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Nano-based ocular drug delivery systems: an insight into the preclinical/clinical studies and their potential in the treatment of posterior ocular diseases

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Numerous novel nano-based ocular drug delivery systems have been developed to overcome the limitations of conventional drug delivery systems, which have demonstrated promising results in ocular disease models and clinical practice. Of all the nano-based drug delivery systems approved or under clinical investigation, topical instillation of eye drops is the most common route for administering therapeutics to the eye. Although this pathway is a viable way of ocular drug delivery to treat many ocular diseases because of its potential to eliminate the risks of intravitreal injection and the toxicity of systemic drug delivery, it remains a major challenge to efficiently treat posterior ocular diseases through topical administration of eye drops. So far, relentless efforts have been dedicated to the development of novel nano-based drug delivery systems with the aim of possible clinical translation. They are designed or modified to facilitate drug delivery to the retina by increasing the retention time, promoting drug penetration across barriers, and targeting specific cells or tissues. In this paper, we provided a snapshot of nano-based drug delivery systems that are currently marketed and under investigation in clinical trials for the treatment of ocular diseases and highlighted some examples of recent preclinical research on novel nano-based systems as eye drops to the posterior segment of the eye.

1. Introduction

The eye is one of the most complicated organs in the human body with distinctive anatomical and physiological structures. Anatomically, the eye can be divided into anterior and posterior segments with the anterior segment including the cornea, conjunctiva, anterior chamber, aqueous humor, iris, and lens and the posterior segment consisting of the vitreous humor, retina, choroid, sclera, and optic nerve. The complexity of the eye's structure, such as the cornea, blood–aqueous barrier, and blood–retinal barrier, prevents the drug from penetrating deeply into the eye. Other major barriers, including tear dilution, tear turnover, and nasolacrimal drainage, also lead to a reduced residence time of the drug. Conventional drug delivery systems, such as eye drops, ointments, and suspensions, are mostly effective in the treatment of ocular diseases in the anterior segment of the eye due to limited ocular bioavailability. For the treatment of posterior segment diseases, invasive procedures are commonly used to achieve higher concentrations, but the eye is at risk of complications from repeated injection. Therefore, the introduction of an ocular drug delivery system is one of the most promising ways to deliver drugs to the target site in a therapeutic dose.

Nanomedicine is an emerging field that combines nanotechnology with pharmaceutical and biomedical sciences to improve medical interventions for the prevention, diagnosis, and treatment of diseases.[1] It intends to develop drugs and imaging agents with increased clinical efficacy, decreased degradation or physiologic clearance rate, and enhanced toxicological profiles. Many of these properties are not inherent to specific particles. They are controllable under the precise design of drug delivery systems with the most favorable physical properties.[2,3]

Recently, a number of nano-based ocular drug delivery systems have been developed to overcome the limitations of conventional ones, which have demonstrated promising results in both *in vitro* and *in vivo* ocular disease models and clinical practice. They are designed or modified to facilitate drug delivery to the eye by increasing the retention time, promoting drug penetration across barriers, and targeting specific cells and tissues.[4]

In this review, we aim to provide a snapshot of the nano-based ocular drug delivery systems that have been approved by

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the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in ocular diseases, along with a description of key drug delivery systems that are emerging in the clinical trial pipeline, and to highlight some examples for topical delivery to the posterior segment of the eye as potential pathways for translational development in recent preclinical studies.

2. Approved and investigational nano-based drug delivery systems

Over the last three decades, various nano-based drug delivery systems have already been approved by the FDA and EMA.[5] To date, about nine nano-based ophthalmic drugs have been approved by the FDA and/or EMA (Table 1), while others remain under Phase I, II, and III clinical trials (Table 2).

2.1 Approved nano-based drug delivery systems

The first FDA-approved nano-based drug delivery system was Visudyne®, a verteporfin-loaded liposomal system, used as a photosensitizing agent along with laser light treatment for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). Visudyne® is administered intravenously, followed by directing a red laser through the pupil into the eye 10 minutes after injection. After absorbing the light, it is boosted into an excited state and transmits its energy to ambient oxygen to produce singlet oxygen. This reactive oxygen can stop and even reverse the progressive loss of vision by damaging the newly produced leaking blood vessels.[6,7] The results of the "Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP)" study, composed of two multicenter, double-masked, randomized phase-III clinical trials, revealed that, as opposed to the placebo, photodynamic therapy with verteporfin significantly reduced the risk of moderate and severe vision loss in patients with neovascular AMD with 61% *versus* 46% at 12 months and 53% *versus* 38% at 24 months ($p < 0.001$).[8] After 20 years of its approval, this drug continues to be widely used and remains the only intravenously injected nano-based drug delivery system, for the treatment of retinal diseases.[9,10]

In the real sense, Macugen®, a pegaptanib sodium-loaded polyethylene glycol (PEG) aptamer, is the first approved nano-based drug delivery system, for the treatment of neovascular AMD. It is the first in a new class of ophthalmic drugs to specifically target vascular endothelial growth factor (VEGF), a protein that acts as a signal in the case of abnormal blood vessel growth and leakage in neovascular AMD.[11] In two pivotal phase II/III, randomized, multicenter, double-blinded clinical trials involving approximately 1190 patients with all subtypes of neovascular AMD, intravitreally injected with 0.3 mg of Macugen®, 70% of patients achieved less vision loss compared with 55% in the placebo group ($p < 0.001$) at 54 weeks.[12] At year 2, patients receiving 0.3 mg of Macugen® experienced a change in vision that was approximately 50% better than those receiving placebo injections. Macugen®, therefore, has the notable distinction of being the first aptamer therapeutic approved for use in humans, shedding light on future aptamer applications.

Other nanocarriers, such as nanomicellar and nanoemulsion, have been widely explored for their potential to treat various ocular disorders. The treatment of anterior segment disease, including dry eye disease, glaucoma, and postoperative ocular inflammation, is the major principal therapeutic target for these delivery systems. Cequa® is a nanotechnology-derived ophthalmic delivery system approved by the FDA for dry eye disease. It is a transparent nanomicellar drug delivery system of a highly hydrophobic drug, cyclosporine A (CsA). In fact, as a highly hydrophobic compound, it is mostly administered as an oily emulsion, but oil-based preparations are poorly tolerated by patients and lead to low bioavailability because CsA is more attracted to the hydrophobic vehicle than the highly hydrophilic tissue. However, the unique CsA nanomicellar delivery system of Cequa® can offer improved stabi-

Table 1 Clinically approved nanodrugs for ocular diseases

Formulation	Drug name	Active drug	Route	Approved application/indication	Approval (year)
Anterior segment disease					
Nano-emulsion	Durezol	Difluprednate	Topical	Postoperative ocular inflammation and pain	FDA (2008)
Polymeric hydrogel	Zirgan	Ganciclovir	Topical	Acute herpetic keratitis	FDA (2009)
Nano-emulsion	Ikervis	Cyclosporine	Topical	Dry eye disease	EMA (2015)
Nanomicelles	Cequa	Cyclosporine	Topical	Dry eye disease	FDA (2018)
Polymeric hydrogel	Timoptic-XE	Timolol maleate	Topical	Ocular hypertension or open-angle glaucoma	FDA (2018)
Nanoparticles	Inveltys	Loteprednol etabonate	Topical	Postoperative ocular inflammation and pain	FDA (2018)
Nanoparticles	Eysuvis	Loteprednol etabonate	Topical	Dry eye disease	FDA (2020)
Posterior segment disease					
Liposome	Visudyne	Verteporfin	Intravenous	Subfoveal choroidal neovascularization secondary to age-related macular degeneration	FDA (2000) and EMA (2000)
Polymer	Macugen	Pegaptanib sodium	Intravitreal	Neovascular age-related macular degeneration	FDA (2004) and EMA (2006)

Table 2 Nanodrugs still under investigation (not yet recruiting, recruiting, completed but not clinically approved)

Formulation	Drug name	Active drug	Disease	Route	Clinical trial phase	Clinical trials gov ID	Status
Dry eye disease							
Nanomicelles	VOS (voclosporin ophthalmic solution)	Voclosporin	Dry eye disease	Topical	III	NCT04147650	Completed
Nanoparticles	KPI-121	Loteprednol etabonate	Meibomian gland disease	Topical	II	NCT02218489	Completed
Nanoparticles	Haporine-S	Cyclosporine	Dry eye disease	Topical	III	NCT01804361	Completed
Nano-emulsion	NOVA22007 (Ikervis® approved by EMA)	Cyclosporine	Dry eye disease	Topical	III	NCT00814515	Completed
Nano-emulsion	TJCS eye drops	Cyclosporine	Dry eye disease	Topical	III	NCT02461719	Completed
Nano-emulsion	Nanodrop (PRO-176)	Propylene glycol	Dry eye disease	Topical	Iand II	NCT04111965	Not yet recruiting
Nano-emulsion	OCU-310	Brimonidine Tartrate	Dry eye disease	Topical	III	NCT03785340	Completed
Glaucoma							
Liposome	POLAT-001	Latanoprost	Ocular hypertension, open-angle glaucoma	Subconjunctival injection	II	NCT02466399	Completed
Nanoparticles Intracameral implant	ENV515	Travoprost	Ocular hypertension, open-angle glaucoma	Topical	II	NCT02371746	Completed
Ocular inflammations							
Nanocrystal	NCX 4251	Fluticasone propionate	Blepharitis	Topical	II	NCT03926026	Completed
Nano-emulsion	OCU300	Brimonidine tartrate	Ocular graft *versus* host disease	Topical	III	NCT03591874	Terminated
Nanoparticles	DexNP (OCS-01)	Dexamethasone	Inflammation and pain following cataract surgery	Topical	II	NCT04130802	Completed
Nano-emulsion	SVT-15473	Clobetasol propionate	Inflammation and pain following cataract surgery	Topical	III	NCT04246801	Completed
Nanomicellar	LX211	Voclosporin	Non-infectious uveitis	Oral	III	NCT00404612	Completed
Nano-emulsion	NOVA22007	Cyclosporine	Vernal keratoconjunctivitis	Topical	II and III	NCT00328653 and NCT01751126	Completed
Retinal diseases							
Nanoparticles	Dexamethasone-cyclodextrin eye drops	Dexamethasone	Diabetic macular edema	Topical	II and III	NCT01523314	Unknown
Nanoparticles	DexNP (OCS-01)	Dexamethasone	Diabetic macular edema	Topical	II and III	NCT05066997	Recruiting
Nanoparticles	TLC399 (ProDex)	Dexamethasone	Retinal vein occlusion, macula edema	Intravitreal	II	NCT03093701	Completed
Nanoparticles	KPI-121	Loteprednol etabonate	Intra- or subretinal fluid due to retinal vein occlusion, macula edema	Topical	II	NCT02245516	Completed
Other diseases							
Nanoparticles	Pluronic®F-127	Urea	Cataract	Topical	II	NCT03001466	Completed
Liposomes	Coenzyme Q10	Coenzyme Q10	Ataxia-oculomotor apraxia 1	Oral	III	NCT02333305	Completed
Liposomes	Marqibo	Vincristine sulfate	Metastatic malignant uveal melanoma	Intravenous	II	NCT00506142	Completed
		Vincristine sulfate	Intraocular retinoblastoma	Intravenous	III	NCT00072384	Completed
Nanoparticles	Nab-paclitaxel	Paclitaxel	Intraocular melanoma	Intravenous	II	NCT00738361	Completed

lity, safety, and efficacy, as well as lower cost.[13] Its safety can be confirmed by low toxicity from the preclinical results performed in human-derived corneal and retinal cells.[14] In addition, the insignificant charge of the system helps to prevent rejection by negatively charged cell surfaces, which contributes to improved interaction with the ocular cells.[15] In clinical practice, in phase III clinical trial with a total of 745 patients with dry eye disease, both the primary endpoints of the trial, Schirmer's test (a measure of tear production), and secondary endpoints indicated a statistically significant

increase.[16] It was also clarified in the trial that Cequa® was a highly efficient and safe ophthalmic solution resulting in a clinically meaningful increase in tear production and a large reduction in signs and symptoms of ocular surface inflammation compared to the vehicle in dry eye disease.[17–19]

2.2 Investigational nano-based drug delivery systems

There are a handful of novel nano-based eye drops currently being investigated in clinical trials to establish their safety and efficacy for the treatment of ocular disorders. A phase III clinical trial was conducted to examine the effects of clobetasol propionate nanoemulsion eye drops (SVT-15473) in patients on the reduction of inflammation and pain after cataract surgery between June 2020 and May 2021 (NCT04246801). SVT-15473 was developed using a patented nanoemulsion technology, IMPACT-SVT® nanoemulsion (emulsion with nanometric-sized droplets), to improve drug–mucus penetration and bioadhesion, and to reduce irritation to the eye.[20] The trial involved 212 patients who had recently undergone cataract surgery from 22 hospitals in the United States. Recently, the company submitted a New Drug Application (NDA) to the FDA for approval with favorable results for this innovative nano-based delivery systems. In addition, a randomized, double-masked, vehicle-controlled phase II study of loteprednol etabonate nanoparticle eye drop for the treatment of meibomian gland disease was completed at approximately 8 centers in the United States (NCT02218489).

Although nano-based drug delivery systems intended for topical instillation exhibit the ability to penetrate through the biological membrane and accumulate in the ocular tissues, few have received clinical use approval for the market. There are limited clinical trials that have been conducted for the clinical transition of topical instillation in the management of posterior segment diseases. One is a phase II/III clinical trial under investigation for dexamethasone nanoparticle eye drops (OCS-01) in the treatment of diabetic macular edema (DME) (NCT05066997). The OCS-01 ophthalmic suspension is 1.5% dexamethasone formulated in OPTIREACH technology, which leverages unique characteristics of drug/cyclodextrin nanoparticles to enhance drug permeability and bioavailability in eye tissues. Animal studies and preliminary clinical trials have proven that this cyclodextrin nanoparticle technology has the potential to increase drug concentrations in ocular tissues, particularly the retina, for the treatment of retinal diseases such as DME. It has successfully completed a phase II trial (NCT05343156). The trial achieved its pre-defined efficacy endpoints and demonstrated that OCS-01 eye drops were superior to vehicle eye drops (identical to the active treatment but without dexamethasone) in reducing the central macular thickness and improving visual acuity in 133 patients with DME.[21]

2.3 Complications in clinical trials

Safety is one of the most important issues relevant to the clinical development of nano-based drug delivery systems intended for ocular application. The significance of eye safety is highlighted by the FDA's guidance for the industry: safety of nanomaterials in cosmetic products (Docket number: FDA-2011-D-0489). The standard eye irritation test for measuring the ocular toxicity of nano-based drug delivery systems is established by The Organization for Economic Co-operation and Development. Although there has been certain attention paid to the safe use of these delivery systems to the eye, research on their toxicity effect on eyes is still in the early stage.

Even though the ocular surface is the first layer that comes in contact with nanomaterials, once they are absorbed into the eyes, the toxic effect may also be caused within the eye or on the inner surface of the retina. Specific literature on the complications of nanoparticles in ocular application remains scarce. The main toxicity caused by nanoparticles is the generation of oxidative stress, inflammation, and interaction with the cell membrane.[22]

KPI-121 is a nano-based drug delivery system using mucus-penetrating particles to deliver a custom-engineered ocular corticosteroid, loteprednol etabonate, to the ocular surface tissues.[23–26] In the clinical trial of its application in dry eye disease, there was a low incidence of treatment-related adverse events (AEs), severe AEs, and serious AEs. The only AE reported with an incidence of more than 1% was pain at the site of instillation, which was reported by 5.2% of subjects in the KPI-121 group and 4.4% of subjects in the placebo group.[24] But the pain was transient and mild or moderate in severity.[25,26]

NOVA22007 is a proprietary cationic emulsion that enables an optimal penetration of CsA through the ocular surface by Novasorb cationic emulsion technology.[27] In a multicenter phase III trial of NOVA22007 for the treatment of vernal keratoconjunctivitis in children, instillation site pain was also the most common adverse event, reported by six patients (10.5%) in the four-times-daily treatment regimen group, three patients (5.6%) in the twice-daily treatment regimen group, and two patients (3.4%) in the placebo group.[28] In the phase III study for its application in dry eye disease, 31 (4%) patients had a serious adverse event during the initial 6 months period including 15 (3.8%) in the NOVA22007 group and 16 (4.7%) in the vehicle group (cationic emulsion without CsA). Two patients were considered to be drug-related with one related to NOVA22007 (epithelial erosion of the cornea) and the other related to the vehicle (reduced visual acuity).[29]

3. Topical instillation of eye drops to the posterior segment of the eye

Of all the nano-based drug delivery systems approved and under investigation, topical instillation of eye drops is the most common route for administering therapeutics to the eye. Although this pathway is a viable way of drug delivery for the treatment of anterior segment diseases, such as dry eye disease, glaucoma, inflammation, and pain following ocular surgery, it remains a major challenge to efficiently deliver

drugs topically to treat diseases of the posterior segment of the eye.

At present, all commercially available ophthalmic products used for the management of posterior segment diseases are invasive. It is true that intravitreal injection is the most efficient route for the administration of drugs to the posterior segment of the eye. However, this route is associated with various complications, including endophthalmitis, retinal detachment, vitreous hemorrhage, and cataract.[30] Even though intravitreal injection is widely used in the clinic, it still demands high patient compliance. In fact, patients may receive fewer injections than those taking part in clinical trials, and thus their treatment outcomes may be worse than anticipated.[31] Therefore, patients would benefit greatly if effective delivery could be achieved by a less invasive route of administration.

The absorption of drugs on the ocular surface is limited by various barriers, such as static (cornea, conjunctiva, sclera), dynamic (tear turnover, reflex blinking, conjunctival blood flow, and nasolacrimal drainage), metabolic barriers (phase I & II enzymes, efflux pumps) and intraocular environment (blood–retinal and blood–aqueous barriers), resulting in extremely low drug bioavailability which is usually less than 5% and difficult to be delivered to the posterior segment of the eye.[32–35] After topical instillation, drugs may penetrate into the posterior segment *via* the corneal or/and conjunctival route. Drugs can penetrate through the cornea to the anterior chamber, then pass through the lens/iris to reach the vitreous and retina. Drugs can also diffuse through the sclera, choroid and eventually reach the retina following absorption into the conjunctiva, or they can diffuse from the cornea to the conjunctiva. In addition, a small number of drugs can reach the retina by overcoming the blood–retinal barrier after systemic absorption *via* nasolacrimal drainage, conjunctival blood vessels, or choroidal circulation (Fig. 1).[36]

Recently, a lot of nano-based drug delivery systems have been developed to overcome the limitations of conventional eye drops and deliver drugs to the retina.[37–63] These advanced delivery systems have shown promising outcomes in the ocular disease models both *in vitro* and *in vivo* by increasing the retention time of drugs on the cornea, enhancing drug penetration, or promoting drug delivery to the posterior segment of the eye through the corneal or conjunctival–scleral pathway. Herein, we provide a summary of preclinical research on novel nano-based drug delivery systems for topical delivery to the posterior segment of the eye in the recent five years (Table 3).

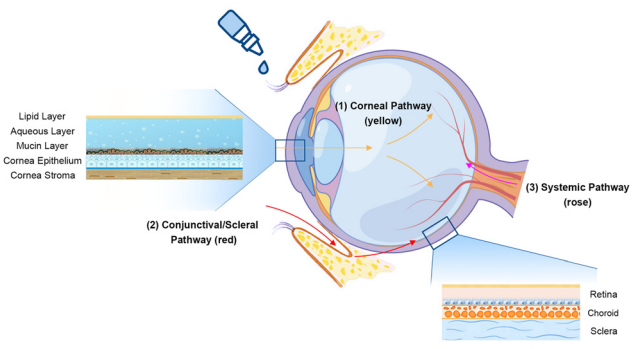

Fig. 1 Drug absorption pathways through the cornea/conjunctiva–sclera pathways following topical administration. (1) Corneal pathway is marked in yellow. (2) Conjunctival–scleral pathway is marked in red. (3) Systemic absorption is marked in rose.

3.1 Liposomes

Liposomes are spherical vesicles composed of one or more lipid bilayers and an aqueous core. Both hydrophilic and lipophilic drugs can be encapsulated in liposomes, with hydrophilic drugs encapsulated in the core and lipophilic drugs in the bilayer. Liposomes have been widely used in the development of topical therapeutics with increased residence time for drug absorption, protection of the encapsulated drug from the external environment, and enhanced drug penetration to ocular tissues.[63,64] A recent study developed and evaluated the potential of triamcinolone acetonide-loaded liposomes, formed by soybean phosphatidylcholine and cholesterol, coated with chitosan by the calcium acetate gradient method as a novel drug delivery system enhancing the efficacy of triamcinolone acetonide as eye drops to the retina. Chitosan was chosen as the surface modification of liposomes due to its special properties of bioadhesion to the cornea and enhanced penetration. After modification, the cationic liposomes have a high binding affinity to the corneal surface, which interacts with the negative charge of the ocular surface to prolong drug retention and improve local drug concentration. This system was found to have a prolonged retention time on the ocular surface, which enhanced the absorption of cargo through the corneal pathway.[37,38] Altamirano-Vallejo *et al.* also developed triamcinolone acetonide-loaded liposome formulations (TALF), self-forming synthetic PEGylated lipids (QuSomes®) containing TA, to enhance the delivery of TA into the posterior segment of the eye. TALF was able to cross the cornea and deliver TA to the vitreous body and retina, reaching the highest peak at 12 h.[40] Moreover, in the phase I clinical study, TALF was able to reduce the thickness of the fovea in patients with adequate glycemic control but the presence of DME with good ocular tolerability.[41]

Liposomes modified by penetration-enhanced polymers can not only entrap drug molecules but also target the desired sites *via* binding to the cornea surface. Gu *et al.* prepared a novel nanocomposite eye drop by hybridizing dexamethasone-loaded liposomes, made by soybean phospholipids and cholesterol, with glycylsarcosine (GS)-anchored layered double hydroxides (LDH).[43] GS is a classical substrate for PepT-1, which is used for targeting PepT-1 of the ocular surface and was modified on LDH. LDH, a kind of positive carrier, can increase precorneal retention through electrostatic adsorption. Combining the advantages of all compounds mentioned above, the formulation showed prolonged precorneal retention time by 2.0 times and superior *in vitro* permeability than commercial dexamethasone eye drops. Furthermore, the formulations also displayed higher drug concentrations in choroid-

Table 3 Representative topical nano-formulations in preclinical study in recent 5 years

Formulation	Drug	Function	Pathway	Disease	Ref.
Liposomes	Diclofenac	Enhance penetration	Corneal	Choroidal neovascularization	Shimazawa *et al.*[37]
	Triamcinolone acetonide	Enhance penetration, increase retention time	Corneal	Retinal edema	Chen *et al.*[38] and Li *et al.*[39]
	Triamcinolone acetonide	Enhance penetration	Corneal	Diabetic macular edema	Altamirano-Vallejo *et al.*[40] and Navarro-Partida *et al.*[41]
	Triamcinolone acetonide	Increase retention time	Corneal	Choroidal neovascularization	Khalil *et al.*[42]
	Dexamethasone	Enhance penetration, increase retention time	Non-corneal	Posterior ocular tissues	Gu *et al.*[43]
	TGFβ1	Enhance penetration	Corneal	Age-related macular degeneration	Platania *et al.*[44]
Lipid nanoparticles	Myriocin	Enhance penetration	Conjunctival/ scleral	Retinitis pigmentosa	Platania *et al.*[45]
	Atorvastatin	Enhance penetration, increase retention time	Corneal, conjunctival/ scleral	Age-related macular degeneration	Yadav *et al.*[46]
	Triamcinolone acetonide	Enhance penetration, increase retention time	Corneal	Posterior ocular tissues	Tatke *et al.*[47]
	Melatonin	Enhance penetration, increase retention time	Corneal	Diabetic retinopathy	Romeo *et al.*[48]
	Verteporfin	Enhance penetration	Conjunctival/ scleral	Age-related macular degeneration	Ran *et al.*[49]
Polymer nanoparticles	Apatinib	Enhance penetration, increase retention time	Corneal	Diabetic retinopathy	Radwan *et al.*[50]
	siRNA/antisense oligonucleotides	Enhance penetration	Non-corneal	Retinoblastoma	Jiang *et al.*[51]
Inorganic nanoparticles	Cerium oxide nanoparticles	Enhance penetration	Conjunctival/ Scleral	Age-related macular degeneration	Badia *et al.*[52]
	Gold nanoparticles	Enhance penetration	Corneal	Diabetic retinopathy	Apaolaza *et al.*[53]
	Guanabenz and valproic acid (magnetic nanoparticles)	Enhance penetration by MRI	Corneal	Barded–Biedl syndrome related retinal degeneration	Bassetto *et al.*[54]
Nanomicelles	Aflibercept	Enhance penetration, increase retention time	Corneal, conjunctival/ scleral	Choroidal neovascularization	Zhao *et al.*[55]
	Doxorubicin	Enhance penetration, increase retention time	Conjunctival/ scleral	Oxygen-induced retinopathy	Li *et al.*[56]
	Anti-PDL1, anti-VEGFA	Enhance penetration	Conjunctival/ scleral	Choroidal neovascularization, choroidal melanoma	Shen *et al.*[57]
Nanoemulsion	Lutein	Enhance penetration, increase retention time	Non-corneal	Age-related macular degeneration	Ge *et al.*[58]
	Ro5-3335	Increase retention time	Not mentioned	Ocular neovascularization, proliferative vitreoretinopathy	Delgado-Tirado *et al.*[59] and Delgado-Tirado *et al.*[60]
Dendrimer	Not mentioned	Enhance penetration	Conjunctival/ scleral	Choroidal neovascularization	Yang *et al.*[61]
	Antisense oligonucleotides	Enhance penetration	Corneal	Posterior ocular tissues	Tai *et al.*[62]
	Berberine hydrochloride, chrysophanol	Enhance penetration	Conjunctival/ scleral	Age-related macular degeneration	Lai *et al.*[63]

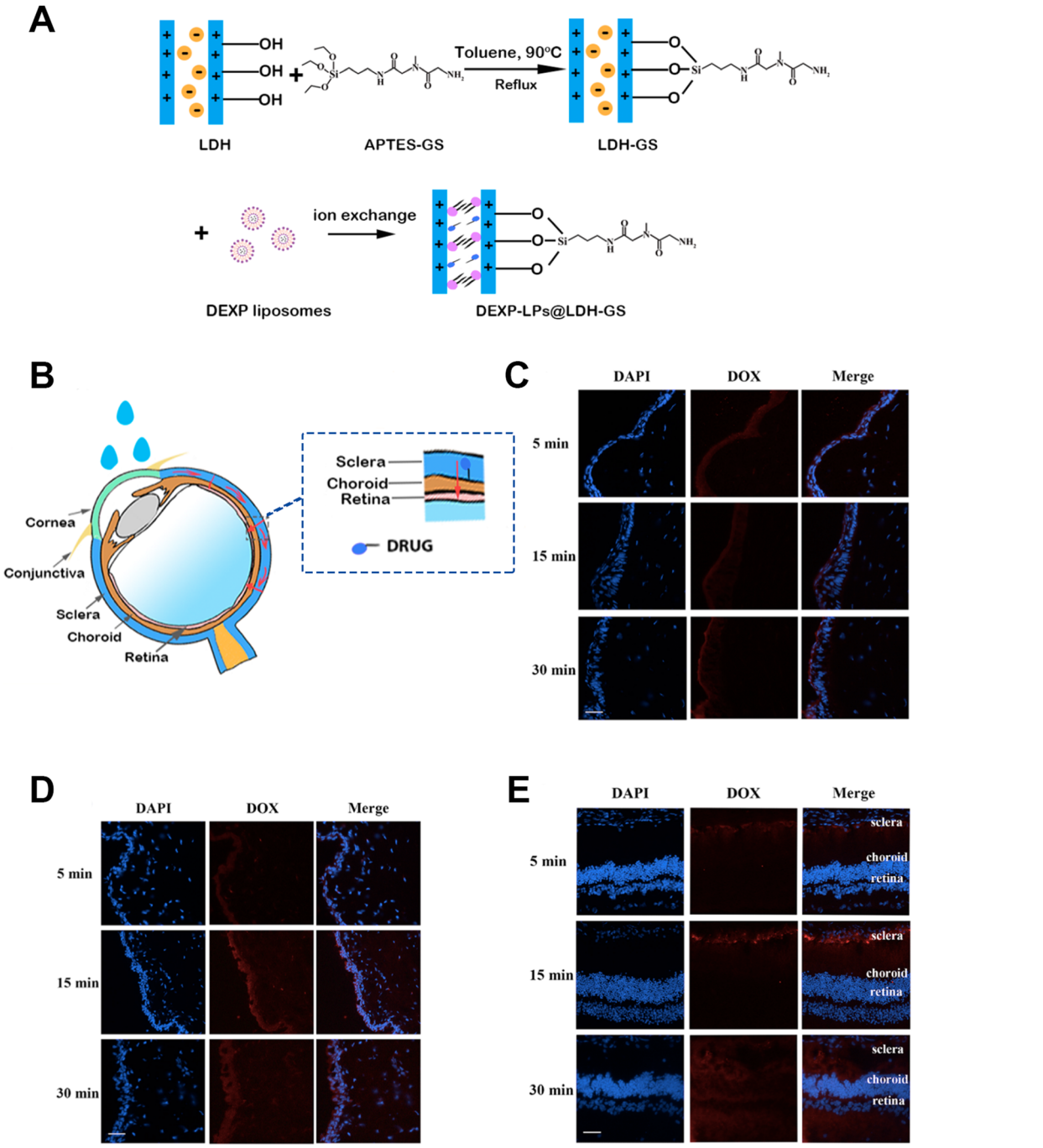

Fig. 2 Dexamethasone (DEXP)-loaded liposomes with glycylsarcosine (GS)-anchored layered double hydroxides (LDH) can facilitate the noninvasive delivery of drugs to the posterior segment of the eye. (A) Synthesis of DEXP-HSPC@LDH-GS nanocomposites by an ion-exchange method. (B) Schematic illustration of topical delivery of DEXP to the posterior segment of the eye through a non-corneal pathway. Fluorescent images of frozen sections of cornea (C), conjunctiva (D), and sclera–choroid–retina (E) of rabbit eyes after topical administration of DOX-HSPC@LDH-GS nanocomposites. Scale bar, 50 μm.[43] Copyright © 2019, American Chemical Society.

retina tissue compared with other formulations composed of single LDH (Fig. 2).

3.2 Lipid nanoparticles

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) play a key role in a major shift in eye disease therapy. These lipid-based systems have compatible characteristics with biological membranes, which may promote mucus adhesion, thus improving drug uptake when compared to conventional drug delivery systems. In addition, they also allow modified drug release and a reduction in the required dose for topical instillation.[65] Yadav *et al.* designed an SLN system

loaded with atorvastatin (ATS-SLNs) as topical therapeutics for AMD. The ATS-SLNs, comprising atorvastatin, Compritol® 888 ATO, PEG400, Poloxamer 188 (P188) and Phospholipon 90H (P 90H), were prepared by a high-pressure homogenization method and were suitable to provide enhanced permeation through the cornea and attained higher drug bioavailability in both the aqueous and vitreous humor.

They found that ATS-SLNs were 8 and 12 times more bioavailable in the aqueous and vitreous humor, respectively, compared to free ATS. The AST-SLNs were observed on the corneal surface for up to 7 h, 4.7 times longer than the free solution after topical instillation. The prolonged residence on the eye may be attributed to their mucus penetration effects because the particles contain PEG400 and P188, and both these polymers have been established as effective mucopenetrating agents. The particles were able to penetrate through the mucus and reach the corneal surface with the help of P188, which coats the particle surfaces by adhering hydrophobic poly-propylene oxide segments and leaving a dense brush of uncharged, hydrophilic segments sticking out from the particle surface.[46] Tatke *et al.* developed a similar TA-loaded SLN *in situ* gel (TA-SLN-IG), comprising TA, Compritol® 888 ATO, glyceryl monostearate, Tween® 80, P188 and glycerin, for enhanced topical ocular delivery to the posterior segment of the eye. The introduction of the *in situ* gelling agent with SLN will keep the formulation for a longer period of time, thus increasing the pre-corneal residence time. The rheological and trans-corneal permeability of TA-SLN and TA-SLN-IG were 10.2 and 9.3 fold higher, respectively, compared to the TA-control, with a higher tear concentration of 13.3 μg mL^{-1} at 2 hours, indicating an enhanced precorneal residence time. The enhanced retention time of TA-SLN-IG on the ocular surface was mainly due to cross-linking of the polymer chains mediated by the cations in the tear fluid, resulting in gel formation on the ocular surface, which contributes to an extended corneal contact time.[47]

In order to improve the encapsulation efficiency and achieve well-controlled release kinetics, a new generation of nanoparticles, lipid–polymer hybrid nanoparticles (LPHNs), has been designed.[66] Romeo *et al.* developed and optimized melatonin-loaded LPHNs (mel-LPHNs) using the Design of Experiment as a safe hybrid platform suitable for topical instillation of diabetic retinopathy. With the aim of enhancing corneal retention time, the nanoparticles consisted of the PLGA-PEG polymer coated with a cationic lipid shell. PLGA-PEG was used as a mucopenetrating agent and cationic lipids were used to enhance mucoadhesion through electrostatic interaction with the anionic ocular mucosa. After topical instillation, mel-LPHNs displayed a high encapsulation efficiency of 79.8%, suitable pH and osmolarity values, good mucoadhesive properties, and a controlled release profile for over 8 days. Furthermore, biological evaluation in an *in vitro* model of diabetic retinopathy demonstrated enhanced neuroprotective and antioxidant activities of mel-LPHNs, when compared to melatonin aqueous solution at the same concentration.[48]

Ran *et al.* designed a low-density lipoprotein-inspired nanoparticle (PEN-rLDL-VP) with high verteporfin (VP) encapsulation efficacy and neovascularization recognizability for the targeted photodynamic (PDT) of wet AMD. VP was protected inside the hydrophobic core of reconstituted LDL (rLDL) vectors, and 5-carboxyfluorescein (FAM) conjugated penetratin (PEN) was anchored on the surface of the rLDL carrier, which allowed the nanoparticles (PEN-rLDL-VP) to pass across the blood–retina barrier to enable visual therapy. After topical instillation for only a single dose, PEN-rLDL-VP was able to deliver VP into the neovasculature to respond to PDT therapy, and decreased neovascularization and inflammation were observed afterwards (Fig. 3).[49]

3.3 Polymer nanoparticles

Polymer nanoparticles are ideal for ocular drug delivery to the desired sites due to the diversity of polymers in their compositions. Recently, several hybrid polymer nanoparticle-based eye drop delivery systems have been prepared mainly focusing on the ability to penetrate deeper into the posterior segments of the eye, resulting in the localized delivery of drugs at high dosages and enriching the local drug concentration in the retina.

Radwan *et al.* investigated the feasibility of bovine serum albumin (BSA) nanoparticles coated with hyaluronic acid (HA), containing apatinib, a selective inhibitor of VEGF receptor 2, to the retina *via* topical instillation in diabetic retinopathy. The mucoadhesive nature of HA, as well as its interaction with hyaluronan receptors, on corneal epithelial cells may result in prolonged precorneal retention. The characteristics of BSA-NPs prepared in this work, including the highly negative surface charge (−29.5 ± 0.05 and −37.3 ± 1.8 mV) and the relatively small particle size (212 ± 0.35 and 222.2 ± 3.56 nm) of uncoated and HA-coated nanoparticles, respectively, allowed avoiding particle trapping within the vitreous meshwork, thus allowing them to freely diffuse towards the retina. In addition, the HA coating also worked to enhance apatinib delivery to actively target CD44 receptor positive retinal cells by receptor-mediated endocytosis.[50]

Polymer nanoparticles can also be used as carriers for gene delivery to the retina with the assistance of cell-penetrating peptides. An octopus-like 8-valent penetratin (VP) composed of a biocompatible multi-arm PEG core and several outspread penetratin tentacles was designed to effectively deliver siRNA or antisense oligonucleotides (ASOs) into retinoblastoma-bearing mice. The formation of a branched spatial structure and flexible cationic penetratin tentacles of 8VP significantly improved cancer cellular efficiency (approaching 100%) and transfection rate (over 75%). After topical instillation in the retinoblastoma-bearing mice model, 8VP enabled rapid (<10 min) and prolonged (>6 h) distribution of nucleic acids in the retina *via* a noncorneal pathway and efficiently inhibited the protein expression of intraocular tumor without toxicity (Fig. 4). This non-viral vector nanostructure provided a promising strategy for non-invasive gene delivery therapies for retinoblastoma treatment.[51]

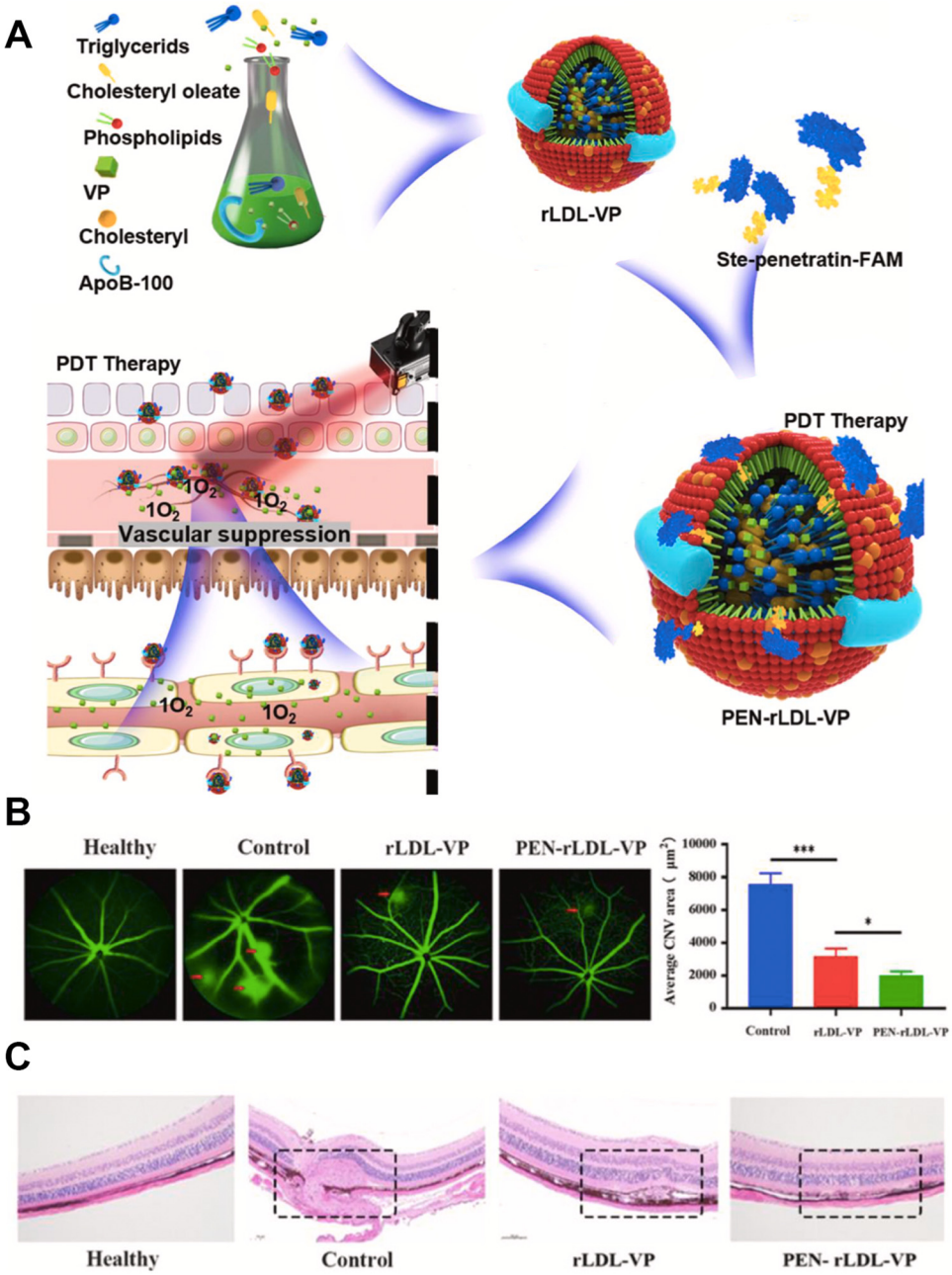

Fig. 3 Neovascularization-directed bionic eye drops for the treatment of age-related macular degeneration. (A) Schematic illustration of the composition of PEN-rLDL-VP nanoparticles and treatment of wet age-related macular degeneration after topical instillation. (B) Representative images of fluorescence fundus angiograms from the healthy, untreated, rLDL-VP, and PEN-rLDL-VP groups and quantification analyses of CNV areas on the 24th day of CNV induction. (C) Representative images for retinal sections of experimental groups stained with H&E on the 28th day (400×).[49]

3.4 Inorganic nanoparticles

Inorganic nanoparticles, including silicone, iron oxide, zinc oxide, cerium oxide, gold, silver, and magnetic nanoparticles have been investigated for their potential in ocular drug delivery.[67] These nanoparticles are gaining popularity as a result of their antioxidant, anti-inflammatory, antiangiogenic and magnetic properties. Cerium oxide nanoparticles (CeO_2NPs) were found to have minimal toxicity to normal tissues while providing cellular protection from ROS-dependent oxidative damage. Badia *et al.* prepared a delivery system of 3 nm CeO_2NPs which were monodispersed in an aqueous suspension stabilized by sodium citrate. The ultrasmall nanoparticles usually have a strong propensity to aggregate, making it difficult to create single CeO_2NP colloidal dispersions in water. To overcome this problem, Badia *et al.* were able to make CeO_2NPs stable in

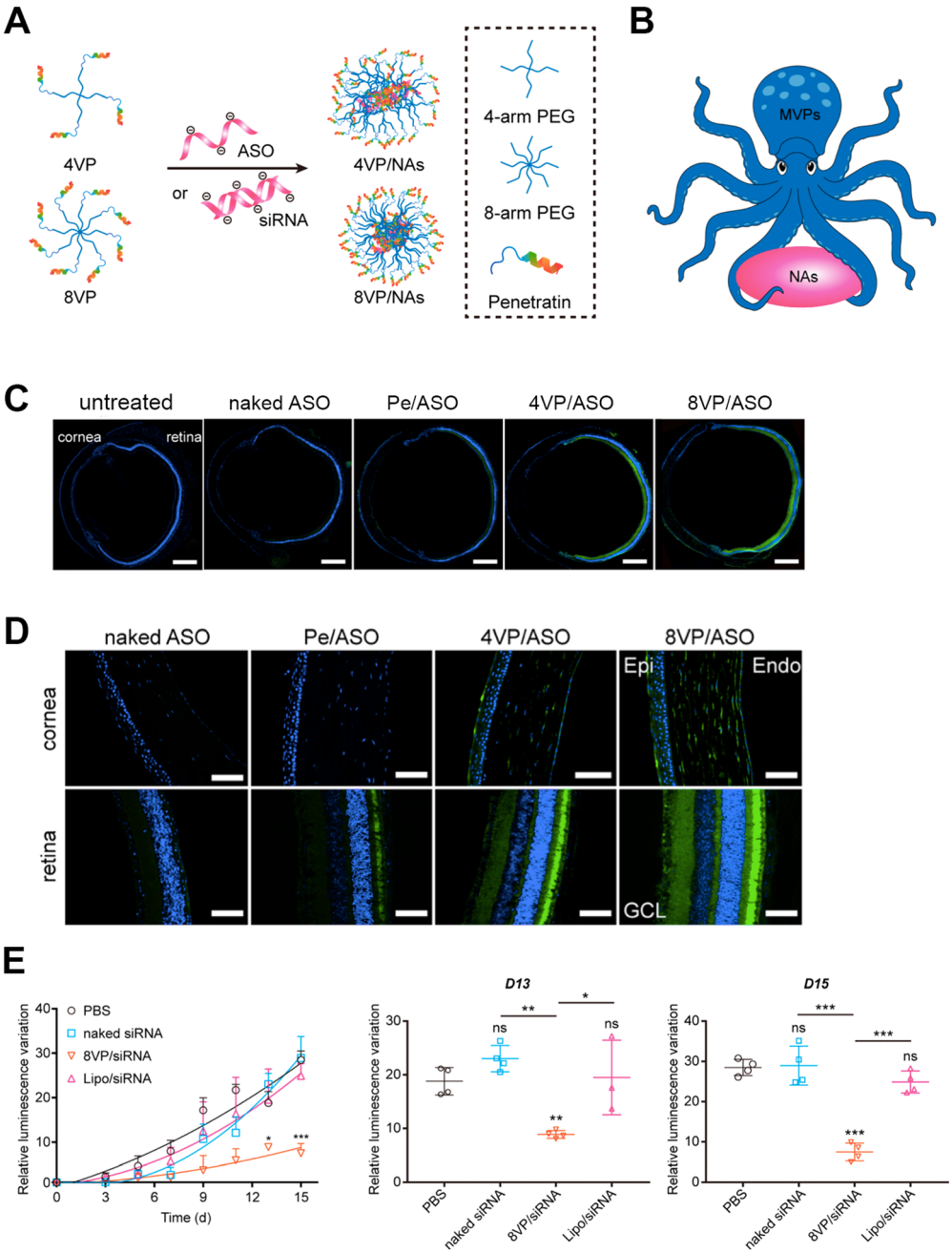

Fig. 4 Topical delivery of nucleic acids by octopus-like 8-valent penetratin polymer nanoparticles for the treatment of retinoblastoma. (A) Construction of multivalent penetratin (MVP) forms polyplexes with antisense oligonucleotides (ASO). (B) The polyplexes are formed as an octopus-like nanostructure that carry some cargo (nucleic acids) by binding cationic penetratin tentacles with anionic nucleic acids and moving forward by nonbinding tentacles to mediate the noninvasive intraocular delivery. (C and D) Intraocular distribution of aso in the whole eye, cornea, and retina treated with different polyplexes. Epi, epithelium; *endo*, endothelium; gcl, ganglion cell layer. (E) Semiquantitative inhibition efficiency on bioluminescence fluc expression of the tumor. Scale bars, 500 μm for (C) and 100 μm for (D).[51] Copyright © 2019, American Chemical Society.

water by starting with sodium citrate complexed cerium ions rather than conventional cerium nitrate and using TMAOH as the base. The non-aggregation characteristics helped in the topical instillation of the nanoparticles to reach the retina and achieved a beneficial therapeutic effect. The system displayed the capacity to activate the expression of genes related to the antioxidant response, reduce the expression of inflammatory lesions, and decrease CNV both *in vitro* and *in vivo* (Fig. 5).[52]

Gold nanoparticles possess several advantages, such as relatively small size, high biocompatibility, antioxidant and anti-angiogenic features.[68] Apaolaza *et al.* designed HA-coated gold

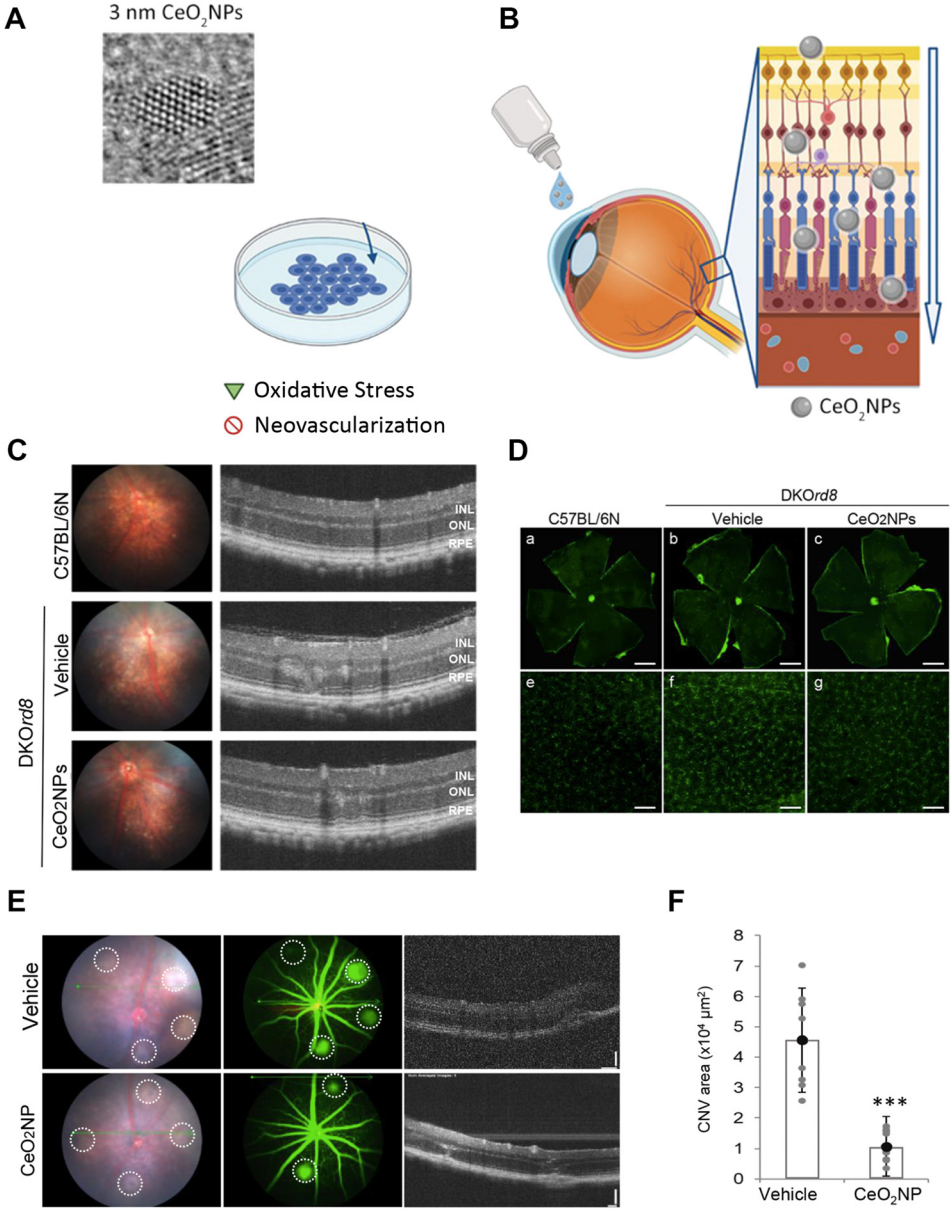

Fig. 5 Non-aggregated biocompatible cerium oxide nanoparticles (CeO_2NPs) in the treatment of dry and wet forms of AMD as a beneficial antioxidant and a neuroprotective agent. (A) *In vitro* results indicated the biocompatible and protective character of 3 nm CeO_2NPs in reducing oxidative stress in arpe19 cells and inhibiting neovascularization in both huvec and *in vitro* models of neovascular growth. (B) Schematic illustration of topical delivery of CeO_2NPs to the retina through the conjunctival–scleral pathway. (C) Fundoscopy and optical coherence tomography (oct) images of DKOrd8 mice 2 months after treatment with CeO_2NPs or vehicle, and C57BL/6N mice used as control. (D) Microglia quantification in RPE a–c and retinal flatmounts e–g of DKOrd8 mice stained with iba1 after the 2-month treatment. Scale bars, 500 µm for a–c and 100 µm for e–g. (E) Representative fundus, fluorescein angiography and oct images of laser induced CNV mouse eyes treated with CeO_2NPs or vehicle for 7 days (F) Graphs comparing CNV area measured from RPE–choroid–sclera flatmounts.[52] Copyright © 2023, American Chemical Society.

nanoparticles for topical instillation to reach the retina. By modifying with HA, the gold nanoparticles were able to cross the physiological barrier of the eye and reach the retina. The HA coating helped to enhance the mobility of the nanoparticles in the vitreous and increase stability and distribution by a specific CD44 receptor interaction. As a result, protective and antiangiogenic effect was achieved by significant suppression of neovascularization and advanced glycation end mediated retinal pigment epithelial cell death after topical instillation.[53]

Magnetic nanoparticles are different from other nanocarriers due to the magnetic properties that make them unique for drug delivery. Recently, Bassetto *et al.* developed a topical, noninvasive, and magnetically aided delivery system that cargo guanabenz and valproic acid on the surface of Fe_3O_4 nanoparticles through anti-unfolded protein response towards

the retina. Assisted by magnetic resonance imaging, the nanoparticles were successfully delivered to the photoreceptors after being topically applied onto the ocular surface of *Bbs* knockout and wild-type mice. Moreover, a therapeutic effect was seen in the mice models with significant amelioration of the photoreceptors' functionality by electroretinogram.[54]

3.5 Nanomicelles

Nanomicelles are nanosized amphiphilic core–shell structures with a hydrophobic core, hydrophilic shell, and polymeric surfactants.[69] Nanomicelles are emerging as a promising platform for the delivery of poorly water-soluble drugs to the eye due to their increased bioavailability, enhanced corneal permeation, and increased solubility and stability of drugs.[70–73] Zhao *et al.* reported a nanomicelle drug delivery system made of a copolymer EPC (nEPC), comprising PEG, polypropylene glycol (PPG), and polycaprolactone (PCL) for the topical instillation of aflibercept to the posterior segment of the eye. nEPCs were made by concentrating EPC above the critical micelle concentration but below the concentration required for sol–gel transition. Aflibercept was then encapsulated by nEPCs through direct mixing. The systems of nEPC loaded with aflibercept could penetrate the cornea and deliver aflibercept to the retina with a therapeutic effect on CNV murine models. Interestingly, nEPCs exhibit intrinsic antiangiogenic properties by inhibiting VEGF-driven angiogenesis pathways responsible for endothelial cell proliferation and tube formation instead of haptotaxis, which is driven by extracellular matrix components such as collagen. The intrinsic antiangiogenic properties of nEPCs and their ability to deliver anti-VEGF drugs may result in a synergistic effect for the treatment of CNV.[55]

Li *et al.* designed a co-assembled glycopeptide nanotransforrs (GPNTs), consisting of glycopeptide, cationic peptide, and doxorubicin, which can effectively penetrate the cornea and sclera barriers, and then target M2 macrophages and release drugs to alleviate fundus neovascularization. The two peptide amphiphiles were modularly designed with hydrophobic, enzyme-responsive, and hydrophilic motifs. The appropriate ratio of these components enabled the legumain trigged transformation. This was not a typical delivery system of nanomicelles, because it was transformed from nanoparticles to a fiber-like structure induced by legumain cleavage intracellularly after mannose receptor-mediated phagocytosis. This dynamic transformation not only strengthened lysosome escape and prevented exocytosis, but also enhanced drug accumulation and M2 macrophage apoptosis. After topical instillation, pathological neovascularization branches and cell nuclei that broke through the inner limiting membrane were reduced by 55% and 72%, respectively, 25% and 20% less than those in the non-transformed controls (Fig. 6).[56]

Shen *et al.* prepared a fluorocarbon-modified chitosan (FCS) for macromolecular ophthalmic drug delivery, which was able to self-assemble with therapeutic proteins *via* electronic interactions to form stable nanocomplexes. The delivery system showed effective ocular penetration ability by temporally opening the tight junctions in both cornea and conjunctiva tissue barriers. Furthermore, the fluorocarbon chains in FCS are nonhydrophilic and nonlipophilic by nature, which would probably make such nanocomplexes less "sticky", facilitating their intraocular penetration. In both choroidal melanoma-bearing mouse model and choroidal neovascularization-bearing mouse/rabbit models, FCS/anti-programmed cell death ligand 1 (PDL1) or FCS/anti-VEGFA eyedrops showed excellent therapeutic outcomes, comparable to those with intravenous or intravitreal injections.[57]

3.6 Nanoemulsions

Nanoemulsions are one of the most promising carriers applied topically onto the eye with a variety of properties, such as improved bioavailability, good *in vivo* biocompatibility, prolonged residence time, and enhanced corneal drug permeation.[74] Ge *et al.* prepared a penetratin-modified lutein nanoemulsion for the treatment of AMD. Lutein was loaded into the nanoemulsion to improve water solubility. Stearyl penetratin was added to the nanoemulsion to enhance penetration *via* a noninvasive administration route. In order to extend corneal retention duration and enable penetratin to reach its full effect, the penetratin nanoemulsion was prepared as an ion-responsive *in situ* gel. With the aid of penetratin, the nanoemulsion was rapidly delivered to the posterior segment of the eye and distributed in the retinal region. This system showed good efficacy in the protection of the retinal cells from damage caused by ROS and apoptosis in the dry AMD mouse model.[58] In addition, nanoemulsions can also be ideal nanocarriers when exploring the mechanism of small-molecule drugs. With the aim to deliver a hydrophobic small molecule, Ro5-3335, a runt-related transcription factor 1 (RUNX1) inhibitor, to the retina, Delgado-Tirado *et al.* designed a nanoemulsion delivery system utilizing surfactants as the encapsulation matrix within an aqueous phase. After topical instillation of this system, Ro5-3335 was detected to be 2.67 ng mL^{-1} within the vitreous cavity and effectively reduced the progression of proliferative vitreoretinopathy in the rabbit model.[59] Such a system was also effective in the treatment of both corneal and choroidal neovascularization in animal models.[60]

3.7 Dendrimers

Dendrimers are spherical, tree-like nanostructures consisting of one core and many side-chain molecules that branch out to form a three-dimensional structure.[75] With plenty of peripheral functional groups, dendrimers can receive surface modifications, which endow them with various properties for ocular drug delivery, such as enhanced permeation, and targeted delivery to specific sites.[76]

Recent studies on dendrimers for topical instillation and delivering the drug to the posterior segment of the eye mainly focused on enhancing their ability of penetration. As a powerful permeation enhancer in ophthalmic administration, modification of penetratin on dendrimers is an effective strategy.[77] Yang *et al.* designed a novel penetratin and cyclic arginine–glycine–aspartate (RGD) co-modified PEGylation polyamidoa-

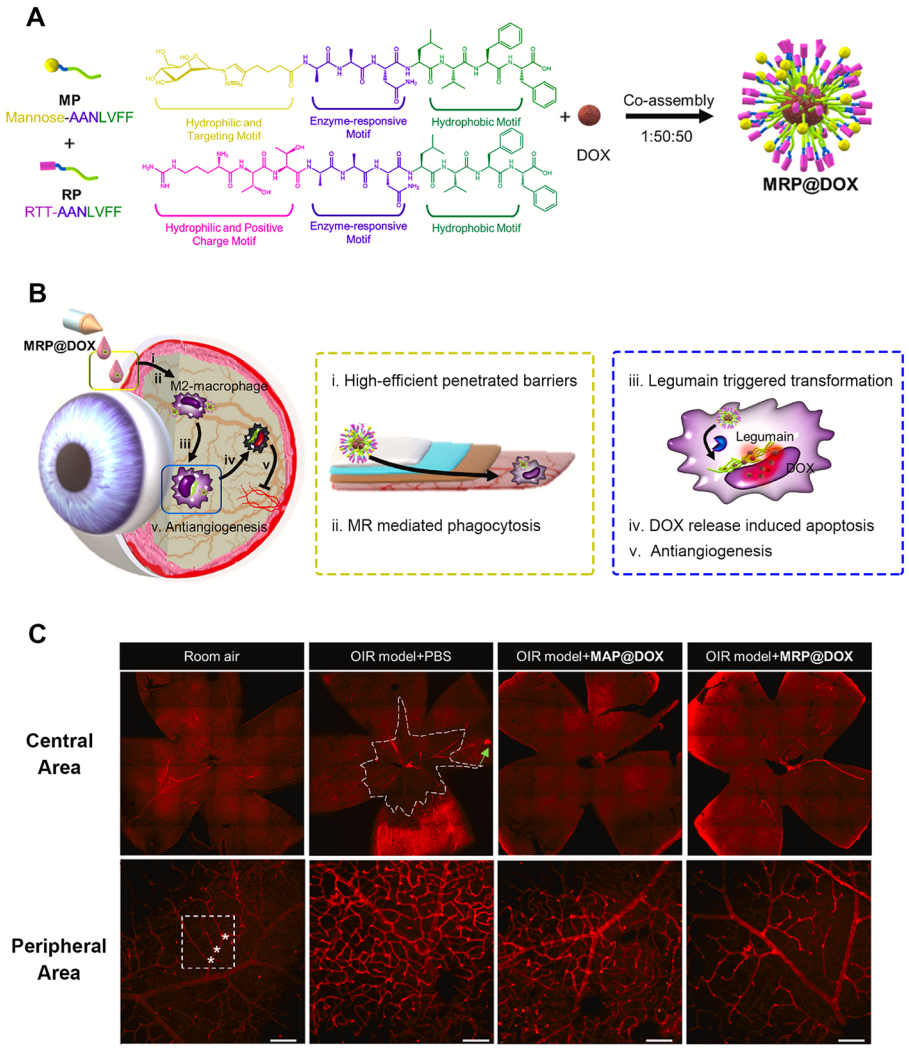

Fig. 6 The therapeutic effect of co-assembled glycopeptide nanotransforrs (GPNTs), MRP@DOX, on fundus neovascularization. (A) Construction of MRP@DOX, by the co-assembly of amphiphilic peptides of glycopeptide, cationic peptide, and doxorubicin. (B) Schematic illustration of topical delivery of MRP@DOX for the treatment of neovascularization in five steps: (i) penetration through the cornea and sclera barriers efficiently; (ii) mannose receptor (MR) targeting mediated phagocytosis into M2 macrophages; (iii) legumain triggered transformation instructed lysosome escape; (iv) DOX induced M2 macrophages apoptosis; (v) M2 macrophages elimination strengthened neovascularization. (C) Representative images of retinal flatmounts in the central area and enlarged view of peripheral neovascularization area treated by different agents. The white dashed line represented no perfusion area. The green arrow indicated the hemorrhagic point. The asterisk marked the branch site of the blood vessels in the unit area. Scale bar, 100 μm.[56] Copyright © 2021, Elsevier.

mine (PAMAM) G4.0 as a nanocarrier with a significantly improved permeability of 1.5 times and extended retinal retention time of more than 12 h, as compared to PAMAM without modifications. At the same time, the RGD peptide worked to enhance the affinity toward integrin αγβ3, which validated the targeting of neovascularization.[61] Penetratin also plays an important role in ocular gene delivery to the posterior segment of the eye. In the study of Tai *et al.*, a penetratin-modified PAMAM G5.0/HA complex was established to deliver ASOs to the retina *via* topical instillation. Compared with other nano-based drug delivery systems, this complex exhibited much more distribution in the retina and prolonged the retention time of ASOs in the retina for more than 8 h.[62]

The amino groups in PAMAM have mucoadhesive properties by interacting with the negatively charged cellular membrane, thus improving the therapeutic effects.[78] Lai *et al.* developed a liposome system coated with PAMAM G3.0 that simultaneously entrapped berberine hydrochloride (BBH) and chrysophanol (CHR) for topical instillation drug delivery to the retina. The PAMAM G3.0 coating could not only enhance bioadhesion on corneal epithelium but also allow greater permeability of negatively charged molecules than of positively charged molecules into the corneal layer due to diffusion through the sclera. After topical instillation, the accumulation of BBH and CHR was effectively promoted by the system, and a better therapeutic effect was achieved in reducing ROS levels and protecting against light-induced retinal damage.[63]

4. Future perspectives

Although topical drug delivery to the posterior segment of the eye is challenging, there remains an emerging number of nano-based drug delivery systems aiming at delivering drugs or nucleic acids to the retina *via* this non-invasive pathway. There is a leading trend in the design and development towards active targeting to increase drug concentration in specific sites, increased complexity in the synthesis with multiple functions that combine therapeutic and diagnostic capabilities and leverage the non-corneal pathway to facilitate drug delivery to the retina (Fig. 7).

A lot of novel nanocarriers are introduced to improve ocular permeability and bioavailability, but their distribution in ocular tissues, especially in the retina, after topical instillation still needs to be tested. The actively targeted therapies will be able to increase drug concentration in specific sites, such as RPE, photoreceptors, retinal or choroidal neovascular, thus further enhancing the bioavailability and efficacy with reduced toxicity to normal ocular tissues.[79] But the balance among rates of drug release, absorption, and selective target binding that encourage sufficient and uniform drug distribution throughout the retinal lesions remains a challenge in the design and development.

Simple functional nano-based delivery systems can no longer meet the current need for ocular drug delivery. The trend has moved toward complex and multi-component materials that blur the boundaries in traditional categories, even though the increased complexity may add to the difficulties and costs for the sake of large-scale production for clinical translation in the future. Not only is the design more complicated in the synthesis but delivery systems are also made to be multifunctional that combine diagnostic and therapeutic functions, enabling visual tracking during the ocular disease treatment.[80–82] These delivery systems are still in preclinical trials and not yet in clinical trials.

The conjunctival–scleral pathway, a type of noncorneal pathway, is in principle the one followed by topical instillation to reach the retina, though this pathway is still under investigation and debate regarding the potential for therapeutic concertation. The surface area of the conjunctiva is 17 times larger than that of the cornea. In addition, the conjunctiva showed superior permeability to drugs compared to the cornea.[83] Hydrophilic and small-sized formulations or molecules can diffuse across the conjunctiva and sclera from the ocular surface into the eye without entering the aqueous humor. Given that the openings in the conjunctival epithelium are larger than those in the cornea, it is possible that large-molecule drugs can also penetrate *via* this route.[84] Cell-penetrating peptides are common examples of modifications to nanocarriers to improve drug delivery to the retina from the ocular surface. These peptides often make *in vivo* uptake into the retina easier *via* the conjunctival–scleral pathway.[85]

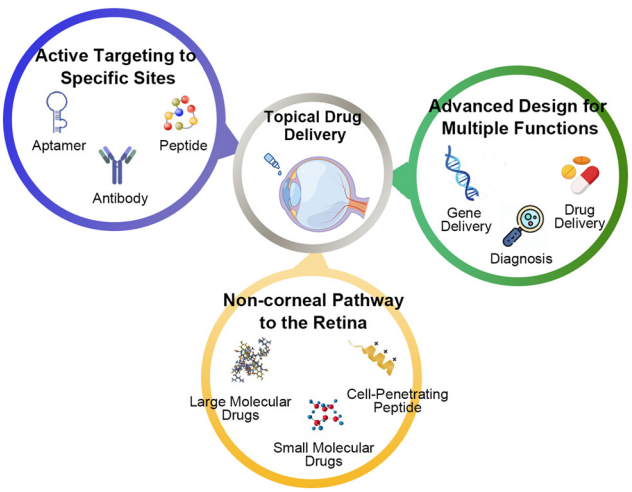

Fig. 7 Summary of future perspectives on topical drug delivery. Increasing attention has been paid to these three aspects aiming at delivering drugs or nucleic acids to the retina through this non-invasive pathway.

5. Conclusions

The involvement of nanomedicine in ocular diseases has brought numerous advancements over conventional treatments. Topical instillation, as a noninvasive way, is an optimal option for many ocular diseases due to its potential for eliminating the risks of intravitreal injection and the toxicity of systemic drug delivery. Although the delivery of drugs safely and efficiently into lesions in the posterior segment of the eye topically is a challenging task, relentless efforts have been dedicated to the development of novel nano-based delivery systems in the hope of possible clinical translation from bench to bedside. With ongoing innovations in this field, safe and effective eye drops are expected to revolutionize the present invasive treatment in the foreseeable future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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