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REVIEW

Nanomedicine-Based Ophthalmic Drug Delivery Systems for the Treatment of Ocular Diseases

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Abstract: Ocular diseases affect over 2.2 billion people globally, imposing a significant socioeconomic burden, with annual productivity losses estimated at US$411 billion. Conventional drug delivery methods—topical, local injection, and systemic administration—face challenges such as low bioavailability (<5%), rapid clearance, and physiological barriers like the cornea and blood-retinal barrier (BRB). Nanomedicine offers promising solutions by enhancing drug bioavailability, prolonging release, and enabling targeted delivery. This review explores nanomedicine-based ophthalmic drug delivery systems, including organic nanomaterials (eg, liposomes, polymer micelles, dendrimers), inorganic nanomaterials (eg, metal nanoparticles, quantum dots), and biological components (eg, exosomes). These systems improve drug penetration, reduce administration frequency, and minimize toxicity, addressing conditions like dry eye disease, keratitis, glaucoma, uveitis, age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinal vascular occlusion (RVO). For instance, Ocular Therapeutix (OTX)-TP, a sustained-release intracanalicular implant combining poly (ethylene glycol)-based hydrogel with travoprost-loaded poly (lactic acid) microspheres, has shown therapeutic efficacy lasting up to three months in the management of glaucoma and ocular hypertension in Phase III clinical trial. Additionally, a liposomal formulation of verteporfin, approved for the treatment of neovascular AMD, administered intravenously and activated by laser photodynamic therapy, demonstrates a durable response, with a marked reduction in treatment frequency from an average of 3.5 sessions in the first year to only 0.1 by the fifth year post-diagnosis. Despite these advantages, challenges such as manufacturing costs, potential toxicity, and limited clinical translation persist. Future advancements in nanomedicine hold potential for personalized, non-invasive ocular therapies, revolutionizing ophthalmology.

Keywords: nanomedicine, ophthalmic drug delivery, ocular diseases, physiological barriers, targeted delivery

Introduction

According to the World Health Organization (WHO), over 2.2 billion individuals worldwide suffer from significant visual impairment and ocular diseases, ranking vision loss as the third leading cause of reduced quality of life after cancer and cardiovascular diseases. The global financial burden is staggering, with annual productivity losses estimated at US$411 billion.[1] This economic impact is compounded by direct healthcare costs and intangible losses in patient well-being. In 2020, approximately 43.3 million people were blind, and 295.09 million experienced moderate-to-severe vision impairment. Projections indicate a worsening trend: by 2050, due to population aging, growth, and urbanization, an estimated 61.0 million will be blind, and 474 million will suffer from moderate-to-severe vision impairment.[2] These statistics underscore the urgent need for innovative therapeutic strategies. Ocular diseases span a wide range, including anterior segment conditions like dry eye disease (DED) and keratitis, and posterior segment disorders such as glaucoma,

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age-related macular degeneration (AMD), diabetic retinopathy (DR), retinal vascular occlusion (RVO), and retinopathy of prematurity (ROP). Traditional treatments often fail to deliver drugs effectively due to the eye's complex anatomical and physiological barriers, necessitating advanced delivery systems like nanomedicine to improve outcomes. This review therefore provides a comprehensive evaluation of nanomedicine-based strategies designed to overcome the ocular anatomical and physiological barriers for enhanced therapeutic efficacy. Through systematic analysis of cutting-edge nanocarrier innovations and their clinical translation, we place particular emphasis on quantifying clinically relevant outcomes, including treatment frequency reduction and sustained-release duration, a distinct departure from conventional reviews limited to preclinical findings. Furthermore, we present timely updates on both FDA-approved nanoformulations and emerging technologies to provide better treatments and even fundamentally change the treatment way in ocular diseases.

Conventional Ophthalmic Drug Delivery Systems

Ocular drug delivery is primarily achieved through topical application, local injection, and systemic administration (Figure 1). Each method encounters significant obstacles that limit therapeutic efficacy, driving the need for nanotechnology-based alternatives (Figure 2).

Topical Drug Delivery

Topical administration, such as eye drops, is the preferred method for anterior segment diseases due to its non-invasive nature and high patient compliance.[3] However, ocular bioavailability remains low (<5%) due to multiple barriers. These barriers include conjunctiva barrier, tear film barrier, corneal barrier, blood-aqueous barrier, vitreal barrier, blood-retinal barrier, from anterior to posterior segments. The conjunctival barrier exhibits significant permeability due to its capillaries and lymphatic vessels. This structural characteristic facilitates substantial drug diffusion into systemic

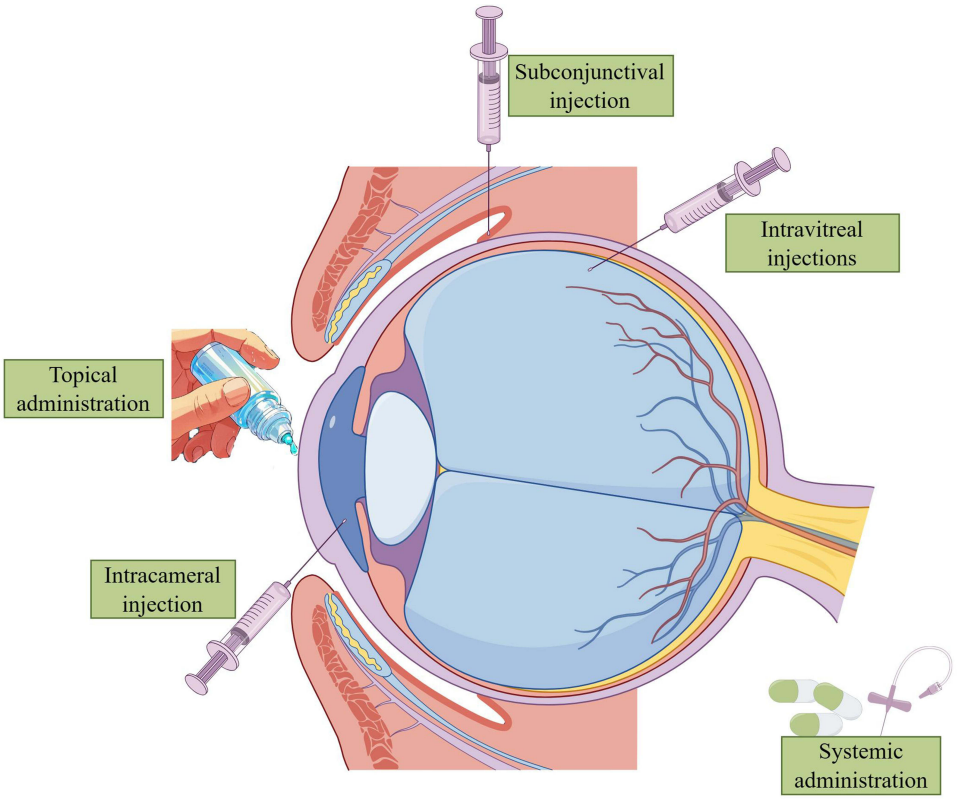

Figure 1 Routes of ocular administration for drug delivery systems, including the topical application, local injection (subconjunctival injection, intracameral injection, intravitreal injection), and systemic administration. By Figdraw.

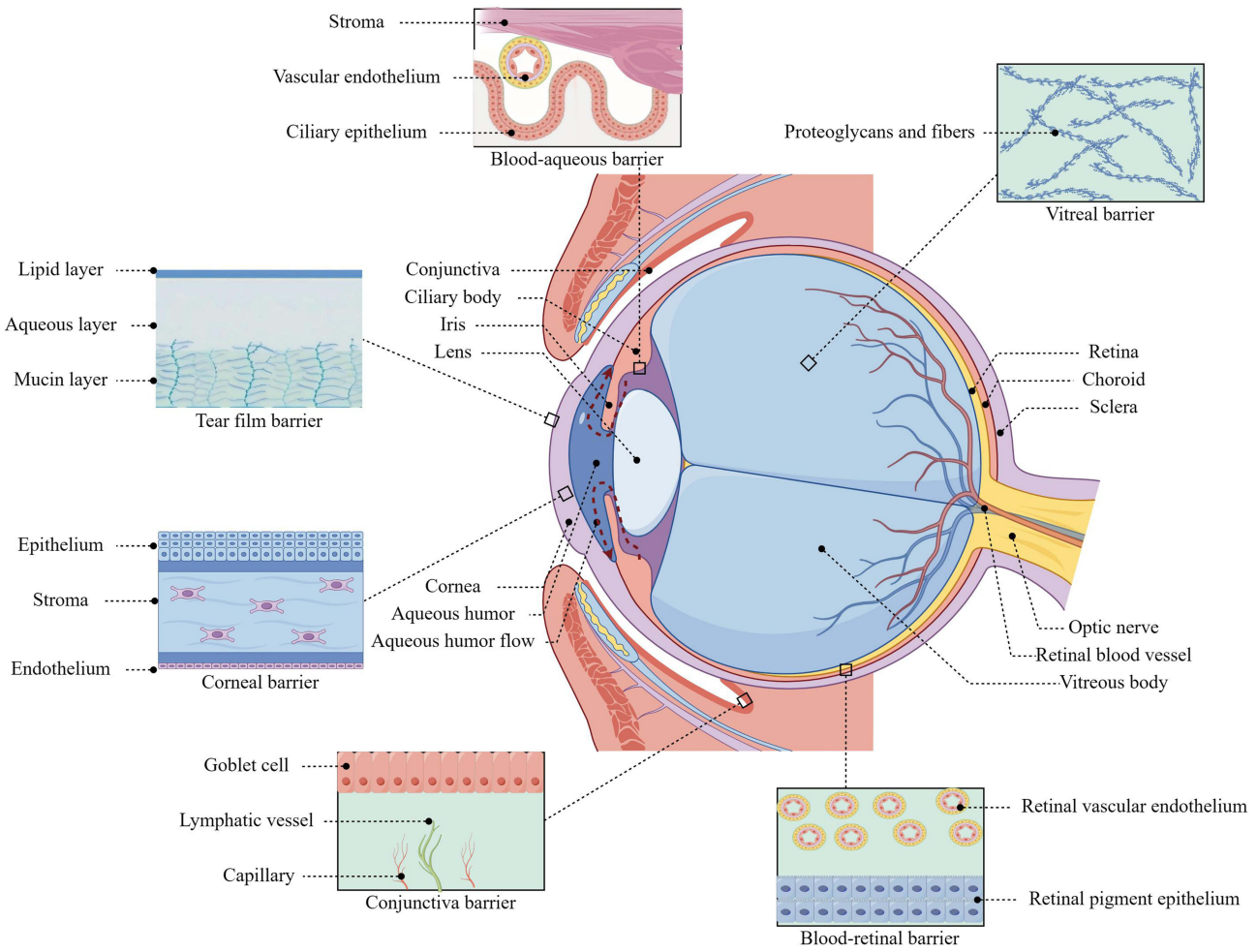

Figure 2 Drugs can face several challenges during delivery, including the tear film barrier, the conjunctiva barrier, the corneal barrier, the vitreal barrier, the blood-aqueous barrier (BAB), and the blood-retinal barrier (BRB). By Figdraw.

circulation, consequently reducing ocular bioavailability.[4] The tear film barrier, tear film turnover (tears secretion rate of 1~3uL/min), blinking (reducing drug residence time to <1 min) and metabolic enzymatic (present on the tear film degrade the drug).[5,6] The corneal barrier, the cornea's multilayered epithelium (3–6 layers of tightly connected cells), blocks hydrophilic drugs, while the stroma (90% of corneal thickness, rich in collagen) impedes lipophilic drugs, in addition efflux transporters like P-glycoprotein, breast cancer-associated protein and multidrug resistance proteins on the cornea actively expel drugs, reducing uptake.[7] Drugs that enter the anterior chamber through the cornea are further rapidly eliminated by the distribution of intraocular tissues and fluid to non-target tissues, further into the posterior chamber is blocked by the annular iris and aqueous humor flow (aqueous humor secretion rate of 2.4 ± 0.6μL/min).[8] The blood-aqueous barrier (BAB)—formed by tight junctions in ciliary epithelium and iris vascular endothelium—restricts bidirectional hydrophilic compound movement, blocking both blood-to-aqueous influx and aqueous-to-blood efflux; concurrently, active efflux transporters expressed in the ciliary body and iris epithelium mediate drug expulsion, collectively limiting therapeutic permeation.[9] The vitreal barrier, the viscosity of vitreous fluid impedes the diffusion of more extensive and heavier therapeutic cargoes (eg, proteins), and positively charged molecules binding with the vitreous proteoglycans (negatively charged) appear to be permeate-hindered.[10,11] The blood-retinal barrier (BRB) restrict access to deeper tissues. BRB consists of two functionally coupled layers—the outer retinal pigment epithelium (RPE) with tight junction complexes and the inner retinal vascular endothelium.[12,13] This dual architecture restricts paracellular transport through both interfaces: RPE junctions block choroidal-to-retinal hydrophilic substance movement, while retinal endothelial tight junctions impede systemic drug penetration. Their coordinated action creates bidirectional

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obstruction of aqueous-phase compound exchange between blood and vitreous compartments. Successful BRB permeation necessitates either optimal drug lipophilicity for transcellular diffusion or specific affinity for active transport systems expressed at RPE/endothelial interfaces.[14–17]

Local Injections

Local injections, including subconjunctival, intracameral, and intravitreal routes, are the mainstay for posterior segment diseases, delivering drugs directly to target sites.[18] However, macromolecules like anti-vascular endothelial growth factor (VEGF) agents, proteins, and peptides exhibit poor stability and short half-lives.[19–21] For instance, intravitreal dexamethasone (400 μg) in primates, which is commonly used as an anti-inflammatory therapy, showed negligible choroid/retinal retention (<100 ng/g, <0.002%) at 48 hours.[22,23] Anti-VEGF agents are the first-line drug macromolecules for ocular neovascularization. There are currently 5 drugs on the market, Bevacizumab (Avastin®), Ranibizumab (Lucentis®), Aflibercept (Eylea®), Pegaptanib sodium(Macugen®), Brolucizumab (Beovu®), and the half-lives of the five drugs are 4.9 days, 9 days, 7.1 days, 10 days, and 2.4 days, respectively—demonstrate half-lives under 10 days, with retention as low as 0.04% for Aflibercept at 48 hours.[24–27] So local injections often need to be given repeatedly, resulting in low patient satisfaction and an increased risk of numerous complications. Short-term complications, including eye pain, redness, swelling, and inflammation. In rare cases, it can lead to serious and lasting complications such as macular dysfunction, retinal detachment, and endophthalmitis.[28,29] Systemic risks also arise, as VEGF suppression may elevate cerebrovascular and cardiovascular event rates.[30] These limitations necessitate delivery systems that prolong drug action and reduce injection frequency.

Systemic Administration

Systemic administration targets the posterior segment via three pathways: diffusion through leaky ciliary body vessels into the aqueous humor, crossing the BRB, or penetrating the vitreous from the posterior chamber.[3] However, ocular drug concentrations remain low due to multiple factors. Drugs must remain stable in blood, evade systemic clearance, and possess physicochemical properties to cross the BRB and BAB, which selectively filters plasma components.[31,32] The BRB's tight junctions and the aqueous humor's regulated composition further restrict access. High systemic doses are often required, increasing off-target effects and reducing efficacy, making this route less viable for ocular therapy without advanced delivery enhancements.

Nanomedicine Components in Ophthalmic Applications

Nanomedicine utilizes a diverse array of nanomaterials—organic (eg, liposomes, micelles, dendrimers), inorganic (eg, metal nanoparticles, silica), and biological (eg, exosomes)—to address the shortcomings of conventional delivery systems.[33] For convenient reference and comparison, we have organized all described nanomedicines with their respective properties in Table 1 (contains nanoformulations, cargos, diseases, administrations, efficacy, phase, ClinicalTrials.gov Identifier and Reference).

Lipid-Based Nanoparticles

Lipid-based nanoparticles constitute a versatile drug delivery platform primarily categorized into three systems: conventional liposomes (Figure 3A), solid lipid nanoparticles (SLNs) (Figure 3B), and nanostructured lipid carriers (NLCs)[33] (Figure 3C). Liposomes are spherical vesicles composed of phospholipids that self-assemble into concentric bilayers surrounding an aqueous core.[83] These amphiphilic structures typically exhibit a size distribution ranging from 30 nm to micrometer-scale dimensions, with individual phospholipid bilayers maintaining a characteristic thickness of 4–5 nm.[84] As pharmaceutical carriers, liposomes demonstrate exceptional capabilities including: (1) protection of encapsulated therapeutics against physiological degradation, (2) extended plasma circulation half-life through surface modification, (3) controlled drug release kinetics, and (4) inherent biocompatibility with minimized systemic toxicity.[85,86] Their targeting efficiency derives from both passive accumulation via the enhanced permeability and retention effect and active targeting through surface-conjugated ligands, collectively enabling dose reduction while maximizing therapeutic efficacy at disease sites.[87,88] SLNs consist of a physiological lipid that is solid at room temperature and body temperature,

Table 1 Examples of Studies Performed with Nanomedicines. The Nanomedicine's Components, Features and Information, Nanoformulations (Product), Cargos, Diseases, Administrations, Efficacy, Phase, ClinicalTrials.gov Identifier, Reference

Nanoformulations(Product)	Cargos	Diseases	Administrations	Efficacy	Phase	ClinicalTrials. gov Identifier	Reference
Liposomes	Sodium hyaluronate	DED	Eye drops	Maintain ocular surface moisture while restoring the lipid layer	–	Cells (in vitro) Animals (in vivo)	[34]
Hydroxyl PAMAM dendrimers	Dexamethasone	DED	Subconjunctival injection	Prolong drug release to 1 month	–	Cells (in vitro) Animals (in vivo)	[35]
Methoxy PEG-PLA micelles	Cyclosporine A	DED	Eye drops	4.5 times of 0.05% CsA emulsion	-	Cells (in vitro) Animals (in vivo)	[36]
Cationized HA-coated spanlastics	Cyclosporine A	DED	Eye drops	Enhance ocular retention, improve corneal permeability, and increase tear production	-	Cells (in vitro) Animals (in vivo)	[37]
Palladium-coated gold nanorods hydrogels (GNRs@Pd)	-	DED	Attached to the surface of lacrimal gland	Minimizes the damage caused by preservatives in artificial tears	-	Animals (in vivo)	[38]
SLNs	Natamycin	Fungal keratitis	Eye drops	Prolong drug release (10 hours), improve corneal penetration (1.59-fold more than natamycin in Papp), increase antifungal activity (2.5-fold more than econazole in MICs)	-	Goat corneas (ex vivo)	[39]
SLNs	Econazole	Fungal keratitis	Eye drops	Extend corneal residence time (1.58-fold more than econazole), good bioavailability (2.64-fold more than econazole in Papp), enhanced antifungal activity (1.75 to 2.43-fold more than econazole in MICs)	-	Rabbit corneas (ex vivo) Animals (in vivo)	[40]
PBA-CS-VE	Voriconazole	Fungal keratitis	Eye drops	Extend corneal residence time, increasing voriconazole's bioavailability (1.65-fold more than voriconazole in aqueous humor), increasing therapeutic efficacy (0.09-fold than voriconazole in CFU/g)	-	Cells (in vitro) Animals (in vivo)	[41]
Cationic NLCs	Voriconazole	Fungal keratitis	Eye drops	Maintain effective drug concentrations for 30 minutes in corneal tissue, enhancing retention time	-	Cells (in vitro)	[42]
Liposomes	Fluconazole	Fungal keratitis	Eye drops	Extend corneal residence time (12 hours), a faster therapeutic effect	-	Cells (in vitro) Animals (in vivo)	[43]
Mucoinert nanosuspension	Moxifloxacin	Bacterial keratitis	Eye drops	Increases drug exposure and intraocular concentration (1.7-fold and 4.4-fold more than moxifloxacin, respectively), reduce dosing frequency (once daily)	-	Animals (in vivo)	[44]
Polymer micelles (PαGal50-b-PGRB20)	-	Bacterial keratitis	Photodynamic therapy	Effectively killing *Pseudomonas aeruginosa*, improving recovery from keratitis	-	Animals (in vivo)	[45]
Silver nanoparticles	-	Bacterial keratitis	Eye drops	Kill infectious pathogens, enhance eye wound healing	-	Cells (in vitro)	[46]
Hydrogels (Tiopex®)	Timolol Maleate	Glaucoma	Eye drops	Reduce dosing frequency (once daily)	-	FDA approved	[47]

(*Continued*)

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Table 1 (Continued).

Nanoformulations(Product)	Cargos	Diseases	Administrations	Efficacy	Phase	ClinicalTrials. gov Identifier	Reference
Hydrogels (Timoptic® GFS)	Timolol maleate	Glaucoma	Eye drops	Reduce dosing frequency (once daily)	-	FDA approved	[48]
Hydrogels (Timoptic-XE®)	Timolol maleate	Glaucoma	Eye drops	Reduce dosing frequency (once daily)	-	FDA approved	[48]
Hydrogels (Pilopine HS®)	Pilocarpine	Glaucoma	Eye drops	Reduce dosing frequency (once daily)	-	FDA approved	[49]
PEG-based hydrogel (OTX-TP)	Travoprost	Glaucoma, ocular hypertension	Intracanalicular punctal plug	Prolong drug release to 3 months	III	NCT02914509	[50]
PEG-based hydrogel (OTX-TIC)	Travoprost	Glaucoma, ocular hypertension	Intracameral injections	Prolong drug release to 4–6 months	I	NCT04360174	[50]
Liposomes	Latanoprost	Glaucoma, ocular hypertension	Subconjunctival injection	Prolong drug release to 3 months	I/ II	NCT01987323	[51]
Cubosomes	Latanoprost	Glaucoma	Eye drops	Increasing drug efficacy (maximum IOP reduction of 30% lasting for 9 days)	-	Cells (in vitro) Animals (in vivo)	[52]
Hollow PLA nanoparticles	Pilocarpine	Glaucoma	Intracameral injections	Prolong drug release to 56 days	-	Cells (in vitro) Animals (in vivo)	[53]
Lipid DNA Nanoparticles	Brimonidine	Glaucoma	Eye drops	Improved IOP lowering efficacy (IOP reduction of 74% and can reach 7.8 mmHg after 5 weeks)	-	Animals (in vivo)	[54]
PAMAM dendrimers hydrogel nanoparticles	Timolol maleate	Glaucoma	Eye drops	Improved IOP lowering efficacy (3.35 mmHg and 4.32 mmHg at 1 hour and 24 hours post-treatment, respectively)	-	Animals (in vivo) Rabbit (ex vivo)	[55]
MSNs	Sodium nitroprusside	Glaucoma	Eye drops	Extend efficacy to 48 hours	-	Cells (in vitro) Animals (in vivo)	[56]
PLGA (Ozurdex®)	Dexamethasone	Non-infectious uveitis, RVO, DME	Intravitreal injections	Prolong drug release to 3 months	-	FDA approved	[57]
LCGH, HCGH	Adalimumab	Non-infectious uveitis	Eye drops	Improved ocular drug retention time (2.8-fold and 2.1-fold, respectively) and penetration into the anterior chamber (5.2-fold and 1.4-fold, respectively) compared to Adalimumab	-	Cells (in vitro) Animals (in vivo)	[58]

Liposomes	Infliximab	Autoimmune uveoretinitis	Intravitreal injections	Improved ocular drug retention time in vitreous humor and retina (more than 28 days), and decrease in retinal damage and intraocular inflammation compared to Infliximab	-	Animals (in vivo)	[59]
Liposomes (Visudyne®)	Verteporfin	nAMD	Intravenous	A progressive reduction in treatment frequency: from 3.5 annual sessions during the first year post-diagnosis to just 0.1 by the fifth year	-	FDA approved	[60]
Hydroxyl dendrimers VEGF receptor (D-4517.2)	Tyrosine kinase inhibitor	nAMD, DME	Subcutaneous	The efficacy is equivalent to Aflibercept intravitreal injection	I/ II	NCT05105607 NCT05387837	[61]
PEG-based hydrogel (OTX-TKI)	Axitinib	nAMD	Intravitreal injections	Prolong drug release to 12 months	I	NCT03630315	[62]
Natural Polymers	Lycium barbarum poly saccharides	Atrophic AMD	Eye drops	A potential treatment avenue for atrophic AMD	-	Cells (in vitro)	[63]
LNCs	Astragaloside-IV	AMD	Eye drops	A potential treatment avenue for atrophic AMD	-	Cells (in vitro) Animals (in vivo)	[64]
Albuminated-PLGA nanoparticles	Bevacizumab	CNV	Intravitreal injections	Prolong drug release to months	-	Cells (in vitro) Animals (in vivo)	[65]
PLGA nanoparticles	Angiopoietin-1	CNV	Intravenous	Achieving non-invasive treatment of CNV with targeted, long-acting sustained-release drugs (28 days)	-	Cells (in vitro) Animals (in vivo)	[66]
Ultraviolet-sensitive polymer nanoparticles	-	CNV	Intravitreal injections	Stably retain in the vitreous for up to 30 weeks, non-invasive control of drug release timing under ultraviolet irradiation	-	Cells (in vitro) Animals (in vivo)	[67]
PLGA microspheres (RETAAC)	Triamcinolone acetonide	DME	Intravitreal injections	Prolong drug release to months	I/ II	NCT00407849	[68]
Cyclodextrin nanoparticles	Dexamethasone	DME	Eye drops	Achieving non-invasive treatment of DME	II/ III	NCT01523314	[69]
CS nanoparticles	Bevacizumab	DR	Intravitreal injections	Prolong drug release to 8 weeks	-	Animals (in vivo)	[70]
Gold nanoparticles	Resveratrol	DR	Oral	Protective effect of retina and amelioration of retinal inflammation	-	Animals (in vivo)	[71]
CS nanoparticles	Plasminogen kringle 5	DR, ROP	Intravitreal injections	Reduce retinal vascular leakage and decrease retinal leukostasis for at least 4 weeks	-	Animals (in vivo)	[72]
PLGA-PEG-PLGA hydrogel	Insulin	DR	Subconjunctival injection	Protecting retinal function up to 4 weeks	-	Animals (in vivo)	[73]
Hydrogels (Verisome®)	Triamcinolone acetonide	RVO	Intravitreal injections	Prolong drug release to 12 months	I/ II	ACTRN12608000603314	[74]

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Table 1 (Continued).

Nanoformulations(Product)	Cargos	Diseases	Administrations	Efficacy	Phase	ClinicalTrials. gov Identifier	Reference
Liposomes (TLC399)	Dexamethasone sodium phosphate	RVO	Intravitreal injections	Prolong drug release to 12 months	II	NCT02006147 NCT03093701	[75]
Hydroxyl PAMAM dendrimers	Triamcinolone acetonide	ROP, PDR, RVO, nAMD	Intravitreal injections	Improved efficacy (100-fold higher than free TA)	-	Cells (in vitro) Animals (in vivo)	[76]
Multivesicular Liposomes	Bevacizumab	nAMD, DR, RVO	Intravitreal injections	Prolong drug release to 56 days	-	Cells (in vitro) Animals (in vivo)	[77]
Annexin A5 Liposomes	Bevacizumab	nAMD, DR, RVO	Eye drops	Achieving non-invasive treatment of nAMD, DR and RVO	-	Cells (in vitro) Animals (in vivo)	[78]
MSNs	Bevacizumab	nAMD, DR, RVO	Intravitreal injections	Prolong residence time (28 days),	-	Cells (in vitro) Animals (in vivo)	[79]
Liposomes	Bevacizumab	nAMD, DR, RVO	Intravitreal injections	Prolong drug release to 42 days and 2-fold more than free Bevacizumab on day 28	-	Animals (in vivo)	[80]
Polyvinyl alcohol liposomes	Diclofenac	Macular edema	Eye drops	Improved efficacy (1.8-fold more than conventional diclofenac eye drops)	-	Animals (in vivo)	[81]
Gold nanoparticles	-	DR, nAMD, ROP	Intravitreal injections	A potential treatment avenue for ROP	-	Cells (in vitro) Animals (in vivo)	[82]

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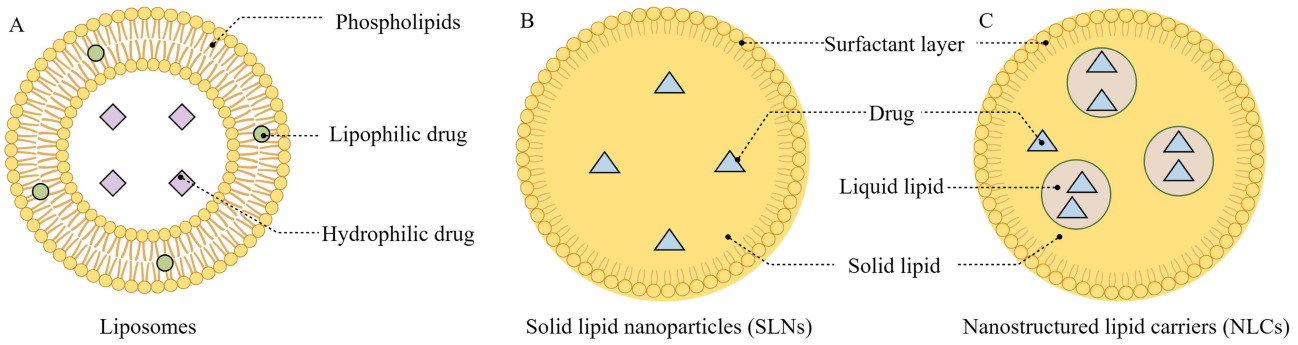

Figure 3 Liposomes are spherical vesicles composed of phospholipids that self-assemble into concentric bilayers surrounding an aqueous core (**A**); Lipid nanoparticles (SLNs) consist of a physiological lipid that is solid, a surfactant, and water (**B**); Nanostructured lipid carriers (NLCs) consist of a physiological lipid that are solid and liquid lipid, a surfactant, and water (**C**). By Figdraw.

a surfactant, and water.[89–91] These systems exhibit distinct advantages over liposomal formulations, including superior physical stability during storage and enhanced drug encapsulation efficiency for both hydrophobic and hydrophilic active pharmaceutical ingredients. The nanoscale dimensions combined with matrix lipid crystallinity enable sustained drug release profiles while maintaining efficient physiological barrier penetration through lipid-mediated transport mechanisms.[92,93] NLCs constitute a third-generation optimization of SLNs technology, engineered through strategic blending of solid and liquid lipid phases stabilized by surfactant co-emulsifiers.[94,95] This hybrid architecture creates an imperfect crystalline matrix with amorphous domains, resolving key limitations of SLNs by: (1) increasing active pharmaceutical ingredients loading capacity through lattice defect incorporation, (2) preventing drug expulsion during storage via reduced crystallinity, and (3) enhancing biocompatibility through tailored lipid phase combinations. Comparative studies confirm that NLCs exhibit greater drug payload capacity and improved long-term stability versus SLNs, establishing them as the current preferred choice among lipid nanoparticles systems for controlled delivery applications.[93]

Polymer Micelles

Polymer micelles (Figure 4A), typically ranging from 10 to 100 nm in diameter, are nanocarriers formed through the spontaneous self-assembly of amphiphilic block copolymers in aqueous media.[96] These supramolecular structures exhibit a core-shell architecture, where hydrophobic polymer segments aggregate into an inner core capable of solubilizing poorly water-soluble therapeutic agents, while hydrophilic segments form an outer corona that stabilizes the colloidal system and prevents micellar aggregation.[97] The hydrophilic corona fulfills dual critical functions: (1) steric stabilization against intermicellar coalescence through hydration repulsion forces, and (2) protection of encapsulated payloads from enzymatic degradation and opsonization.[98,99] Conversely, the hydrophobic core enables high-capacity loading of lipophilic drugs via non-covalent interactions, achieving solubilization efficiencies up to 1000-fold greater than aqueous solubility limits.[98] Convenient surface modification and targeted delivery improve the bioavailability of the drug, which can enhance the permeability of the drug by prolonging the residence time of the drug on the ocular surface.[54]

Dendrimers

Dendrimers represent a class of three-dimensional nanostructured polymers (2–10 nm) characterized by radially symmetric branching architectures and monodisperse molecular weight distributions.[100,101] These hyperbranched macromolecules are synthesized through iterative reaction sequences, predominantly via either divergent (core-to-periphery) or convergent (periphery-to-core) methodologies, enabling precise control over generation-dependent physicochemical properties.[102] The well-defined topology of dendrimers governs critical pharmaceutical parameters including: (1) aqueous solubility through terminal group modification, (2) in vivo stability via steric shielding of labile bonds, and (3) bioactivity modulation via multivalent ligand presentation.[103] In ocular therapeutics, dendrimers exhibit macrophage/microglia-specific tropism through size-dependent passive targeting.[18] Intravitreal administration of hydroxyl-terminated

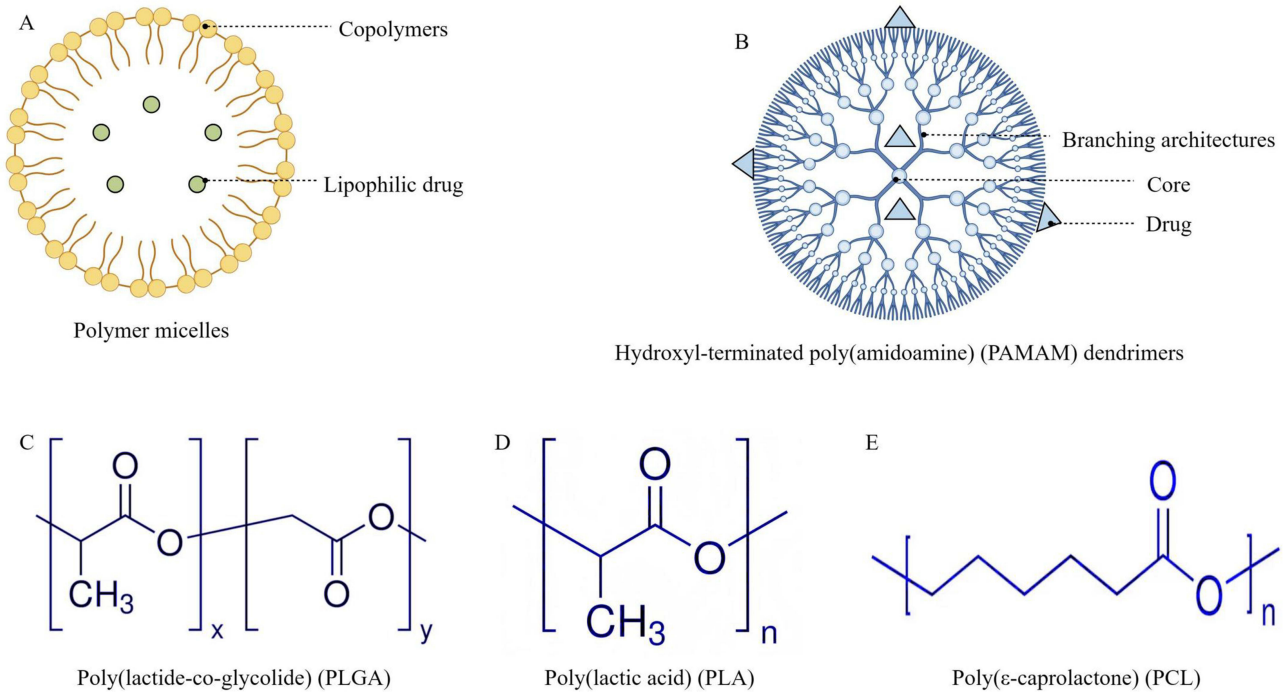

Figure 4 Polymer micelles structure exhibit a core-shell architecture, the shell formed through the amphiphilic block copolymers and the core carried the lipophilic drugs (**A**); Hydroxyl-terminated poly(amidoamine) (PAMAM) dendrimers structure exhibit a core-branching architecture, the drug entrapment by using various mechanisms: void spaces (by molecular entrapment), branching points (by hydrogen bonding) and outside surface groups by (charge–charge interactions) (**B**); Chemical formula of poly(lactide-co-glycolide) (PLGA) (**C**), poly(lactic acid) (PLA) (**D**), and poly(ε-caprolactone) (PCL) (**E**). By Figdraw.

poly(amidoamine) (PAMAM) dendrimers (Figure 4B) in ischemic retinopathy models demonstrated selective accumulation in activated microglia, with retinal retention extending beyond 21 days post-injection—a 7-fold increase compared to healthy controls during the acute phase (Days 0–3).[104–107] This pathological targeting paradigm arises from two synergistic mechanisms: (1) Enhanced Vascular Permeability: breakdown of the inner blood-retinal barrier during ischemia increases paracellular transport, and (2) Cellular Uptake Optimization: the small size (4–6 nm) and neutral hydroxyl termini enable rapid interstitial diffusion meanwhile minimize non-specific protein adsorption while enhancing microglial phagocytosis.[108,109]

Polyester Nanoparticles

Polyester-based nanoparticles, particularly those fabricated from poly(lactide-co-glycolide) (PLGA) (Figure 4C), poly (lactic acid) (PLA) (Figure 4D), and poly(ε-caprolactone) (PCL) (Figure 4E), have established themselves as cornerstone platforms in precision drug delivery and biomedical engineering due to their programmable degradation kinetics, tunable surface chemistry, and proven biocompatibility.[110–113] PLGA systems, with adjustable lactide:glycolide ratios (50:50 to 85:15), demonstrate superior pharmaceutical versatility—achieving >90% encapsulation efficiency for both hydrophobic and hydrophilic agents through emulsion-based techniques while enabling sustained release over 7–60 days via hydrolytic chain scission mechanisms.[114–117] This degradation-profile programmability, coupled with surface functionalization strategies enhanced cellular uptake, positions PLGA as the excellent way for intracellular targeted delivery.[118] In contrast, PLA and PCL leverage their distinct mechanical properties for structural biomedical applications: PLA's high tensile strength (50–70 MPa) and extended degradation timeline (12–24 months) suit tissue-engineered stents, while PCL's low glass transition temperature (−60°C) enables shape-memory vascular stents with 98% radial recovery.[119] Collectively, these polyester systems bridge therapeutic delivery and medical consumables applications through material-specific property optimization, with PLGA dominating controlled drug release paradigms and PLA/PCL excelling in medical consumables (eg, tissue-engineered stents, implantable medical devices and surgical meshes).[120]

Natural Polymers

Natural polymers exhibit distinctive advantages as ocular drug delivery platforms due to their enzyme-responsive biodegradation pathways, intrinsic bioactivity (eg, anti-inflammatory and angiogenic modulation), exceptional biocompatibility, and enhanced mucosal penetration through transient tight junction regulation.[121] Among natural biopolymers clinically deployed for ophthalmic applications, three dominant systems emerge:[33] (1) Hydrogel (Figure 5) networks—hydrophilic crosslinked matrices (mesh size 10–100 nm) that immobilize therapeutics via physical entrapment and controlled release mechanisms governed by Fickian diffusion and polymer relaxation kinetics, achieving times prolonged corneal residence versus eye drops while enabling zero-order release over 7–14 days and synergistic multi-drug co-delivery;[25,122–126] (2) Chitosan (CS) (Figure 6A)—a cationic linear polysaccharide composed of β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine units that mediates mucoadhesion through hydrogen bond formation with functional groups (hydroxyl, carboxyl, and amino groups) which significantly prolong their retention time in ocular tissues, and hinder drug clearance.[127–130] Meantime, CS has certain immunomodulation that enables it to be used for wound healing, tissue regeneration, and vaccine rejuvenation.[131,132] Hyaluronic acid (HA) (Figure 6B)—a linear anionic polysaccharide composed of repeating disaccharide units (D-glucuronic acid and N-acetyl-D-glucosamine) linked through β-1,3 and β-1,4 glycosidic bonds, serves as a natural ligand for CD44 receptors on macrophages and demonstrates exceptional drug diffusion and delivery capabilities, making it an outstanding therapeutic carrier for ocular disease treatment.[133,134] Emerging natural nano-sized pharmaceutical polymers, such as *Lycium barbarum* polysaccharides (LBPS) (Figure 6C) and cyclodextrin, exemplify versatile therapeutic platforms: LBPS, a multifunctional nanomedicine composed of polysaccharides, monosaccharides, uronic acid, acidic heteropolysaccharides, polypeptides, and proteins, exhibits potent antioxidative activity, while cyclodextrin (Figure 6D)—oligosaccharides characterized by a hydrophilic exterior and a lipophilic core—enhance nanomaterial adhesion, improve bioavailability, enable controlled ocular drug release, and prolong ocular retention time through superior permeability.[135–139]

Inorganic Nanomaterials

Inorganic nanomaterials (eg, metal nanoparticles, quantum dots, silica nanoparticles) have emerged as transformative platforms in ophthalmic applications due to their intrinsic physicochemical advantages, including high physiological stability, tunable morphostructural properties, and versatile surface functionalization capabilities.[140] Metal nanoparticles (MNPs) (Figure 7A), particularly silver (Ag) and gold (Au) variants, demonstrate potent antimicrobial efficacy through multimodal mechanisms: (1) direct membrane disruption via surface charge interactions, (2) sustained ion release profiles, and (3) Reactive oxygen species (ROS) generation, achieving reduction in bacterial load while enhancing corneal permeability versus conventional antibiotics.[141–145] Additionally, gold nanorods enhance the photoacoustic signal-to-noise ratio, making them highly compatible with advanced imaging technique.[146] Quantum dots (QDs) (Figure 7B), with size-tunable emission wavelengths (the radiation wavelength range of QDs depends not on their

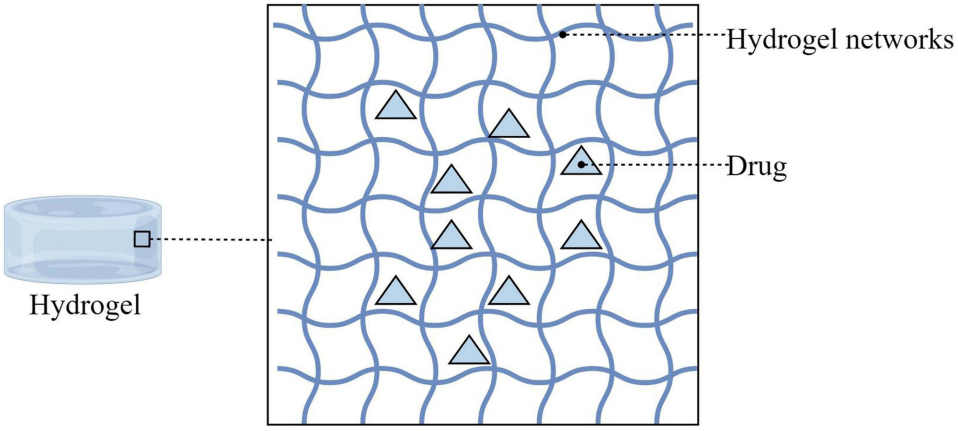

Figure 5 Hydrogel creates networks (hydrophilic crosslinked matrices) to catch the drug. By Figdraw.

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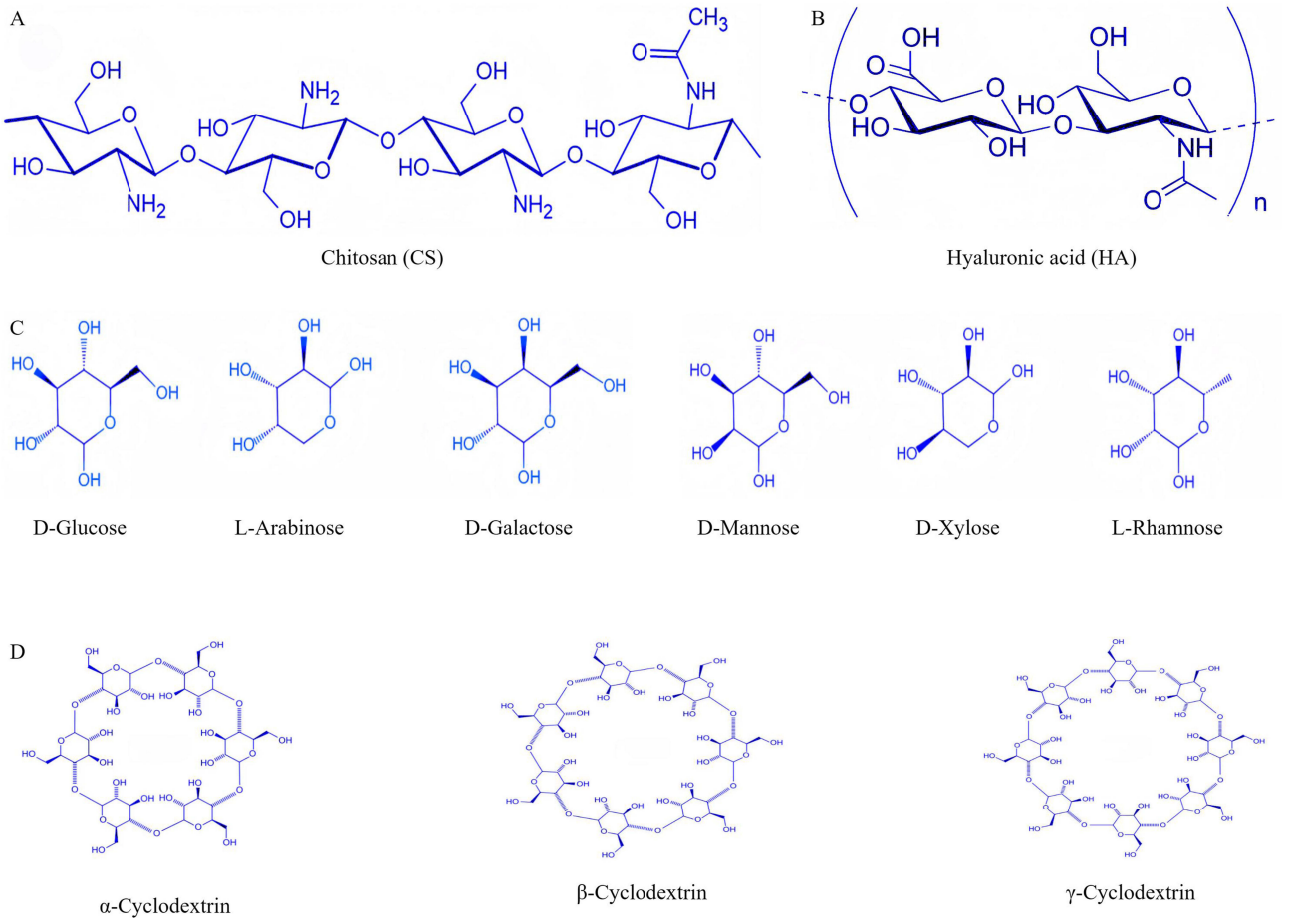

Figure 6 Chemical formula of chitosan (CS) (**A**), hyaluronic acid (HA) (**B**), Lycium barbarum polysaccharides (LBPS) mainly contain six monosaccharides (glucose, arabinose, galactose, mannose, xylose, and rhamnose) (**C**), and cyclodextrin (α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin) (**D**). By Figdraw.

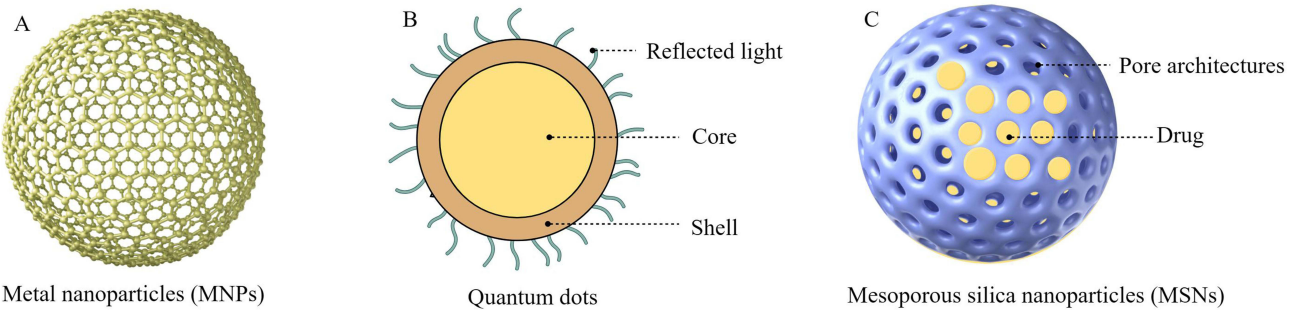

Figure 7 The structure of metal nanoparticles (MNPs) (**A**), quantum dots (QDs) (composed of core, shell, and reflected light) (**B**), and mesoporous silica nanoparticles (MSNs) (pore architectures carry drugs) (**C**). By Figdraw.

constituent materials but on their structural properties; thus, accurately tuning their dimensions enables precise control over the reflected light's wavelength and color), serve as advanced ocular imaging modalities (eg, contrast agents, optical coherence tomography, photoacoustic imaging) to provide better visualization of ocular structures and information.[147–150] Silica-based systems, particularly mesoporous silica nanoparticles (MSNs) (Figure 7C), combine exceptional biocompatibility (the growth rates of cells exposed to MSNs are similar to those of cells grown without MSNs, and there are no toxic side effects observed over a period of 42 days), tailorable pore architectures, and biodegradation kinetics, achieving highly drug loading efficiency for sustained agent delivery over 28 days.[151–158]

Biological Components

Exosomes (Figure 8A) are nanoscale (40–160 nm diameter) lipid bilayer-enclosed vesicles originating from multivesicular bodies through inward budding of endosomal membranes, subsequently released into the extracellular matrix via plasma membrane fusion.[159–162] This endogenous biogenesis pathway endows exosomes with natural intercellular communication capabilities, positioning them as promising drug delivery vectors with distinct advantages: (1) Enhanced targeting efficiency through both passive and active mechanisms;[163] (2) Innate biocompatibility with low immunogenicity in syngeneic models due to autologous membrane proteins;[164] (3) High payload capacity accommodating diverse therapeutics (eg, nucleic acids, proteins, small molecules) through electroporation or sonication methods;[165] (4) Synergistic therapeutic effects via co-delivery;[166] (5) Structural stability retaining high integrity with controlled multi-drug release.[167] Complementing exosomal systems, lipid-deoxyribonucleic acid (DNA) nanoparticles (Figure 8B)—hybrid nanostructures integrating programmable DNA frameworks with cationic lipid shells—demonstrate high loading drugs efficiency and increasing bioavailability.[54,168]

Applications of Nanomedicine in Ocular Diseases

Dry Eye Disease (DED)

DED is a multifactorial ocular surface disorder characterized by tear film instability, chronic inflammation of the ocular surface, and a secondary immune response. Inflammation is central to the pathogenesis of DED.[169] With the increasing use of electronic devices and higher rates of contact lens wear, the incidence of DED has risen significantly.[170,171] Current treatments for DED, including artificial tears, topical secretagogues, glucocorticoids, and immunosuppressants, have notable drawbacks. These include issues with patient compliance, eye discomfort, and side effects such as increased intraocular pressure, cataracts, and glaucoma.[172] To address tear film instability, phosphatidylcholine-based liposomes dispersed in sodium hyaluronate can help maintain ocular surface moisture while restoring the lipid layer of the tear film,

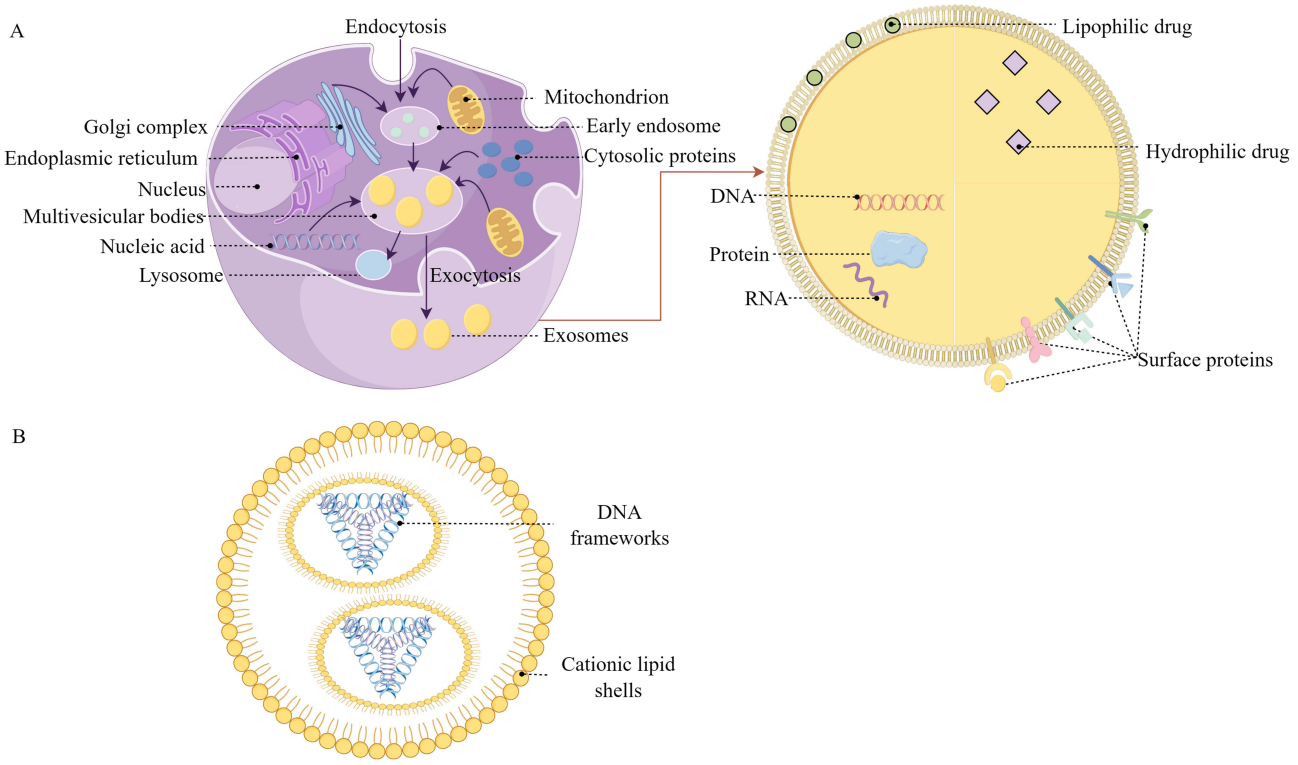

Figure 8 Exosomes are nanoscale lipid bilayer-enclosed vesicles originating from multivesicular bodies through inward budding of endosomal membranes (endocytosis), subsequently released to the extracellular matrix via plasma membrane fusion (exocytosis). Exosomes contain bilayer lipid (carry lipophilic drug hydrophilic drug), DNA, RNA, proteins, and surface proteins (**A**); Lipid-deoxyribonucleic acid (DNA) nanoparticles are nanostructures integrating DNA frameworks with cationic lipid shells (**B**). By Figdraw.

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thus reducing dry eye symptoms.[34,173] Compared to traditional eye drops, these formulations not only alleviate symptoms but also target the underlying causes. In studies involving a rabbit model of autoimmune dacryoadenitis related to DED, subconjunctival injections of hydroxyl-terminated PAMAM dendrimers-dexamethasone conjugate nanoparticles have demonstrated the ability to selectively localize in the inflammatory lacrimal gland and be taken up by infiltrating cells for up to one month, resulting in enhanced therapeutic efficacy.[35] For secondary immune responses, topical Cyclosporine A (CsA) is the first drug approved by the Food and Drug Administration (FDA) to inhibit T cell-mediated immune responses and improve tear production affected by ocular inflammation.[174] However, due to its hydrophobic structure, poor solubility, and low permeability, surfactants or permeability enhancers are often required to improve the water solubility and permeability of CsA, which can increase eye irritation.[175–177] Currently, several CsA formulations have received FDA approval, including RESTASIS™ (cyclosporine ophthalmic emulsion) 0.05%, CEQUA™ (cyclosporine ophthalmic solution) 0.09%, Verkazia® (cyclosporine ophthalmic emulsion) 0.1%, and VEVYE (cyclosporine ophthalmic solution) 0.1%, all requiring a minimum dosing frequency of twice daily. CsA-loaded methoxy poly(ethylene glycol)-PLA (mPEG-PLA) micelles have shown a maximum concentration in the rabbit cornea that is 4.5 times higher than that of 0.05% CsA emulsion, with continuous release and significantly prolonged residence time on the ocular surface.[36,178] Additionally, cationized HA-coated spanlastics are being utilized for the delivery of ocular CsA to enhance ocular retention, improve corneal permeability, and increase tear production.[37] Furthermore, GNRs@Pd (palladium-coated gold nanorods) hydrogel eye masks can sense various visible light irradiations and promote tear secretion through heating. This approach not only improves DED treatment but also minimizes the damage caused by preservatives in artificial tears and avoids interference from red light eye patches on normal eyes.[38,179]

Keratitis

Keratitis is a vision-threatening corneal infection caused by bacteria, fungi, viruses, or amebae. If not properly treated, it can lead to corneal opacity, perforation, and even eye atrophy.[169] The first-line treatment options depend on the causative agent and typically include eye drops containing antibacterial agents (eg, besifloxacin, moxifloxacin, and ofloxacin), antifungal agents (eg, natamycin, econazole, voriconazole, and fluconazole), or antiviral drugs (such as acyclovir).[180–184] However, the low bioavailability of these eye drops often hampers treatment efficacy. Innovative formulations have been developed to enhance therapeutic outcomes. For instance, natamycin SLNs (NAT-SLNs) can prolong drug release (10 hours), improve corneal penetration (1.59-fold more than natamycin in apparent permeability coefficient—Papp), and increase antifungal activity (2.5-fold more than econazole in minimum inhibitory concentrations—MICs) without causing cytotoxic effects on corneal tissue, achieving a lower minimum inhibitory concentration and enhanced absorption in the deeper corneal layers.[39] Similarly, econazole SLNs (E-SLNs) extend corneal residence time (1.58-fold more than econazole) and demonstrate good bioavailability (2.64-fold more than econazole in Papp) and enhanced antifungal activity (1.75 to 2.43-fold more than econazole in MICs).[40] Voriconazole-loaded phenylboronic acid conjugated chitosan-vitamin E (PBA-CS-VE) polymer micelles can prolong the drug's residence time in the cornea, thereby increasing voriconazole's bioavailability (1.65-fold more than voriconazole in aqueous humor) and therapeutic efficacy against fungal keratitis (0.09-fold than voriconazole in CFU/g).[41] Cationic NLCs loaded with voriconazole maintain effective drug concentrations in corneal tissue even after 30 minutes of in vitro application, enhancing retention time and improving treatment for fungal keratitis.[42] Additionally, liposomal formulations of fluconazole provide a longer duration of action (12 hours) and a faster therapeutic effect in a Candida albicans keratitis model compared to traditional fluconazole.[43] An insoluble ion-paired complex of moxifloxacin (MOX) with pamoic acid (PAM), formulated into a mucus-penetrating nanosuspension (MOX-PAM NS) eye drops, increases drug exposure and intraocular concentration (1.7-fold and 4.4-fold more than moxifloxacin, respectively), proving to be as effective when administered once daily as MOX given three times a day in cases of *Staphylococcus aureus*-infected keratitis.[44] Treating multidrug-resistant (MDR) *Pseudomonas aeruginosa* is particularly challenging due to its natural resistance to antibiotics and ability to form stable biofilms. Photodynamic therapy using photosensitizer-based germicidal nanoparticles (PαGal50-b-PGRB20) specifically targets and produces ROS to damage DNA, ribonucleic acid (RNA), proteins, and biofilms, effectively killing *Pseudomonas aeruginosa* and improving recovery from keratitis.[45] Moreover, silver nanoparticles (Ag NPs) are recognized as highly effective antibacterial agents, with mechanisms that include direct interaction with bacteria, the

release of silver ions (Ag+), and the ability to kill infectious pathogens associated with bacterial keratitis. Additionally, Ag NP bandages can promote cell proliferation and enhance eye wound healing.[46,185,186]

Glaucoma

Glaucoma is the leading cause of irreversible blindness worldwide, primarily due to damage to retinal ganglion cells, which results in vision loss. The only proven modifiable risk factor for glaucoma is intraocular pressure (IOP).[187,188] Conventional treatments mainly focus on lowering IOP by either reducing the production of aqueous humor—using medications such as β-blockers (eg, timolol maleate) and carbonic anhydrase inhibitors—or increasing the outflow of aqueous humor through parasympathomimetics (eg, pilocarpine), prostaglandin analogues (eg, travoprost, latanoprost), and α-agonists (eg, brimonidine).[189–193] Topical intraocular antihypertensive drugs are a primary treatment for glaucoma; however, the bioavailability of eye drop formulations is often less than 5% due to various physiological barriers in the eye.[194] Additionally, the chronic nature of glaucoma necessitates long-term, repeated medication, which can lead to significant drug-related surface toxicity and decreased patient compliance.[195] Innovative delivery systems have been developed to improve treatment adherence and efficacy. For instance, using hydrogels as carriers for timolol maleate has reduced the frequency of administration from twice daily to once daily, as seen in products like Tiopex®, Timoptic® GFS, and Timoptic-XE.[47,48] Similarly, pilocarpine formulations can be administered once daily instead of four times a day, exemplified by Pilopine HS.[49] Ocular Therapeutix (OTX) has designed an intracanalicular punctal plug, OTX-TP, which consists of a PEG-based hydrogel and travoprost-loaded PLA microspheres, allowing for drug delivery to the ocular surface over a period of up to three months. The phase III clinical trial for this product (NCT02914509) has been completed.[50,196] Another product, OTX-TIC, is a bioresorbable intracameral implant containing travoprost, with a release period of 4 to 6 months; its Phase I clinical trial (NCT04360174) has also been completed.[50] Liposomes encapsulating latanoprost have demonstrated a clinically significant antihypertensive effect through subconjunctival injection for at least three months, with the phase I/II clinical trial (NCT01987323) completed.[51] Nanosized cubic liquid crystals, known as cubosomes, have been developed to carry latanoprost in eye drops, achieving a maximum IOP reduction of 30% lasting for nine days—significantly better than commercial preparations of latanoprost 0.005% (Louten®), which achieve a 20% reduction lasting 24 hours.[52] Hollow PLA nanoparticles can regulate the release of pilocarpine, with an optimal shell thickness of 40 nm providing sustained IOP reduction for 56 days following a single intracameral injection.[53] Additionally, lipid DNA nanoparticles carrying brimonidine applied to the ocular surface of mice showed an improved IOP lowering efficacy, IOP reduction of 74% (brimonidine is 36%) and can reach 7.8 mmHg (brimonidine is 0.6 mmHg) on a weekly basis (every 7 days) for 5 weeks.[54] PAMAM dendrimer hydrogel nanoparticles carrying timolol maleate demonstrated significant IOP reductions in an angiopoietin 1 gene knockout (A1cKO) glaucoma model, achieving average reductions of 3.35 mmHg and 4.32 mmHg at 1 hour and 24 hours post-treatment, respectively, which were markedly more effective than timolol maleate eye drops (0.72 mmHg and 1.85 mmHg).[55] Nitric oxide (NO) is a key signaling molecule that mediates various physiological responses and can reduce IOP by increasing aqueous humor outflow through the trabecular meshwork (TM) and Schlemm's canal (SC).[197–199] Sodium nitroprusside (SNP), a NO donor, has been incorporated into a SNP@MSNs delivery system, successfully developed as an eye drop that continuously reduces IOP by delivering SNP to the TM and SC, activating downstream signaling pathways and achieving sustained IOP reduction for up to 48 hours.[56]

Uveitis

Uveitis is an inflammation of the eye that affects the uvea, which includes the iris, ciliary body, and choroid. It is primarily categorized into infectious and non-infectious uveitis, both of which can lead to vision loss in severe cases.[200,201] Appropriate treatment for infectious uveitis often involves antibacterial, antifungal, or antiparasitic medications, which typically resolve the inflammation.[201,202] However, frequent eye drops are still necessary. Traditional treatment for non-infectious uveitis has relied on systemic or topical steroid drugs and immunosuppressants.[203] Unfortunately, these methods may be associated with significant side effects and limited intraocular distribution and penetration. Dexamethasone implant (Ozurdex®) is a biodegradable, rod-shaped implant containing 0.7 mg of dexamethasone, made from PLGA, and is FDA-approved for treating macular edema due to RVO, DME, and non-infectious

uveitis.[57] This implant allows for intravitreal injections followed by a slow, sustained release of dexamethasone over three months. Tumor necrosis factor-alpha (TNF-α) is considered a key factor in the development of various inflammatory eye diseases, including uveitis, scleritis, and ocular surface disease.[204–207] Adalimumab (HUMIRA®), a TNF-α inhibitor, is the only systemic non-corticosteroid drug approved by the FDA for the treatment of non-infectious uveitis.[208] It is administered via subcutaneous injection, but systemic therapy can lead to immunosuppression, increasing the risk of infections and tumorigenesis.[209,210] To enhance the delivery of Adalimumab for uveitis treatment, low-deacetylated chitosan/β-glycerophosphate (β-GP) hydrogel (LCGH) and high-deacetylated chitosan/β-GP hydrogel (HCGH) have been developed as carriers for eye drops. In studies using an endotoxin-induced uveitis (EIU) rabbit model, both LCGH and HCGH improved ocular drug retention time (2.8-fold and 2.1-fold, respectively) and penetration into the anterior chamber (5.2-fold and 1.4-fold, respectively) compared to Adalimumab solution.[58] Furthermore, Adalimumab-loaded LCGH and HCGH significantly reduced EIU symptoms (including anterior chamber cells, iris hyperemia, pupillary adhesions, and exudate) and inflammatory cytokines (TNF-α and interleukin-6), with LCGH showing superior therapeutic effects compared to HCGH.[58] Infliximab, another TNF-α inhibitor, has proven effective in reducing chronic uveitis.[211] Intravitreal injections of Infliximab-loaded liposomes in a rat model of autoimmune uveoretinitis resulted in significant improved ocular drug retention time in vitreous humor and retina (more than 28 days), and decrease in retinal damage and intraocular inflammation compared to conventional Infliximab treatments.[59]

Age-Related Macular Degeneration (AMD)

AMD is the third leading cause of blindness globally and the primary cause of irreversible vision loss among older populations in developed countries.[212] AMD can be classified into atrophic AMD and neovascular AMD (nAMD), with 10–15% of AMD cases progressing to nAMD due to choroidal neovascularization (CNV), which accounts for over 80% of vision impairment in AMD patients.[213] Currently, there are no regulatory-approved therapies to slow the progression of AMD or the growth of geographic atrophy.[214] Treatments for nAMD primarily focus on anti-VEGF drugs, laser photocoagulation, and corticosteroids, but the limited efficacy of laser photocoagulation and the potential risks of glucocorticoids leading to cataracts and glaucoma restrict their clinical use.[215] Intravitreal VEGF antagonists are gradually replacing these methods as the primary treatment strategy;[216] however, anti-VEGF therapy necessitates repeated lifelong intravitreal injections, which can result in complications such as hemorrhage, retinal detachment, and endophthalmitis. Moreover, long-term use of VEGF antagonists, the most effective drugs for treating neovascular diseases, can lead to macular dysfunction, with only 25–40% of patients experiencing significant improvements in visual acuity. Visudyne® is currently the only FDA-approved nanoparticle formulation that achieves targeted delivery to the eye through systemic administration.[18] This liposomal formulation containing Verteporfin is administered intravenously and activated intraocularly using a diode laser, resulting in reactive oxygen species-mediated vascular thrombosis, and is approved for treating CNV associated with AMD, thus avoiding the complications and surgical risks of vitreous injection of anti-VEGF.[60,217] Besides, clinical data reveal a progressive reduction in treatment frequency: from 3.5 annual sessions during the first year post-diagnosis to just 0.1 by the fifth year, indicating durable therapeutic effects. The hydroxyl dendrimer VEGF receptor tyrosine kinase inhibitor (D-4517.2) has shown effectiveness in nAMD and diabetic macular edema (DME) treatments; a single subcutaneous injection of 40 μg of D-4517.2 was compared to an intravitreal injection of Aflibercept over two weeks, demonstrating that the subcutaneous dendritic conjugate significantly reduced mean CNV compared to the intravitreal Aflibercept group, with oral administration also proving effective and non-toxic.[18,61,218] A Phase II clinical study (NCT05105607, NCT05387837) is currently underway.[61] Axitinib, a multi-receptor tyrosine kinase inhibitor (TKI), blocks VEGF-R and platelet-derived growth factor (PDGF)-B receptor signaling pathways.[219] OTX-TKI, a dry PEG-based hydrogel containing dispersed small molecule Axitinib microcrystals, has completed a phase I clinical trial (NCT03630315) in nAMD patients, showing efficacy lasting up to 12 months.[62] LBPS inhibits NLRP3 inflammasome activation through its anti-amyloid β1-40 oligomerization properties in AMD models, exerting anti-apoptotic effects and alleviating inflammation and cytopathological changes, thus providing a potential treatment avenue for atrophic AMD.[63] Astragaloside-IV (ASIV) exhibits anti-inflammatory and antioxidant properties, protecting RPE cell lines and reducing neurodegenerative changes in RPE cells.[220–222] ASIV loaded into lipid nanocapsules (ASIV-LNCs) can reduce the apoptosis rate from 5.12% to 0.533% and effectively protect retinal cells from apoptosis by delivering the

drug to the retinal layer via topical eye drops in the NaIO3-induced atrophic AMD mice.[64] Albuminated-PLGA nanoparticles encapsulating Bevacizumab for treating CNV utilize albumin to prevent inactivation and aggregation of Bevacizumab protein, stabilizing its activity and maintaining concentrations above 500 ng/mL for over 8 weeks, with stable release for 4 months.[65,223,224] Angiopoietin-1 (Ang1) improves the internal environment of ischemic organs, promotes the tightening of endothelial junctions, stabilizes blood vessels, and protects the vascular system from VEGF-induced plasma leakage.[225–230] CD105, a hypoxia-inducible protein associated with proliferation, is upregulated in endothelial cells under hypoxic conditions, enhancing angiogenesis, particularly at the edges of neovascularization.[231,232] Angiopoietin-1-anti-CD105-PLGA nanoparticles (AAP NPs) slowly release Ang1 and target the CD105 marker on CNV, increasing drug accumulation and enhancing cadherin expression between vascular endothelial cells, significantly reducing neovascularization and achieving non-invasive treatment of CNV with targeted, long-acting sustained-release drugs (28 days).[66,233] Ultraviolet-sensitive polymer nanoparticles represent a brief, low-power, far-ultraviolet light-responsive degradable system that enables on-demand delivery of anti-angiogenic molecules, effectively inhibiting CNV in rats. This nanosystem can stably retain encapsulated molecules in the vitreous for up to 30 weeks post-injection, allowing for non-invasive control of drug release timing under 365 nm ultraviolet irradiation.[67]

Diabetic Retinopathy (DR)

DR is a specific microvascular complication of diabetes mellitus and ranks among the leading causes of vision impairment and preventable blindness worldwide, affecting both the adult working population and older adults.[234–237] DR is categorized into several stages: no DR, mild non-proliferative DR, moderate non-proliferative DR, severe non-proliferative DR, and proliferative DR (PDR).[238] Current treatment options include laser photocoagulation, surgical vitrectomy, and intravitreal drug therapy, which often employ various strategies to manage the disease; however, these methods primarily serve to delay and alleviate some symptoms while carrying a significant risk of further vision loss.[239] Evidence suggests that dexamethasone implant can inhibit peripheral retinal ischemia, potentially delaying the progression of DR and PDR while improving DR severity within 24 months.[240–243] In patients with diffuse DME, intravitreal injection of 1 mg triamcinolone acetonide (TA) loaded in PLGA microspheres (RETAAC system) resulted in decreased macular center thickness and improved visual acuity after 6 and 12 months, with PLGA microspheres demonstrating superior long-term pharmacological properties compared to 4 mg of free TA, which showed no functional or anatomical improvement after the same period.[68,244,245] A phase I/II clinical study (NCT00407849) is currently underway.[68] Dexamethasone-cyclodextrin nanoparticle eye drops at 1.5% have been evaluated in a clinical study (NCT01523314) for diabetic macular edema, showing an average reduction of 20% in central macular thickness in 74% of eyes by week 4, along with improvements in visual acuity exceeding 0.1 logMAR, without serious adverse effects.[69] Compared to Bevacizumab, intravitreal injection of Bevacizumab-loaded chitosan nanoparticles demonstrated a longer inhibitory effect on diabetic retinal VEGF expression in rats (lasting over 8 weeks).[70] Resveratrol exhibits antifibrotic, anti-inflammatory, and antioxidant properties; in streptozotocin (STZ)-diabetic rats, oral administration of AU nanoparticles-coated resveratrol promoted increased retinal expression of pigment epithelium-derived factor (PEDF) while decreasing mRNA expression of VEGF-1, TNF-α, monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), interleukin-6 (IL-6), and interleukin-1β (IL-1β) by inhibiting retro-transcribed NF-κB and reducing diabetes-induced retinal ERK1/2 activation, consequently reducing BRB permeability and retinal inflammation.[71] Plasminogen kringle 5, a natural angiogenesis inhibitor, Chitosan nanoparticles containing the Plasminogen kringle 5 can reduce retinal vascular leakage and decrease leukostasis in the retina for at least 4 weeks.[72] Subconjunctival injection of insulin-loaded chitosan nanoparticles/PLGA-PEG-PLGA thermosensitive hydrogel (ICNPH) mitigates retinal microstructural and ultrastructural changes, reduces apoptosis, decreases glial fibrillary acidic protein (GFAP) and VEGF expression, and enhances globin expression, thereby protecting retinal function in STZ-diabetic rats for up to 4 weeks.[73]

Retinal Vascular Occlusion (RVO)

Retinal vein occlusion (RVO) is one of the most common causes of sudden, painless unilateral blindness and ranks as the second most prevalent retinal vascular disease after DR.[246] Vision loss typically results from macular edema caused by increased permeability of retinal vessels due to hypoxia and inflammation following vascular occlusion, which

stimulates retinal cells to release growth factors that promote neovascularization.[247] The current mainstay of treatment involves intravitreal injections of anti-VEGF agents and dexamethasone implants, often requiring multiple vitreous injections. Verisome® technology, a hydrogel-based drug delivery system, is currently undergoing a Phase I clinical trial (ACTRN12608000603314) for the delivery of TA to treat macular edema associated with RVO.[74] This technology allows for injection through the vitreous cavity, where the released fluid forms a sphere, extending the sustained release time to one year.[74,248] Additionally, dexamethasone sodium phosphate (DSP), a derivative of dexamethasone, is being investigated in phase II clinical trials (NCT02006147, NCT03093701) using DSP-loaded liposomes (TLC399) for RVO treatment, with the primary outcome measure being a best corrected visual acuity (BCVA) gain of at least 15 letters from baseline after 12 months.[75]

Common Retinal Diseases (AMD, DR, RVO)

AMD, DR, and RVO are the most common retinal diseases and leading causes of permanent vision loss in developed countries.[249] Clinically, similar strategies are employed for treating neovascularization and macular edema associated with these conditions. TA is FDA-approved for treating diabetic macular edema, macular edema due to RVO, PDR, and uveitis, and is used off-label for certain forms of AMD.[250–256] Microglial cells play a crucial role in ambulatory immune monitoring and maintaining normal retinal health.[257] However, under pathological conditions, these cells become activated, leading to breakdown of the BRB, cytokine production, and stimulation of RPE cells, which are significant contributors to VEGF production, ultimately resulting in neovascularization.[258,259] Hydroxyl PAMAM dendrimers conjugated with TA (D-TA) have been shown to deliver TA effectively, inhibiting retinal microglial inflammation for up to 72 hours while selectively targeting activated microglia, achieving concentrations in RPE cells that are 100-fold higher than free TA.[260] D-TA significantly outperforms free TA in inhibiting retinal inflammatory cytokines, microglial activation, retinopathy-related neovascularization, and protecting retinal nerve and visual function at equivalent doses.[76] Bevacizumab-loaded multivesicular liposomes (MVLs) allow for extended release in the vitreous and aqueous humor for over 56 days, prolonging drug action and reducing injection frequency.[77] Annexin A5, which interacts with cells and biological membranes in a calcium-dependent manner, is conjugated with Bevacizumab in liposomes, enhancing corneal permeability and resulting in significant Bevacizumab concentrations in the posterior segment.[78] MSNs encapsulating Bevacizumab prolong its residence time (28 days) in the vitreous and aqueous humor, maintaining long-lasting drug concentrations. MSNs-encapsulated Bevacizumab nanoparticles are more effective than free Bevacizumab in inhibiting endothelial growth factor-induced endothelial cell proliferation, migration, and neovascularization.[79] Bevacizumab-loaded liposomes administered intravitreally in rabbit eyes can sustain drug release for over 42 days, with concentrations on day 28 being double that of free Bevacizumab and five times higher on day 42.[80] Additionally, diclofenac, a non-steroidal anti-inflammatory drug, is effective for treating macular edema of various origins.[261] Using a calcium acetate gradient method to encapsulate diclofenac in liposomes achieves a 97% encapsulation efficiency, resulting in a 1.8-fold increase in retinal-choroid drug concentration compared to conventional diclofenac eye drops.[81]

Retinopathy of Prematurity (ROP)

ROP is one of the leading causes of severe vision impairment and blindness in children.[262] The typical developmental process of retinal vascularization is disrupted in various ways at different stages.[263] ROP progresses through two distinct pathological phases: The initial phase involves delayed physiological vascularization or even regression of developing retinal vasculature. This is followed by a secondary phase marked by reactive pathological angiogenesis, characterized by disorganized vascular proliferation that extends abnormally from the retinal surface into the vitreous cavity.[264] Therefore, both anti-VEGF and laser therapy have limited efficacy on ROP, and even have a negative effect. The oxygen-induced retinopathy (OIR) mouse model effectively mimics the pathological mechanisms of ROP. In these models, AU NPs have been shown to inhibit VEGF-induced endothelial cell proliferation and retinal neovascularization by blocking VEGFR-2 autophosphorylation and subsequent ERK1/2 activation.[82] Meanwhile, the AU NPs never affected to cellular viability of retinal microvascular endothelial cells.[82] So, Au NPs demonstrate therapeutic benefits for Phase I ROP treatment while avoiding adverse effects on Phase II pathological progression. And these mechanisms hold potential for application in the treatment of DR and nAMD also.

Advantages and Challenges of Nanomedicine-Based Systems

Nanomedicine-based ophthalmic drug delivery systems offer several advantages, including enhanced drug bioavailability, prolonged release, targeted delivery, drug protection, improved ocular penetration, reduced administration frequency, minimized toxicity, non-invasive delivery, combination therapy, and potential for personalized medicine. These benefits are related to several factors: (1) Size: Nanoparticles with diameters of 100–200 nm are evenly distributed in the vitreous, while those around 50 nm can cross the retinal barrier and accumulate in the retina. Smaller nanoparticles tend to be excreted through lymphatic, choroidal blood, or systemic circulation, whereas larger particles (preferably >100 nm) can avoid rapid clearance, prolonging circulation within ocular tissues. Drug-loaded nanoparticles sized between 50 and 400 nm are optimal for ocular delivery, providing efficient adhesion, high penetration of ocular barriers, and reduced intraocular irritation.[265] Nanocarriers smaller than 200 nm are readily absorbed in the precorneal region via topical administration.[266,267] For the posterior segment, small particles (<350 nm) can reach the retina through intravitreal injection.[268,269] (2) Charge: At physiological pH, corneal epithelia are negatively charged, allowing positively charged nanoparticles to electrostatically interact with corneal cells and surface mucins, enhancing adhesion and permeability.[270] In contrast, neutral or anionic molecules diffuse more rapidly through the negatively charged lens capsule, while positive ions face limited diffusion.[271] Negatively charged nanocarriers can diffuse freely in the vitreous, whereas positive ions experience restricted movement.[272] Cationic nanoparticles can enhance cellular internalization due to their interaction with anionic cell surfaces, whereas negatively charged nanoparticles may promote tear retention by avoiding adhesion to healthy ocular surfaces. (3) Hydrophilicity/Lipophilicity: Increasing the hydrophilicity of nanoparticle surfaces can improve drug bioavailability on the ocular surface. The hydrophilic barrier formed by lens epithelial cells restricts the penetration of hydrophilic molecules, while lipophilic molecules can achieve better penetration in the RPE due to their ability to diffuse through intracellular pathways.[273]

Despite these advantages, nanomedicine-based ophthalmic drug delivery systems face challenges in specific applications. Clinical use of liposomes has been associated with blurred vision, inflammation during cationic liposome delivery, and aggregation due to poor colloidal stability, along with high manufacturing costs.[274,275] SLNs have limited biopharmaceutical load and rapid elimination by mononuclear phagocytic systems.[276] Polymeric micelles face several limitations in ocular drug delivery, including inadequate potential for gene delivery applications, inefficient entrapment of macromolecular agents, and challenges in scalable manufacturing processes.[33] Dendrimers face toxicological issues, complex synthesis, inadequate in vivo quality control, and high preparation costs, hindering their clinical advancement.[277] Polyester nanoparticles exhibit biological inertness, limiting progress, while natural polymers present challenges in chemical synthesis, purity, and structural identification.[278] Natural polymers present persistent challenges as ocular nanocarriers, particularly regarding their complex synthesis, inconsistent purity levels, and insufficient structural identification. For examples, hydrogels have a higher viscosity, which may lead to (longer lasting) blurred vision and foreign body sensation,[54] and LBPS displays low absorption, poor bioavailability, and unstable chemical structures in ocular tissues.[134] Additionally, inorganics such as metal nanoparticles may pose toxic risks to the retina and overall eye health.[279] To biological components, the rapid removal in the body is still a problem that needs to be solved, including exosomes and lipid DNA nanoparticles. To harness the full potential of nanomaterials in ophthalmology while mitigating their associated risks, several approaches can be adopted: (1) Comprehensive understanding of nanomedicine physicochemical properties: As critical parameters including particle size distribution and morphological characteristics directly govern their biodistribution and interactions with ocular tissues. These intrinsic material properties may precipitate unanticipated biological consequences, particularly given the propensity of some nanomaterials to undergo aggregation in physiological conditions—a phenomenon that can manifest clinically as microvascular occlusion or trigger inflammatory cascades.[280] Optimizing size, shape, and surface properties: Precise control of nanoparticle size and morphology directly enhances therapeutic efficacy by improving tissue penetration and biodistribution profiles. Furthermore, advanced surface engineering approaches can significantly improve biocompatibility while mitigating potential toxicological concerns through enhanced ocular tolerance and reduced non-specific interactions.[281] Preclinical assessment: Thorough preclinical evaluation of nanomaterials in relevant animal models and in vitro assays is essential to identify and address potential safety concerns before progressing to clinical trials.[282]

Conclusion

Nanomedicine-based ophthalmic drug delivery systems represent a transformative approach to treating ocular diseases, addressing the limitations of conventional methods such as low bioavailability, rapid clearance, and physiological barriers. By leveraging organic nanomaterials (eg, liposomes, polymer micelles, dendrimers), inorganic nanomaterials (eg, metal nanoparticles, quantum dots), and biological components (eg, exosomes), these systems enhance drug penetration, prolong therapeutic effects, and enable targeted delivery. Notable advancements include sustained-release implants like OTX-TP for glaucoma and liposomal formulations such as Verteporfin for neovascular AMD, which significantly reduce treatment frequency and improve patient outcomes.

Despite these promising developments, challenges remain, including manufacturing costs, potential toxicity, and the need for further clinical validation. Future research should focus on optimizing nanoparticle properties (size, charge, hydrophilicity/lipophilicity) to improve efficacy and safety, as well as exploring personalized and non-invasive delivery methods. The integration of nanomedicine into ophthalmology holds the potential to revolutionize treatment paradigms, offering more effective, patient-friendly solutions for a wide range of ocular diseases. Continued innovation and collaboration across disciplines will be essential to overcome existing barriers and fully realize the therapeutic potential of these advanced delivery systems.

Abbreviations

WHO, World Health Organization; DED, dry eye disease; AMD, age-related macular degeneration; DR, diabetic retinopathy; RVO, retinal vascular occlusion; ROP, retinopathy of prematurity; BAB, blood-aqueous barrier; BRB, blood-retinal barrier; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor; SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers; PAMAM, poly(amidoamine); PLGA, poly(lactide-co-glycolide); PLA, poly(lactic acid); PCL, poly(ε-caprolactone); CS, chitosan; HA, hyaluronic acid; LBPS, *Lycium barbarum* polysaccharides; DNA, deoxyribonucleic acid; MNPs, metal nanoparticles; Ag, silver; Au, gold; ROS, reactive oxygen species; QDs, quantum dots; MSNs, mesoporous silica nanoparticles; CsA, cyclosporine A; FDA, Food and Drug Administration; mPEG-PLA, methoxy poly(ethylene glycol)-PLA; NAT-SLNs, natamycin SLNs; Papp, apparent permeability coefficient; MICs, minimum inhibitory concentrations; E-SLNs, econazole SLNs; PBA-CS-VE, phenylboronic acid conjugated chitosan-vitamin E; MOX, moxifloxacin; PAM, pamoic acid; MOX-PAM NS, MOX with PAM formulated into a mucus-penetrating nanosuspension; MDR, treating multidrug-resistant; Ag NPs, silver nanoparticles; Ag+, silver ions; RNA, ribonucleic acid; IOP, intraocular pressure; OTX, Ocular Therapeutix; A1cKO, angiopoietin 1 gene knockout; NO, nitric oxide; TM, trabecular meshwork; SC, Schlemm's channel; SNP, sodium nitroprusside; TNF-α, tumor necrosis factor-alpha; β-GP, β-glycerophosphate; LCGH, low-deacetylated chitosan/β-GP hydrogel; HCGH, high-deacetylated chitosan/β-GP hydrogel; EIU, endotoxin-induced uveitis; CNV, choroidal neovascularization; nAMD, neovascular AMD; DME, diabetic macular edema; TKI, tyrosine kinase inhibitor; PDGF, platelet-derived growth factor; ASIV, Astragaloside-IV; ASIV-LNCs, ASIV loaded into lipid nanocapsules; Ang1, Angiopoietin-1; AAP NPs, Angiopoietin-1-anti-CD105-PLGA nanoparticles; TA, triamcinolone acetonide; STZ, streptozotocin; PEDF, pigment epithelium-derived factor; MCP-1, monocyte chemotactic protein-1; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; IL-1β, interleukin-1β; ICNPH, insulin-loaded chitosan nanoparticles/PLGA-PEG-PLGA thermosensitive hydrogel; GFAP, glial fibrillary acidic protein; DSP, dexamethasone sodium phosphate; BCVA, best corrected visual acuity; D-TA, dendrimers-TA conjugate; MVLs, multivesicular liposomes; OIR, oxygen-induced retinopathy.

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The authors have declared that there are no conflicts of interest.

References

1. Burton MJ, Ramke J, Marques AP, et al. The Lancet Global Health Commission on Global Eye Health: vision beyond 2020. *Lancet Glob Health*. 2021;9(4):e489–e551. doi:10.1016/S2214-109X(20)30488-5
2. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Trends in prevalence of blindness and distance and near vision impairment over 30 years: an analysis for the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9(2):e130–e143. doi:10.1016/S2214-109X(20)30425-3
3. Hughes P, Olejnik O, Changlin J, Wilson C. Topical and systemic drug delivery to the posterior segments. *Adv Drug Deliv Rev*. 2005;57 (14):2010–2032. doi:10.1016/j.addr.2005.09.004
4. Huang D, Chen Y, Rupenthal ID. Overcoming ocular drug delivery barriers through the use of physical forces. *Adv Drug Deliv Rev*. 2018;126:96–112. doi:10.1016/j.addr.2017.09.008
5. Yanez-Soto B, Mannis MJ, Schwab IR, et al. Interfacial phenomena and the ocular surface. *Ocul Surf*. 2014;12(3):178–201. doi:10.1016/j.jtos.2014.01.004
6. Achouri D, Alhanout K, Piccerelle P, Andrieu V. Recent advances in ocular drug delivery. *Drug Dev Ind Pharm*. 2013;39(11):1599–1617. doi:10.3109/03639045.2012.736515
7. Mannermaa E, Vellonen KS, Urtti A. Drug transport in corneal epithelium and blood-retina barrier: emerging role of transporters in ocular pharmacokinetics. *Adv Drug Deliv Rev*. 2006;58(11):1136–1163. doi:10.1016/j.addr.2006.07.024
8. Meng T, Kulkarni V, Simmers R, Brar V, Xu Q. Therapeutic implications of nanomedicine for ocular drug delivery. *Drug Discov Today*. 2019;24(8):1524–1538. doi:10.1016/j.drudis.2019.05.006
9. Lee J, Pelis RM. Drug transport by the blood-aqueous humor barrier of the eye. *Drug Metab Dispos*. 2016;44(10):1675–1681. doi:10.1124/dmd.116.069369
10. El Sanharawi M, Kowalczuk L, Touchard E, Omri S, de Kozak Y, Behar-Cohen F. Protein delivery for retinal diseases: from basic considerations to clinical applications. *Prog Retin Eye Res*. 2010;29(6):443–465. doi:10.1016/j.preteyeres.2010.04.001
11. Radhakrishnan K, Sonali N, Moreno M, et al. Protein delivery to the back of the eye: barriers, carriers and stability of anti-VEGF proteins. *Drug Discov Today*. 2017;22(2):416–423. doi:10.1016/j.drudis.2016.10.015
12. Cunha-Vaz JG. The blood-retinal barriers system. Basic concepts and clinical evaluation. *Exp Eye Res*. 2004;78(3):715–721. doi:10.1016/s0014-4835(03)00213-6
13. Raviola G. The structural basis of the blood-ocular barriers. *Exp Eye Res*. 1977;25(Suppl):27–63. doi:10.1016/s0014-4835(77)80009-2
14. Hammes HP, Lin J, Renner O, et al. Pericytes and the pathogenesis of diabetic retinopathy. *Diabetes*. 2002;51(10):3107–3112. doi:10.2337/diabetes.51.10.3107
15. Motiejunaite R, Kazlauskas A. Pericytes and ocular diseases. *Exp Eye Res*. 2008;86(2):171–177. doi:10.1016/j.exer.2007.10.013
16. Kansara V, Mitra AK. Evaluation of an ex vivo model implication for carrier-mediated retinal drug delivery. *Curr Eye Res*. 2006;31 (5):415–426. doi:10.1080/02713680600646890
17. Sarin H. Physiologic upper limits of pore size of different blood capillary types and another perspective on the dual pore theory of microvascular permeability. *J Angiogenes Res*. 2010;2:14. doi:10.1186/2040-2384-2-14
18. Kannan RM, Pitha I, Parikh KS. A new era in posterior segment ocular drug delivery: translation of systemic, cell-targeted, dendrimer-based therapies. *Adv Drug Deliv Rev*. 2023;200:115005. doi:10.1016/j.addr.2023.115005
19. Ding D, Zhu Q. Recent advances of PLGA micro/nanoparticles for the delivery of biomacromolecular therapeutics. *Mat Sci Eng C-Mater*. 2018;92:1041–1060. doi:10.1016/j.msec.2017.12.036
20. Mandal A, Pal D, Agrahari V, Trinh HM, Joseph M, Mitra AK. Ocular delivery of proteins and peptides: challenges and novel formulation approaches. *Adv Drug Deliv Rev*. 2018;126:67–95. doi:10.1016/j.addr.2018.01.008
21. Fan X, Jiang K, Geng F, Lu W, Wei G. Ocular therapies with biomacromolecules: from local injection to eyedrop and emerging noninvasive delivery strategies. *Adv Drug Deliv Rev*. 2023;197:114864. doi:10.1016/j.addr.2023.114864
22. Horita S, Watanabe M, Katagiri M, et al. Species differences in ocular pharmacokinetics and pharmacological activities of regorafenib and pazopanib eye-drops among rats, rabbits and monkeys. *Pharmacol Res Perspe*. 2019;7(6):e00545. doi:10.1002/prp2.545
23. Shen J, Durairaj C, Lin T, Liu Y, Burke J. Ocular pharmacokinetics of intravitreally administered brimonidine and dexamethasone in animal models with and without blood-retinal barrier breakdown. *Invest Ophth Vis Sci*. 2014;55(2):1056–1066. doi:10.1167/iovs.13-13650
24. Park SJ, Choi Y, Na YM, et al. Intraocular pharmacokinetics of intravitreal Aflibercept (Eylea) in a Rabbit Model. *Invest Ophth Vis Sci*. 2016;57 (6):2612–2617. doi:10.1167/iovs.16-19204
25. Ilochonwu BC, Urtti A, Hennink WE, Vermonden T. Intravitreal hydrogels for sustained release of therapeutic proteins. *J Control Release*. 2020;326:419–441. doi:10.1016/j.jconrel.2020.07.031
26. Lau CML, Yu Y, Jahanmir G, Chau Y. Controlled release technology for anti-angiogenesis treatment of posterior eye diseases: current status and challenges. *Adv Drug Deliv Rev*. 2018;126:145–161. doi:10.1016/j.addr.2018.03.013
27. Seah I, Zhao X, Lin Q, et al. Use of biomaterials for sustained delivery of anti-VEGF to treat retinal diseases. *Eye*. 2020;34(8):1341–1356. doi:10.1038/s41433-020-0770-y
28. Brambati M, Bettin P, Ramoni A, Battista M, Bandello F. A case of endophthalmitis following needling procedure after PRESERFLO((R)) Micro Shunt implantation. *Eur J Ophthalmol*. 2022;32(3):NP83–NP86. doi:10.1177/11206721211019548
29. Lee RM, Thompson JR, Eke T. Severe adverse events associated with local anaesthesia in cataract surgery: 1 year national survey of practice and complications in the UK. *Brit J Ophthalmol*. 2016;100(6):772–776. doi:10.1136/bjophthalmol-2015-307060
30. Avery RL, Gordon GM. Systemic safety of prolonged monthly anti-vascular endothelial growth factor therapy for diabetic macular edema: a systematic review and meta-analysis. *JAMA Ophthalmol*. 2016;134(1):21–29. doi:10.1001/jamaophthalmol.2015.4070
31. Bai X, Wang J, Mu Q, Su G. In vivo protein corona formation: characterizations, effects on engineered nanoparticles' biobehaviors, and applications. *Front Bioeng Biotech*. 2021;9:646708. doi:10.3389/fbioe.2021.646708
32. Coca-Prados M, Escribano J. New perspectives in aqueous humor secretion and in glaucoma: the ciliary body as a multifunctional neuroendocrine gland. *Prog Retin Eye Res*. 2007;26(3):239–262. doi:10.1016/j.preteyeres.2007.01.002
33. Tang Z, Fan X, Chen Y, Gu P. Ocular nanomedicine. *Adv Sci*. 2022;9(15):e2003699. doi:10.1002/advs.202003699

34. Vicario-de-la-torre M, Caballo-Gonzalez M, Vico E, et al. Novel nano-liposome formulation for dry eyes with components similar to the preocular tear film. *Polymers-Basel*. 2018;10(4). doi:10.3390/polym10040425
35. Lin H, Liu Y, Kambhampati SP, Hsu CC, Kannan RM, Yiu SC. Subconjunctival dendrimer-drug therapy for the treatment of dry eye in a rabbit model of induced autoimmune dacryoadenitis. *Ocul Surf*. 2018;16(4):415–423. doi:10.1016/j.jtos.2018.05.004
36. Yu Y, Chen D, Li Y, Yang W, Tu J, Shen Y. Improving the topical ocular pharmacokinetics of lyophilized cyclosporine A-loaded micelles: formulation, in vitro and in vivo studies. *Drug Deliv*. 2018;25(1):888–899. doi:10.1080/10717544.2018.1458923
37. Liu Y, Wang Y, Yang J, Zhang H, Gan L. Cationized hyaluronic acid coated spanlastics for cyclosporine A ocular delivery: prolonged ocular retention, enhanced corneal permeation and improved tear production. *Int J Pharm*. 2019;565:133–142. doi:10.1016/j.ijpharm.2019.05.018
38. Pang Y, Wei C, Li R, et al. Photothermal conversion hydrogel based mini-eye patch for relieving dry eye with long-term use of the light-emitting screen. *Int J Nanomed*. 2019;14:5125–5133. doi:10.2147/IJN.S192407
39. Khames A, Khaleel MA, El-Badawy MF, El-Nezhawy A. Natamycin solid lipid nanoparticles - sustained ocular delivery system of higher corneal penetration against deep fungal keratitis: preparation and optimization. *Int J Nanomed*. 2019;14:2515–2531. doi:10.2147/IJN.S190502
40. Liang Z, Zhang Z, Yang J, et al. Assessment to the antifungal effects in vitro and the ocular pharmacokinetics of solid-lipid nanoparticle in rabbits. *Int J Nanomed*. 2021;16:7847–7857. doi:10.2147/IJN.S340068
41. Sun X, Sheng Y, Li K, et al. Mucoadhesive phenylboronic acid conjugated chitosan oligosaccharide-vitamin E copolymer for topical ocular delivery of voriconazole: synthesis, in vitro/vivo evaluation, and mechanism. *Acta Biomater*. 2022;138:193–207. doi:10.1016/j.actbio.2021.10.047
42. Andrade LM, Rocha KAD, De Sa FAP, et al. Voriconazole-loaded nanostructured lipid carriers for ocular drug delivery. *Cornea*. 2016;35(6):866–871. doi:10.1097/ICO.0000000000000825
43. Habib FS, Fouad EA, Abdel-Rhaman MS, Fathalla D. Liposomes as an ocular delivery system of fluconazole: in-vitro studies. *Acta Ophthalmol*. 2010;88(8):901–904. doi:10.1111/j.1755-3768.2009.01584.x
44. Josyula A, Omiadze R, Parikh K, et al. An ion-paired moxifloxacin nanosuspension eye drop provides improved prevention and treatment of ocular infection. *Bioeng Transl Med*. 2021;6(3):e10238. doi:10.1002/btm2.10238
45. Zhu Y, Wu S, Sun Y, et al. Bacteria-targeting photodynamic nanoassemblies for efficient treatment of multidrug-resistant biofilm infected keratitis. *Adv Funct Mater*. 2022;32(14):2111066. doi:10.1002/adfm.202111066
46. Yan D, Yao Q, Yu F, et al. Surface modified electrospun poly(lactic acid) fibrous scaffold with cellulose nanofibrils and Ag nanoparticles for ocular cell proliferation and antimicrobial application. *Mat Sci Eng C-Mater*. 2020;111:110767. doi:10.1016/j.msec.2020.110767
47. El Hoffy NM, Abdel Azim EA, Hathout RM, Fouly MA, Elkheshen SA. Glaucoma: management and future perspectives for nanotechnology-based treatment modalities. *Eur J Pharm Sci*. 2021;158:105648. doi:10.1016/j.ejps.2020.105648
48. Chowhan A, Giri TK. Polysaccharide as renewable responsive biopolymer for in situ gel in the delivery of drug through ocular route. *Int J Biol Macromol*. 2020;150:559–572. doi:10.1016/j.ijbiomac.2020.02.097
49. Wu Y, Liu Y, Li X, et al. Research progress of in-situ gelling ophthalmic drug delivery system. *Asian J Pharm Sci*. 2019;14(1):1–15. doi:10.1016/j.ajps.2018.04.008
50. Belamkar A, Harris A, Zukerman R, et al. Sustained release glaucoma therapies: novel modalities for overcoming key treatment barriers associated with topical medications. *Ann Med*. 2022;54(1):343–358. doi:10.1080/07853890.2021.1955146
51. Wong TT, Novack GD, Natarajan JV, Ho CL, Htoon HM, Venkatraman SS. Nanomedicine for glaucoma: sustained release latanoprost offers a new therapeutic option with substantial benefits over eyedrops. *Drug Deliv Transl Res*. 2014;4(4):303–309. doi:10.1007/s13346-014-0196-9
52. Bessone C, Akhlaghi SP, Tartara LI, Quinteros DA, Loh W, Allemandi DA. Latanoprost-loaded phytantriol cubosomes for the treatment of glaucoma. *Eur J Pharm Sci*. 2021;160:105748. doi:10.1016/j.ejps.2021.105748
53. Nguyen DD, Luo L, Lai J. Effects of shell thickness of hollow poly(lactic acid) nanoparticles on sustained drug delivery for pharmacological treatment of glaucoma. *Acta Biomater*. 2020;111:302–315. doi:10.1016/j.actbio.2020.04.055
54. Schnichels S, Hurst J, de Vries JW, et al. Improved treatment options for glaucoma with brimonidine-loaded lipid DNA nanoparticles. *Acs Appl Mater Inter*. 2021;13(8):9445–9456. doi:10.1021/acsami.0c18626
55. Wang J, Li B, Huang D, et al. Nano-in-nano dendrimer gel particles for efficient topical delivery of antiglaucoma drugs into the eye. *Chem Eng J*. 2021:425. doi:10.1016/j.cej.2021.130498.
56. Hu C, Sun J, Zhang Y, et al. Local delivery and sustained-release of nitric oxide donor loaded in mesoporous silica particles for efficient treatment of primary open-angle glaucoma. *Adv Healthc Mater*. 2018;7(23):e1801047. doi:10.1002/adhm.201801047
57. OZURDEX® (Dexamethasone Intravitreal Implant) 0.7 mg as Initial Therapy in Pseudophakic Patients With Diabetic Macular Edema, Macular Edema Following Retinal Vein Occlusion, and Noninfectious Posterior Segment Uveitis: A Case-Based Discussion. *Retina-J Ret Vit Dis*. 2019;39(Suppl 1):S1–S28. doi:10.1097/01.iae.0000574292.81105.b2
58. Chen Z, Yang M, Wang Q, et al. Hydrogel eye drops as a non-invasive drug carrier for topical enhanced Adalimumab permeation and highly efficient uveitis treatment. *Carbohyd Polym*. 2021;253:117216. doi:10.1016/j.carbpol.2020.117216
59. Zhang R, Qian J, Li X, Yuan Y. Treatment of experimental autoimmune uveoretinitis with intravitreal injection of infliximab encapsulated in liposomes. *Brit J Ophthalmol*. 2017;101(12):1731–1738. doi:10.1136/bjophthalmol-2016-310044
60. Ruiz-Moreno JM, Montero JA, Arias L, et al. Photodynamic therapy in subfoveal and juxtafoveal idiopathic and postinflammatory choroidal neovascularization. *Acta Ophthalmol Scand*. 2006;84(6):743–748. doi:10.1111/j.1600-0420.2006.00691.x
61. Cleland J, Sharma R, Appiani S, Moore J, Rogers B. Safety and tolerability of a single subcutaneous dose of anti-angiogenesis drug to treat neovascular age-related macular degeneration (wet AMD) and Diabetic Macular Edema (DME). *Invest Ophth Vis Sci*. 2022;63(7):1347–F0181–1347–F0181.
62. Wong JG, Chang A, Guymer RH, et al. Phase 1 study of an intravitreal axitinib hydrogel-based implant for the treatment of Neovascular Age-Related Macular Degeneration (nAMD). *Invest Ophth Vis Sci*. 2021;62(8):218.
63. Yang M, So KF, Lo A, Lam WC. The effect of Lycium barbarum polysaccharides on pyroptosis-associated amyloid beta(1-40) oligomers-induced adult retinal pigment Epithelium 19 cell damage. *Int J Mol Sci*. 2020;21(13). doi:10.3390/ijms21134658
64. Sun R, Zhang A, Ge Y, et al. Ultra-small-size Astragaloside-IV loaded lipid nanocapsules eye drops for the effective management of dry age-related macular degeneration. *Expert Opin Drug Deliv*. 2020;17(9):1305–1320. doi:10.1080/17425247.2020.1783236

65. Varshochian R, Riazi-Esfahani M, Jeddi-Tehrani M, et al. Albuminated PLGA nanoparticles containing bevacizumab intended for ocular neovascularization treatment. *J Biomed Mater Res A*. 2015;103(10):3148–3156. doi:10.1002/jbm.a.35446
66. Yao H, Xu H, Wu M, et al. Targeted long-term noninvasive treatment of choroidal neovascularization by biodegradable nanoparticles. *Acta Biomater*. 2023;166:536–551. doi:10.1016/j.actbio.2023.05.021
67. Huu VAN, Luo J, Zhu J, et al. Light-responsive nanoparticle depot to control release of a small molecule angiogenesis inhibitor in the posterior segment of the eye. *J Control Release*. 2015;200:71–77. doi:10.1016/j.jconrel.2015.01.001
68. Lavinsky D, Cardillo JA, Filho AASL, et al. Phase I/II study of intravitreal triamcinolone acetonide microspheres for treatment of diffuse diabetic macular edema unresponsive to conventional laser photocoagulation treatment. *Invest Ophth Vis Sci*. 2008;49(13):2698.
69. Tanito M, Hara K, Takai Y, et al. Topical dexamethasone-cyclodextrin microparticle eye drops for diabetic macular edema. *Invest Ophth Vis Sci*. 2011;52(11):7944–7948. doi:10.1167/iovs.11-8178
70. Lu Y, Zhou N, Huang X, et al. Effect of intravitreal injection of bevacizumab-chitosan nanoparticles on retina of diabetic rats. *Int J OphthalmolChi*. 2014;7(1):1–7. doi:10.3980/j.issn.2222-3959.2014.01.01
71. Dong Y, Wan G, Yan P, Qian C, Li F, Peng G. Fabrication of resveratrol coated gold nanoparticles and investigation of their effect on diabetic retinopathy in streptozotocin induced diabetic rats. *J Photoch Photobio B*. 2019;195:51–57. doi:10.1016/j.jphotobiol.2019.04.012
72. Park K, Chen Y, Hu Y, et al. Nanoparticle-mediated expression of an angiogenic inhibitor ameliorates ischemia-induced retinal neovascularization and diabetes-induced retinal vascular leakage. *Diabetes*. 2009;58(8):1902–1913. doi:10.2337/db08-1327
73. Rong X, Ji Y, Zhu X, et al. Neuroprotective effect of insulin-loaded chitosan nanoparticles/PLGA-PEG-PLGA hydrogel on diabetic retinopathy in rats. *Int J Nanomed*. 2019;14:45–55. doi:10.2147/IJN.S184574
74. Lim JI, Fung AE, Wieland M, Hung D, Wong V. Sustained-release intravitreal liquid drug delivery using triamcinolone acetonide for cystoid macular edema in retinal vein occlusion. *Ophthalmology*. 2011;118(7):1416–1422. doi:10.1016/j.ophtha.2010.12.029
75. Bremond-Gignac D. Investigational drugs for retinal vein occlusion. *Expert Opin Inv Drug*. 2016;25(7):841–850. doi:10.1080/13543784.2016.1181750
76. Cho H, Kambhampati SP, Lai MJ, et al. Dendrimer-triamcinolone acetonide reduces neuroinflammation, pathological angiogenesis, and neuroretinal dysfunction in ischemic retinopathy. *Adv Ther-Germany*. 2021;4(2). doi:10.1002/adtp.202000181
77. Mu H, Wang Y, Chu Y, et al. Multivesicular liposomes for sustained release of bevacizumab in treating laser-induced choroidal neovascularization. *Drug Deliv*. 2018;25(1):1372–1383. doi:10.1080/10717544.2018.1474967
78. Davis BM, Normando EM, Guo L, et al. Topical delivery of Avastin to the posterior segment of the eye in vivo using annexin A5-associated liposomes. *Small*. 2014;10(8):1575–1584. doi:10.1002/smll.201303433
79. Sun J, Jiang Q, Zhang X, et al. Mesoporous silica nanoparticles as a delivery system for improving antiangiogenic therapy. *Int J Nanomed*. 2019;14:1489–1501. doi:10.2147/IJN.S195504
80. Abrishami M, Zarei-Ghanavati S, Soroush D, Rouhbakhsh M, Jaafari MR, Malaekeh-Nikouei B. Preparation, characterization, and in vivo evaluation of nanoliposomes-encapsulated bevacizumab (avastin) for intravitreal administration. *Retina-J Ret Vit Dis*. 2009;29(5):699–703. doi:10.1097/IAE.0b013e3181a2f42a
81. Fujisawa T, Miyai H, Hironaka K, et al. Liposomal diclofenac eye drop formulations targeting the retina: formulation stability improvement using surface modification of liposomes. *Int J Pharmaceut*. 2012;436(1–2):564–567. doi:10.1016/j.ijpharm.2012.07.024
82. Kim JH, Kim MH, Jo DH, Yu YS, Lee TG, Kim JH. The inhibition of retinal neovascularization by gold nanoparticles via suppression of VEGFR-2 activation. *Biomaterials*. 2011;32(7):1865–1871. doi:10.1016/j.biomaterials.2010.11.030
83. Liu P, Chen G, Zhang J. A review of liposomes as a drug delivery system: current status of approved products, regulatory environments, and future perspectives. *Molecules*. 2022;27(4):1372. doi:10.3390/molecules27041372
84. Mazur F, Bally M, Stadler B, Chandrawati R. Liposomes and lipid bilayers in biosensors. *Adv Colloid Interfac*. 2017;249:88–99. doi:10.1016/j.cis.2017.05.020
85. Niu M, Lu Y, Hovgaard L, et al. Hypoglycemic activity and oral bioavailability of insulin-loaded liposomes containing bile salts in rats: the effect of cholate type, particle size and administered dose. *Eur J Pharm Biopharm*. 2012;81(2):265–272. doi:10.1016/j.ejpb.2012.02.009
86. Wang N, Wang T, Li T, Deng Y. Modulation of the physicochemical state of interior agents to prepare controlled release liposomes. *Colloid Surf B*. 2009;69(2):232–238. doi:10.1016/j.colsurfb.2008.11.033
87. Zeng H, Qi Y, Zhang Z, Liu C, Peng W, Zhang Y. Nanomaterials toward the treatment of Alzheimer's disease: recent advances and future trends. *Chinese Chem Lett*. 2021;32(6):1857–1868. doi:10.1016/j.cclet.2021.01.014
88. Li C, Zhang Y, Wan Y, et al. STING-activating drug delivery systems: design strategies and biomedical applications. *Chinese Chem Lett*. 2021;32(5):1615–1625. doi:10.1016/j.cclet.2021.01.001
89. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv Drug Deliv Rev*. 2002;54:S131–S155. doi:10.1016/S0169-409X(02)00118-7
90. Fonte P, Andrade F, Araujo F, Andrade C, Neves J, Sarmento B. Chitosan-coated solid lipid nanoparticles for insulin delivery. *Method Enzymol*. 2012;508:295–314. doi:10.1016/B978-0-12-391860-4.00015-X
91. Parhi R, Suresh P. Preparation and characterization of solid lipid nanoparticles-a review. *Curr Drug Discov Technol*. 2012;9(1):2–16. doi:10.2174/157016312799304552
92. Lakshminarayanan R, Ye E, Young DJ, Li Z, Loh XJ. Recent advances in the development of antimicrobial nanoparticles for combating resistant pathogens. *Adv Healthc Mater*. 2018;7(13):e1701400. doi:10.1002/adhm.201701400
93. Viegas C, Patricio AB, Prata JM, Nadhman A, Chintamaneni PK, Fonte P. Solid lipid nanoparticles vs nanostructured lipid carriers: a comparative review. *Pharmaceutics*. 2023;15(6). doi:10.3390/pharmaceutics15061593
94. Beloqui A, Solinis MA, Rodriguez-Gascon A, Almeida AJ, Preat V. Nanostructured lipid carriers: promising drug delivery systems for future clinics. *Nanomedicine-UK*. 2016;12(1):143–161. doi:10.1016/j.nano.2015.09.004
95. Doktorovova S, Souto EB. Nanostructured lipid carrier-based hydrogel formulations for drug delivery: a comprehensive review. *Expert Opin Drug Deliv*. 2009;6(2):165–176. doi:10.1517/17425240802712590
96. Morita T, Mukaide S, Chen Z, et al. Unveiling the interaction potential surface between drug-entrapped polymeric micelles clarifying the high drug nanocarrier efficiency. *Nano Lett*. 2021;21(3):1303–1310. doi:10.1021/acs.nanolett.0c03978

97. Hwang D, Ramsey JD, Kabanov AV. Polymeric micelles for the delivery of poorly soluble drugs: from nanoformulation to clinical approval. *Adv Drug Deliv Rev*. 2020;156:80–118. doi:10.1016/j.addr.2020.09.009
98. Gaucher G, Dufresne M, Sant VP, Kang N, Maysinger D, Leroux J. Block copolymer micelles: preparation, characterization and application in drug delivery. *J Control Release*. 2005;109(1–3):169–188. doi:10.1016/j.jconrel.2005.09.034
99. Cagel M, Tesan FC, Bernabeu E, et al. Polymeric mixed micelles as nanomedicines: achievements and perspectives. *Eur J Pharm Biopharm*. 2017;113:211–228. doi:10.1016/j.ejpb.2016.12.019
100. Tomalia DA, Henderson SA, Diallo MS. Dendrimers—an enabling synthetic science to controlled organic nanostructures. *Handbook Nanosci Eng Technol*. 2007;2.
101. Hsu HJ, Bugno J, Lee SR, Hong S. Dendrimer-based nanocarriers: a versatile platform for drug delivery. *Wires Nanomed Nanobi*. 2017;9(1). doi:10.1002/wnan.1409
102. Pearson RM, Sunoqrot S, Hsu HJ, Bae JW, Hong S. Dendritic nanoparticles: the next generation of nanocarriers? *Ther Deliv*. 2012;3 (8):941–959. doi:10.4155/tde.12.76
103. Khandare J, Calderon M, Dagia NM, Haag R. Multifunctional dendritic polymers in nanomedicine: opportunities and challenges. *Chem Soc Rev*. 2012;41(7):2824–2848. doi:10.1039/c1cs15242d
104. Kambhampati SP, Clunies-Ross AJ, Bhutto I, et al. Systemic and intravitreal delivery of dendrimers to activated microglia/macrophage in ischemia/reperfusion mouse retina. *Invest Ophth Vis Sci*. 2015;56(8):4413–4424. doi:10.1167/iovs.14-16250
105. Shen L, You Y, Sun S, Chen Y, Qu J, Cheng L. Intraocular and systemic pharmacokinetics of triamcinolone acetonide after a single 40-mg posterior subtenon application. *Ophthalmology*. 2010;117(12):2365–2371. doi:10.1016/j.ophtha.2010.03.033
106. Sigurdsson HH, Konraethsdottir F, Loftsson T, Stefansson E. Topical and systemic absorption in delivery of dexamethasone to the anterior and posterior segments of the eye. *Acta Ophthalmol Scand*. 2007;85(6):598–602. doi:10.1111/j.1600-0420.2007.00885.x
107. Kato A, Kimura H, Okabe K, et al. Suppression of laser-induced choroidal neovascularization by posterior sub-tenon administration of triamcinolone acetonide. *Retina-J Ret Vit Dis*. 2005;25(4):503–509. doi:10.1097/00006982-200506000-00017
108. Nance E, Zhang F, Mishra MK, et al. Nanoscale effects in dendrimer-mediated targeting of neuroinflammation. *Biomaterials*. 2016;101:96–107. doi:10.1016/j.biomaterials.2016.05.044
109. Zhang F, Nance E, Alnasser Y, Kannan R, Kannan S. Microglial migration and interactions with dendrimer nanoparticles are altered in the presence of neuroinflammation. *J Neuroinflammation*. 2016;13(1):65. doi:10.1186/s12974-016-0529-3
110. Markovsky E, Baabur-Cohen H, Eldar-Boock A, et al. Administration, distribution, metabolism and elimination of polymer therapeutics. *J Control Release*. 2012;161(2):446–460. doi:10.1016/j.jconrel.2011.12.021
111. Nishiyama N, Kataoka K. Current state, achievements, and future prospects of polymeric micelles as nanocarriers for drug and gene delivery. *Pharmacol Therapeut*. 2006;112(3):630–648. doi:10.1016/j.pharmthera.2006.05.006
112. Perez-Herrero E, Fernandez-Medarde A. Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy. *Eur J Pharm Biopharm*. 2015;93:52–79. doi:10.1016/j.ejpb.2015.03.018
113. Slomkowski S, Basinska T, Gadzinowski M, Mickiewicz D. Polyesters and polyester nano- and microcarriers for drug delivery. *Polymers-Basel*. 2024;16(17). doi:10.3390/polym16172503
114. Makadia HK, Siegel SJ. Poly Lactic-co-Glycolic Acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers-Basel*. 2011;3 (3):1377–1397. doi:10.3390/polym3031377
115. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Preat V. PLGA-based nanoparticles: an overview of biomedical applications. *J Control Release*. 2012;161(2):505–522. doi:10.1016/j.jconrel.2012.01.043
116. Sanchez-Lopez E, Egea MA, Davis BM, et al. Memantine-loaded PEGylated biodegradable nanoparticles for the treatment of glaucoma. *Small*. 2018;14(2). doi:10.1002/smll.201701808
117. Jiang G, Jia H, Qiu J, et al. PLGA nanoparticle platform for trans-ocular barrier to enhance drug delivery: a comparative study based on the application of oligosaccharides in the outer membrane of carriers. *Int J Nanomed*. 2020;15:9373–9387. doi:10.2147/IJN.S272750
118. Park K, Skidmore S, Hadar J, et al. Injectable, long-acting PLGA formulations: analyzing PLGA and understanding microparticle formation. *J Control Release*. 2019;304:125–134. doi:10.1016/j.jconrel.2019.05.003
119. Nair LS, Laurencin CT. Biodegradable polymers as biomaterials. *Prog Polym Sci*. 2007;32(8):762–798. doi:10.1016/j.progpolymsci.2007.05.017
120. Longobardi G, Moore TL, Conte C, Ungaro F, Satchi-Fainaro R, Quaglia F. Polyester nanoparticles delivering chemotherapeutics: learning from the past and looking to the future to enhance their clinical impact in tumor therapy. *Wires Nanomed Nanobi*. 2024;16(5):e1990. doi:10.1002/wnan.1990
121. Than A, Liu C, Chang H, et al. Self-implantable double-layered micro-drug-reservoirs for efficient and controlled ocular drug delivery. *Nat Commun*. 2018;9(1):4433. doi:10.1038/s41467-018-06981-w
122. Fang G, Yang X, Wang Q, Zhang A, Tang B. Hydrogels-based ophthalmic drug delivery systems for treatment of ocular diseases. *Mat Sci Eng C-Mater*. 2021;127:112212. doi:10.1016/j.msec.2021.112212
123. Skotak M, Ragusa J, Gonzalez D, Subramanian A. Improved cellular infiltration into nanofibrous electrospun cross-linked gelatin scaffolds templated with micrometer-sized polyethylene glycol fibers. *Biomed Mater*. 2011;6(5):055012. doi:10.1088/1748-6041/6/5/055012
124. Grassiri B, Zambito Y, Bernkop-Schnurch A. Strategies to prolong the residence time of drug delivery systems on ocular surface. *Adv Colloid Interfac*. 2021;288:102342. doi:10.1016/j.cis.2020.102342
125. Chang D, Park K, Famili A. Hydrogels for sustained delivery of biologics to the back of the eye. *Drug Discov Today*. 2019;24(8):1470–1482. doi:10.1016/j.drudis.2019.05.037
126. Arranz-Romera A, Esteban-Perez S, Garcia-Herranz D, Aragon-Navas A, Bravo-Osuna I, Herrero-Vanrell R. Combination therapy and co-delivery strategies to optimize treatment of posterior segment neurodegenerative diseases. *Drug Discov Today*. 2019;24(8):1644–1653. doi:10.1016/j.drudis.2019.03.022
127. Pandit J, Sultana Y, Aqil M. Chitosan-coated PLGA nanoparticles of bevacizumab as novel drug delivery to target retina: optimization, characterization, and in vitro toxicity evaluation. *Artif Cell Nanomed B*. 2017;45(7):1397–1407. doi:10.1080/21691401.2016.1243545
128. Enriquez De Salamanca A, Diebold Y, Calonge M, et al. Chitosan nanoparticles as a potential drug delivery system for the ocular surface: toxicity, uptake mechanism and in vivo tolerance. *Invest Ophth Vis Sci*. 2006;47(4):1416–1425. doi:10.1167/iovs.05-0495

129. Balijepalli AS, Sabatelle RC, Chen M, Suki B, Grinstaff MW. A synthetic bioinspired carbohydrate polymer with mucoadhesive properties. *Angew Chem Int Edit*. 2020;59(2):704–710. doi:10.1002/anie.201911720
130. Joseph SM, Krishnamoorthy S, Paranthaman R, Moses JA, Anandharamakrishnan C. A review on source-specific chemistry, functionality, and applications of chitin and chitosan. *Carbohydr Polym Technol Appl*. 2021;2:100036. doi:10.1016/j.carpta.2021.100036
131. Kalam MA. The potential application of hyaluronic acid coated chitosan nanoparticles in ocular delivery of dexamethasone. *Int J Biol Macromol*. 2016;89:559–568. doi:10.1016/j.ijbiomac.2016.05.016
132. Dmour I, Islam N. Recent advances on chitosan as an adjuvant for vaccine delivery. *Int J Biol Macromol*. 2022;200:498–519. doi:10.1016/j.ijbiomac.2021.12.129
133. Tiwari S, Bahadur P. Modified hyaluronic acid based materials for biomedical applications. *Int J Biol Macromol*. 2019;121:556–571. doi:10.1016/j.ijbiomac.2018.10.049
134. Wei J, Mu J, Tang Y, Qin D, Duan J, Wu A. Next-generation nanomaterials: advancing ocular anti-inflammatory drug therapy. *J Nanobiotechnol*. 2023;21(1):282. doi:10.1186/s12951-023-01974-4
135. Zhang Q, Lv X, Wu T, et al. Composition of Lycium barbarum polysaccharides and their apoptosis-inducing effect on human hepatoma SMMC-7721 cells. *Food Nutr Res*. 2015;59:28696. doi:10.3402/fnr.v59.28696
136. Tian X, Liang T, Liu Y, Ding G, Zhang F, Ma Z. Extraction, structural characterization, and biological functions of Lycium barbarum polysaccharides: a review. *Biomolecules*. 2019;9(9). doi:10.3390/biom9090389
137. Varela-Fernandez R, Garcia-Otero X, Diaz-Tome V, et al. Design, optimization, and characterization of lactoferrin-loaded Chitosan/TPP and Chitosan/Sulfobutylether-beta-cyclodextrin nanoparticles as a pharmacological alternative for Keratoconus treatment. *Acs Appl Mater Inter*. 2021;13(3):3559–3575. doi:10.1021/acsami.0c18926
138. Hu D, Li H, Wang B, et al. Surface-adaptive gold nanoparticles with effective adherence and enhanced photothermal ablation of methicillin-resistant staphylococcus aureus biofilm. *Acs Nano*. 2017;11(9):9330–9339. doi:10.1021/acsnano.7b04731
139. Shulman S, Johannesson G, Stefansson E, Loewenstein A, Rosenblatt A, Habot-Wilner Z. Topical dexamethasone-cyclodextrin nanoparticle eye drops for non-infectious Uveitic macular oedema and vitritis - a pilot study. *Acta Ophthalmol*. 2015;93(5):411–415. doi:10.1111/aos.12744
140. Wang X, Zhong X, Li J, Liu Z, Cheng L. Inorganic nanomaterials with rapid clearance for biomedical applications. *Chem Soc Rev*. 2021;50(15):8669–8742. doi:10.1039/d0cs00461h
141. Qamar Z, Qizilbash FF, Iqubal MK, et al. Nano-based drug delivery system: recent strategies for the treatment of ocular disease and future perspective. *Recent Pat Drug Deliv Formul*. 2019;13(4):246–254. doi:10.2174/1872211314666191224115211
142. Lemire JA, Harrison JJ, Turner RJ. Antimicrobial activity of metals: mechanisms, molecular targets and applications. *Nat Rev Microbiol*. 2013;11(6):371–384. doi:10.1038/nrmicro3028
143. Franco D, Calabrese G, Guglielmino SPP, Conoci S. Metal-based nanoparticles: antibacterial mechanisms and biomedical application. *Microorganisms*. 2022;10(9). doi:10.3390/microorganisms10091778
144. Fan W, Han H, Chen Y, et al. Antimicrobial nanomedicine for ocular bacterial and fungal infection. *Drug Deliv Transl Res*. 2021;11(4):1352–1375. doi:10.1007/s13346-021-00966-x
145. Ghafoorianfar S, Ghorani-Azam A, Mohajeri SA, Farzin D. Efficiency of nanoparticles for treatment of ocular infections: systematic literature review. *J Drug Deliv Sci Technol*. 2020;57:101765. doi:10.1016/j.jddst.2020.101765
146. Nguyen VP, Qian W, Li Y, et al. Chain-like gold nanoparticle clusters for multimodal photoacoustic microscopy and optical coherence tomography enhanced molecular imaging. *Nat Commun*. 2021;12(1):34. doi:10.1038/s41467-020-20276-z
147. Mosleh-Shirazi S, Abbasi M, Moaddeli MR, et al. Nanotechnology advances in the detection and treatment of cancer: an overview. *Nanotheranostics*. 2022;6(4):400–423. doi:10.7150/ntno.74613
148. Smith AM, Nie S. Semiconductor nanocrystals: structure, properties, and band gap engineering. *Acc Chem Res*. 2010;43(2):190–200. doi:10.1021/ar9001069
149. Wakaskar RR. General overview of lipid-polymer hybrid nanoparticles, dendrimers, micelles, liposomes, spongosomes and cubosomes. *J Drug Target*. 2018;26(4):311–318. doi:10.1080/1061186X.2017.1367006
150. Sarwat S, Stapleton F, Willcox M, Roy M. Quantum dots in ophthalmology: a literature review. *Curr Eye Res*. 2019;44(10):1037–1046. doi:10.1080/02713683.2019.1660793
151. Slowing II, Vivero-Escoto JL, Wu C, Lin VS. Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. *Adv Drug Deliv Rev*. 2008;60(11):1278–1288. doi:10.1016/j.addr.2008.03.012
152. He Q, Shi J. MSN anti-cancer nanomedicines: chemotherapy enhancement, overcoming of drug resistance, and metastasis inhibition. *Adv Mater*. 2014;26(3):391–411. doi:10.1002/adma.201303123
153. Niu D, Li Y, Shi J. Silica/organosilica cross-linked block copolymer micelles: a versatile theranostic platform. *Chem Soc Rev*. 2017;46(3):569–585. doi:10.1039/c6cs00495d
154. Lee JE, Lee N, Kim T, Kim J, Hyeon T. Multifunctional mesoporous silica nanocomposite nanoparticles for theranostic applications. *Acc Chem Res*. 2011;44(10):893–902. doi:10.1021/ar2000259
155. Li Z, Barnes JC, Bosoy A, Stoddart JF, Zink JI. Mesoporous silica nanoparticles in biomedical applications. *Chem Soc Rev*. 2012;41(7):2590–2605. doi:10.1039/c1cs15246g
156. Yang P, Quan Z, Lu L, Huang S, Lin J. Luminescence functionalization of mesoporous silica with different morphologies and applications as drug delivery systems. *Biomaterials*. 2008;29(6):692–702. doi:10.1016/j.biomaterials.2007.10.019
157. Xing L, Zheng H, Cao Y, Che S. Coordination polymer coated mesoporous silica nanoparticles for pH-responsive drug release. *Adv Mater*. 2012;24(48):6433–6437. doi:10.1002/adma.201201742
158. Ow V, Loh XJ. Recent developments of temperature-responsive polymers for ophthalmic applications. *J Polym Sci*. 2022;60(9):1429–1447. doi:10.1002/pol.20210907
159. Xu Y, Pu S, Li X, et al. Exosomal ncRNAs: novel therapeutic target and biomarker for diabetic complications. *Pharmacol Res*. 2022;178:106135. doi:10.1016/j.phrs.2022.106135
160. Song H, Liu B, Dong B, et al. Exosome-based delivery of natural products in cancer therapy. *Front Cell Dev Biol*. 2021;9:650426. doi:10.3389/fcell.2021.650426

161. Yang B, Chen Y, Shi J. Exosome biochemistry and advanced nanotechnology for next-generation theranostic platforms. *Adv Mater*. 2019;31(2):e1802896. doi:10.1002/adma.201802896
162. Bu T, Li Z, Hou Y, et al. Exosome-mediated delivery of inflammation-responsive Il-10 mRNA for controlled atherosclerosis treatment. *Theranostics*. 2021;11(20):9988–10000. doi:10.7150/thno.64229
163. Sanghani A, Andriesei P, Kafetzis KN, Tagalakis AD, Yu-Wai-Man C. Advances in exosome therapies in ophthalmology-from bench to clinical trial. *Acta Ophthalmol*. 2022;100(3):243–252. doi:10.1111/aos.14932
164. Rehman FU, Liu Y, Zheng M, Shi B. Exosomes based strategies for brain drug delivery. *Biomaterials*. 2023;293:121949. doi:10.1016/j.biomaterials.2022.121949
165. Zhang Y, Bi J, Huang J, Tang Y, Du S, Li P. Exosome: a review of its classification, isolation techniques, storage, diagnostic and targeted therapy applications. *Int J Nanomed*. 2020;15:6917–6934. doi:10.2147/IJN.S264498
166. Fan L, Liu C, Chen X, et al. Exosomes-loaded electroconductive hydrogel synergistically promotes tissue repair after spinal cord injury via immunoregulation and enhancement of myelinated axon growth. *Adv Sci*. 2022;9(13):e2105586. doi:10.1002/advs.202105586
167. Chavda VP, Pandya A, Kumar L, et al. Exosome nanovesicles: a potential carrier for therapeutic delivery. *Nano Today*. 2023;49:101771. doi:10.1016/j.nantod.2023.101771
168. Willem De Vries J, Schnichels S, Hurst J, et al. DNA nanoparticles for ophthalmic drug delivery. *Biomaterials*. 2018;157:98–106. doi:10.1016/j.biomaterials.2017.11.046
169. Han H, Li S, Xu M, et al. Polymer- and lipid-based nanocarriers for ocular drug delivery: current status and future perspectives. *Adv Drug Deliv Rev*. 2023;196:114770. doi:10.1016/j.addr.2023.114770
170. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15(3):276–283. doi:10.1016/j.jtos.2017.05.008
171. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15(3):334–365. doi:10.1016/j.jtos.2017.05.003
172. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. *Ocul Surf*. 2017;15(3):575–628. doi:10.1016/j.jtos.2017.05.006
173. Obeid MA, Alsaadi M, Aljabali AA. Recent updates in curcumin delivery. *J Liposome Res*. 2023;33(1):53–64. doi:10.1080/08982104.2022.2086567
174. Huang D, Li Z. Multidimensional immunotherapy for dry eye disease: current status and future directions. *Front Ophthalmol*. 2024;4:1449283. doi:10.3389/fopht.2024.1449283
175. Yavuz B, Bozdag Pehlivan S, Kaffashi A, et al. In vivo tissue distribution and efficacy studies for cyclosporin A loaded nano-decorated subconjunctival implants. *Drug Deliv*. 2016;23(9):3279–3284. doi:10.3109/10717544.2016.1172368
176. Kang H, Cha K, Cho W, et al. Cyclosporine Amicellar delivery system for dry eyes. *Int J Nanomed*. 2016;11:2921–2933. doi:10.2147/IJN.S107569
177. Prete M, Dammacco R, Fatone MC, Racanelli V. Autoimmune uveitis: clinical, pathogenetic, and therapeutic features. *Clin Exp Med*. 2016;16(2):125–136. doi:10.1007/s10238-015-0345-6
178. Shen Y, Yu Y, Chaurasiya B, et al. Stability, safety, and transcorneal mechanistic studies of ophthalmic lyophilized cyclosporine-loaded polymeric micelles. *Int J Nanomed*. 2018;13:8281–8296. doi:10.2147/IJN.S173691
179. Baudouin C, Labbe A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res*. 2010;29(4):312–334. doi:10.1016/j.preteyeres.2010.03.001
180. Date AA, Kates M, Yoshida T, et al. Preclinical evaluation of a hypotonic docetaxel nanosuspension formulation for intravesical treatment of non-muscle-invasive bladder cancer. *Drug Deliv Transl Re*. 2021;11(5):2085–2095. doi:10.1007/s13346-020-00870-w
181. Polat HK, Kurt N, Aytekin E, Bozdag Pehlivan S, Calis S. Novel drug delivery systems to improve the treatment of keratitis. *J Ocul Pharmacol Therap*. 2022;38(6):376–395. doi:10.1089/jop.2021.0127
182. El-Emam GA, Girgis GNS, El-Sokkary MMA, El-Azeem Soliman OA, Abd El Gawad AEGH. Ocular inserts of voriconazole-loaded proniosomal gels: formulation, evaluation and microbiological studies. *Int J Nanomed*. 2020;15:7825–7840. doi:10.2147/IJN.S268208
183. Cochereau-Massin I, Bauchet J, Marrakchi-Benjaafar S, et al. Efficacy and ocular penetration of sparfloxacin in experimental streptococcal endophthalmitis. *Antimicrob Agents Chemother*. 1993;37(4):633–636. doi:10.1128/AAC.37.4.633
184. Diamond JP, White L, Leeming JP, Bing Hoh H, Easty DL. Topical 0.3% ciprofloxacin, norfloxacin, and ofloxacin in treatment of bacterial keratitis: a new method for comparative evaluation of ocular drug penetration. *Brit J Ophthalmol*. 1995;79(6):606–609. doi:10.1136/bjo.79.6.606
185. Zhang M, Cheng Y, Li H, et al. Metallic nano-warriors: innovations in nanoparticle-based ocular antimicrobials. *Mater Today Bio*. 2024;28:101242. doi:10.1016/j.mtbio.2024.101242
186. Qing Y, Cheng L, Li R, et al. Potential antibacterial mechanism of silver nanoparticles and the optimization of orthopedic implants by advanced modification technologies. *Int J Nanomed*. 2018;13:3311–3327. doi:10.2147/IJN.S165125
187. Zhang K, Zhang L, Weinreb RN. Ophthalmic drug discovery: novel targets and mechanisms for retinal diseases and glaucoma. *Nat Rev Drug Discov*. 2012;11(7):541–559. doi:10.1038/nrd3745
188. Jayaram H, Kolko M, Friedman DS, Gazzard G. Glaucoma: now and beyond. *Lancet*. 2023;402(10414):1788–1801. doi:10.1016/S0140-6736(23)01289-8
189. Timolol maleate-a new drug for glaucoma. *Med Lett Drugs Ther*. 1978;20(25):109–110.
190. Zimmerman TJ. Pilocarpine. *Ophthalmology*. 1981;88(1):85–88. doi:10.1016/s0161-6420(81)35072-6
191. Waugh J, Jarvis B. Travoprost. *Drug Aging*. 2002;19(6):465–71;discussion472–3. doi:10.2165/00002512-200219060-00005
192. Strier SE. The additive effect of latanoprost 0.005% in patients on maximally tolerated medical therapy. *Clin Eye Vision Care*. 1997;9(4):189–196. doi:10.1016/S0953-4431(97)10015-7
193. Greenfield DS, Liebmann JM, Ritch R. Brimonidine: a new alpha 2-adrenoreceptor agonist for glaucoma treatment. *J Glaucoma*. 1997;6(4):250–258.
194. Mazet R, Yameogo J, Wouessidjewe D, Choisnard L, Geze A. Recent advances in the design of topical ophthalmic delivery systems in the treatment of ocular surface inflammation and their Biopharmaceutical evaluation. *Pharmaceutics*. 2020;12(6). doi:10.3390/pharmaceutics12060570

195. Ahmed I, De Francesco T, Rhee D, et al. Long-term outcomes from the HORIZON randomized trial for a Schlemm's Canal Microstent in combination cataract and glaucoma surgery. *Ophthalmology*. 2022;129(7):742–751. doi:10.1016/j.ophtha.2022.02.021
196. Singh RB, Ichhpujani P, Thakur S, Jindal S. Promising therapeutic drug delivery systems for glaucoma: a comprehensive review. *Ther Adv Ophthalmol*. 2020;12:2515841420905740. doi:10.1177/2515841420905740
197. Wiederholt M, Sturm A, Lepple-Wienhues A. Relaxation of trabecular meshwork and ciliary muscle by release of nitric oxide. *Invest Ophth Vis Sci*. 1994;35(5):2515–2520.
198. Dismuke WM, Mbadugha CC, Ellis DZ. NO-induced regulation of human trabecular meshwork cell volume and aqueous humor outflow facility involve the BKCa ion channel. *Am J Physiol-Cell Physiol*. 2008;294(6):C1378–86. doi:10.1152/ajpcell.00363.2007
199. Schneemann A, Dijkstra BG, van den Berg TJ, Kamphuis W, Hoyng PFJ. Nitric oxide/guanylate cyclase pathways and flow in anterior segment perfusion. *Graef Arch Clin Exp*. 2002;240(11):936–941. doi:10.1007/s00417-002-0559-7
200. Krishna U, Ajanaku D, Denniston AK, Gkika T. Uveitis: a sight-threatening disease which can impact all systems. *Postgrad Med J*. 2017;93(1106):766–773. doi:10.1136/postgradmedj-2017-134891
201. Burkholder BM, Jabs DA. Uveitis for the non-ophthalmologist. *BMJ-Brit Med J*. 2021;372:m4979. doi:10.1136/bmj.m4979
202. Shahab MA, Mir TA, Zafar S. Optimising drug therapy for non-infectious uveitis. *Int Ophthalmol*. 2019;39(7):1633–1650. doi:10.1007/s10792-018-0984-1
203. Taylor SRJ, Isa H, Joshi L, Lightman S. New developments in corticosteroid therapy for uveitis. *Ophthalmologica*. 2010;224(Suppl 1):46–53. doi:10.1159/000318021
204. Doycheva D, Zierhut M, Blumenstock G, et al. Immunomodulatory therapy with tumour necrosis factor alpha inhibitors in children with antinuclear antibody-associated chronic anterior uveitis: long-term results. *Brit J Ophthalmol*. 2014;98(4):523–528. doi:10.1136/bjophthalmol-2013-303935
205. Takeuchi M, Kezuka T, Sugita S, et al. Evaluation of the long-term efficacy and safety of infliximab treatment for uveitis in Behcet's disease: a multicenter study. *Ophthalmology*. 2014;121(10):1877–1884. doi:10.1016/j.ophtha.2014.04.042
206. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology*. 2014;121(3):785–96.e3. doi:10.1016/j.ophtha.2013.09.048
207. Cordero-Coma M, Sobrin L. Anti-tumor necrosis factor-alpha therapy in uveitis. *Surv Ophthalmol*. 2015;60(6):575–589. doi:10.1016/j.survophthal.2015.06.004
208. Lamattina KC, Goldstein DA. Adalimumab for the treatment of uveitis. *Expert Rev Clin Immun*. 2017;13(3):181–188. doi:10.1080/1744666X.2017.1288097
209. Burmester GR, Panaccione R, Gordon KB, Mcilraith MJ, Lacerda APM. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis*. 2013;72(4):517–524. doi:10.1136/annrheumdis-2011-201244
210. Llorenc V, Cordero-Coma M, Blanco-Esteban A, et al. Drug retention rate and causes of discontinuation of adalimumab in uveitis: real-world data from the biotherapies in uveitis (BioUvea) Study Group. *Ophthalmology*. 2020;127(6):814–825. doi:10.1016/j.ophtha.2019.11.024
211. Chauhan K, Tyagi M. Update on non-infectious uveitis treatment: anti-TNF-alpha and beyond. *Front Ophthalmol*. 2024;4:1412930. doi:10.3389/fopht.2024.1412930
212. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet*. 2018;392(10153):1147–1159. doi:10.1016/S0140-6736(18)31550-2
213. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *New Engl J Med*. 2008;358(24):2606–2617. doi:10.1056/NEJMra0801537
214. Guymer RH, Campbell TG. Age-related macular degeneration. *Lancet*. 2023;401(10386):1459–1472. doi:10.1016/S0140-6736(22)02609-5
215. Jampol LM, Glassman AR, Sun J. Evaluation and care of patients with diabetic retinopathy. *New Engl J Med*. 2020;382(17):1629–1637. doi:10.1056/NEJMra1909637
216. Schmidt-Erfurth UM, Pruente C. Management of neovascular age-related macular degeneration. *Prog Retin Eye Res*. 2007;26(4):437–451. doi:10.1016/j.preteyeres.2007.03.002
217. Schmidt-Erfurth U, Hasan T. Mechanisms of action of photodynamic therapy with verteporfin for the treatment of age-related macular degeneration. *Surv Ophthalmol*. 2000;45(3):195–214. doi:10.1016/s0039-6257(00)00158-2
218. Wu S, Xu Z, Wu T, et al. Suppression of subretinal neovascularization in Vldlr knockout mice by systemic administration of a targeted VEGF-receptor inhibitor. *Invest Ophth Vis Sci*. 2023;64(8):3900.
219. Giddabasappa A, Lalwani K, Norberg R, et al. Axitinib inhibits retinal and choroidal neovascularization in in vitro and in vivo models. *Exp Eye Res*. 2016;145:373–379. doi:10.1016/j.exer.2016.02.010
220. Leng B, Zhang Y, Liu X, et al. Astragaloside IV suppresses high glucose-induced NLRP3 inflammasome activation by inhibiting TLR4/NF-kappaB and CaSR. *Media Inflam*. 2019;2019:1082497. doi:10.1155/2019/1082497
221. Chen Q, Su Y, Ju Y, Ma K, Li W, Li W. Astragalosides IV protected the renal tubular epithelial cells from free fatty acids-induced injury by reducing oxidative stress and apoptosis. *Biomed Pharmacother*. 2018;108:679–686. doi:10.1016/j.biopha.2018.09.049
222. Chen P, Shang A, Wang W, Yang J. Astragaloside suppresses tumor necrosis factor receptor-associated factor 5 signaling pathway and alleviates neurodegenerative changes in retinal pigment epithelial cells induced by isoflurane. *J Cell Biochem*. 2019;120(1):1028–1037. doi:10.1002/jcb.27599
223. Yandrapu SK, Upadhyay AK, Petrash JM, Kompella UB. Nanoparticles in porous microparticles prepared by supercritical infusion and pressure quench technology for sustained delivery of bevacizumab. *Mol Pharm*. 2013;10(12):4676–4686. doi:10.1021/mp400487f
224. Varshochian R, Jeddi-Tehrani M, Mahmoudi AR, et al. The protective effect of albumin on bevacizumab activity and stability in PLGA nanoparticles intended for retinal and choroidal neovascularization treatments. *Eur J Pharm Sci*. 2013;50(3–4):341–352. doi:10.1016/j.ejps.2013.07.014
225. Fagiani E, Christofori G. Angiopoietins in angiogenesis. *Cancer Lett*. 2013;328(1):18–26. doi:10.1016/j.canlet.2012.08.018
226. Koh GY. Orchestral actions of angiopoietin-1 in vascular regeneration. *Trends Mol Med*. 2013;19(1):31–39. doi:10.1016/j.molmed.2012.10.010
227. Whitehead M, Osborne A, Widdowson PS, Yu-Wai-Man P, Martin KR. Angiopoietins in diabetic retinopathy: current understanding and therapeutic potential. *J Diabetes Res*. 2019;2019:5140521. doi:10.1155/2019/5140521

228. Nambu H, Nambu R, Oshima Y, et al. Angiopoietin 1 inhibits ocular neovascularization and breakdown of the blood-retinal barrier. *Gene Ther*. 2004;11(10):865–873. doi:10.1038/sj.gt.3302230
229. Lee J, Park D, Park DY, et al. Angiopoietin-1 suppresses choroidal neovascularization and vascular leakage. *Invest Ophth Vis Sci*. 2014;55 (4):2191–2199. doi:10.1167/iovs.14-13897
230. Gavard J, Patel V, Gutkind JS. Angiopoietin-1 prevents VEGF-induced endothelial permeability by sequestering Src through mDia. *Dev Cell*. 2008;14(1):25–36. doi:10.1016/j.devcel.2007.10.019
231. Duff SE, Li C, Garland JM, Kumar S. CD105 is important for angiogenesis: evidence and potential applications. *FASEB J*. 2003;17(9):984–992. doi:10.1096/fj.02-0634rev
232. Nassiri F, Cusimano MD, Scheithauer BW, et al. Endoglin (CD105): a review of its role in angiogenesis and tumor diagnosis, progression and therapy. *Anticancer Res*. 2011;31(6):2283–2290.
233. Zhou Y, Xu M, Shen W, et al. Recent advances in nanomedicine for ocular fundus neovascularization disease management. *Adv Healthc Mater*. 2024;13(17):e2304626. doi:10.1002/adhm.202304626
234. Antonetti DA, Klein R, Gardner TW. Diabetic retinopathy. *New Engl J Med*. 2012;366(13):1227–1239. doi:10.1056/NEJMra1005073
235. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376(9735):124–136. doi:10.1016/S0140-6736(09)62124-3
236. Klein R, Lee KE, Gangnon RE, Klein BE. The 25-year incidence of visual impairment in type 1 diabetes mellitus the Wisconsin epidemiologic study of diabetic retinopathy. *Ophthalmology*. 2010;117(1):63–70. doi:10.1016/j.ophtha.2009.06.051
237. Ting DS, Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Exp Ophthalmol*. 2016;44(4):260–277. doi:10.1111/ceo.12696
238. Wong TY, Cheung CM, Larsen M, Sharma S, Simo R. Diabetic retinopathy. *Nat Rev Dis Primers*. 2016;2:16012. doi:10.1038/nrdp.2016.12
239. Stitt AW, Curtis TM, Chen M, et al. The progress in understanding and treatment of diabetic retinopathy. *Prog Retin Eye Res*. 2016;51:156–186. doi:10.1016/j.preteyeres.2015.08.001
240. Chang-Lin J, Attar M, Acheampong AA, et al. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. *Invest Ophth Vis Sci*. 2011;52(1):80–86. doi:10.1167/iovs.10-5285
241. Querques L, Parravano M, Sacconi R, Rabiolo A, Bandello F, Querques G. Ischemic index changes in diabetic retinopathy after intravitreal dexamethasone implant using ultra-widefield fluorescein angiography: a pilot study. *Acta Diabetol*. 2017;54(8):769–773. doi:10.1007/s00592-017-1010-1
242. Borrelli E, Parravano M, Querques L, et al. One-year follow-up of ischemic index changes after intravitreal dexamethasone implant for diabetic macular edema: an ultra-widefield fluorescein angiography study. *Acta Diabetol*. 2020;57(5):543–548. doi:10.1007/s00592-019-01435-1
243. Iglicki M, Zur D, Busch C, Okada M, Loewenstein A. Progression of diabetic retinopathy severity after treatment with dexamethasone implant: a 24-month cohort study the 'DR-Pro-DEX Study'. *Acta Diabetol*. 2018;55(6):541–547. doi:10.1007/s00592-018-1117-z
244. Cardillo JA, Souza-Filho AA, Oliveira AG. Intravitreal Bioerudivel sustained-release triamcinolone microspheres system (RETAAC). Preliminary report of its potential usefulnes for the treatment of diabetic macular edema. *Arch Soc Esp Oftalmol*. 2006;81(12):675–7,679–81.
245. Cardillo JA, Paganelli F, Costa RA, et al. Intravitreal bioerudivel sustained–Release Triamcinolone Microspheres System (RETAAC): safety and pharmacokinetic in the rabbit eye and a preliminary report of its potential usefulness for the treatment diabetic macular edema. *Invest Ophthalmol Visual Sci*. 2006;47(13):3886.
246. Kiire CA, Chong NV. Managing retinal vein occlusion. *BMJ*. 2012;344:e499. doi:10.1136/bmj.e499
247. Chong V. Branch retinal vein occlusion. *BMJ*. 2012;345:e8373. doi:10.1136/bmj.e8373
248. Lu L, Jiang Y, Jaganathan R, Hao Y. Current advances in pharmacotherapy and technology for diabetic retinopathy: a systematic review. *J Ophthalmol*. 2018;2018:1694187. doi:10.1155/2018/1694187
249. Triantafylla M, Massa HF, Dardabounis D, et al. Ranibizumab for the treatment of degenerative ocular conditions. *Clin Ophthalmol*. 2014;8:1187–1198. doi:10.2147/OPTH.S40350
250. Zhang X, Wang N, Schachat AP, Bao S, Gillies MC. Glucocorticoids: structure, signaling and molecular mechanisms in the treatment of diabetic retinopathy and diabetic macular edema. *Curr Mol Med*. 2014;14(3):376–384. doi:10.2174/1566524014666140128114414
251. Zhang X, Bao S, Lai D, Rapkins RW, Gillies MC. Intravitreal triamcinolone acetonide inhibits breakdown of the blood-retinal barrier through differential regulation of VEGF-A and its receptors in early diabetic rat retinas. *Diabetes*. 2008;57(4):1026–1033. doi:10.2337/db07-0982
252. Salek SS, Leder HA, Butler NJ, Gan TJ, Dunn JP, Thorne JE. Periocular triamcinolone acetonide injections for control of intraocular inflammation associated with uveitis. *Ocul Immunol Inflamm*. 2013;21(4):257–263. doi:10.3109/09273948.2013.767353
253. Li W, He B, Dai W, Zhang Q, Liu Y. Evaluations of therapeutic efficacy of intravitreal injected polylactic-glycolic acid microspheres loaded with triamcinolone acetonide on a rabbit model of uveitis. *Int Ophthalmol*. 2014;34(3):465–476. doi:10.1007/s10792-013-9829-0
254. Becerra EM, Morescalchi F, Gandolfo F, et al. Clinical evidence of intravitreal triamcinolone acetonide in the management of age-related macular degeneration. *Curr Drug Targets*. 2011;12(2):149–172. doi:10.2174/138945011794182746
255. Penfold PL, Wong JG, Gyory J, Billson FA. Effects of triamcinolone acetonide on microglial morphology and quantitative expression of MHC-II in exudative age-related macular degeneration. *Clin Exp Ophthalmol*. 2001;29(3):188–192. doi:10.1046/j.1442-9071.2001.00407.x
256. Wang Y, Wang VM, Chan C. The role of anti-inflammatory agents in age-related macular degeneration (AMD) treatment. *Eye*. 2011;25 (2):127–139. doi:10.1038/eye.2010.196
257. Mccarthy CA, Widdop RE, Deliyanti D, Wilkinson-Berka JL. Brain and retinal microglia in health and disease: an unrecognized target of the renin-angiotensin system. *Clin Exp Pharmacol Physiol*. 2013;40(8):571–579. doi:10.1111/1440-1681.12099
258. Ma W, Zhao L, Fontainhas AM, Fariss RN, Wong WT. Microglia in the mouse retina alter the structure and function of retinal pigmented epithelial cells: a potential cellular interaction relevant to AMD. *PLoS One*. 2009;4(11):e7945. doi:10.1371/journal.pone.0007945
259. Blaauwgeers HG, Holtkamp GM, Rutten H, et al. Polarized vascular endothelial growth factor secretion by human retinal pigment epithelium and localization of vascular endothelial growth factor receptors on the inner choriocapillaris. Evidence for a trophic paracrine relation. *Am J Pathol*. 1999;155(2):421–428. doi:10.1016/S0002-9440(10)65138-3
260. Kambhampati SP, Mishra MK, Mastorakos P, Oh Y, Lutty GA, Kannan RM. Intracellular delivery of dendrimer triamcinolone acetonide conjugates into microglial and human retinal pigment epithelial cells. *Eur J Pharm Biopharm*. 2015;95(Pt B):239–249. doi:10.1016/j.ejpb.2015.02.013

261. Soheilian M, Karimi S, Ramezani A, Peyman GA. Pilot study of intravitreal injection of diclofenac for treatment of macular edema of various etiologies. *Retina-J Ret Vit Dis*. 2010;30(3):509–515. doi:10.1097/IAE.0b013e3181bdfa43
262. Solebo AL, Teoh L, Rahi J. Epidemiology of blindness in children. *Arch Dis Child*. 2017;102(9):853–857. doi:10.1136/archdischild-2016-310532
263. Hellstrom A, Smith LEH, Dammann O. Retinopathy of prematurity. *Lancet*. 2013;382(9902):1445–1457. doi:10.1016/S0140-6736(13)60178-6
264. Dammann O, Hartnett ME, Stahl A. Retinopathy of prematurity. *Dev Med Child Neurol*. 2023;65(5):625–631. doi:10.1111/dmcn.15468
265. Almeida H, Amaral MH, Lobao P, Silva AC, Loboa JM. Applications of polymeric and lipid nanoparticles in ophthalmic pharmaceutical formulations: present and future considerations. *J Pharm Pharm Sci*. 2014;17(3):278–293. doi:10.18433/j3dp43
266. Hagigit T, Abdulrazik M, Valamanesh F, Behar-Cohen F, Benita S. Ocular antisense oligonucleotide delivery by cationic nanoemulsion for improved treatment of ocular neovascularization: an in-vivo study in rats and mice. *J Control Release*. 2012;160(2):225–231. doi:10.1016/j.jconrel.2011.11.022
267. Liu D, Lian Y, Fang Q, Liu L, Zhang J, Li J. Hyaluronic-acid-modified lipid-polymer hybrid nanoparticles as an efficient ocular delivery platform for moxifloxacin hydrochloride. *Int J Biol Macromol*. 2018;116:1026–1036. doi:10.1016/j.ijbiomac.2018.05.113
268. Joseph RR, Venkatraman SS. Drug delivery to the eye: what benefits do nanocarriers offer? *Nanomedicine-UK*. 2017;12(6):683–702. doi:10.2217/nnm-2016-0379
269. Bisht R, Mandal A, Jaiswal JK, Rupenthal ID. Nanocarrier mediated retinal drug delivery: overcoming ocular barriers to treat posterior eye diseases. *Wires Nanomed Nanobi*. 2018;10(2). doi:10.1002/wnan.1473
270. Petrou G, Crouzier T. Mucins as multifunctional building blocks of biomaterials. *Biomater Sci UK*. 2018;6(9):2282–2297. doi:10.1039/c8bm00471d
271. Winkler J, Wirbelauer C, Frank V, Laqua H. Quantitative distribution of glycosaminoglycans in young and senile (cataractous) anterior lens capsules. *Exp Eye Res*. 2001;72(3):311–318. doi:10.1006/exer.2000.0952
272. Xu Q, Boylan NJ, Suk JS, et al. Nanoparticle diffusion in, and microrheology of, the bovine vitreous ex vivo. *J Control Release*. 2013;167(1):76–84. doi:10.1016/j.jconrel.2013.01.018
273. Ranta VP, Mannermaa E, Lummepuro K, et al. Barrier analysis of periocular drug delivery to the posterior segment. *J Control Release*. 2010;148(1):42–48. doi:10.1016/j.jconrel.2010.08.028
274. Chaw SY, Novera W, Chacko A, Wong TTL, Venkatraman S. In vivo fate of liposomes after subconjunctival ocular delivery. *J Control Release*. 2021;329:162–174. doi:10.1016/j.jconrel.2020.11.053
275. Bochot A, Fattal E. Liposomes for intravitreal drug delivery: a state of the art. *J Control Release*. 2012;161(2):628–634. doi:10.1016/j.jconrel.2012.01.019
276. Date AA, Joshi MD, Patravale VB. Parasitic diseases: liposomes and polymeric nanoparticles versus lipid nanoparticles. *Adv Drug Deliv Rev*. 2007;59(6):505–521. doi:10.1016/j.addr.2007.04.009
277. Villaraza AJL, Bumb A, Brechbiel MW. Macromolecules, dendrimers, and nanomaterials in magnetic resonance imaging: the interplay between size, function, and pharmacokinetics. *Chem Rev*. 2010;110(5):2921–2959. doi:10.1021/cr900232t
278. Darie-Nita RN, Rapa M, Frackowiak S. Special features of polyester-based materials for medical applications. *Polymers-Basel*. 2022;14(5). doi:10.3390/polym14050951
279. Zhu S, Gong L, Li Y, Xu H, Gu Z, Zhao Y. Safety assessment of nanomaterials to eyes: an important but neglected issue. *Adv Sci*. 2019;6(16):1802289. doi:10.1002/advs.201802289
280. Zhang J, Jiao J, Niu M, et al. Ten years of knowledge of nano-carrier based drug delivery systems in ophthalmology: current evidence, challenges, and future prospective. *Int J Nanomed*. 2021;16:6497–6530. doi:10.2147/IJN.S329831
281. Li X, Li L, Zhang Z, Chen H. An overview on pharmacokinetics, disposition, and safety of nanoparticles in ocular applications. *Curr Drug Metab*. 2013;14(8):857–862. doi:10.2174/138920021131400107
282. Wilson SL, Ahearne M, Hopkinson A. An overview of current techniques for ocular toxicity testing. *Toxicology*. 2015;327:32–46. doi:10.1016/j.tox.2014.11.003