

Ocular Nanomedicine: Emerging Nanotechnology-Based Drug Delivery Systems for Eye Diseases

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Abstract

Ocular drug delivery remains one of the most demanding challenges in pharmaceutical science because the eye is protected by a dense array of static and dynamic barriers, including the tear film, corneal epithelium, conjunctiva, sclera, and the blood–aqueous and blood–retinal barriers. Conventional dosage forms such as eye drops, ointments, and suspensions typically achieve ocular bioavailability of less than five percent, and their short residence time on the ocular surface forces frequent instillation, which compromises patient adherence and therapeutic outcomes (Franco & De Marco, 2021; Rajan et al., 2022). Over the past decade, nanotechnology has emerged as a transformative strategy for overcoming these obstacles. This review synthesises the current literature on nanotechnology-based ocular drug delivery systems, covering liposomes and niosomes, polymeric nanoparticles, solid lipid nanoparticles and nanostructured lipid carriers, dendrimers and nanomicelles, nanosuspensions and nanoemulsions with in situ gelling systems, and device-based platforms such as drug-eluting contact lenses, iontophoresis, and microneedles. Evidence from preclinical and translational studies indicates that these nanocarriers can enhance corneal permeability, prolong precorneal residence time, protect labile drugs from enzymatic and hydrolytic degradation, and enable targeted delivery to the anterior and posterior segments of the eye, thereby reducing dosing

frequency and systemic toxicity. Applications spanning dry eye disease, glaucoma, keratitis, uveitis, diabetic retinopathy, and age-related macular degeneration are discussed, alongside toxicological considerations and the regulatory and manufacturing hurdles that continue to limit clinical translation. The review concludes that, despite substantial preclinical promise, only a small number of nanotechnology-enabled ocular products have reached the market, and future progress will depend on standardised safety evaluation, scalable manufacturing, and closer alignment between formulation design and regulatory expectations.

Keywords: ocular nanomedicine; nanoparticles; liposomes; drug delivery; ophthalmic; blood–retinal barrier; nanotechnology

1. Introduction

The human eye is anatomically and physiologically isolated from the rest of the body by a combination of static barriers, dynamic clearance mechanisms, and efflux transport systems that collectively protect intraocular tissue from pathogens and xenobiotics. While this isolation is essential for visual health, it is precisely what makes the eye one of the most inaccessible organs for pharmacological intervention. Conventional ophthalmic therapeutics were designed within the constraints of this hostile delivery environment, and as a result the field has historically relied on high drug concentrations, frequent dosing, and invasive routes of administration such as intravitreal

injection to achieve therapeutic effect. The emergence of nanotechnology has reframed this problem: instead of forcing more drug through the eye's barriers, nanocarriers are engineered to interact with those barriers directly, exploiting mucoadhesion, controlled release, and barrier-specific transport pathways to deliver therapeutic payloads more efficiently (Rajan et al., 2022). This introductory section outlines the anatomical and physiological context of ocular drug delivery, the burden of the diseases that this review addresses, the limitations of existing therapies, the rationale for nanotechnology-based intervention, and the specific aims and scope of the present review.

Interest in ocular nanomedicine has accelerated sharply over the past decade, tracking a broader expansion of nanotechnology across pharmaceutical science, but the ophthalmic application space carries several features that distinguish it from other organ systems. Unlike the gastrointestinal tract or the skin, the eye is a small, enclosed, and optically transparent organ in which even modest changes in formulation turbidity, particle aggregation, or local inflammation can compromise vision directly, so the tolerance for formulation defects is considerably narrower than in most other therapeutic areas. At the same time, the eye is uniquely accessible for direct visual and instrumental monitoring, allowing researchers to track nanocarrier distribution, corneal integrity, and inflammatory response non-invasively using tools such as slit-lamp biomicroscopy, optical coherence tomography, and confocal microscopy, which has made ophthalmology something of a proving ground for nanomedicine concepts that may later be extended to other tissues. These distinctive features, taken together with the severe unmet clinical need represented by chronic and

vision-threatening ocular disease, explain why ocular nanomedicine has developed into one of the most active and rapidly evolving subfields of nanotechnology-enabled drug delivery.

1.1 Anatomy and Physiological Barriers of the Eye

The eye is conventionally divided into anterior and posterior segments, each presenting a distinct set of barriers to drug penetration. The anterior segment comprises the cornea, conjunctiva, sclera, iris, ciliary body, aqueous humor, and lens, and is principally responsible for diseases such as dry eye disease, conjunctivitis, keratitis, cataract, and glaucoma. The posterior segment comprises the choroid, retina, and vitreous humor, and is the site of vision-threatening diseases including diabetic retinopathy, retinal vein occlusion, and age-related macular degeneration (AMD). Topically instilled drugs must first cross the tear film, which is rapidly diluted and drained through the nasolacrimal duct, before penetrating the corneal epithelium, a tightly packed layer of cells joined by zonula occludens that severely restricts paracellular diffusion of hydrophilic molecules. Lipophilic drugs can traverse the epithelium but are then impeded by the hydrophilic corneal stroma, creating a differential permeability requirement often described as the need for balanced amphiphilicity. Beyond the cornea, the blood–aqueous barrier restricts systemic drug access to the anterior chamber, while the blood–retinal barrier, composed of tight junctions in the retinal pigment epithelium and retinal capillary endothelium, severely limits the delivery of systemically or topically administered drugs to the retina and choroid (López-Cano et al., 2021; Rajan et al., 2022). Collectively, these barriers mean that less than five percent of a topically applied dose typically reaches intraocular tissues,

and reaching the posterior segment from the ocular surface is considered exceptionally difficult without invasive administration.

The efflux transport systems embedded within corneal and conjunctival epithelia add a further layer of complexity to this barrier landscape. Multidrug resistance-associated proteins and P-glycoprotein transporters, expressed on both the corneal epithelium and the retinal pigment epithelium, actively pump a range of therapeutic substrates back out of the tissue, further reducing the fraction of an applied dose that achieves an intracellular or transcellular concentration sufficient for pharmacological effect. Enzymatic degradation compounds this problem: the tear film and corneal epithelium contain esterases, peptidases, and other catabolic enzymes that can rapidly inactivate labile drug molecules, particularly peptide- and protein-based therapeutics, before they ever reach their intended site of action. For posterior segment targets, the vitreous humor itself constitutes an additional diffusional barrier; although it is largely aqueous, its viscoelastic gel-like structure, composed of a dilute collagen and hyaluronic acid network, slows the diffusion of larger macromolecules and nanoparticles, meaning that intravitreally injected therapeutics must be engineered with an appropriate balance of size and surface chemistry to avoid both premature clearance through the anterior chamber angle and entrapment within the vitreous meshwork. It is precisely this combination of static anatomical barriers, active efflux, enzymatic degradation, and diffusional resistance within ocular compartments that has motivated the shift toward nanoscale delivery platforms capable of being engineered around each of these obstacles individually.

1.2 Burden of Ocular Diseases

Ocular disease represents a substantial and growing global health burden. Glaucoma alone was estimated to affect approximately 76 to 80 million people in 2020, with projections rising to over 111 million by 2040, and it remains a leading cause of irreversible blindness worldwide because of progressive optic nerve damage driven by elevated intraocular pressure (Juliana et al., 2019). Age-related macular degeneration is similarly a major cause of irreversible central vision loss in people over the age of fifty, with the global burden projected to increase substantially as populations age (Yang et al., 2021). Diabetic retinopathy, dry eye disease, corneal infections, and uveitis further add to the cumulative burden, and many of these conditions require chronic, sometimes lifelong, pharmacological management. The economic and quality-of-life costs associated with repeated clinic visits for intravitreal injections, frequent self-administration of eye drops, and the systemic side effects of orally or intravenously administered ocular therapeutics are considerable, and they provide strong motivation for the development of delivery systems that can reduce dosing frequency while improving therapeutic precision.

Beyond glaucoma and AMD, several other ocular conditions contribute substantially to the global burden of visual impairment and warrant consideration in the context of nanomedicine development. Dry eye disease is estimated to affect several hundred million people worldwide, causing chronic discomfort, visual disturbance, and, in severe cases, corneal damage, and its multifactorial pathophysiology, involving tear film instability, hyperosmolarity, and ocular surface inflammation, makes it a particularly attractive target for lipid-based nanocarriers capable of directly restoring the tear film

architecture. Diabetic retinopathy, a leading cause of vision loss among working-age adults, is projected to affect an increasing proportion of the global population as the prevalence of diabetes mellitus rises, and its management similarly depends heavily on repeated intravitreal anti-VEGF therapy, carrying the same adherence and treatment-burden challenges observed in AMD. Infectious and inflammatory conditions, including bacterial and fungal keratitis, uveitis, and post-surgical endophthalmitis, though individually less prevalent, carry a disproportionately high risk of rapid and irreversible vision loss if not treated promptly and effectively, underscoring the value of nanocarrier platforms capable of achieving high local drug concentrations quickly. Collectively, these conditions illustrate that the clinical need addressed by ocular nanomedicine spans the full spectrum from chronic, slowly progressive disease requiring sustained low-level drug exposure to acute, sight-threatening emergencies requiring rapid and potent local therapeutic action.

1.3 Limitations of Conventional Ocular Drug Delivery

Conventional ocular formulations, principally aqueous eye drops, suspensions, and ointments, suffer from several interlinked limitations. First, precorneal residence time is short because of reflex blinking, tear turnover, and nasolacrimal drainage, meaning that the majority of an instilled dose is lost within minutes of administration. Second, ocular bioavailability is low, generally below five percent, necessitating frequent dosing that reduces patient adherence, particularly in chronic diseases such as glaucoma where long-term compliance is essential to preserving vision (Rajan et al., 2022). Third, systemic absorption via the nasolacrimal duct and conjunctival vasculature can produce unwanted systemic side

effects, as seen historically with beta-blocker eye drops used in glaucoma management. Fourth, for posterior segment diseases, topical and systemic routes are largely ineffective, forcing reliance on intravitreal injection, which is invasive, carries risk of endophthalmitis, retinal detachment, and elevated intraocular pressure, and is poorly tolerated for chronic conditions requiring monthly or bimonthly re-administration (Yang et al., 2021). These shortcomings collectively underscore the need for delivery platforms capable of prolonging residence time, improving barrier penetration, and enabling sustained release from a single administration.

1.4 Rationale for Nanotechnology-Based Approaches

Nanotechnology offers a set of engineering strategies that directly address the limitations described above. Nanocarriers in the size range of roughly ten to a thousand nanometres can be engineered with tunable surface charge, mucoadhesive coatings, and stimuli-responsive release profiles that collectively enhance ocular retention and barrier permeation without requiring an increase in administered dose (Begines et al., 2020). Cationic nanocarriers, for example, exploit electrostatic interaction with the negatively charged mucin layer of the tear film and corneal glycocalyx to extend residence time, while nanoscale particle size allows carriers to be internalised by corneal and conjunctival epithelial cells through endocytic pathways that are inaccessible to conventional molecular solutions (Yang et al., 2022). For posterior segment disease, nanocarriers injected intravitreally can be formulated to achieve sustained release over weeks to months, reducing the frequency of invasive injections, while some systems are being engineered to cross or bypass the blood–retinal barrier following topical or periocular

administration, a goal often described in the literature as nanomedicine's central objective for retinal therapeutics (American Academy of Ophthalmology, 2021). The regulatory precedent set by nanotechnology-enabled products already approved for ocular use, including a liposome-based cyclosporine emulsion for dry eye disease and an adeno-associated viral nanocarrier for inherited retinal disease, demonstrates that nanoscale engineering can be translated into approved clinical therapeutics, providing further rationale for continued investment in this field.

1.5 Aim and Scope of the Study

This review aims to provide a comprehensive and up-to-date synthesis of nanotechnology-based ocular drug delivery systems reported in the peer-reviewed literature between 2015 and 2022. The review is organised into a literature review section covering six major categories of nanocarrier: liposomes and vesicular systems; polymeric nanoparticles; lipid nanoparticles, including solid lipid nanoparticles and nanostructured lipid carriers; dendrimers and nanomicelles; nanosuspensions, nanoemulsions, and in situ gelling systems; and device-integrated platforms including drug-eluting contact lenses, iontophoresis, and microneedles. For each category, representative formulation strategies, model drugs, and reported performance outcomes are summarised in tabular form to facilitate comparison. The review then considers disease-specific applications across the anterior and posterior segments, toxicological and safety considerations associated with nanomaterial exposure to ocular tissue, the regulatory and manufacturing challenges that continue to constrain clinical translation, and future directions for the field, before concluding with an integrated perspective on the state of ocular nanomedicine.

2. Literature Review

Nanotechnology-based ocular drug delivery systems can be broadly classified according to their structural composition into vesicular carriers, polymeric particulate systems, lipid-based particulate systems, dendrimeric and micellar carriers, dispersed liquid or colloidal systems, and device-integrated nanocarrier platforms. Each class offers a distinct combination of drug-loading capacity, release kinetics, biocompatibility, and manufacturability, and the choice of carrier is generally guided by the physicochemical properties of the therapeutic agent, the target ocular tissue, and the desired duration of action. The following subsections review the literature for each of these six categories, drawing on formulation studies published largely between 2015 and 2022.

2.1 Liposomes and Vesicular Carriers

Liposomes are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core, and their amphiphilic architecture allows simultaneous encapsulation of hydrophilic drugs within the aqueous compartment and lipophilic drugs within the bilayer itself. Because the phospholipid bilayer closely resembles the lipid layer of the natural tear film, liposomes have been particularly well studied for dry eye disease, where they can help restore tear film stability in addition to acting as drug carriers (López-Cano et al., 2021). Liposomal formulations have also been extensively investigated for glaucoma therapeutics; cationic liposomes composed of specific lipid blends have demonstrated superior corneal permeation relative to conventional eye drops, and fixed-dose combination liposomes co-encapsulating timolol maleate and brimonidine tartrate have shown significantly greater reduction of intraocular pressure than free drug solutions in rabbit models of induced glaucoma

(Bigdeli et al., 2021). Hyaluronic acid-coated latanoprost liposomes have similarly been shown to improve long-term ocular surface tolerance while maintaining hypotensive efficacy, addressing the ocular surface toxicity historically associated with chronic prostaglandin analogue use. Beyond glaucoma, dendritic oligoethylenimine-decorated liposomes have been engineered to markedly extend corneal retention and permeation of antiglaucoma drugs relative to unmodified vesicles (Qiu et al., 2021), while niosomes, which replace phospholipids with non-ionic surfactants, offer a more chemically stable and cost-effective alternative for encapsulating

anti-infective agents for transcorneal delivery. Cationic niosomal systems have additionally attracted interest as non-viral vectors for ocular gene delivery because their surface charge facilitates electrostatic complexation with nucleic acids, and lipophilic polyamine-modified cationic liposomes have been proposed as efficient carriers for gene therapy applications relevant to inherited and acquired retinal disease (Grijalvo et al., 2019; Puchkov & Maslov, 2021). Table 1 summarises representative liposomal and niosomal ocular delivery systems reported in the literature.

Table 1. Representative liposomal and niosomal ocular drug delivery systems

Carrier / Modification	Model Drug	Target Indication	Key Reported Outcome	Source
Cationic liposome (thin-layer hydration)	Timolol maleate + brimonidine tartrate	Glaucoma	Significant IOP reduction versus aqueous solution in rabbit model	Bigdeli et al. (2021)
Hyaluronic acid-coated liposome	Latanoprost	Chronic glaucoma	Improved long-term ocular surface tolerance and sustained IOP control	López-Cano et al. (2021)
Dendritic oligoethylenimine-decorated liposome	Antiglaucoma agents	Glaucoma	Augmented corneal retention and permeation versus plain liposomes	Qiu et al. (2021)
Cationic-charged liposome (DoE-optimised)	Brimonidine tartrate	Glaucoma	Optimised particle size, zeta potential and entrapment via design of experiments	Soni & Saini (2022)
Standard phospholipid liposome	Cyclosporine / tear-film lipids	Dry eye disease	Restoration of tear film lipid layer stability	López-Cano et al. (2021)

Cationic niosome	Nucleic acids (siRNA/plasmid)	Retinal gene delivery (experimental)	Effective electrostatic nucleic-acid complexation and cellular uptake	Grijalvo et al. (2019)
Bioadhesive niosome	Anti-infective agent	Transcorneal infection	Enhanced in vitro and ex vivo corneal permeation	Zubairu et al. (2015)

2.2 Polymeric Nanoparticles

Polymeric nanoparticles are solid colloidal particles, typically 10 to 1000 nanometres in diameter, formed from biodegradable natural or synthetic polymers such as chitosan, hyaluronic acid, sodium alginate, poly(lactic-co-glycolic acid) (PLGA), poly(ϵ -caprolactone), and poly(ethylene glycol) (PEG) conjugates (Begines et al., 2020). Their principal advantages for ocular delivery include tunable drug release kinetics, protection of labile therapeutic cargo from enzymatic degradation, and the capacity for surface functionalisation with mucoadhesive or cell-penetrating ligands. PLGA nanoparticles surface-modified with 2-hydroxypropyl- β -cyclodextrin have been shown to increase the maximum aqueous humor concentration of triamcinolone acetonide by more than fifty-fold relative to a conventional aqueous suspension following topical instillation, illustrating the magnitude of bioavailability enhancement achievable through rational surface engineering. Studies evaluating the ocular biodistribution of topically administered PLGA nanoparticles loaded with the antioxidant lutein found that nanoparticles were preferentially taken up by the cornea, episclera, and sclera, with detectable accumulation extending to the choroid, supporting the feasibility of topical nanoparticle delivery for select posterior structures

(Chittasupho et al., 2018). Subconjunctivally administered PLGA nanoparticles loaded with dexamethasone sodium phosphate have demonstrated sustained drug release over approximately sixteen days and were able to prevent corneal allograft rejection in a rat keratoplasty model across a nine-week weekly dosing regimen, an outcome not achievable with free drug. Chitosan-coated PLGA nanoparticles loaded with bevacizumab, delivered subconjunctivally in a diabetic retinopathy model, achieved higher and more sustained retinal drug concentrations than bevacizumab solution, with effects persisting for up to twelve weeks. Intravitreal polymeric nanocarriers engineered for long ocular retention have additionally demonstrated targeted accumulation in the retina and optic nerve head region, a feature of particular relevance to glaucomatous neurodegeneration and optic neuropathies (Junnuthula et al., 2021). Polymeric nanoparticles loaded with immunosuppressive agents such as tacrolimus, cyclosporine A, and the Janus kinase inhibitor baricitinib have similarly shown promise for dry eye disease, uveitis, and corneal graft rejection by prolonging local immunosuppressive exposure while limiting systemic absorption. Table 2 summarises selected polymeric nanoparticle systems reported for ocular applications.

Table 2. Representative polymeric nanoparticle systems for ocular drug delivery

Polymer System	Model Drug	Route / Target	Key Reported Outcome	Source
2-HP- β -cyclodextrin/PLGA nanoparticle	Triamcinolone acetonide	Topical / aqueous humor	C _{max} approximately 52-fold higher than aqueous suspension	Rajan et al. (2022)
PLGA nanoparticle (lutein-loaded)	Lutein	Topical / cornea, sclera, choroid	Stable colloidal dispersion; preferential external-tissue uptake	Chittasupho et al. (2018)
PLGA nanoparticle	Dexamethasone sodium phosphate	Subconjunctival / cornea	16-day sustained release; prevented corneal allograft rejection over 9 weeks	Begines et al. (2020)
Chitosan-coated PLGA nanoparticle	Bevacizumab	Subconjunctival / retina	Sustained retinal drug levels for up to 12 weeks	Yang et al. (2022)
Intravitreal polymeric nanocarrier	Model therapeutic payload	Intravitreal / retina, optic nerve head	Long ocular retention with targeted retinal/ONH accumulation	Junnuthula et al. (2021)
Polymeric nanoparticle (topical)	Baricitinib	Topical / ocular surface	Reduced ocular inflammation in uveitis and dry eye models	Rajan et al. (2022)
Hyaluronic acid-coated PLGA nanoparticle	Lutein	Topical / retina (antioxidant)	Non-toxic to retinal pigment epithelial cells	Chittasupho et al. (2018)

2.3 Lipid Nanoparticles: Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLNs) are colloidal carriers composed of lipids that remain solid at both room and body temperature, dispersed in an aqueous surfactant solution, a technology first proposed in the early 1990s (Naseri et al., 2015).

Nanostructured lipid carriers (NLCs) represent a second-generation evolution in which a liquid lipid is blended into the solid lipid matrix to create a less ordered crystal structure with higher drug-loading capacity and reduced drug expulsion during storage. Both platforms are attractive for ocular use because they are composed of physiologically well-tolerated lipids, can be sterilised by autoclaving, a critical requirement

for ophthalmic preparations, and readily undergo surface modification with cationic compounds such as stearylamine or chitosan to promote mucoadhesion and prolong precorneal residence time (Gugleva & Andonova, 2021). A systematic review of SLN-based ocular formulations reported bioavailability enhancements of up to twelve-fold in the vitreous humor for atorvastatin-loaded SLNs, sustained drug release over twenty-four to ninety-six hours, and corneal permeability improvements of up to 287 percent relative to control formulations, with no significant ocular toxicity observed across the included in vitro and in vivo studies. Cationic nanostructured lipid carriers in particular have

demonstrated superior electrostatic bioadhesion to the negatively charged ocular surface, translating into extended residence time and improved therapeutic response relative to conventional SLNs. SLNs and NLCs have been investigated across a broad range of indications including dry eye syndrome, fungal and bacterial keratitis, glaucoma, and posterior segment disorders, with transscleral permeation studies of triamcinolone acetate-loaded NLCs demonstrating meaningful drug flux across excised scleral tissue, supporting feasibility for non-invasive delivery toward the posterior segment. Table 3 summarises representative SLN and NLC ocular delivery studies.

Table 3. Representative solid lipid nanoparticle (SLN) and nanostructured lipid carrier (NLC) ocular systems

Carrier Type	Model Drug	Target Indication	Key Reported Outcome	Source
Solid lipid nanoparticle	Atorvastatin	Posterior segment (statin repurposing)	Up to 12-fold bioavailability increase in vitreous humor	Gugleva & Andonova (2021)
Solid lipid nanoparticle	Econazole	Fungal keratitis	Sustained release 24–96 h; improved corneal permeability	Gugleva & Andonova (2021)
Cationic nanostructured lipid carrier	Model anti-inflammatory agent	Ocular surface inflammation	Enhanced electrostatic bioadhesion and residence time	Gugleva & Andonova (2021)
Nanostructured lipid carrier (transscleral)	Triamcinolone acetate	Posterior segment (macular edema)	Measurable transscleral drug flux ex vivo	Naseri et al. (2015)
Cannabinoid-loaded SLN	Cannabinoid derivative	Glaucoma (IOP control, investigational)	Improved corneal permeability versus free drug	Gugleva & Andonova (2021)
PEGylated lipid nanoparticle	Model hydrophobic drug	Anterior segment (general)	Improved colloidal stability and reduced clearance	Naseri et al. (2015)

2.4 Dendrimers and Nanomicelles

Table 4. Representative dendrimer and nanomicelle ocular drug delivery systems

Carrier Type	Model Drug	Target Indication	Key Reported Outcome	Source
PAMAM dendrimer–drug conjugate	Triamcinolone acetonide	Choroidal neovascularisation (AMD)	Single low dose outperformed 10-fold higher free-drug dose	Kalomiraki et al. (2016)
Hydroxyl-terminated dendrimer	Anti-inflammatory payload	Posterior segment inflammation	Sustained systemic/intravenous targeting to activated retinal cells	Kalomiraki et al. (2016)
PLGA-PLA co-polymeric nanomicelle	Ranibizumab	Age-related macular degeneration	Low CMC (6.2 µg/mL); 10–50 nm spherical micelles for long-acting delivery	Xu et al. (2022)
Block-copolymer nanomicelle	Hesperidin (natural antibacterial)	Bacterial keratitis	Improved aqueous solubility and antibacterial ocular bioavailability	Yang et al. (2022)
Amphiphilic polymeric micelle	Poorly water-soluble corticosteroids	Anterior and posterior segment disease	Enhanced solubilisation and corneal permeability	Durgun et al. (2020)

2.5 Nanosuspensions, Nanoemulsions, and In Situ Gelling Systems

Nanosuspensions are colloidal dispersions of poorly water-soluble drug particles stabilised by surfactants or polymers, formulated without an auxiliary carrier matrix, which increases the effective surface area available for dissolution and corneal absorption. Ion-pairing strategies applied to moxifloxacin, for example, produced a mucus-penetrating moxifloxacin-pamoate nanosuspension that achieved approximately 1.6-fold greater maximum plasma concentration and superior antibacterial activity relative to a commercial moxifloxacin eye drop in healthy rats. Slow-release nanosuspension formulations incorporating thiol-based antioxidant–nitric oxide

donor hybrid molecules have similarly demonstrated substantial and sustained intraocular pressure reduction in ocular hypertensive mouse models, with effects persisting up to seventy-two hours after a single dose (Amankwa et al., 2021). Nanoemulsions, thermodynamically or kinetically stabilised dispersions of oil droplets typically below 200 nanometres in an aqueous continuous phase, are already represented in the approved ophthalmic pharmacopoeia through a cyclosporine-based nanoemulsion indicated for dry eye disease. Travoprost-loaded nanoemulsions have demonstrated superior bioavailability and a more sustained intraocular pressure-lowering effect than a conventional commercial travoprost

formulation in glaucoma models, while cyclosporine nanoemulsions have been shown to relieve dry eye symptoms through sustained ocular surface residence. In situ gelling systems, which undergo a sol-to-gel phase transition upon exposure to physiological triggers such as temperature, pH, or ionic strength after instillation, are frequently combined with nanoparticulate or nanomicellar carriers to further

extend precorneal residence time; chitosan and carbomer nanoparticle-laden in situ gels loaded with timolol, for instance, have shown improved ocular retention and sustained intraocular pressure control relative to nanoparticle suspension alone. Table 5 summarises representative nanosuspension, nanoemulsion, and in situ gel systems for ocular delivery.

Table 5. Representative nanosuspension, nanoemulsion, and in situ gelling ocular systems

System Type	Model Drug	Target Indication	Key Reported Outcome	Source
Ion-paired mucus-penetrating nanosuspension	Moxifloxacin-pamoate	Bacterial ocular infection	~1.6-fold greater C _{max} and improved antibacterial effect versus commercial drops	Yang et al. (2022)
Slow-release antioxidant–NO donor nanosuspension	Thiol-based hybrid small molecule	Glaucoma (IOP reduction)	61% IOP reduction at 3 h, sustained to 72 h post-dose	Amankwa et al. (2021)
Nanoemulsion	Cyclosporine A	Dry eye disease	Sustained relief of dry eye symptoms; marketed nanoemulsion precedent	Rajan et al. (2022)
Nanoemulsion	Travoprost	Glaucoma	Prolonged IOP-lowering effect versus conventional commercial drops	Yang et al. (2022)
Chitosan/carbomer nanoparticle in situ gel	Timolol	Glaucoma	Improved ocular retention and sustained IOP control	Rajan et al. (2022)
Self-assembling peptide hydrogel	Timolol + brimonidine	Glaucoma (fixed-dose combination)	Feasible co-delivery vehicle in vitro and ex vivo	Taka et al. (2020)

2.6 Contact Lenses, Iontophoresis, Microneedles, and Emerging Device-Integrated Platforms

A parallel and increasingly influential strand of ocular nanomedicine integrates nanocarriers with drug-eluting medical devices, most prominently therapeutic contact lenses. Because a soft contact lens sits directly on the tear film for extended wear periods, embedding nanoparticles, nanoliposomes, or drug-loaded nanogels within the lens polymer matrix converts the device into a sustained-release drug reservoir, in principle overcoming the residence time limitations of conventional eye drops (Franco & De Marco, 2021; Rykowska et al., 2021). Contact lenses incorporating layered double hydroxide nanoparticles combined with a thermogel carrier have achieved sustained brimonidine release over 168 hours and produced greater intraocular pressure reduction than a commercial brimonidine eye drop in comparative studies. Chitosan/hyaluronic acid nanoparticle-laden lenses loaded with methotrexate have similarly demonstrated improved drug retention and reduced initial burst release relative to lenses soaked with drug alone, with monthly-replacement lens materials showing slower,

diffusion-controlled release profiles suited to prolonged ocular surface therapy. Beyond contact lenses, transcorneal iontophoresis uses a low-intensity electric current to drive charged nanoparticles or drug ions across the cornea, offering a non-invasive means of enhancing penetration to both anterior and posterior tissues without the residence-time constraints of passive diffusion. Microneedle arrays, which create transient microchannels through the conjunctiva or sclera, have been combined with nanoparticle-loaded tips or coatings to enable minimally invasive, targeted, and painless drug delivery to the anterior segment, circumventing the need for full-thickness intraocular injection. Emerging platforms such as nanowafers, thin transparent polymeric films embedded with drug-loaded nanoparticles that dissolve upon contact with the tear film, and exosome-based nanocarriers exploiting endogenous extracellular vesicle biology for targeted retinal delivery, represent further innovation at the interface of nanotechnology and ocular device engineering (Rajan et al., 2022). Table 6 summarises representative device-integrated and emerging nanotechnology platforms for ocular drug delivery.

Table 6. Representative device-integrated and emerging nanotechnology platforms for ocular drug delivery

Platform	Nanocomponent	Target Indication	Key Reported Outcome	Source
Therapeutic contact lens	Layered double hydroxide nanoparticle + thermogel	Glaucoma	Sustained brimonidine release over 168 h; greater IOP reduction than eye drop	Rykowska et al. (2021)
Therapeutic contact lens	Chitosan/hyaluronic acid nanoparticle	Ocular surface / immune disease	Improved retention and reduced burst release of methotrexate	Franco & De Marco (2021)

Transcorneal iontophoresis	Charged nanoparticle / drug ion	Anterior and posterior segment disease	Non-invasive enhancement of transcorneal/transscleral penetration	Rajan et al. (2022)
Microneedle array	Nanoparticle-coated microneedle tip	Anterior segment / minimally invasive delivery	Targeted delivery bypassing full-thickness intraocular injection	Rajan et al. (2022)
Nanowafer	Drug-loaded nanoparticle film	Corneal and ocular surface disease	Tear-film-triggered dissolution and sustained release	Rajan et al. (2022)
Exosome-based nanocarrier	Endogenous extracellular vesicle	Retinal disease (experimental)	Biocompatible, low-immunogenicity vehicle for targeted retinal delivery	Wu, Li et al. (2022)

Taken together, the six categories of nanocarrier reviewed above illustrate both convergent and complementary design strategies within ocular nanomedicine: convergent, in that nearly all platforms rely on some combination of increased mucoadhesion, protection from enzymatic degradation, and controlled release to overcome the eye's barrier properties; and complementary, in that each carrier class offers particular advantages for specific drug physicochemical properties, target tissues, and durations of therapeutic need. Table 7 provides a comparative synthesis of the principal advantages and limitations associated with each nanocarrier category discussed in this review

Table 7. Comparative summary of nanocarrier platforms for ocular drug delivery

Nanocarrier Class	Typical Size Range	Principal Advantages	Principal Limitations
Liposomes / niosomes	50–500 nm	Amphiphilic loading; tear-film compatibility; biocompatible	Physical instability on storage; moderate scalability
Polymeric nanoparticles	10–1000 nm	Tunable, sustained release; surface functionalisation	Potential polymer degradation by-product toxicity
Solid lipid nanoparticles / NLCs	50–1000 nm	Autoclave sterilisable; physiological lipids; mucoadhesive	Drug expulsion on storage (SLN); limited drug loading (SLN)
Dendrimers	1–10 nm	Precise, multivalent conjugation; high potency at low dose	Higher-generation cationic dendrimers may be cytotoxic

Nanomicelles	10–100 nm	Excellent solubilisation of lipophilic drugs; simple self-assembly	Dilution instability below critical micelle concentration
Nanosuspensions / nanoemulsions	20–500 nm	High drug loading without carrier matrix; marketed precedent	Ostwald ripening; surfactant-related irritation risk
Device-integrated (contact lenses, microneedles, iontophoresis)	Device-scale with embedded nanocomponents	Prolonged, controllable release; minimally invasive delivery	Manufacturing complexity; optical clarity and comfort constraints

An important cross-cutting theme emerging from the six carrier categories reviewed above is the growing use of hybrid and multifunctional nanosystems that combine features of more than one platform in order to capture complementary advantages. Lipid-polymer hybrid nanoparticles, for example, encapsulate a polymeric core within a lipid shell, aiming to combine the sustained-release characteristics of polymeric matrices with the biocompatibility and membrane-fusogenic properties of lipid bilayers, and have been proposed as a next-generation nanocarrier class for ocular applications where neither a purely polymeric nor a purely lipid-based system alone

provides an optimal release profile. Similarly, several of the dendrimer and nanomicelle systems discussed in Section 2.4 have been further modified with mucoadhesive polysaccharide coatings, effectively borrowing surface-engineering strategies originally developed for liposomal and polymeric nanoparticle systems, illustrating that the boundaries between nanocarrier categories are increasingly permeable in contemporary formulation design. Stimuli-responsive functionalisation, whether through pH-sensitive polymers that respond to the mildly acidic microenvironment of inflamed or neovascular tissue, or through thermosensitive polymers that undergo sol-to-gel transition at ocular surface temperature, is likewise being layered onto essentially every one of the carrier classes reviewed here, reflecting a broader trend in the field toward combining passive barrier-penetration strategies with active, disease-responsive release control.

3. Applications of Ocular Nanomedicine Across Anterior and Posterior Segment Diseases

The nanocarrier platforms reviewed above have been evaluated across a broad spectrum of ocular diseases, and the choice of carrier is generally matched to the anatomical target and chronicity of the underlying condition. In dry eye disease, liposomal and nanoemulsion formulations dominate the therapeutic landscape because their lipid-based architecture directly addresses the tear film lipid layer deficiency that underlies aqueous-deficient and evaporative subtypes of the disease; the clinical success of a cyclosporine nanoemulsion in this indication has served as a proof of concept that continues to motivate development of next-generation lipid nanocarriers for ocular surface disease (López-Cano et al., 2021). In glaucoma, the dominant unmet need is

prolonging the duration of intraocular pressure control from a single administration to improve adherence in a lifelong condition, and liposomes, nanosuspensions, nanostructured lipid carriers, and drug-eluting contact lenses have all been investigated toward this end, with several formulations demonstrating multi-day sustained pressure reduction in animal models (Juliana et al., 2019; Rykowska et al., 2021). Corneal infections and bacterial keratitis benefit from nanocarrier-mediated enhancement of antibiotic penetration through the corneal epithelium, with nanosuspension and nanomicelle formulations achieving higher local drug concentrations than conventional eye drops while potentially reducing the emergence of antimicrobial resistance associated with subtherapeutic dosing. For posterior segment diseases such as diabetic retinopathy and age-related macular degeneration, the central translational goal remains extending the duration of anti-VEGF activity from intravitreal injection, and polymeric nanoparticles, nanomicelles, and dendrimer conjugates loaded with anti-VEGF biologics or small molecules have consistently demonstrated extended retinal or vitreous residence relative to free drug, potentially reducing injection frequency from monthly to quarterly or longer intervals (Xu et al., 2022; Yang et al., 2021). Gene therapy nanocarriers, including cationic niosomes, lipid nanoparticles, and mesoporous silica nanoparticles for siRNA delivery, are being explored as a means of achieving durable, potentially single-administration control of VEGF expression in wet AMD, complementing the viral vector gene therapy approaches already under clinical investigation for this indication. Nanoparticle-based diagnostic applications, including gold nanoparticles used as contrast agents for optical coherence tomography and

photoacoustic imaging, further illustrate the theranostic potential of nanotechnology in ophthalmology, extending its relevance beyond therapeutic delivery alone (Yang et al., 2022).

Cross-cutting themes also emerge when applications are compared directly against one another. Anterior segment applications, including dry eye disease, glaucoma, and corneal infection, benefit primarily from strategies that extend precorneal residence time and enhance transcorneal permeation, since the target tissues are directly accessible from the ocular surface and the principal barrier to overcome is rapid clearance rather than deep tissue penetration. Posterior segment applications, in contrast, confront the more fundamental challenge of reaching tissue that is largely inaccessible from the ocular surface under normal physiological conditions, meaning that intravitreal or periocular administration remains the dominant route even for nanocarrier-based therapeutics, and the primary translational benefit sought is not enhanced initial delivery but rather prolongation of the interval between invasive injections. This distinction has practical implications for formulation strategy: anterior segment nanomedicines are typically optimised for surface mucoadhesion and epithelial transport, whereas posterior segment nanomedicines are typically optimised for intravitreal stability, controlled degradation, and retinal or choroidal targeting following local injection. Recognising this divide helps to explain why certain nanocarrier classes, such as nanoemulsions and drug-eluting contact lenses, are disproportionately represented in anterior segment applications, while others, such as dendrimer conjugates and long-acting polymeric nanomicelles, are disproportionately represented in posterior segment and gene therapy applications.

4. Toxicological and Safety Considerations

The clinical adoption of any ocular nanomedicine depends critically on a favourable safety profile, and the unique anatomy of the eye, characterised by limited clearance mechanisms and direct exposure of highly sensitive neural tissue in the retina, makes toxicological evaluation particularly important. Nanoparticle toxicity to ocular tissue is influenced by several physicochemical parameters, including particle size, surface charge, shape, and surface coating, with smaller and more positively charged particles generally showing greater tissue penetration but also greater potential for cytotoxicity (Yang et al., 2022). Organic nanocarriers such as liposomes and PEGylated polymeric nanoparticles have generally demonstrated favourable biocompatibility in preclinical studies, with PEGylation in particular reducing cytotoxicity relative to unmodified polyester nanoparticles in retinal pigment epithelial cell models. In contrast, inorganic nanoparticles, including gold, silver, titanium dioxide, and cerium oxide nanoparticles, have shown more variable toxicological profiles: while several studies report antioxidant or anti-angiogenic benefit from cerium oxide and gold nanoparticles at low concentrations, other studies have documented dose-dependent oxidative stress, mitochondrial dysfunction, and disruption of the inner blood-retinal barrier following intravitreal exposure to titanium dioxide nanoparticles, mediated in part through rapid activation of the metalloproteinase ADAM17 and degradation of the tight-junction protein claudin-5 (Chan et al., 2021). These findings underscore that ocular nanotoxicology cannot be generalised across nanomaterial classes, and safety must be established on a formulation-specific basis. Long-term and chronic exposure data remain comparatively sparse relative to acute toxicity

studies, and there is a recognised need for advanced three-dimensional human organoid and microphysiological ocular tissue models to bridge the translational gap between animal toxicology and human clinical risk, given known interspecies differences in ocular anatomy and clearance kinetics (Yang et al., 2022). Developmental toxicity, particularly the potential for nanoparticles to cross the placental barrier following systemic exposure, represents an additional and currently underexplored dimension of ocular nanomedicine safety assessment that will require further attention as intravenous and periocular nanoparticle-based therapies advance toward clinical use.

5. Translational Challenges and Regulatory Perspectives

Despite the substantial body of preclinical evidence reviewed above, only a small number of nanotechnology-enabled ocular products have achieved regulatory approval, reflecting a persistent gap between laboratory promise and clinical translation. A central obstacle is manufacturing scale-up: many nanocarrier fabrication methods that perform well at laboratory scale, including nanoprecipitation, thin-film hydration, and emulsification-solvent evaporation, are difficult to reproduce with the batch-to-batch consistency required for pharmaceutical manufacturing, and ensuring sterility of colloidal nanosystems without compromising particle integrity remains technically demanding (Rajan et al., 2022). Regulatory agencies evaluating nanomedicines must additionally characterise properties that have no direct precedent in conventional small-molecule or biologic regulatory frameworks, including particle size distribution, surface charge, morphology, and the potential for nanoparticle-specific immunogenicity or

biodistribution outside the intended ocular compartment, and the application of quality-by-design frameworks has been proposed as a systematic means of building safety and efficacy assurance into nanocarrier formulation and process design from the earliest stages of development. Cost-effectiveness represents a further translational barrier, since many nanocarrier manufacturing processes involve specialised equipment and quality control infrastructure that increase production costs relative to conventional formulations, a consideration of particular importance for ocular diseases that disproportionately affect ageing and lower-income populations globally. Intellectual property fragmentation across nanocarrier platforms, drug-loading technologies, and device integration methods has also been identified as a barrier to consolidated clinical development programmes, and closer collaboration between formulation scientists, ophthalmologists, and regulatory bodies will likely be necessary to establish standardised characterisation and safety testing pathways specific to ocular nanomedicines going forward.

6. Future Directions and Conclusion

Several converging trends are likely to shape the next phase of ocular nanomedicine research. Stimuli-responsive nanocarriers that release their payload in response to disease-specific biochemical triggers, such as elevated matrix metalloproteinase activity in inflamed ocular tissue or the acidic microenvironment associated with neovascularisation, offer the prospect of spatially and temporally precise drug release that could further reduce systemic and off-target exposure. Combination platforms that integrate nanocarriers with wearable or implantable devices, including smart contact lenses capable of both sensing intraocular pressure and delivering

therapeutic nanoparticles on demand, represent a particularly promising convergence of nanotechnology, materials science, and digital health monitoring. Advances in gene-editing delivery, including CRISPR/Cas9 systems packaged within non-viral lipid or polymeric nanocarriers, may eventually offer curative rather than merely palliative options for inherited and acquired retinal disease, building on the regulatory precedent already established by viral gene therapy for inherited retinal disorders.

Continued refinement of three-dimensional human ocular organoid models will be essential for closing the translational gap between animal toxicology and clinical safety prediction, while artificial intelligence-assisted formulation design is beginning to be explored as a means of accelerating the optimisation of nanocarrier composition for target physicochemical and pharmacokinetic profiles. In conclusion, nanotechnology has fundamentally reshaped the conceptual and technical landscape of ocular drug delivery, offering credible solutions to the bioavailability, residence time, and barrier penetration challenges that have long constrained conventional ophthalmic therapeutics. The literature reviewed here demonstrates consistent and often substantial improvements in drug bioavailability, sustained release duration, and target-tissue specificity across liposomal, polymeric, lipid-based, dendrimeric, micellar, and device-integrated nanocarrier platforms, spanning applications from dry eye disease to age-related macular degeneration. Nonetheless, the translation of this preclinical promise into approved clinical products remains limited, constrained by manufacturing scalability, incomplete long-term toxicological characterisation, and regulatory frameworks still adapting to the unique properties of nanoscale

therapeutics. Sustained interdisciplinary investment in formulation science, ocular toxicology, and regulatory science will be required to fully realise the potential of nanotechnology to transform the treatment of blinding ocular disease.

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