Dopamine HCl indicated for correction of hemodynamic imbalances	×	Biocompatible, biodegradable, low toxicity, superior adhesion	Complex, poorly understood synthesis; toxicology, degradation, elimination require further investigation
	Pullulan	✓	Hydrogels, NPs, eye drops, fibers	✓ food additives, tablet coatings, stabilizer, and thickener	×	Readily sourced, stable, excellent film-forming, biodegradable, non-toxic	Unexpectedly sluggish diffusion, necessitates functionalization for drug loading

documented across various ocular diseases, with numerous studies highlighting their clinical translation potential.[124] However, despite these advances, significant knowledge gaps remain regarding their long-term ocular safety, as comprehensive monitoring data are still lacking. Additionally, while polysaccharides are generally biodegradable, their degradation kinetics within the unique ocular microenvironment require further refinement to achieve optimal performance.[125] Recent innovations in this field include two particularly noteworthy developments: First, a sophisticated resveratrol-loaded polycaprolactone nanoparticle system (R@PCL NP) that was functionalized with cell-penetrating peptide and metformin through amide bond formation. This design achieved an impressive 15-fold enhancement in retinal permeability following single intravitreal injection.[126] Second, an advanced surface-engineered ceria nanocage platform (SRCN) incorporating poly(L-histidine) coatings that enabled multiple therapeutic functions, including enhanced corneal penetration and lesion-specific dual-drug release. This innovative formulation demonstrated remarkable efficacy, showing a 19-fold greater wound reduction than commercial eye drops, 93% suppression of pathological angiogenesis, and nearly complete corneal clarity restoration within just four days.[127] These cutting-edge systems exemplify how engineered polysaccharide-based nanocarriers are pushing the boundaries of ocular therapeutics through enhanced delivery efficiency and superior treatment outcomes.

Lipid-Based Materials for the Treatment of Ocular Diseases

Solid lipid NPs (SLNs) and liposomes represent two distinct types of lipid-based drug carriers with different structural and functional characteristics. SLNs are composed of solid lipids (such as glyceryl palmitate) that form a crystalline matrix, enabling high encapsulation efficiency and sustained release of hydrophobic drugs. In contrast, liposomes feature phospholipid bilayers surrounding an aqueous core, making them particularly suitable for hydrophilic payloads and rapid drug release.[128–130]

Solid lipid NPs (10–1000 nm) offer multiple advantages as ocular delivery vehicles, including enhanced permeability, prolonged retention, improved solubility, reduced toxicity, and targeted delivery capabilities.[131] Their self-assembly properties, arising from lipid-aqueous phase interactions, have shown therapeutic potential for various ocular conditions including conjunctivitis, glaucoma, and retinal diseases (Table 4). The therapeutic efficacy of SLNs largely depends on formulation strategies that maximize drug concentration in target tissues. Co-loading of multiple drugs in SLNs enables sophisticated delivery paradigms, significantly increasing therapeutic payloads to specific ocular sites.[132,133]

Currently, both unilamellar and multilayer vesicular liposomes have been developed to carry hydrophilic and lipophilic substances, quickly absorbed by the reticuloendothelial system. However, SLNs face non-specific uptake by the mononuclear phagocytic system. By attaching different ligands to the surface of SLNs, circulation time and targeted drug delivery to specific sites can be enhanced, thereby overcoming these limitations.[177] Selecting surface biomarkers can improve targeting specificity.[130] Additionally, widespread clinical application faces challenges related to the reproducibility and reliability of methods. Production requires a multi-component processing line involving centrifugation, filtration, freeze-drying, emulsification, crosslinking, ultrasonication, solvent evaporation, homogenization, and milling, making it difficult to optimize process parameters for stable key quality attributes at a commercial scale, even though small-scale prototypes are relatively easy to obtain.[178]

Extracellular Vesicles for Ophthalmic Applications

Extracellular vesicles (EVs), including exosomes (50–150 nm), microvesicles, and apoptotic bodies, originate from cellular membrane structures and play roles in biological metabolism, immune responses, cell communication, and disease progression.[179] Exosomes, in particular, possess therapeutic potential and value as disease biomarkers due to their low immunogenicity, low toxicity, and membrane marker characteristics.[180] However, the high complexity and heterogeneity of EVs, including variations in size, content, function, and source, can significantly influence their effects on recipient cells. Moreover, the super-physiological injection doses and administration frequencies of EVs in different studies contribute to uncertainties regarding their safety. As our understanding of EVs, their cargo, and functional heterogeneity continues to evolve, the demand for precise and accurate characterization of EVs in the context of ocular disease mechanisms and therapies will persist and flourish (Table 5).

Table 4 Representative Lipid-Based Materials for Ophthalmic Application

Indication	Modification	Application	Model	Function	Ref.
Dry eye diseases	Drugs (eg, atorvastatin, dexamethasone…)	Topical	Rat, ex vivo	Improved mucus-penetrating capacity	[134–136]
	Drugs(Loteprednol etabonate)	Topical	Bovine eye and rabbit eye	Enhanced bioavailability and decreased side effects.	[137]
	Baricitinib	Topical	In vitro, ex vivo	Higher flux and permeation in the cornea.	[138]
	Sebocyte membranes, Drugs (e.g, dexamethasone…)	Topical	Ex vivo human and in vivo mouse studies	Prolonged retention time	[139]
	Lactoferrin	Topical	New Zealand rabbits	Reverse dry eye symptoms and possess anti-inflammatory efficacy	[140]
	Drug(Apigenin)	Topical	Mice	Reversed DED by reducing ocular surface cellular damage and increasing tear volume.	[141]
Ocular infection	Cyclodextrin complexation, thermosenstive in situ gel	Topical	Candida albicans	Enhanced antifungal activity and prolonged action in Fungal keratitis and endopthalmitis.	[142]
	Luliconazole (LCZ)	Topical	New Zealand white rabbits	Improved bioavailability in whole eye tissues	[143]
	mRNA	Topical	Mice	Obtaining of a higher transfection efficiency than naked mRNA	[144]
	Ciprofloxacin (CIP), Natamycin (NT)	Topical	In vitro release, and ex vivo	With better performance than commercial CIP and NT ophthalmic eye drops	[145,146]
	Ganciclovir	Topical	ARPE-19 cells	Targeted GCV delivery to the retina in the treatment of CMV retinitis	[147]
Keratoconus	Lactoferrin	Topical	In vivo Rat, ex vivo(eg HET-CAM, BCOP)	A controlled release could delay the drug release and prolonged adherension.	[148,149]
Corneal damage	Dual-drug(curcumin, vancomycinloaded)	Topical	Rabbit corneal cells	Anti-inflammatory and anti-bacterial agents for the treatment of corneal alkali burn injuries	[150]
Allergy/Immune	Drugs(Mizolastine, tacrolimus)	Topical	Invitro,Rabbits eye model	Stable sustained-release and effective antiallergy ocular delivery systems	[151,152]
Corneal neovascularization	Drug(Sunitinib)	Topical	Rabbit, mice	Suppressed alkali burn-induced CNV in mice	[153]
	Sorafenib	Topical	In-vitro, Rabbit	Possess equal ability in suppressing neovascularization to dexamethasone	[154]

Glaucoma and optic nerve in-jury	Ferrostatin-1	Topical	C57BL/6 mice	Suppression of ferroptosis, inflammation, and neovascularization.	[155]
	Bimatoprost	Topical	In-vitro and ex-vivo	Drug release for a prolonged period of time.	[156]
	Betaxolol hydrochloride (BH)	Topical	In vitro	Prolonged the retention time at the ocular surface and improved bioavailability	[157,158]
	Brinzolamide- and latanoprost	Topical	Rabbit	Effectively reduced IOP in glaucoma patients	[159]
	Annexin V-conjugated encapsulated LM22A-4	Topical	New Zealand white rabbit, mouse	Targetly delivering neurotrophic factors to the injured retinal ganglion cells (RGCs) could promote the survival of RGCs in glaucoma	[160]
	Betaxolol hydrochloride	Topical	Mice	Efficiently decreased the IOP in glaucoma and prolonged maximum reduction.	[161]
	Agomelatine	Topical	Rabbits	Remained over three months, improved ocular delivery and the bioavailability of agomelatine.	[162]
	Deferoxamine	Intravitreal	Rat	Effective delivery of DFO, iron chelator, to the RGCs might rescue RGC ferroptosis from TON-induced injury	[163]
Uveitis	Triamcinolone acetonide	Topical	Wistar rats, Rabbits	Increased corticosteroid penetration after topical application	[164,165]
Uveal melanoma	Sorafenib	Topical	Statens Seruminstitut Rabbit Cornea cells	Sorafenib encapsulation allowed obtaining a sustained and prolonged drug release	[166]
	Gallic acid-Fe (III) and paclitaxel	Topical	Rat	Internalized into tumor cells, leading to mitochondrial damage, lipid per-oxidation, and apoptosis.	[167]
	Drugs, eg, (S)-(-)-MRJF22, Melatonin	Topical	New Zealand albino rabbits	Be able to reach the posterior segment of the eye, antiangiogenic capability and preventive antiinflammatory	[168,169]
Retinal neovascularization	Astragaloside-IV	Topical	NaIO3 induced dAMD mice	Possessed the ability to reach the fundus, and decreases ROS production and reduces the apoptosis	[170]
	siRNA, 2N12H	Intravitreal Injection	Mouse	Therapeutic effect was comparable to that of the clinical drug ranibizumab	[171]
Retinal delivery	mRNA	Topical	Ai9 reporter mouse model	Delivering mRNA and gene editors' to the retinal pigment epithelium and photoreceptors	[172]
	DNA	Intravitreal Injection/ subconjunctival injections	Ex Vivo Pig Eyes	Reach and penetrate the retina Safe and long-term carrier systems for small molecules or nucleotide-based therapies	[173]
	mRNA	Subretinal injection	Mice	Provided applications that are directed towards retinal reprogramming or genome editing	[174]
Inherited retinal degenerations	cGMP analogues	Topical/periocular and intravitreal	Porcine eyes	Suitable for intraocular administration and drug delivery to both the retina and the ciliary body.	[175]
Stargardt Disease	plasmid DNA (pGRK1-ABCA4-S/MAR)	Intravitreal injections	Pigmented Abca4-/- knockout mice	ABCA4 expressed at both mRNA level and protein level 6 months after 2 intravitreal injections	[176]

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Table 5 Representative Exosomes-Associated Nanomaterial Therapeutics

Indication	Modification/Target	Source	Application	Model	Function	Ref.
Dry eye disease		Mouse macrophage RAW264.7	Topical	Benzalkonium chloride (BAC) mice model	Improved dry eye syndrome, decreased	[181]
	miR-21-5p	Bone marrow mesenchymal stem cell	Intravenous injection	BAC induced dry eye mouse model	Modulate the Treg/Th17 balance, and ameliorate DED progression	[182]
	miR-125b inhibitors	Induced pluripotent stem cell derived MSCs	Intravenous injection	NOD.B10.H2b mice model of Sjögren's Syndrome	Repress sialadenitis onset and regulate immunomodulatory splenocytes	[183]
	PKH26 labeled	Bone-marrow-derived MSCs	Subconjunctival injection	Rat model of corneal allograft Wistar rats to Lewis rats	Prolong corneal allograft survival	[184]
	miR-204	Bone-marrow-derived MSCs	Topical	Mouse model of dry eye induced by benzalkonium chloride and NCG-GVHD mouse model	Restore ocular surface immune homeostasis and ameliorate inflammatory injuries	[185]
	miR-100-5p inhibitor	Human umbilical cord MSCs	Subconjunctival injection	Rabbit model of autoimmune dacryoadenitis	Alleviate the development of rabbit Autoimmune dacryoadenitis	[186]
	miRNAs	Human umbilical cord derived MSCs	Topical	Mouse model of dry eye induced by desiccating environment combined with scopolamine administration	Alleviate dry eye signs, suppress inflammation, and restore homeostasis of the corneal surface	[187]
Glaucoma and optic nerve injury	miR-29b-3p	Embryonic stem cell	Intravitreal injection	Chronic ocular hypertension (COH) mice.	Delivery of miR-29b-3p by engineered sEVs protected retinal ganglion cells	[188]
	Anti-neuroinflammatory effect of human adipose tissue	Mesenchymal stem cell	Intravitreal injection	Microbead-induced ocular hypertension rat model	Promoted RGC survival and function, reduced neuroinflammatory response	[189]
Uveitis	CD73	Mesenchymal stem cell	Tail vein injection	Mice with interphotoreceptor retinoid-binding protein (IRBP)-induced experimental autoimmune uveitis (EAU)	Decreased proportion of Th1 cells in the spleen, draining lymph nodes, and eyes	[190]
	IL-10	Mesenchymal stem cell	Tail vein injection	Mouse model of EAU	Decreased the percentage of Th17 cells, regulatory T cells in the eye, and draining lymph nodes.	[191]
	MicroRNA-410-3p	Plasma-Derived From VKH Patients	Co-incubation	In vitro, CD4+ T cells	Inhibited the proliferation of autol-ogous CD4+ T cells.	[192]
	Rapamycin	Mesenchymal Stem Cells	Subconjunctival injection	EAU mice	Penetrate to the retina, and reduce ocular inflammatory cell infiltration	[193]
Age-related macular degeneration	PEDF	Mesenchymal Stem Cells	Intravitreal injection	Oxygen induced retinopathy (OIR) mouse model,	Better anti-Inflammation, and neuronal degeneration compared with the VEGF drug	[194]
	ML385 (Nrf2 inhibitor)	Mesenchymal Stem Cells	Intravitreal injection	ARPE-19 cellsNaIO3-induced damage in male Sprague-Dawley (SD)	Protect RPE cells from oxidative damage by regulating Nrf2/Kepa1 signaling pathway	[195]
		Dental stem cells (DSCs) from apical papilla (SCAP).	Subretinal injection	Royal College of Surgeons (RCS) rat model	Preserved visual function, reduced retinal cell apoptosis, and prevented thinning of the outer nuclear layer.	[196]
Diabetic Retin-opathy	miR-143-3p	Mesenchymal Stem Cells	Intravitreal injection	Streptozotocin (STZ) along with a high-fat diet	Induced inflammation and reducing vascular leakage	[197]
	miR-5068 and miR-10228	Mesenchymal Stem Cells	Intravitreal injection	db/db mice and streptozotocin-induced diabetic rats	Enhance retinal repair efficiency	[198]
	Bevacizumab	Mesenchymal Stem Cells	Intravitreal injection	STZ induced DR rat model	Maintain more than two months in the eye, and the retinal cell death was consistently lower in this period than only bevacizumab	[199]

Nanofibers

Electrospun nanofibers (100–500 nm in diameter) have emerged as a transformative platform for ocular drug delivery by biomimetically replicating key features of the extracellular matrix.[200] These advanced systems offer three major therapeutic advantages: First, their sustained release capability has been demonstrated through innovative coaxial electrospun constructs, such as the corn-derived core (zein)-shell (PLA) nanofibers dual-loaded with rutin and celastrol for conjunctival repair.[201] This design enables sequential drug release - an initial anti-inflammatory phase from the PLA shell followed by prolonged antifibrotic activity from the zein core. Second, their therapeutic versatility extends to oxidative stress management, as shown by Juan Ye team's ROS-scavenging dual-network system comprising a poly (PEGMA-co-GMA) hydrogel integrated with electrospun polyurethane membranes for corneal burn treatment.[202]

The exceptional performance of electrospun nanofibers in ocular applications stems from their unique structural characteristics produced via this established biomedical technique.[101,203,204] Their high surface area-to-volume ratio and optimal porosity enable: (1) precise spatiotemporal control of drug release profiles, (2) enhanced biocompatibility and biodegradability matching ocular tissues, (3) significant reduction of administration side effects, and (4) marked improvement in therapeutic outcomes compared to conventional formulations.[123,205] These advantages, combined with the ability to incorporate multiple active compounds and functional components in a single system, position electrospun nanofibers as a next-generation platform capable of addressing complex ocular disease pathophysiology through sophisticated, biomimetic drug delivery approaches.

Nucleic Acid-Based Nanomaterials for Ophthalmic Applications

Nucleic acid-based nanomaterials (Table 6) are assembled through hybridization and self-folding processes, encompassing DNA nanomaterials, RNA nanomaterials, RNA-based motifs, and DNA/RNA origami structures. Their notable advantages include high biocompatibility and low immunogenicity. Additionally, these materials can be structurally and functionally programmed for highly selective target binding via aptamers, demonstrating immense potential in biomedical applications such as biosensing, bioimaging, cell reprogramming, gene expression, and targeted delivery.[206,207] DNA nanostructures, particularly the tetrahedral framework pioneered by Turberfield in 2005, show promise due to their structural stability and capabilities in scavenging reactive oxygen species, enhancing membrane permeability, and programmable stimuli responsiveness.[208] Furthermore, by embedding stimulus-sensitive sequences—such as lysosome-activated, nucleotide-sensitive, or pH-sensitive sequences—dynamic targeting and precise release of cargo are achieved.[209] RNA nanostructures also display unique advantages in in vivo isothermal transcription. However, challenges such as susceptibility to degradation, off-target effects, and cross-reactivity still need to be addressed.

The strategic selection of materials for NIM platforms plays a pivotal role in determining both drug-loading capacity and biocompatibility, necessitating meticulous optimization to achieve optimal therapeutic outcomes. Different material classes offer distinct advantages and challenges: polymeric matrices (eg, PLGA, chitosan) achieve high drug encapsulation efficiency through their porous architectures and adjustable degradation kinetics,[226,227] though their inherent immunogenicity can be effectively addressed through innovative erythrocyte membrane coatings that substantially reduce reticuloendothelial system recognition and clearance.[228] Inorganic carriers such as mesoporous silica and gold NPs provide exceptionally large surface areas for small molecule loading,[229] yet require biocompatible surface modifications to mitigate potential oxidative stress effects. Lipid-based systems demonstrate superior biocompatibility through their endogenous components that minimize immune clearance, but require stabilization with agents like trehalose to prevent lipid leakage.[230–232]

The true innovation of NIM platforms lies in their ability to synergistically combine these materials through hierarchical engineering. A prime example is the encapsulation of silica NPs within phosphatidylserine (PS)-modified liposomes, which creates an advanced hybrid system that simultaneously achieves: (1) targeted drug delivery, (2) enhanced cellular uptake, (3) controlled release profiles, (4) excellent biocompatibility, and (5) preserved cell viability. This materials integration approach represents a paradigm shift in ocular therapeutics, as it enables precise balancing of drug payload capacity with biological safety parameters. The modular design philosophy underlying NIM technology

Table 6 Representative Nucleic Acid-Associated Nanomaterial Therapeutics

Vector/Forms of Nucleic Acids		Nucleic Acid	Delivery Route	Disease	Ref.
Liposome	DSPE-PEG, DOPE/DOPC/Cholesterol PEGylated cationic liposomes	siRNA	Eye drop	Dry eye Acanthamoeba keratitis	[210,211]
		miRNA	Intravitreal injection	Retinoblastoma, AMD	[212]
		Messenger RNA (mRNA)	Intravitreal injection Subretinal injection	Uveal melanoma Genetic abnormalities resulting in retinal degeneration	[174,213]
		shRNA	Intravitreal injection	Glaucoma	[214,215]
		Plasmid DNA	Intravitreal injection	Retinal neovascularization Blinding diseases	[216,217]
Polymeric NPs	PLGA Chitosan/Hyaluronic acid…	miRNA		Choroidal neovascularization	[218]
		siRNA	Intravitreal injection	Choroidal neovascularization	[219]
Dendrimers		Oligonucleotide	Intravitreal injection	Choroidal neovascularization	[220]
Polyplexes		polysiRNA	Intravitreal injection	Choroidal Neovascularization	[221]
Polymeric micelles		plasmid	Eye drop	Anterior diseases	[222]
RNA	pRNA	Three-way junction/ four-way X-shape extension	Subconjunctival injection	Posterior diseases	[223]
DNA	Tetrahedral framework nucleic acids	Nanoassembly	Eye drop	Dry eye	[224]
	Solid-phase synthesis of amphiphilic DNA strands	Nanoassembly	Eye drop	Glaucoma	[225]

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allows for rational combination of material advantages while systematically addressing their individual limitations, thereby creating optimized delivery systems that transcend the capabilities of single-component platforms.

Commonality of the Properties of Nano-Micro Particles for Different Administration Approaches (Figure 4)

Nanoparticle interactions and biological behavior in the eye largely depend on their diverse characteristics, particularly size, surface charge, shape, and other physicochemical properties that determine the nano-bio interface interactions in various biological systems.[233] For instance, positively charged NPs tend to have longer retention times in the cornea and facilitate penetration through phospholipid membranes.[121] Thus, when designing nanoparticle platforms for ocular applications, balancing physicochemical properties (eg, size, surface charge) with biological compatibility is critical to ensure optimal performance.

While various types of nanomaterials exist, they often share common properties under specific delivery routes. In vitreous injections, the nano-biointerface between NPs and the vitreous cavity plays a key role in cellular uptake, particularly regarding targeting.[234] The vitreous is mainly composed of 98–99% water, glycosaminoglycans, salts, and various matrix proteins, all of which influence nanoparticle behavior.[235] Research indicates that smaller NPs (approximately 100 nm) move more easily within the vitreous matrix, while larger particles encounter significant obstacles.

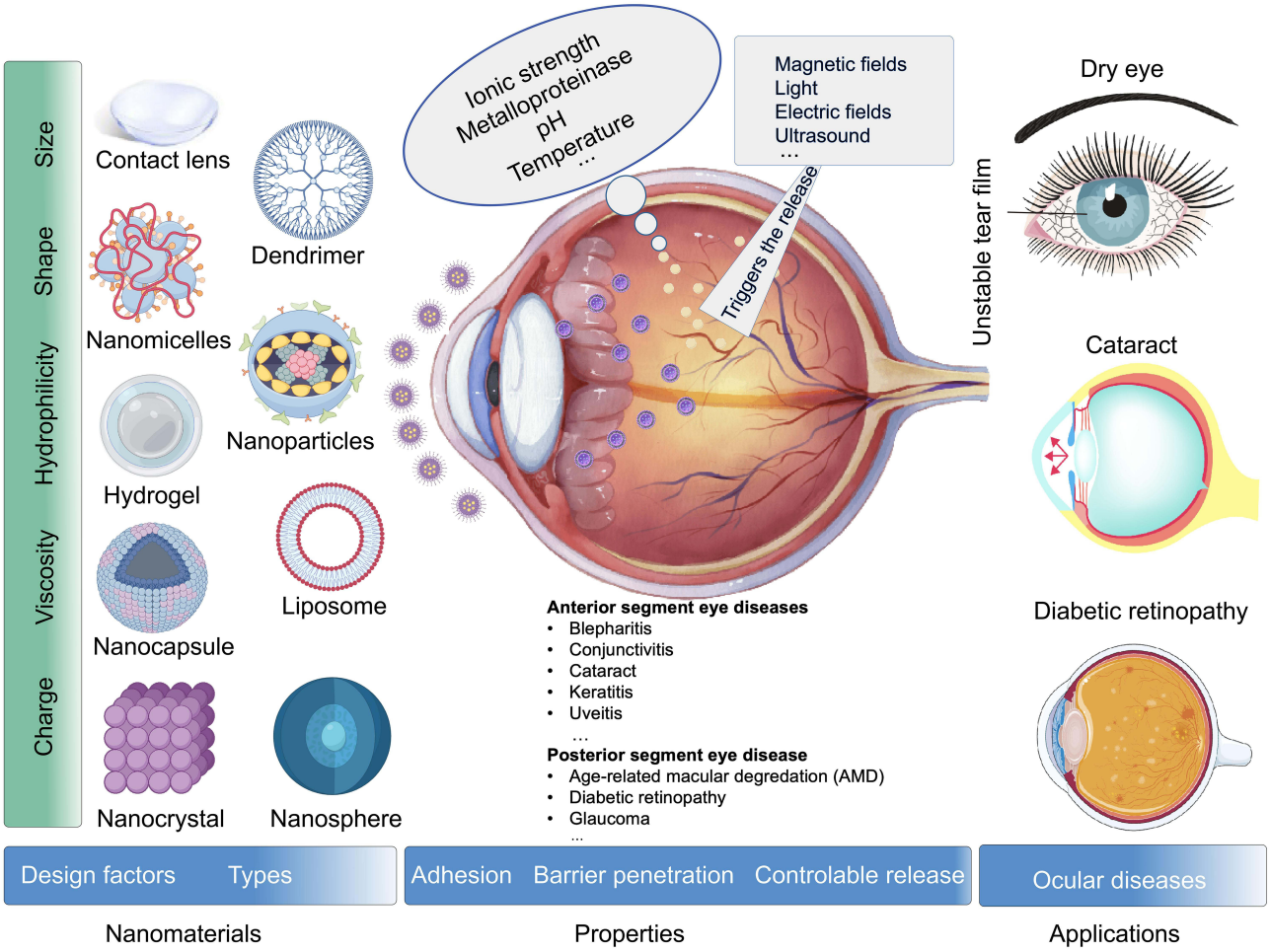

Figure 4 The application of drug delivery systems in the treatment of various ocular diseases. It illustrates the diverse applications of drug carriers in various ocular diseases. It showcases how these innovative delivery systems are tailored to address a spectrum of eye conditions, each demanding unique therapeutic strategy. It underscores the versatility and significance of drug carriers in ophthalmology, demonstrating how they are pivotal in advancing the treatment of a wide range of eye diseases, ultimately aiming to enhance patient quality of life and visual health. Created in BioRender. Lin, E. (2025) https://BioRender.com/tgyfyi1.

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Anionic NPs are observed to penetrate the vitreous more effectively than cationic ones,[236] and the shape of NPs also impacts their mobility.[237]

Topical eye drops are a non-invasive and convenient method for delivering drugs to the anterior eye tissues, widely used for conditions like dry eye, glaucoma, and infections.[238] Given that the ocular surface carries a negative charge, positively charged drug carriers generally exhibit better permeability.[239] Beyond charge and size, factors like lubricity, muco-adhesiveness, viscosity, and biocompatibility are critical in eye drop formulations. Recent studies have explored novel nanoparticle platforms for local delivery, such as hydrogels, fluid gels, and lipid NPs, significantly enhancing corneal retention time and drug bioavailability in anterior tissues.[240] A notable example is the development of rosmarinic acid-conjugated gelatin nanogels co-loaded with diquafosol sodium, which has demonstrated remarkable improvements in ocular surface retention time and therapeutic efficacy for dry eye treatment.[241] This dual-functional system combines the anti-inflammatory properties of rosmarinic acid with the mucin secretagogue action of diquafosol, exemplifying the potential of multifunctional nanocarriers in optimizing ocular drug delivery.

Systemic injections face challenges in effectively reaching the retina due to the tight junctions of the blood-retinal barrier (BRB). In this route, NPs may circulate to non-target organs with the bloodstream, necessitating careful evaluation of their biosafety, including biodistribution, excretion, tissue clearance, and potential side effects or toxicity. Insights from blood-brain barrier (BBB) or cancer therapy research suggest that the ideal size for NPs suitable for systemic injection ranges between 2 to 200 nm, providing valuable reference for BRB-related studies.[242] For example, 20 nm gold NPs (AuNPs) can successfully penetrate the BRB, while those larger than 100 nm cannot.[243] Although smaller NPs facilitate retinal penetration, unmodified conventional NPs struggle to accurately target pathological cells or accumulate at lesions.

Recent advancements in ocular drug delivery have led to the development of sophisticated smart nanoparticle platforms engineered with precision-targeting ligands and aptamers to address the challenges of ocular therapy.[244] These next-generation systems employ innovative ligand engineering strategies to overcome existing limitations in drug delivery. A prime example is the PLGA@AST/AXI nanoparticle system,[226] which utilizes FDA-approved poly (lactic-co-glycolic acid) to co-encapsulate astaxanthin (a multifunctional carotenoid with antioxidant, anti-inflammatory, and anti-apoptotic properties) and axitinib (a selective VEGF receptor tyrosine kinase inhibitor). This dual-drug platform demonstrates four key advantages: (1) multi-targeted action against wet AMD pathogenesis, (2) sustained release kinetics from a single subconjunctival administration, (3) excellent ocular biocompatibility without tissue damage, and (4) significant therapeutic potential for posterior segment diseases.

The field has further expanded to include several breakthrough platforms: the bioadhesive nanoparticle network system (BNP/CA-PEG) combining cefuroxime axetil with 8-arm polyethylene glycol for enhanced antibiotic delivery,[245] and the chondroitin sulfate-cysteine modified nanostructured lipid carriers (Dex-cNLC) that specifically target ocular mucin substructures for efficient dry eye treatment.[246] These systems exemplify the growing sophistication in ocular nanomedicine through their targeted delivery mechanisms and improved therapeutic profiles.

However, the translation of these technologies faces substantial challenges, particularly in optimizing ligand-receptor interactions and addressing interspecies variability in ocular biology. Future progress requires a concerted effort to:

1. Standardize ligand density and binding parameters
2. Elucidate species-specific differences in ocular receptor expression
3. Develop scalable, reproducible manufacturing processes
4. Establish comprehensive biocompatibility assessment protocols

The integration of these considerations with continued nanoplatform innovation will be crucial for advancing precision ocular therapeutics from laboratory concepts to clinically viable treatments, ultimately enabling more effective management of complex ocular diseases while minimizing systemic side effects. This holistic approach represents the next frontier in ophthalmic drug delivery, combining cutting-edge nanotechnology with rigorous translational science.

Biosafety and Toxicity Profiles of Ocular Nanomaterials: Mechanistic Insights and Interspecies Variability

The NIM platform represents a paradigm shift in ocular drug delivery biosafety, offering transformative advantages over conventional nanocarriers through its innovative hierarchical architecture. This sophisticated design fundamentally addresses the longstanding "toxicity-efficacy paradox" in ocular therapeutics by simultaneously enhancing treatment precision while reducing systemic and local toxicity (Figure 5). The platform's success stems from three synergistic safety mechanisms: (1) Barrier-shielded delivery exemplified by the PVA/PDA-PBA@MT eye drop system, which combines polydopamine NPs' exceptional radical scavenging capacity with prolonged ocular retention and controlled melatonin release for dry eye management;[247] (2) Spatiotemporal release control demonstrated by pH-responsive hydrogels and transformable microneedle patches that precisely target pathological microenvironments while minimizing off-target effects - particularly the remarkable soft MN patch that delivers antimicrobial NPs to infected corneas before converting to a sustained-release contact lens for wound healing;[248] and (3) Enhanced immune evasion through PEGylated microcarriers that significantly reduce dendritic cell activation and promote immune tolerance compared to bare NPs.[249]

These technological breakthroughs are supported by the platform's unique ability to decouple and optimize two critical safety parameters: microscale components control systemic exposure through regulated retention, while nanoscale

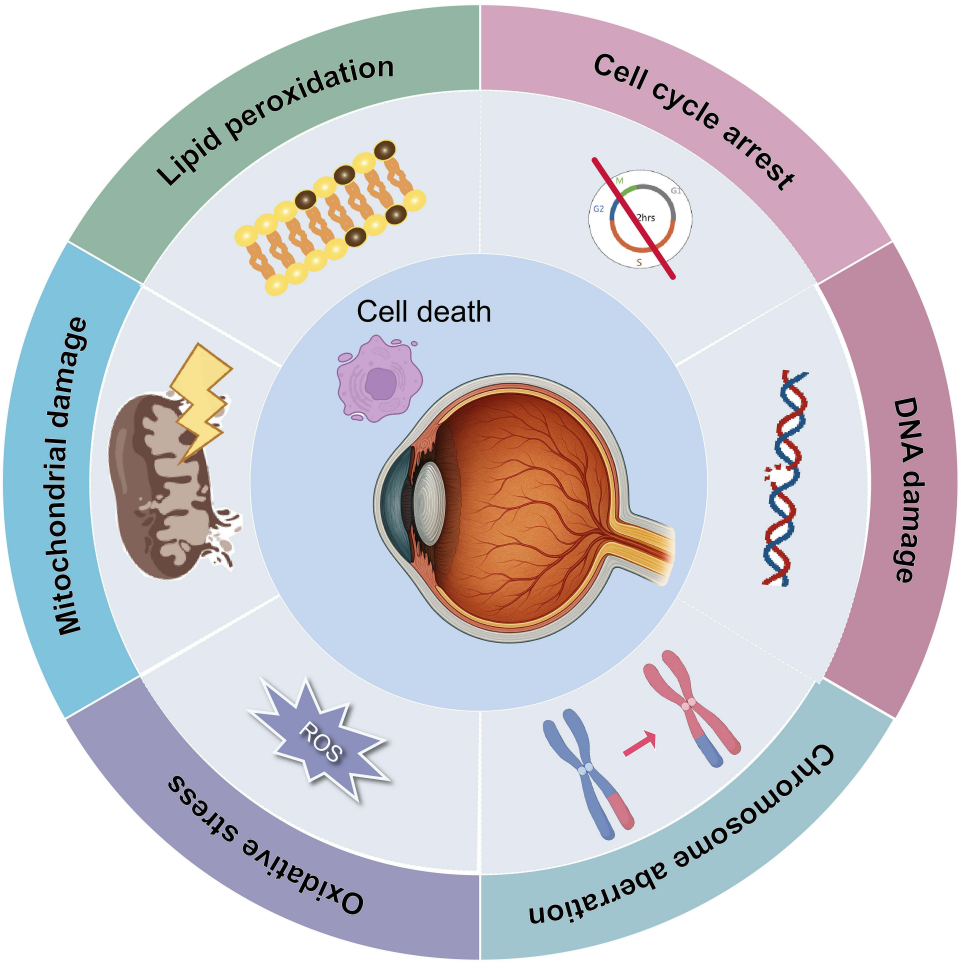

Figure 5 Potential toxicity of nanomaterials. It depicts potential drug toxicities that may arise from the administration of nanomedicines. These toxicities encompass a wide spectrum of adverse effects, including disruptions to the cell cycle, which can lead to abnormal cell proliferation or arrest, as well as DNA damage, a critical concern given its potential to induce mutations and genomic instability. It underscores the importance of rigorous toxicity assessments and the development of safer nanocarriers to minimize these risks, ensuring the safe and effective application of nanomedicines in therapeutic interventions. Created in BioRender. Lin, E. (2025) https://BioRender.com/wcw3s1r.

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elements modulate local cytotoxicity via precision engineering. However, comprehensive safety assessment requires addressing several key challenges: nanoparticle-specific toxicity mechanisms including oxidative stress and DNA damage,[35] size- and surface charge-dependent biological interactions,[250] species variability in ocular physiology, long-term exposure effects, and dynamic nanoparticle-protein corona formation in ocular fluids. Moving forward, the field must prioritize standardized safety evaluation protocols that bridge preclinical and clinical studies, with particular emphasis on surface engineering strategies to mitigate risks while maintaining therapeutic efficacy. The NIM platform's success in harmonizing these complex parameters positions it as a groundbreaking approach in ocular therapeutics, offering new hope for treating challenging eye diseases while setting a new standard for drug delivery biosafety.

Factors Affecting the Bio-Performance of Nano/Micro Delivery Systems

The biological performance of nano- and microparticle delivery systems, including biodistribution and bioavailability, is influenced by multiple factors including size, surface charge, solubility, and biodegradability.[251] To enhance these performances, researchers aim to prolong bioavailability, broaden biodistribution, and reduce toxicity. The loading capacity of the delivery system is crucial for in vivo performance and primarily depends on the manufacturing process. For chronic disease treatment, matrices with good biodegradability or intelligent responsiveness are more suitable, as they can prevent preloaded drugs from directly interacting with specific tissues, which is essential for intracellular applications like genome editing.[252]

Release kinetics is another important indicator for assessing the performance of delivery systems.[253] Particulate and hydrogel formulations excel in improving drug release profiles. Additionally, enhanced cellular uptake is particularly critical for intracellular applications. While small-sized NPs have advantages, their size must be optimized to avoid rapid clearance or ocular irritation.

The surface charge of NPs affects cellular uptake and intracellular transport.[254] Positively charged NPs may disrupt cell membranes or exhibit toxicity, while anionic NPs are internalized via specific endocytic pathways. Therefore, selecting NPs requires a balance between size and charge to maximize cellular uptake and minimize toxicity.

Beyond surface charge, the stiffness, hydrophobicity, and topology of nano/microsystems also influence cell adhesion, thereby affecting biocompatibility and uptake mechanisms.[255] To enhance biocompatibility, researchers have explored various coating materials to modify the nanoparticle interface.

In summary, optimizing nano/microparticle delivery systems necessitates a comprehensive consideration of factors such as size, surface charge, solubility, biodegradability, and other surface characteristics. Through meticulous design and appropriate surface modifications, more efficient and safe drug delivery can be achieved, with the introduction of smart release capabilities further enhancing system performance (Figure 6).

FDA Approved and Under Clinical Trial Nanomedicine for Ocular Diseases

Nanocarriers, due to their nanoscale size and surface characteristics, hold great promise for penetrating ocular barriers and delivering drugs precisely to target sites. Extensive research on nanoformulations for anterior and posterior segment diseases has yielded positive results in clinical trials (Table 7). Commercially available products like Restasis[256] and Durezol[257] are used for treating dry eye syndrome and ocular inflammation, respectively. Other marketed nanostructured products include Cequa®[258] and Cyclokat®[259] (both cyclosporine A nanoemulsions), Lacrisek®[260] (liposomal vitamin), and Artelac Rebalance®[261] (lubricant). Visudyne[262] is indicated for conditions like choroidal neovascularization. InSite Vision's Durasite® is a novel drug delivery system, with its besifloxacin formulation approved by the FDA.[263] Several nanoformulations, such as Ozurdex,[264] Iluvien[265] and Trivaris[266] are used for treating macular edema and uveitis. Currently, various nanoformulations, including TLC399 (ProDex),[267] latanoprost-coated liposomes (POLAT-001),[268] and SYSTANE®,[269] are undergoing clinical trials for conditions like ocular hypertension, glaucoma, AMD, diabetic macular edema, and ocular infections.

The rapid development of nanotechnology and microsystems has integrated NPs with micro-matrices (such as hydrogels, microspheres, and liposomes), combining the advantages of both to provide a larger drug-loading surface area. However, the biocompatibility of inorganic NPs is relatively poor, which can lead to side effects or cytotoxicity. To address this, researchers have combined inorganic NPs with biocompatible polymers to shield encapsulated components

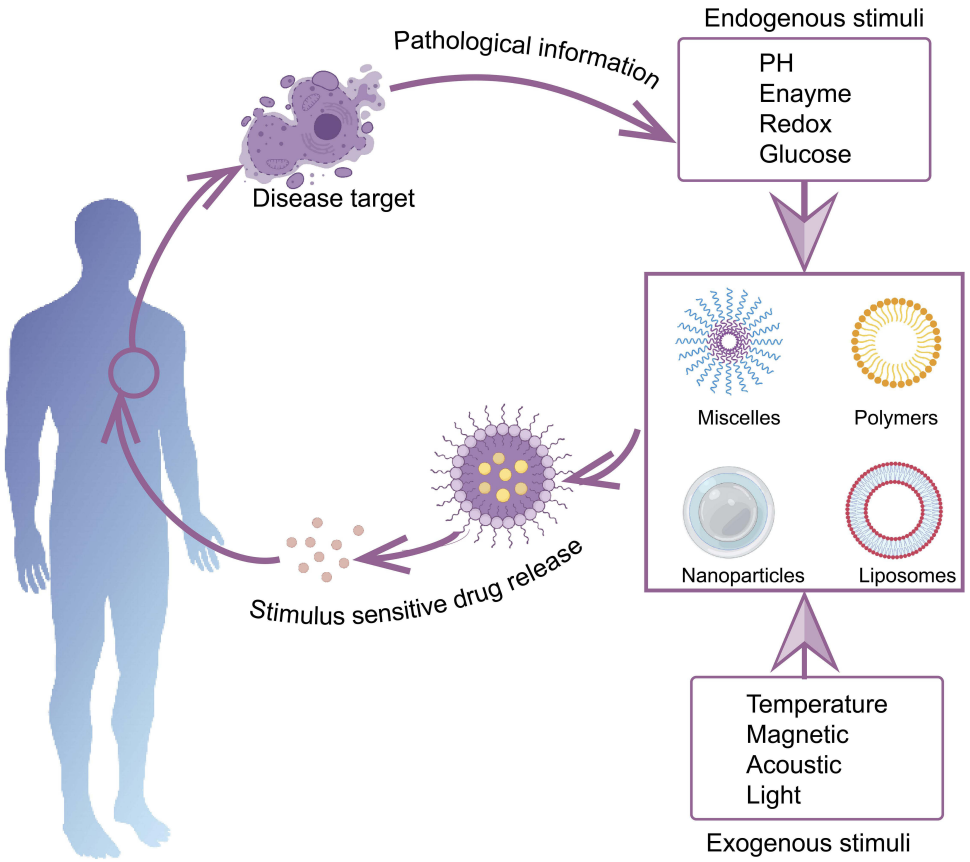

Figure 6 The basic parameters involved in the process of drug delivery. It illustrates the fundamental parameters that are integral to the process of drug delivery. Looking ahead, the trajectory of advancement lies in the continued pursuit of smart drug development, which encompasses the realm of nanomedicines engineered to respond to various physiological factors such as pH levels in bodily fluids and blood glucose concentrations. This evolution toward smarter therapeutic solutions aims to enhance the precision and efficacy of drug administration, tailoring. Created in BioRender. Lin, E. (2025) https://BioRender.com/wcw3s1r.

from in vivo clearance, thereby enhancing biocompatibility and optimizing drug release profiles.[287] In ophthalmic applications, this system demonstrates significant potential for sustained drug delivery, cell encapsulation, and transplantation. Additionally, cell encapsulation technology is being used to create novel therapeutic platforms by encapsulating genetically engineered cells to produce therapeutic factors. Given their longevity, immune privilege characteristics, and ease of gene editing, human retinal pigment epithelial cell lines (ARPE-19) and mesenchymal stem cells are preferred choices. A notable ARPE-19-based delivery system is Neurotech Inc.'s NT-501 device,[288] which has been used clinically for the controlled release of ciliary neurotrophic factor.

A number of FDA-approved drugs have completed or are undergoing clinical trials for further validation. Dexamethasone, a cornerstone anti-inflammatory agent, is increasingly delivered via sustained-release implants to address clinical challenges associated with frequent dosing and poor patient compliance. Ozurdex® and DEXTENZA® are exemplary models of sustained-release systems for dexamethasone delivery, with their applications significantly enhancing patient compliance and clinical outcomes. The Ozurdex® system encapsulates dexamethasone within biodegradable poly(lactic-co-glycolic acid) (PLGA) microspheres, enabling prolonged drug release at the target site. In the DME trial (NCT05372562), patients treated with Ozurdex® demonstrated superior outcomes: 22–28% achieved ≥15-letter visual acuity improvement (vs 12% in controls), alongside central macular thickness reductions of 100–150 μm (vs 30 μm in controls). A multicenter Chinese trial (NCT06548568) is currently underway to further validate these findings. The system's efficacy, lasting up to six months, underscores its potential to reduce treatment burden and improve quality of life. DEXTENZA®, on the other hand, is an FDA-approved intracanalicular insert, employs a polyethylene glycol (PEG)-based plug to deliver dexamethasone nanocrystals for postoperative inflammation/pain management following cataract or glaucoma surgeries. Phase III trial data (NCT02525036) demonstrated significant resolution of inflammation

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Table 7 FDA Approved and Under Clinical Trial Nanomedicine for Ocular Diseases

Target Indication	Route	Target Tissue	Product	Nano Formulation	Drug/Bioactive	FDA Approval Status	Refs
Dry eye	Eye drop	Cornea and Tear film	Restasis	Nanoemulsion	Cyclosporine ophthalmic emulsion	Approved	[256]
			Ikervis	Nanoemulsion	Ciclosporin ophthalmic emulsion 0.1%	Approved	[270]
			Cationorm	Nanoemulsion	Cationic emulsion	Approved	[271]
			Cequa	Micelle	Cyclosporine ophthalmic solution 0.09%	Approved	[258]
			Cyclokat	Cationic nanoemulsion	Cationic emulsion 0.1%	Approved	[259]
			Lacrisek	Liposomal spray	Vitamin A palmitate, vitamin E	Approved	[260]
			Artelac Rebalance	Liposomal eyedrops	Lubricant	Approved	[261]
			SYSTANE	Nanoemulsion	Propylene glycol-based nanoemulsion	Phase IV	[269]
AMD	Intravitreal injection	Retina, Choroid	Visudyne	Liposome	Verteporfin	Approved	[272]
			GB-102	NPs	Sunitinib malate	Phase I	[273]
AMD and diabetic macular edema	Intravitreal injection	Retina, Choroid	AR-13503	Intravitreal implants	AR-13503 implant alone and in combination with aflibercept	Phase I	[274]
			AR-1105	Intravitreal implants	Dexamethasone intravitreal implant	Phase II	[275]
Wet AMD	Intravitreal injection	Retina, Choroid	Macugen	Aptamer-polymer nanoparticle	Pegaptanib	Approved	[276]
Glaucoma	Subconjunctival injection	Anterior segment	POLAT-001	Liposome	Latanoprost-coated liposome	Phase II	[268]
Macular edema	Intravitreal injection	Vitreous, Retina, Choroid	ProDex	Lipid-based nanoparticle	ProDex	Phase II	[277]
	Intravitreal injection, Suprachoroidal injection		Kenalog	Microparticle	Triamcinolone acetonide suspension	Approved	[278]
	Intravitreal injection		Triesence	Microparticle	Triamcinolone acetonide suspension	Approved	[266]
Macular edema, noninfectious uveitis	Intravitreal injection	Vitreous, Retina, Choroid	Ozurdex	Implant	Dexamethasone biodegradable implant	Approved	[279]
Diabetic macular edema	Intravenous	Vitreous, Retina, Choroid	Iluvien	Implant	Fluocinolone acetonide nonbiodegradable implant	Approved	[265]
Intraocular melanoma	Intravenous injection	Retina, Choroid	Taxol	NPs	Paclitaxel albumin-stabilized nanoparticle formulation	Phase II	[280]

Pain and inflammation in ocular surgery	Eye drop	Anterior segment	KPI-121	Mucus penetrating particles	1 and 0.25% loteprednol etabonate	Approved	[281]
	Subconjunctival implant	Anterior segment	Dextenza	Implant	Dexamethasone	Phase III	[282]
	Eye drop	Anterior segment	GPN00833 (APP13007)	Nanoemulsion	Clobetasol propionate	Approved	
Control of Inflammation, Diabetic Macular Edema	Eye drop	Anterior segment, Retina	OCS-01	Nanoparticle	Dexamethasone Cylcodextrin Nanoparticle Ophthalmic Suspension 1.5% mg/mL	Phase II	[283]
Eye inflammation	Eye drop	Mainly anterior segment of the eye, anterior chamber, cornea, conjunctiva	Durezol	Nanoemulsion	Difluprednate ophthalmic emulsion 0.05%	Approved	[257]
Uveitis	Intravitreal injection	Vitreous, Retina, Choroid	Trivaris	Microparticle	Triamcinolone acetonide suspension	Approved	[284]
Non-infectious uveitis	Intravitreal injection	Vitreous, Retina, Choroid	Retisert	Implant	Fluocinolone acetonide nonbiodegradable implant	Approved	[285]
Ocular infection	Eye drop	Conjunctiva, cornea	AzaSite	Micelle	Azithromycin Ophthalmic 1% Solution	Approved	[286]

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and pain reduction, highlighting its clinical viability. Another example based on biodegradable PLGA microsphere-based platform, is OTX-TIC system, incorporating travoprost nanocrystals for glaucoma management. Clinical trials evaluating its efficacy and safety in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) aim to validate its potential as a single-application alternative to daily topical therapies.

The NIM platform demonstrates significant translational potential, with emerging clinical adoption in ophthalmic therapeutics. Clinical evaluations have demonstrated superior therapeutic efficacy compared to traditional drug delivery approaches, particularly in targeting chronic ocular pathologies. Nevertheless, the full clinical translation of NIM formulations continues to face persistent challenges.

Challenges in the Clinical Translation

Nanomaterial drug delivery systems face multiple challenges in ophthalmic applications, leading to slow progress and high costs. The primary obstacles involve safety, regulatory approval, scalability, and cost-effectiveness.[289] The complexity of new nanotherapeutic products makes the approval process time-consuming and challenging. Although the FDA has released draft guidance documents, final guidelines are still pending, and current regulatory requirements remain aligned with small molecules. These testing standards may not be suitable for nanoproducts, potentially resulting in biased outcomes.

The transition to clinical applications hinges on reproducibility and large-scale production; yet the structural and physicochemical complexity of nanomaterials often leads to poor reproducibility. Issues such as inconsistency, inadequate quality control, low yield, and high manufacturing costs are prevalent in nanodrug production, complicating quality assurance and control. Lastly, patient safety is paramount. An ideal nanoplatform should exhibit good biocompatibility and safety, minimizing adverse effects or ocular accumulation. Although extensive research has explored the toxicity of NPs on ocular tissues, most data are based on animal models, which may not accurately reflect human conditions due to significant differences in retinal immune composition.[290] Additionally, the biocompatibility and toxicity of NPs are closely tied to their physicochemical properties, and there remains insufficient evidence to confirm their biocompatibility and toxicity in the human eye.

Conclusion and Prospects

The NIM platform combines nanoscale precision with micron-scale stability to address the ongoing challenges of drug retention, penetration, and biocompatibility in ocular drug delivery, representing a transformative approach in the field of ocular therapy. This innovative technology has shown significant potential, especially in the treatment of genetic retinal diseases. The CRISPR-Cas9 lipid NPs delivered through the NIM platform achieved high gene correction efficiency in a model of retinitis pigmentosa.[291–293] However, there are still some key obstacles hindering its clinical translation. The challenges of materials science, especially at the interface of inorganic polymers, require innovative solutions to ensure optimal performance of the system, while regulatory ambiguity significantly limits the progress of NIM preclinical research towards clinical trials. Clinical translation has shown that only a few ocular nanotherapeutic drugs have entered Phase 3 trials, mainly hindered by inconsistent manufacturing and scalability limitations of microfluidic production systems.[294,295] Safety considerations remain paramount, as evidenced by the heterogeneity of diseases and the large number of mutations in genes such as RPE65, which directly affect the toxicity threshold of nanomaterials.[296,297] These challenges underscore the urgent need to balance efficacy and biocompatibility, especially for long-term treatment regimens. Looking ahead, several key research directions must be prioritized in this field: (1) the development of advanced delivery systems that combine artificial intelligence-guided drug release and sustainable biodegradable matrices; (2) creating enhanced formulations with improved stability and pharmacokinetic characteristics for small molecules and biologics; (3) Expand translational research through comprehensive in vivo studies and optimization of non-invasive delivery methods. When developing solutions for diseases, multidisciplinary collaboration is crucial to addressing these challenges. By successfully overcoming these obstacles, NIM technology has the potential to move beyond incremental improvements and become the foundational platform for the next generation of ophthalmology, effectively bridging the gap between nanoscale innovations and meaningful clinical impact in ophthalmic treatments.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

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Disclosure

The authors declare that they have no competing interests.

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