

# Ten Years of Knowledge of Nano-Carrier Based Drug Delivery Systems in Ophthalmology: Current Evidence, Challenges, and Future Prospective

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**Abstract:** The complex drug delivery barrier in the eye reduces the bioavailability of many drugs, resulting in poor therapeutic effects. It is necessary to investigate new drugs through appropriate delivery routes and vehicles. Nanotechnology has utilized various nano-carriers to develop potential ocular drug delivery techniques that interact with the ocular mucosa, prolong the retention time of drugs in the eye, and increase permeability. Additionally, nano-carriers such as liposomes, nanoparticles, nano-suspensions, nano-micelles, and nano-emulsions have grown in popularity as an effective theranostic application to combat different microbial superbugs. In this review, we summarize the nano-carrier based drug delivery system developments over the last decade, particularly review the biology, methodology, approaches, and clinical applications of nano-carrier based drug delivery system in the field of ocular therapeutics. Furthermore, this review addresses upcoming challenges, and provides an outlook on potential future trends of nano-carrier-based drug delivery approaches in ophthalmology, and hopes to eventually provide successful applications for treating ocular diseases.

**Keywords:** nano-carrier, nanomedicine, ocular disease, drug delivery system

## Key Summary Points

- This review offers a comprehensive overview of nano-medicine-based treatments for ocular disorders in the last decade.
- Nanotechnology-based drug delivery systems will probably be used by ophthalmologists in the near future, allowing benefits such as reduced side effects, and less frequent dosing, among others.
- Active targeting ligands related to nano-medicine in ocular therapeutics have yet to be addressed to test their effects and safety.
- Further nanomedicine clinical trials for ocular disorders are needed until this promising pharmacological innovation becomes available in the ophthalmologist's daily therapeutic practice.

## Introduction

The eye is one of the most sensitive organs and consists of several barriers and defense mechanisms to protect it from the environment. For example, it is challenging to deliver drugs to different compartments of the eye and treat ocular disorders due to this specific anatomy, such as the blood-aqueous barrier (BAB) and blood

retinal barrier (BRB). Additionally, the bioavailability of drugs after ocular administration may be less than 5%, which is often insufficient.<sup>1</sup> At present, commonly used drug dosage forms to treat eye diseases include eye drops, eye ointments, and eye gels. Due to the numerous ocular barriers, including the tear film barrier, the corneal barrier, the conjunctival barrier, the scleral barrier, as well as the BAB and BRB, challenges, such as delivery of drugs to less accessible parts of the eye, are often encountered.<sup>2–4</sup> Therefore, innovating ocular particulate drug delivery systems (DDSs) with sustained release effects or increasing permeability have become a recent research hotspot. These particulate DDSs mainly include liposomes, emulsions, micelles, dendrimers, and microspheres.<sup>5–8</sup> The conventional administration route for an ocular DDS mainly includes the ocular surface and the intraocular (such as intravitreal and suprachoroidal space) and periorbital tissues. Due to the different barrier effects of each part of the eye, the factors affecting the administration of each route are not the same. The design of a novel ocular DDS has become a central issue to achieve efficient delivery of drugs to different parts of the eye. In the past, nanomedicine was mainly concentrated in the treatment of ocular surface diseases and glaucoma. However, in the last 10 years, nanomedicine has rapidly developed in ophthalmology to include fundus lesions and ocular tumors. Loading the drug into an ocular nano-level DDS enhances its solubility, stability, and permeability, while extending residence time, thereby enhancing drug efficacy.<sup>9</sup>

To provide an overview of recent advancements in ocular nanomedicine, we herein review the current evidence of various nano-micro matrices based on several conventional materials (eg, liposomes, nanoparticles, nano-suspensions, nano-micelles, and nano-emulsions) for ophthalmological applications reported over the last decade (2011–2020). Notably, recent advances in nano-carrier DDSs as well as their effects in the treatment of various ophthalmic diseases are comprehensively introduced. Finally, current challenges and future directions and perspectives about nano-carrier-based DDS applications for ocular therapeutics are further discussed.

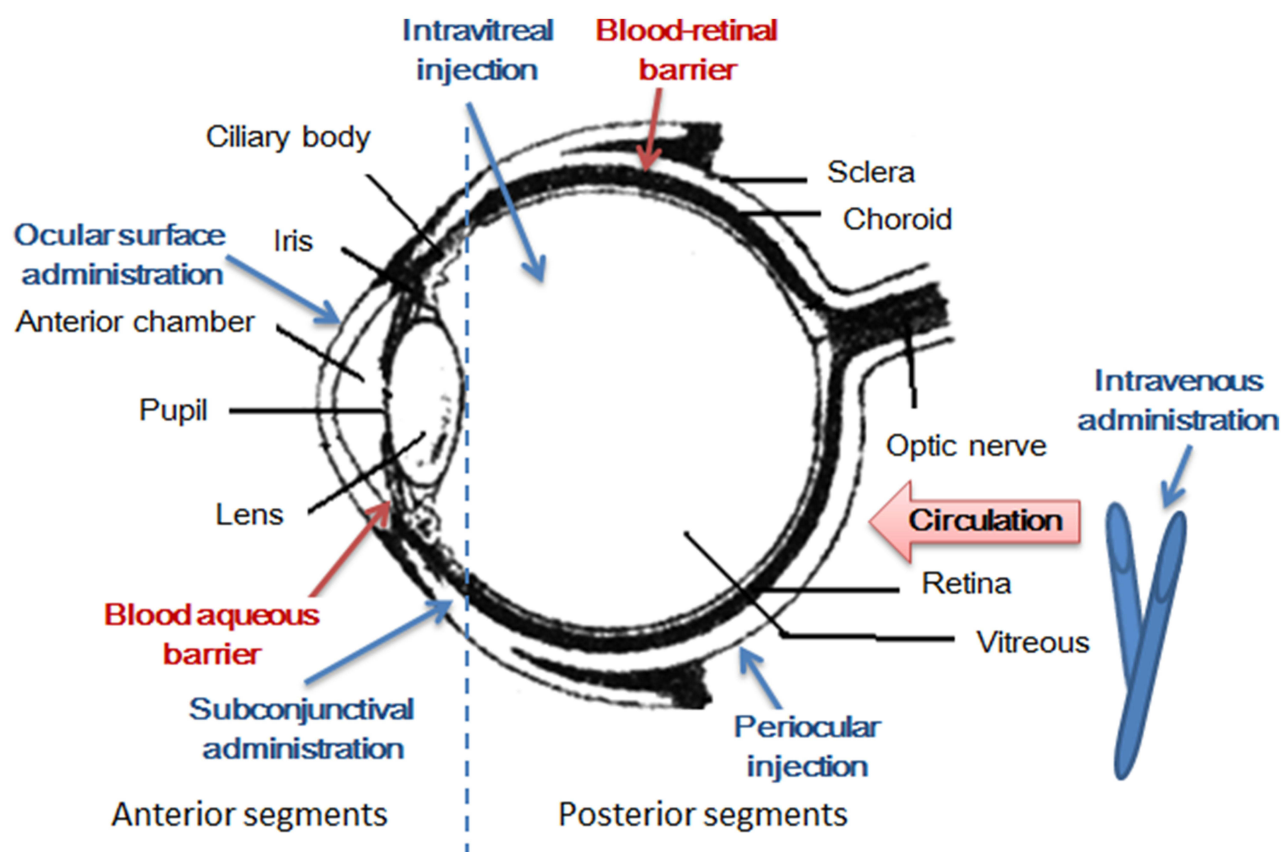
## Structure of the Eyeball for Drug Delivery

The diameter of the adult eyeball is about 24 mm, which is composed of the ocular wall and the contents of the eyeball.<sup>10</sup> The anterior segment of the eyeball mainly consists of the

cornea, conjunctiva, iris, ciliary body, sclera, aqueous humor, and the lens, while the posterior segment mainly includes the vitreous body, retina, choroid, and sclera.<sup>11</sup> The eyeball has a unique anatomical structure called the blood-eye barrier, which makes it difficult to achieve an effective drug concentration.<sup>12,13</sup> Due to the lipophilic surface layer of the cornea and the hydrophilic nature of the inner layer, ointments do not have characteristics of being both fat-soluble and water-soluble, which makes it difficult to achieve an effective intraocular concentration after applying topical medications.<sup>14</sup> The effective intraocular drug concentration is the key to the treatment of many ocular disorders. Therefore, changing the administration route and dosage form of ophthalmic drugs is an important measure to increase the intraocular drug concentration.

## Traditional Delivery of Ocular Drugs

The traditional administration methods for treating eye diseases include local administration or systemic administration (Figure 1). Local administration includes periocular (subconjunctival, subtenon, posterior juxtasclear, retrobulbar, and peribulbar) and intravitreal injections. However, these drug delivery routes are limited. Local administration on the ocular surface (cornea, conjunctiva, sclera, and anterior uvea) is usually adopted in the clinic to treat ocular diseases. Generally, eye drops are quickly discharged from the surface of the eye. In addition, due to technological advancements and drug development, such as antiangiogenic drug (bevacizumab, ranibizumab, aflibercept, and conbercept) therapy and glucocorticoids, intravitreal injections are used for retinal and vitreous diseases.<sup>15,16</sup> This local administration route also has many challenges, such as poor patient compliance and potential adverse effects (eg, endophthalmitis, cataracts, or retinal detachment). Only 1% to 2% of systemically administered drugs reach the target tissue due to the effects of the BAB and the BRB.<sup>17</sup> In addition, large doses and frequent systemic administration can cause adverse effects.<sup>18</sup> Recent studies have shown that nano-carriers are useful to deliver hydrophilic or lipophilic drugs to the eye, prolong the half-life of drugs in the vitreous, and improve the bioavailability of many drugs, including proteins and peptides.<sup>19,20</sup> Interestingly, applications of polymeric nano-micelles have been tested for intraocular and surface ocular disease treatment.<sup>21</sup> Furthermore, nanotechnology protects the drug from degradation both in the *in vivo* circulation and under storage conditions. Consequently, a new ophthalmic DDS with sustained release, strong penetration, and long duration in the eye is needed.



**Figure 1** Structural particularities of the eye. The eye can be divided into two parts of the anterior segment and the posterior segment. There are many barriers to drug delivery to the retina. Drugs cannot be easily delivered to the retina by topical administration, such as eye drops, because of the presence of tear drainage and peribulbar and choroidal blood flow. In contrast, systemically administered drugs rarely enter the retina because of the presence of the blood - aqueous barrier and the inner and outer blood-retinal barriers.

## Ocular Nano-Drug Delivery System Advantages of Nano-Drugs and DDS

A DDS with nanoscale spatial resolution plays a key role in making ocular tissue an attractive pharmacological target for therapies against disorders. Three different advantages of utilizing DDS include: (1) Promoting absorption: promote the passage of the drug through tissues acting as a barrier; (2) Controlled release: local administration effectively controls timed- and sustained release; (3) Targeted drugs: use drugs that are effective and act specifically on the target tissues.<sup>22,23</sup> The development of DDS nanotechnology has made it possible to overcome eye-related obstacles.

Many promising vehicles are available for ocular DDS, such as nanoemulsions, liposomes, nanomicelles, nanosuspensions, and polymeric and lipid nanoparticles.<sup>24</sup> Nano-carriers for eye DDSs have the following advantages: (1) A nano-material carrier can enter the capillaries through the blood circulation, and penetrate the endothelial cell gap, enter the lesion, and be absorbed by pinocytosis to

improve bioavailability of the material. (2) Nano-carrier particles are small with a high specific surface area, which can embed hydrophobic substances, improve solubility, and reduce the side effects of conventional solvents. (3) A nano-material carrier can be modified by the targeting group to realize targeted drug delivery, which can reduce the dosage and side effects, such as folic acid-modified nanoparticles and magnetic nanoparticles.<sup>25</sup> (4) Nano-carriers prolong the elimination half-life ( $t_{1/2\beta}$ ) of a substance, increase effective blood concentration time, increase efficiency, reduce frequency of use, and reduce toxic and side effects. (5) Nanocarriers pass through the barriers of the body that limit the effects of substances, such as the blood-brain barrier, the blood-eye barrier (BAB and BRB) and the cell biomembrane barrier, so substances reach the lesion. (6) Nanocarriers improve the interactions between drugs and the cornea and conjunctival epithelium, which improve the efficiency of delivery and bioavailability of drugs.<sup>24,26-28</sup>

## Common Nano-Carriers for Ocular Drug Delivery

The nano-carrier DDS has become a hotspot in the field of ophthalmic preparation research. Ophthalmic nano-carrier DDSs mainly include liposomes, nanoparticles, nano-suspensions, nano-micelles, and nano-emulsions. Based on the special molecular structure and biological characteristics, the ophthalmic preparations of DDSs have advantages of sustained and controlled drug release as well as targeting and are advantageous for carrying ophthalmic sustained release systems.

### Liposomes

A liposome is a double-layered membrane structure formed spontaneously during the water phase by phospholipid molecules under hydrophobic forces.<sup>29,30</sup> The amphiphilic characteristics make it possible to load fat-soluble drugs between the double-layered membranes and to wrap water-soluble drugs in the center. Liposomes are highly biocompatible and degradable, reduce drug toxicity, and realize sustained drug release. In addition, liposomes interact with cells, including adsorption on the cell surface, fusion with cell membranes, exchange of phospholipid components with cell membranes, and endocytosis.<sup>30-33</sup> Based on these characteristics, the potential of liposomes as drug delivery vehicles has been under development for the past 10 years.

Liposome is an ideal DDS in the field of ophthalmology because their structure is like a cell membrane that encapsulates hydrophilic and hydrophobic drugs. The efficiency of liposomes in the eye is related to their biocompatibility, size, charge, stability, residence time, the encapsulation rate, and distribution of the drug.<sup>22,34,35</sup>

In 1981, Smolin et al first reported the use of liposomes as ophthalmic drug carriers. They demonstrated that liposomes coated with iodides are more effective than ordinary eye drops for treating rabbit herpes simplex virus keratitis.<sup>36</sup> In 1988, Simmons et al injected 5 mg of fluorouracil (5-FU) liposomes under the conjunctiva of rabbits to prevent scarring of the filtering mouth fibers after filtration in cases of glaucoma. It is believed that this improves the success rate of surgery and more secure.<sup>35</sup> Studies have revealed that the clearance rates of liposomes in eyes with aphakia and those that underwent vitrectomy are faster, which is believed to be related to the increase in intraocular convection and molecular movement after vitrectomy. Experiments have also confirmed that the clearance rate of liposomes is inversely proportional to the size of the liposome.<sup>37</sup> Larger liposomes have been speculated to be more stable Barza et al designed

a set of experiments to study the effect of liposome size and lipid composition on pharmacokinetics.<sup>38</sup> Arroyo et al reported that a conventional liposome formulation has the same effects on reducing intraocular pressure (IOP) compared to eye drops, and the effective time was significantly longer using a concentration 10-fold lower.<sup>39</sup> In addition, local delivery of liposomes improves the bioavailability of drugs to posterior eye tissues (such as the retina).<sup>40</sup>

Zhang et al investigated the efficacy of an intravitreal injection of liposomes encapsulating infliximab in rats with experimental autoimmune uveoretinitis (EAU) and reported that liposomes prolong the persistence of the drug in the vitreous body and demonstrated a satisfactory safety and significant therapeutic potential in EAU.<sup>41</sup> Additionally, Tan et al showed that the permeability and bioavailability of chitosan-modified liposomes were 2 and 3.9 times higher than those of unmodified liposomes containing a timolol maleate solution alone (1.71 times). Moreover, chitosan-modified liposomes continuously release drug in the eye tissues for 4 hours and unmodified liposomes release drug for 2 hours, which has a better effect on reducing IOP.<sup>42</sup> The use of biodegradable particles for therapeutic antibody delivery provides a promising approach for treating ocular diseases.

### Nanoparticles

Nanoparticles are formed by self-assembly of natural degradable phospholipids in the water phase and have bi-continuous micro-structural characteristics.<sup>43</sup> Cubic liquid crystal nanoparticles have advantages for lipid soluble and amphiphilic drug loading compared with liposomes due to the size of the bilayer region. Therefore, good bioadhesion is another outstanding advantage of cubic liquid crystal nanoparticles.<sup>44</sup> Furthermore, the common phospholipid used in calcium carbonate liquid crystal nanoparticles is glycerol monooleate.

Nanoparticles have attracted the most attention as a delivery system to locally treat ocular diseases. The distribution of nanoparticles in the eye mainly depends on their size and surface properties. Nanoparticles of 200 to 2000 nm remain in the eye tissue for at least 2 months.<sup>45</sup> Nanoparticles adhere to the mucosa and remain in the anterior corneal tissue for a long time without rapid removal. Drugs can be encapsulated, conjugated, or adsorbed in nanoparticles. Biodegradable polymers, such as alginate, chitosan, gelatin, polycaprolactone, polylactic acid or poly lactic co-glycolic acid (PLGA), are the most widely used polymers for preparing nanoparticles.<sup>46,47</sup> Varshochianand et al<sup>48</sup> used albumin PLGA nanoparticles

containing bevacizumab to treat ocular angiogenesis. The nanoparticles were prepared using the double emulsion method and injected into the rabbit vitreous body in a single dose. The results showed that the concentration of bevacizumab was more than 500 g/L and was extended for about 8 weeks. Mahaling et al<sup>49</sup> prepared a core-shell nanoparticle system to deliver triamcinolone acetonide non-invasively to the retina using a slowly degrading polycaprolactone core. They reported that the drug-loaded nanoparticles significantly improved both structural and functional activities of the retina. Furthermore, expression of retinal inflammatory biomarkers, such as nuclear factor- $\kappa$ B, intercellular adhesion molecule-1 (ICAM-1), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were reduced by the intervention. Wang et al<sup>50</sup> developed biodegradable nanoparticles loaded with dexamethasone sodium phosphate (DSP) using zinc ion bridging (DSP-Zn-NP) with dense coatings of poly (ethylene glycol) (PEG). As results, the nanoparticles were safe after subconjunctival administration in rats and provided continuous DSP administration. A single subconjunctival administration inhibited corneal angiogenesis in rats within 2 weeks. These results suggest that subconjunctival administration of DSP-Zn-NP could be an effective strategy for preventing and treating corneal neovascularization (CNV).

### Nanosuspensions

Unlike traditional matrix-framework nanosystems, nanosuspensions do not require carrier materials. A nanosuspension is a versatile formulation combining conventional and innovative features. It comprises 100% pure drug nanoparticles with sizes in the nano-scale range, generally stabilized by surfactants or polymers. After the drug is prepared in a nanosuspension, reducing the particle size increases the contact area and residence time of the drug with the cornea, and increasing the concentration of the drug in the infected tissue and the solubility of a poorly soluble drug improve bioavailability.<sup>45</sup> Luschmann et al prepared a cyclosporine (CsA) nanosuspension and micellar formulations and evaluated their tolerance and drug release in corneal tissue using the rabbit eye model.<sup>51</sup> The results showed that the drug concentrations in the corneal tissues of the rabbits in the nanosuspension and micelle groups were much higher than that in the commercially available Restasis<sup>®</sup> group. After topical administration of a hydrocortisone nanosuspension prepared by Ali et al, the hydrocortisone nanosuspension had a larger area under the curve (AUC) and a retention time of 9-hours in the local eye tissue, while the drug solution alone

only maintained a 5-hour retention time.<sup>52</sup> Similarly, other studies have suggested that nanosuspensions successfully deliver other drugs, such as pranoprofen,<sup>53</sup> triamcinolone acetonide,<sup>54</sup> and moxifloxacin,<sup>55</sup> to eye tissues.

### Nanomicelles

Nanomicelles are nanostructures formed spontaneously in an aqueous environment by block copolymers with amphiphilic properties.<sup>56</sup> The lipophilic portion is composed of the micelle core that encapsulates the hydrophobic drug, while the hydrophilic part is composed of the outer surface of the micelle to increase drug solubility.

Nanomicelle carriers formed by self-assembly of block polymers containing hydrophilic and hydrophobic segments have attracted increasing attention as non-invasive ophthalmic DDSs. The amphiphilic nature of nanomicelles makes it easy for them to penetrate lipophilic corneal epithelial and endothelial cells, and they can also penetrate a hydrophilic matrix, which overcomes the solubility problems of poorly soluble drugs, promotes drug penetration, and improves bioavailability. In addition, nanomicelles are small in size and are easily taken up by corneal cells.<sup>57</sup> Polymeric micelles have been demonstrated to improve the bioavailability of drugs in anterior eye tissues, help spread the drug in the sclera, and produce a sustained drug delivery effect of ophthalmic applications.<sup>58</sup> Wu et al reported that an intravitreal injection of labeled methoxy polyethylene glycol-block-polycaprolactone (mPEG-PCL) micelles loaded with rapamycin exists in retinal pigment epithelial cells for at least 14 days, which significantly prolongs the retention time of the drug in the retina.<sup>59</sup> The micelle system had a better therapeutic effect on autoimmune uveitis in rats compared with the rapamycin suspension system alone. Cholkar et al prepared cyclosporine-loaded nanomicelles and studied the tissue distribution of CsA in rabbit eyes.<sup>60</sup> The CsA concentration in the anterior eye tissue was highest after local instillation, but a higher level of CsA (53.7 ng/g) was detected in the retina, suggesting that nano-micelles have the potential to deliver drugs to eye tissues.

### Microemulsions/Nanoemulsions

Other nanotechnology-based carriers, particularly nanoemulsion (NEs) and microemulsions (MEs) have various applications in drug delivery research.<sup>61</sup> Furthermore, they are potential drug solubilizers that enhance penetration through their high surfactant/co-surfactant contents.<sup>62</sup> NEs are highly stable, with low toxicity and irritation,

large drug loading capacity, and greatly improved drug bioavailability. NEs are some of the most researched and applied nano-carriers DDSs in the field of ocular local drug delivery. After local administration to the eye, NEs are mainly absorbed through the cornea.<sup>63,64</sup> Furthermore, the emulsion is composed of an oil phase, a water phase, an emulsifier, and a co-emulsion. The emulsion prolongs contact time between the drug and corneal epithelial cells, promotes absorption of the drug by the cornea, sclera or conjunctiva, and improves adhesion of the emulsion.<sup>65</sup> Although NEs have many physical, chemical, and physiological advantages, their absorption and distribution are affected by the structure of the corneal layers.

Kalam et al confirmed that optimized MEs possess good stability, show greater adherence to the corneal surface, and diffuse gatifloxacin into the anterior chamber of the eye, resulting in a two-fold increase in gatifloxacin concentration than the conventional dosage form.<sup>66</sup> Subsequently, Kesavan et al<sup>67</sup> evaluated the mucoadhesive chitosan-coated cationic microemulsions (CH-MEs) to deliver dexamethasone to treat uveitis in vitro and in vivo. The inhibitory rate of CH-MEs on inflammatory cells was 93.4%, and the protein content was reduced to 6.46 g/l, which was better than dexamethasone alone (the inhibitory rate of inflammatory cells was 62.14%, and protein content was 16.15 g/l), indicating that a chitosan-coated dexamethasone emulsion has good mucosal adhesion and slow-release characteristics. In addition, this emulsion interacts with the lipid layer of the tear film, and is retained in the conjunctival sac for a longer time, where it acts as a drug reservoir.

### In situ Gelling Drug Delivery Systems and Others

In situ gelling drug delivery systems have gained enormous attention in the area of ophthalmology over the last decade. In situ gelling drug delivery systems are in a sol-state before administration, and capable of forming gels in response to different endogenous stimuli.<sup>68</sup> Such systems can be administered through different routes, to achieve ocular drug delivery and can also be successfully used as vehicles for drug-loaded nano- and micro-particles to treat ocular diseases.<sup>69</sup> Other nano-preparations, such as liposomes and nanoparticles have been combined to prepare composite systems to further extend the retention time of drugs on the ocular surface and improve their bioavailability.<sup>70</sup> Quality control of the nanocomposite gel system is comprehensive. It is necessary to consider the quality of the entire system, including stability of the gel and the gelling

performance of the in-situ gel at the macro level. Notably, the nano-gel composite system uses many auxiliary materials, and safety should be the focus. The eye irritation test for dorzolamide ME gel composite formulations shows that the it is non-irritating utilizing the Draize technique, but that study did not compare MEs and the gel matrix.<sup>71</sup> It is recommended to set up a comparison between a single formulation and the corresponding matrix for a safety evaluation of a composite system, which provides a reference for designing new composite formulations.

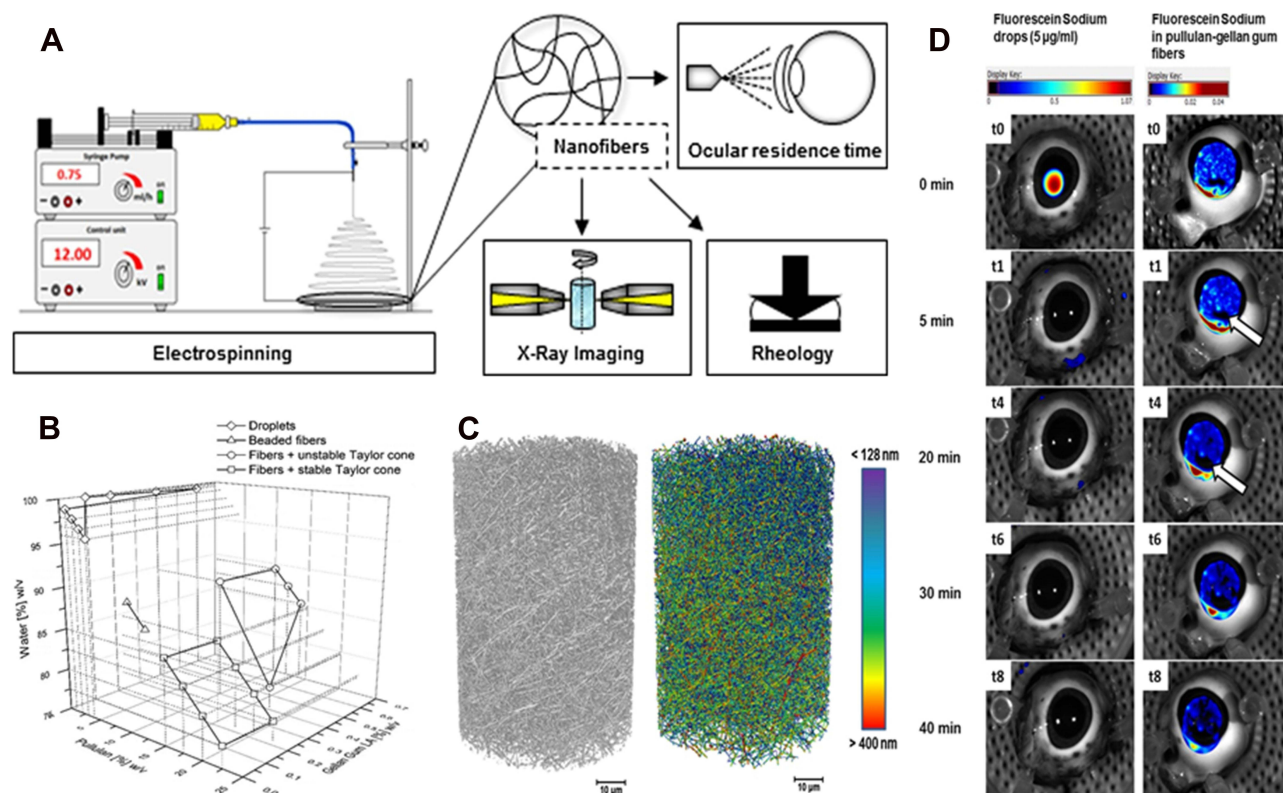
Göttel et al developed a new solid in-situ gelling system for topical ocular therapeutics (Figure 2).<sup>72</sup> Electrospinning an amylopectin-gellan gum solution produces nanofibers with high porosity and a narrow size distribution. Nano-computed tomography (CT) imaging produces a non-invasive and detailed 3D visualization of the internal structure of nanofibers.<sup>73</sup> Rheological experiments showed that gelation behavior continued to occur after spinning. Researchers improved the application of fiber optic lenses in the eye using a 3D printed matrix to produce bending. This system can be easily processed and applied. A new 3D printing model has been developed to determine the residence time in in vitro pig eyes.<sup>74</sup> As results, rapid dissolution and uniform distribution were observed on the porcine cornea with extended eye residence time. In the future, this new solid in-situ gelation system might be an attractive alternative to existing ophthalmic DDSs.

## Nano-Drug Preparations and Therapeutic Effects for Different Eye Diseases

Many studies have focused on evaluating the preliminary therapeutic effects of drug loaded nanoformulations in ocular therapeutics in vitro and in vivo. Few drug loaded nanoformulations have been used in clinical research, possibly because it remains challenging to reach the internal structure of the eye through local infusion, and there are still some problems in nano preparation, such as poor stability, difficulties with sterilization, low drug loading, and high costs. Due to the strong irritation of excipients and incomplete drug release, the research progress on nano-level eye drops is still relatively slow. In the following sections, we describe the application of nano drug delivery systems in different types of ocular disorders.

## Conjunctivitis

The most common ocular surface disease is conjunctivitis, which is a common cause of eye redness and is common in



**Figure 2** Electrospun nanofibers - A promising solid in-situ gel. **(A)** The diagram of study on electrospun nanofibers; **(B)** 3D diagram of the spinning solution composition and the product characteristics; **(C)** 3D X-ray images of the electrospun nanofibers: (black) grayscale and (color) fiber size distribution image with scale bar; **(D)** overlay of regular (photo) and fluorescence images of porcine eyes treated with fluorescein sodium eye drops (5 μg/mL) (left), and with pullulan-gellan gum nanofiber lens (0.0001% fluorescein sodium) (right) after different spray applications. Reprinted from *Eur J Pharm Biopharm*, 146, Göttel B. Electrospun nanofibers - A promising solid in-situ gelling alternative for ocular drug delivery, 125–132, Copyright 2020, with permission from Elsevier.<sup>72</sup>

emergency rooms, as well as emergency care and primary clinics. It can affect people of any age and demographic or socioeconomic status. According to pathogenic examination, the disease is divided into bacterial, viral, fungal, parasitic, allergic, and chlamydial conjunctivitis.<sup>75</sup> The main symptoms of conjunctivitis include red itchy eyes, palpebral edema, excessive tearing, along with a yellowish mucous discharge. It is usually self-limiting and rarely causes loss of vision, but it often requires treatment to relieve symptoms and shorten the disease course.<sup>76</sup> The treatment recommendations for conjunctivitis include pharmacological therapy targeting causes, such as antibiotics,<sup>77</sup> antivirals<sup>78</sup> and antifungals<sup>79</sup> and anti-allergy medications.<sup>80</sup> The common route of administration for ocular diseases is local administration on the ocular surface, of which, eye drops, ointments, and gels are the main dosage forms. However, because the conjunctival sac holds less fluid and affects eye blink behavior as well as orbicularis oculi muscle activity, the drug only stays on the ocular surface for a short time, which

ultimately leads to a short time of the effective therapeutic concentration on the ocular surface.<sup>81</sup> Interestingly, nanotechnology opens a new avenue for treating ocular diseases, particularly ocular surface disorders. Nano-carrier DDSs have the potential to reduce drug degradation, increase permeability and bioavailability, and prolong retention time by tailoring the release profile, thereby achieving sustained drug release and targeted therapeutic concentrations, which have been shown in in-vitro or animal studies.<sup>24</sup>

The main advantage of adding anti-infective/anti-inflammatory drugs to a nano-carrier is to extend the residence time of the drug and improve bioavailability of the drug in the eye. Many studies have been performed on anti-allergy drugs loaded with nano-carrier DDSs for allergic conjunctivitis treatments (Table 1). Allergic conjunctivitis has immune-pathophysiology, in which, topical non-steroidal anti-inflammatory drugs (NSAIDs) and immune modulators are conventional treatment.<sup>24</sup> For example, the NSAID flurbiprofen has low penetration across the cornea

and produces ocular irritation. Deformable chitosan-coated flurbiprofen-loaded liposomes were proposed and these flexible liposomes easily move across the pores which are too small for conventional liposomes to pass, as their bilayers are highly curved.<sup>82</sup> Another NSAID, dexibuprofen, loaded onto biodegradable polymeric PLGA nanoparticles constitutes a suitable alternative to topical eye administration. These nanoparticles improve ocular bioavailability and simultaneously reduce drug-induced side effects.<sup>83</sup> Tacrolimus is a common immune modulator that has been loaded onto PLGA nanoparticle and proglycosomes to provide continuous sustained drug release without side effects (Figure 3).<sup>84,85</sup>

## Keratitis

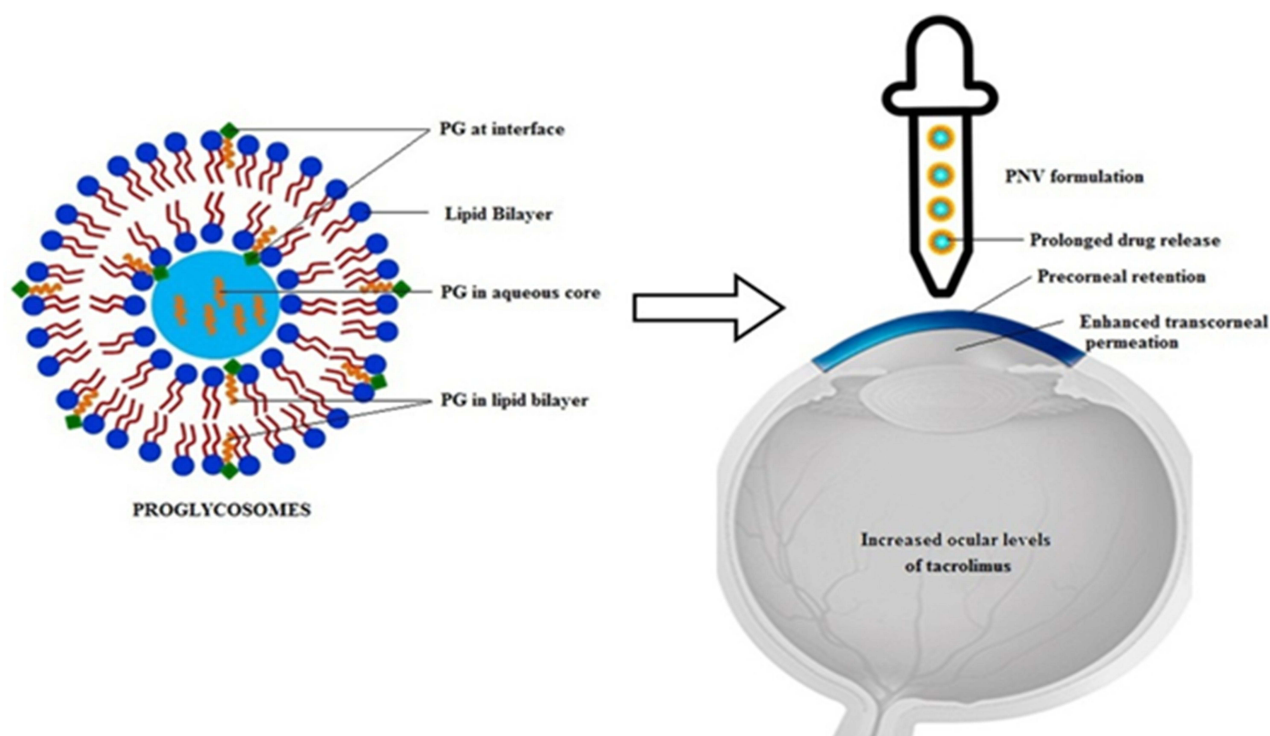
Keratitis is characterized by corneal edema, infiltration of inflammatory cells, and ciliary congestion and has symptoms, such as eye red, decreased vision, photophobia, difficulty opening the eyelids upon awakening, and excessive tearing.<sup>86</sup> Keratitis is classified as infectious or non-infectious based on the etiological agent. The infectious type is subdivided into bacterial, protozoal (*Acanthamoeba*), pythium, fungal, viral, and onchocercal keratitis. Topical chloramphenicol is one of most commonly used drugs against all bacterial isolates, but it has some disadvantages, such as low solubility and short residence time in the conjunctival sac.

**Table I** Nanocarriers to Deliver Anti-Conjunctivitis Agents

Study	Drug	Vehicle/Carriers	Production Method(s)	Results	Conclusion
E. Sanchez-Lopez, et al <sup>159</sup> 2020	Dexibuprofen	PLGA* nanoparticles	Solvent displacement method	Polyethylene glycol (PEG) increased the interaction between Dexibuprofen-NPs and customized corneal membrane.	These formulations containing DXI PLGA 15% PEG prepared using Lutrol as a surfactant were able to release DXI more effectively for the treatment of ocular inflammation.
X. Gai, et al <sup>160</sup> 2018	Ibuprofen	Liposomal	Ethanol injection method	Ibuprofen cationic liposomes could significantly prolong the T max to 100 min and the AUC to 1.53-folds, which indicated that the ibuprofen cationic liposomes could improve the precorneal retention time and bioavailability of ibuprofen.	The ibuprofen cationic liposomes probably are a promising application in ocular drug delivery system.
Y. Xu, et al <sup>84</sup> 2017	Tacrolimus	PLGA nanoparticles	Emulsification-diffusion method	PLGA-NPs improved corneal, conjunctival and aqueous humor bioavailability of Tacrolimus.	The PLGA-NPs significantly enhanced ocular bioavailability of TAC than that of aqueous suspension.
V. Garg, et al <sup>85</sup> 2017	Tacrolimus	Proglycosomes	Film hydration method	Incorporation of proglycosomes enhanced the drug encapsulation, decreased the vesicle aggregation and increased the liposomal elasticity, thereby enhancing the transocular permeation.	The developed proglycosomes are prospective carriers for enhanced ocular delivery of tacrolimus.
H. Chen, et al <sup>82</sup> 2016	Flurbiprofen	Chitosan-coated liposomal	Modified ethanol injection method	Flurbiprofen-loaded deformable liposomes could prolong pre-corneal retention and improve transcorneal penetration. Edge activator, Solutol HS-15, could potentiate its flexibility and penetrability.	Chitosan-coated deformable liposomes appear to be a novel ophthalmic drug delivery system with the potential to overcome the limitations of conventional eye drops.

**Abbreviation:** \*PLGA, poly (lactic-co-glycolic acid).





**Figure 3** Tacrolimus is a common immune modulator that has been loaded onto Poly(lactic-co-glycolic acid) nanoparticle. Hypothetical representation of the location of propylene glycol in the vesicles and its effects as a novel drug delivery system for tacrolimus. Reprinted from *Colloids Surf B Biointerfaces*, 157, Garg V, Suri R, Jain GK, Kohli K. Proglycosomes: a novel nano-vesicle for ocular delivery of tacrolimus, 40–47, Copyright 2017, with permission from Elsevier.<sup>85</sup>

**Abbreviation:** PNVs, Proglycosomes nano-vesicles.

In order to solve these problems, Xu et al prepared chloramphenicol-containing cyclodextrin eye drops containing chloramphenicol to treat acute bacterial keratitis. Furthermore, the drug concentration in the aqueous humor using CHL/SBE- $\beta$ -CD eye drops was higher than that of commercial chloramphenicol eye drops, and the average ocular surface stay time was 1.9 times longer.<sup>84</sup> Zorzi et al developed PEGylated polymeric vesicles encapsulating small interfering RNA (siRNA) sequences to treat keratitis caused by *Acanthamoeba*. The combined therapy of siRNA-loaded polymeric vesicles with chlorhexidine led to a 60% reduction in corneal damage caused by *Acanthamoeba* in a 2 month-old Wistar rat model.<sup>87</sup> Further studies should be performed to confirm the effectiveness of this treatment.

## Dry Eye Disease

Dry eye disease (DED) is one of the most common ocular surface disorders characterized by a deficiency of tear production or excessive tear evaporation. The common symptoms of DED include a dry, foreign body sensation, burning, itching, photophobia, congestion, pain, blurred

vision, fatigue, and a sticky silk secretion. Treatments for DED aim to improve these clinical symptoms using artificial tears and lubricants to moisten the ocular surface.<sup>88</sup> In the last decade, nano-carrier systems have shown great promise to revolutionize drug delivery to treat DED, offering many advantages such as site-specific and sustained delivery of therapeutic agents. A number of studies have shown that nanotechnology drugs have a good therapeutic effect on the dry eye rabbit model (Table 2). For example, cyclosporine A, a poorly soluble immunosuppressant cyclic peptide required in some cases of xerophthalmia (severe drying and thickening of the conjunctiva),<sup>89</sup> has been the subject of previous studies involving micelles.<sup>90</sup> Kang et al used polyoxyl 35 hydrogenated castor oil micelles to demonstrate improved functionality and morphology of the conjunctival epithelium in a New Zealand albino rabbit dry eye model.<sup>91</sup> In 2019, the NSAID amfenac loaded with poly(catechin) capped-gold nanoparticles had a synergistic anti-inflammatory effect in a DED rabbit model.<sup>92</sup> Nagai et al loaded nanoparticles with rebamipide using the breakdown method and reported that this drug increases the mucin levels in the lacrimal fluid and prolongs tear film breakup time.<sup>93</sup> These results will be

**Table 2** Nanocarriers to Deliver Anti-Dry Eye Agents

Study	Experimental Models	Drug	Vehicle/ Carriers	Production Method(s)	Results	Conclusion
N. Nagai, et al <sup>93</sup> 2020	N-acetylcysteine-treated rabbit model	Rebamipide	Nanoparticles	Breakdown method	The rebamipide solid nanoparticle-based ophthalmic formulation increased mucin levels in the lacrimal fluid and healed tear film breakup levels in vivo.	This novel sustained-release drug delivery route and creation of a nano-formulation can be used to design further studies aimed at therapy for dry eye.
F. Yu, et al <sup>161</sup> 2019	Dry eye murine model	Glycol chitosan cerium oxide	Nanoparticles	Unspecified	Glycol chitosan cerium oxide nanoparticles not only ameliorate symptoms but also reverse pathological changes at the cellular and molecular levels in dry eye.	Glycol chitosan cerium oxide nanoparticles are an effective treatment for dry eye and may represent a potential new class of drug for dry eye disease.
Y. J. Li, et al <sup>92</sup> 2019	Rabbits model	Amfenac	Poly(catechin) capped-gold nanoparticles	Unspecified	Poly (catechin) capped-gold nanoparticles (Au@Poly-CH NPs) not only act as an antioxidant to suppress ROS-mediated processes, but also serve as a drug carrier of AF for a synergistic effect on anti-inflammation.	Au@Poly-CH NPs loaded with NSAIDs is a promising multifunctional nanocomposite for treating various inflammation- and oxidative stress-related diseases.
H. Y. Huang, et al <sup>162</sup> 2018	New Zealand White rabbits	Hyaluronic acid	Nanoparticles	Self-assembly method	Large amounts of gelatin-epigallocatechin gallate nanoparticles (GEH-NPs) accumulated in the cytoplasm of human corneal epithelium cells and the ocular surfaces of rats and rabbits, indicating the advantage of GEH NPs for ocular delivery of medication.	GEH NPs are potentially valuable as a new therapeutic agent delivered in eye drops for treating dry eye syndrome.
H. Kang, et al <sup>91</sup> 2016	New Zealand albino rabbits	Cyclosporine A	Micelle solutions	Simple method	The number of goblet cells in rabbit conjunctivas after the administration of cyclosporine A-micelle solutions was significantly higher than that with Restasis.	The potential use of a novel MS for the ophthalmic delivery of CsA in treating dry eyes.
C. Di Tommaso, et al <sup>163</sup> 2011	Female albino New Zealand rabbits	Cyclosporin A	polymeric micelles	Co-solvent method	After incubation with methoxy poly (ethylene glycol)-hexylsubstituted poly(lactides) (MPEG-hexPLA) micelle formulations, the activation of caspase-dependent and -independent apoptosis as well as autophagy was evaluated using immunohistochemistry for localizing antibodies	MPEG-hexPLA micelles are promising drug carriers for ocular diseases involving the activation of cytokines

attractive to both academic and pharmaceutical industry researchers working in DED therapeutics.

## Glaucoma

Glaucoma is the second major cause of blindness worldwide, with a 1% global incidence rate, and a 2% rate in subjects over 45 years old.<sup>94</sup> IOP increases intermittently or continuously in patients with glaucoma, and the dynamic balance in the aqueous circulation is disrupted, causing optic nerve atrophy and visual field defects. The other pathological manifestations of glaucoma are retinal ganglion cell (RGC) apoptosis and chronic progressive degeneration of axons.<sup>95,96</sup> Two major problems are encountered in the clinic when treating glaucoma, such as low drug bioavailability and poor patient compliance. In last 10 years, studies of drug-loaded nano-technology formulations to treat of glaucoma have shown positive outcomes (Table 3).

Latanoprost has been injected into the subconjunctival space once to evaluate the safety and efficacy of a latanoprost nanoliposome carrier in human eyes (n = 6) diagnosed with either ocular hypertension or primary open-angle glaucoma. No significant irritation was detected after subconjunctival injection of the liposomal latanoprost. A significant reduction in IOP was detected from baseline ( $27.55 \pm 3.25$  mmHg) to 1 h later ( $14.52 \pm 3.31$  mmHg). More than a 20% IOP reduction was observed after 3-months, which provided evidence for clinical use of liposomal latanoprost in glaucoma therapeutics.<sup>97</sup>

Furthermore, Rodriguez-Aller et al revealed that latanoprost-propylamino- $\beta$  cyclodextrin has significant solubility and stability compared with a commercial latanoprost formulation in vitro. Additionally, there is less ocular irritation with a latanoprost-propylamino- $\beta$ -CD formulation (9.5%) than that with a commercially marketed formulation of latanoprost (15.5%) in vivo.<sup>98</sup>

Interestingly, acetazolamide has been loaded onto water-soluble mucoadhesive carbosilane dendrimers to evaluate the cytotoxicity and cell viability of dendrimers in normotensive rabbit eyes. The results revealed that G3 (from the third generation of carbosilane cationic dendrimers) cationic carbosilane dendrimers (5  $\mu$ M) produced a rapid (1 hour post-instillation) and sustained (up to 7-hour) hypotensive effect, reaching a peak 22.6% reduction in IOP.<sup>99</sup>

Visual field loss in patients with glaucoma is caused by death of RGCs. Normal physiological ageing is

responsible for an estimated rate of 0.4% RGC loss per year,<sup>100</sup> but this percentage increases to 4% in cases of glaucoma.<sup>101</sup> Considering the complex and multifactorial nature of glaucoma, multiple targets are thought to contribute to the loss of RGCs. The NMDA antagonist memantine loaded in PLGA nanoparticles using the double emulsion solvent evaporation technique significantly reduced loss of RGCs in Morrison's ocular hypertension rat model.<sup>102</sup>

## Posterior Capsular Opacification

Postoperative capsular opacification, particularly posterior capsular opacification (PCO), is one of most common complications of cataract surgery. Residual lens epithelial cells (LECs) on the lens capsule lead to proliferation, migration, and trans-differentiation.<sup>103</sup> Various management strategies to control PCO have been tested, including updates on intraocular lens materials and pharmacological treatments. Nano-carrier-loaded targeted drugs or the material method is effective to mechanically prevent the formation of PCO. However, only a few studies have evaluated the use of nanomaterials to prevent PCO. The antimetabolite drug fluorouracil (5-FU) inhibits cell proliferation directly by disturbing the cells' nucleic acids and proteins. 5-FU is also applied to cure eyes with these characteristics.<sup>104</sup> To evaluate the effects of 5-FU modified intra ocular lens (IOL) to prevent PCO, Huang et al injected 5-FU carried by chitosan nanoparticles into the lens capsule after removing the lens cortex of New Zealand white rabbits during cataract surgery, compared with injecting 5-FU alone. Their findings suggested that 5-FU partially curbs the proliferation of LECs, and the 50% inhibitory concentration (IC50) of 5-FU carried by chitosan nanoparticles was only one-fifth that of direct administration, which significantly lowered damage to the cornea, iris, and ciliary body.<sup>105</sup> In addition, another study found that other cytotoxic drugs, such as daunorubicin and mitomycin C, also inhibit proliferation of LECs, but a suitable method to reduce the toxicity to intraocular tissues is needed. In the future, experiments combining pharmacological treatment of the underlying biological processes and the use of nanomedicine could help prevent PCO.<sup>106</sup>

## Diabetic Cataract

Cataract is a major cause of vision disorders in the population with diabetes mellitus (DM),<sup>107</sup> and they form much faster in patients with DM than in normal subjects.<sup>108</sup> Oxidative stress

Table 3 Nanocarriers to Deliver Anti-Glaucoma Agents

Study	Experimental Models	Drug	Vehicle/ Carriers	Production Method(s)	Results	Conclusion	Future Direction
Schnichels S, et al <sup>164</sup> 2020	DBA/2J mice model	Travoprost	Lipid DNA nanoparticles	Self-assembly of DNA amphiphiles	Travoprost nanoparticles deliver at least twice the amount of the drug at every time-point investigated compared to the pristine drug.	There is applicability of a DNA-based drug delivery system in the field of ophthalmology for the treatment of glaucoma.	In the future, a combination therapy relying on DNA-based NPs and different aptamers might be feasible.
Orasugh JT, et al <sup>165</sup> 2019	In vitro gel	Pilocarpine	Cellulose nanocrystals	Acid hydrolysis process	Have higher sustained drug release and less toxicity.	Cellulose nanocrystals have a significant effect on the gelation behavior, gel strength, and drug release kinetics of poloxamer copolymer-cellulose nanocrystals formulations.	Unspecified
Sánchez-López E, et al <sup>162</sup> 2018	Morrison's ocular hypertension model in Dark Agouti (DA) rats	Memantine	PLGA nanoparticles	Modification of the double emulsion solvent evaporation technique	Well tolerated in vitro (human retinoblastoma cells) and in vivo (Draize test); Reduced RGC loss in vivo.	Topical MEM-NP is safe, well tolerated, and, most promisingly, neuroprotective in an experimental glaucoma model.	Unspecified
Fahmy HM, et al <sup>166</sup> 2018	White albino rabbits	Latanoprost	Liposomes	Film hydration method	Reduced the IOP in glaucomatous white albino rabbits, which lasted for 8 hours.	Lip (LAT + TQ) and Lip (LAT) were the most effective tested formulations, which provided in vivo sustained drug release and showed the maximum IOP lowering effect up to 84 h as compared to other tested formulations.	None of the prepared liposome formulations succeeded in improving the glaucoma-induced oxidative stress damage.
Wang F, et al <sup>167</sup> 2018	White New Zealand rabbits	Brinzolamide	Nanoliposomes	Thin-film dispersion method	Reduced IOP in less than 1 hour, reached peak efficacy at 2 hours, and sustained release effect for 12 hours.	The HP-β-CD/BRZ loaded nanoliposomes might have a promising future as a NODDS for glaucoma treatment.	Further studies are still required to investigate the in vitro release properties of BCL and elucidate how the release profile affects the therapeutic efficacy of BCL.

Tan G, et al <sup>42</sup> 2017	New Zealand albino rabbits	Timolol maleate	Chitosan coated liposomes	Ammonium sulfate gradient coupled with a pH-gradient	Significantly reduced the IOP.	CHL is a potentially useful carrier for ocular drug delivery, which could improve the efficacy of TM.	The formulation reported here will be the subject of future studies aimed at improving its clinical use.
Rathod LV, et al <sup>168</sup> 2017	Goat eyes and albino rabbits	Acetazolamide	Nanoparticles	Solvent displacement method	Displayed better permeability and flow across corneal tissue in vitro.	The nanoparticles impregnated ocular inserts can act as potential platform for delivering drug to posterior segment of eye not only for glaucoma but also for other eye diseases.	Unspecified
Ikuta Y, et al <sup>169</sup> 2017	Male Sprague-Dawley rats	Brinzolamide	Nanoparticles	Reprecipitation method	Increases the eye penetration rate and resulted in high drug efficacy.	The nano-eye-drops may have applications as a next-generation ophthalmic treatment.	Unspecified
Kouchak M, et al <sup>170</sup> 2016	Albino rabbits	Dorzolamide hydrochloride	Nanoliposomes	Reverse-phase evaporation vesicle method	Had greater IOP lowering activity and more prolonged effects.	It could be a candidate for the treatment of ocular hypertension.	Assay of DRZ in aqueous humor following drug instillation into rabbit eye should be done before clinical trials as well.
Bravo-Osuna I, et al <sup>99</sup> 2016	New Zealand white rabbits	Acetazolamide	Dendrimers	Hydroxylation of Boc-protected allylamine and followed by deprotection with HCl	Demonstrated rapid (1 hour post-instillation) and sustained (up to 7 hours) hypotensive effect, reaching a peak 22.6% IOP reduction in normotensive rabbit eyes.	Carbosilane dendrimers can be used in a safe range of concentrations to enhance the bioavailability of drugs topically administered in the eye.	Unspecified
Yu S, et al <sup>171</sup> 2015	New Zealand rabbits	Timolol maleate	Liposome	pH-gradient method	Reduced the IOP and the effective time was significantly longer.	Liposome incorporated ion sensitivity in situ gels has a potential ability for ophthalmic delivery.	Future work will research the pathway and mechanism of the cellular uptake of TM L-ISG.

(Continued)

Table 3 (Continued).

Study	Experimental Models	Drug	Vehicle/ Carriers	Production Method(s)	Results	Conclusion	Future Direction
Rodriguez-Aller M, et al <sup>98</sup> 2015	New Zealand rabbits	Latanoprost	Cyclodextrins	Unspecified	Improved solubility and stability in vitro. In vivo evaluation of ocular tolerability revealed that ocular irritation was 15.5% with the commercially marketed formulation of latanoprost and 9.5% with the latanoprost-propylamino- $\beta$ -CD formulation.	The latanoprost-propylamino- $\beta$ -CD formulation was demonstrated to successfully address the main stability, solubility, and tolerance limitations of topical ocular latanoprost therapy for glaucoma.	Unspecified
Wong TT, et al <sup>97</sup> 2014	Human	Latanoprost	Nanoliposome	Gradient method	Good tolerance with no evident safety issues or adverse events.	This study provided the evidence and support for further clinical studies of liposomal latanoprost in the treatment of glaucoma.	The authors were planning additional controlled clinical studies.
Singh J, et al <sup>172</sup> 2014	Rabbits model	Acetazolamide	Polymeric nanoparticles	Nanoprecipitation method	Sustained release effects and increased transcorneal permeation in vivo.	NP-1SG5 may offer intensive management of glaucoma via higher permeation, prolonged precorneal residence time and sustained drug release along with higher in vitro efficacy, safety and patient compliance.	These systems are emerging as vehicles for the treatment of diseases of posterior portion of eye which is not possible by topical delivery through conventional systems.
Tuomela A, et al <sup>173</sup> 2014	Wistar rats	Brinzolamide	Nanocrystal	Top-down wet milling technique	The IOP lowering effect was investigated using a modern rat ocular hypertensive model and elevated IOP reduction was seen in vivo with all the formulations. The reduction achieved in experimentally elevated IOP was comparable to that obtained with a commercial product.	Various BRA nanocrystal formulations which all showed advantageous dissolution and absorption behavior were successfully formulated.	Unspecified

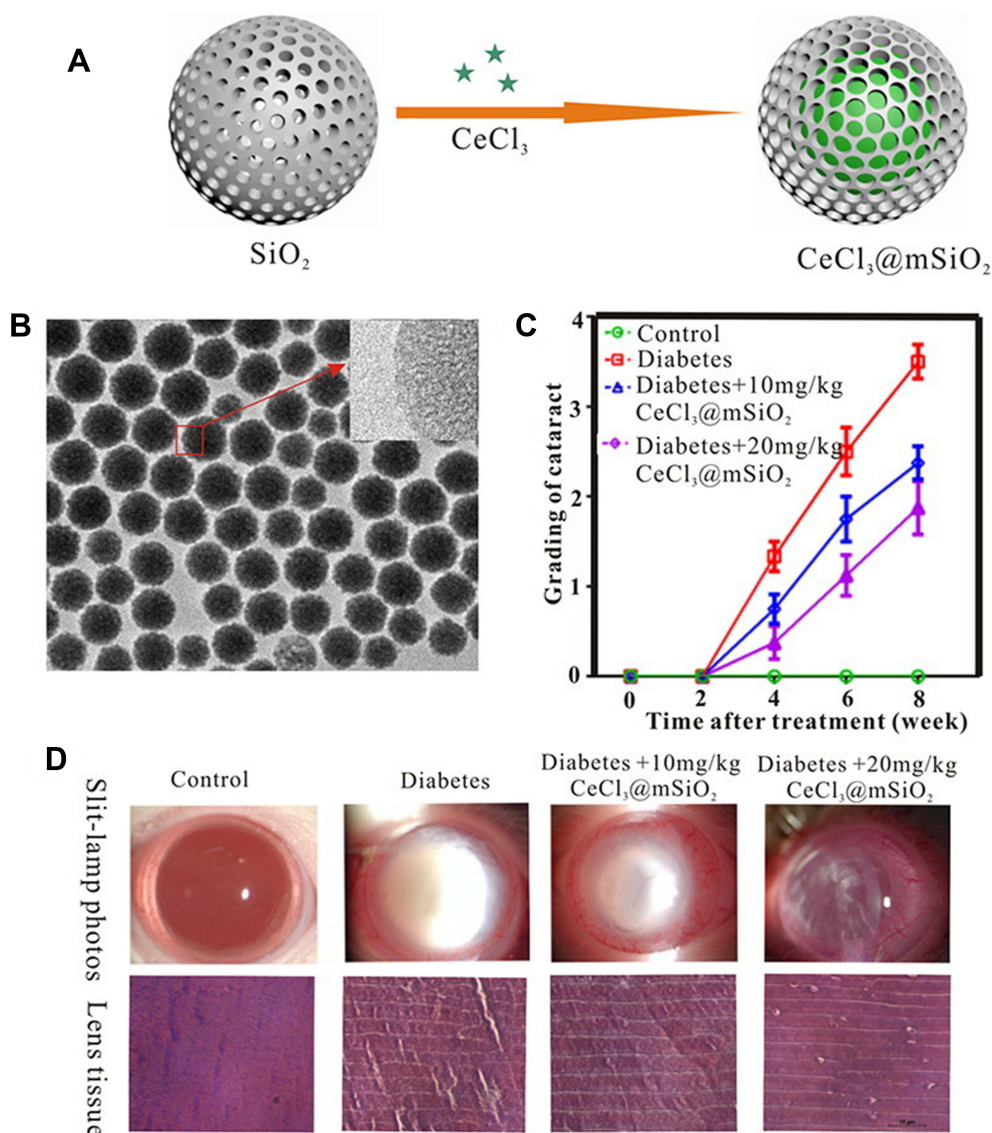
Mishra V, et al <sup>174</sup> 2014	New Zealand albino rabbits	Acetazolamide	Poly(propylene imine) dendrimer nanoarchitectures	Unspecified	The sustained and prolonged reduction in IOP suggested that drug entrapped in dendrimers can be used for higher retention in ocular cul-de sac.	The PPI dendrimer based formulation seems to enhance the ocular drug residence time and exhibits better intraocular pressure lowering effect for glaucoma treatment	Unspecified
Jung HJ, et al <sup>175</sup> 2013	Beagle dogs	Timolol	Nanoparticles of PGT (propoxylated glyceryl triacylate)	Thermal polymerization of a mixture of timolol base and PGT.	Sustained release of the timolol.	Preliminary in vivo animal studies demonstrate safety and efficacy of the particle loaded lenses treating glaucoma.	Further in vivo safety and pharmacokinetics and pharmacodynamics tests particularly with lenses in which particles are loaded prior to lens fabrication are necessary to evaluate the potential of the proposed approach for glaucoma therapy.
Wu W, et al <sup>176</sup> 2013	New Zealand rabbits	Brinzolamide	Liquid crystalline nanoparticles	Modified emulsification method	Had advantages such as lower doses but maintaining the effectiveness, better ocular bioavailability, and patient compliance compared with Azopt®.	BLZ LCNPs would be a promising delivery system used for the treatment of glaucoma	Unspecified
Natarajan JV, et al <sup>177</sup> 2012	New Zealand White rabbits	Latanoprost	Egg PC liposomes	Hydration method	A greater sustained IOP lowering effect compared with daily administration of topical latanoprost beyond 90 days.	A single injection of latanoprost-loaded Egg PC liposomes can lower the IOP for up to 90 days, with a greater IOP lowering effect than daily topical administration of latanoprost.	Further detailed studies on the pharmacodynamics of these liposomes within the ocular tissues will determine its future potential clinical application.

affects the pathogenesis of cataract induced by hyperglycemia.<sup>109</sup> Over the past 10 years, efforts have been made to develop nano-based formulations involving anti-oxidative stress control to treat diabetic cataract.

Cerium, an earth element in the lanthanide series, has oxidation states of  $Ce^{3+}$  and  $Ce^{4+}$ , which scavenge free radicals. Yang et al prepared cerium (III) chloride ( $CeCl_3$ )-loaded mesoporous silica ( $CeCl_3@mSiO_2$ ) nanoparticles and revealed their application for treating diabetes-associated cataract in vitro and in vivo using the

streptozotocin (STZ)-induced male Wistar diabetic rat cataract model (Figure 4).<sup>110</sup> Furthermore, Zhou et al synthesized cerium oxide nanoparticles ( $CeO_2$ -NPs) coated with PEG-PLGA (PCNPs) using the emulsification method, and reported that it protects LECs from oxidative stress damage by scavenging reactive oxygen species (ROS) and attenuating alpha-crystalline glycation in the STZ-induced diabetic rat model.<sup>111</sup>

These findings have opened avenues for developing potential therapeutic strategies to treat diabetic cataract.



**Figure 4** Cerium (III) chloride ( $CeCl_3$ )-loaded mesoporous silica ( $CeCl_3@mSiO_2$ ) nanoparticles. A type of cerium (III) chloride ( $CeCl_3$ )-loaded mesoporous silica ( $CeCl_3@mSiO_2$ ) nanoparticles designed and to prevent the formation of diabetic cataract in vitro and in vivo using a well-established rat model of streptozotocin-induced diabetes. (A) Schematic diagram of  $CeCl_3@mSiO_2$  nanoparticle preparation; (B) The morphology of the  $mSiO_2$  nanoparticles under transmission electron microscopy (spherical, uniform and monodisperse morphology with an average diameter of 85 nm); (C) A line graph, showing the time course of changes in the cataract degrees in different groups of animals; (D) various degrees of cataract and representative images of H&E-stained sections of the lens tissue in experimentally induced diabetic animals 8 weeks after treatment with vehicle or 10 and 20 mg/kg  $CeCl_3@mSiO_2$  nanoparticles, respectively. Reprinted from *Nanomed*, 13, Yang J, Gong X, Fang L, et al. Potential of  $CeCl_3@mSiO_2$  nanoparticles in alleviating diabetic cataract development and progression, 147–1155, Copyright 2017, with permission from Elsevier.<sup>110</sup>



Notably, administering these nanoparticles is invasive, as  $\text{CeCl}_3@\text{mSiO}_2$  nanoparticle is an intraperitoneal injection,<sup>110</sup> and PCNP is a subconjunctival injection.<sup>111</sup> Therefore, studies are necessary to optimize potential non-invasive nanotechnology-based DDS to prevent diabetic cataract.

## Diabetic Retinopathy

Diabetic retinopathy (DR) is one of most common microvascular complications of DM, and is the main cause of blindness in the working-age population. The pathological mechanisms of DR include hyperglycemia and lipid disorder.<sup>112</sup> Quercetin has been isolated from leaves and grains, and is reported to have anti-diabetic activities. Thus, quercetin has been traditionally used to treat DM and its complications.<sup>113</sup> However, poor bioavailability and multiple biological interactions are the major challenges of phytomedicines.<sup>114</sup> Wang et al reported that intravitreal injection of quercetin coated with a freeze-dried nano-formulation had significant therapeutic effects against DR, and reduced lipid peroxidation in a zebrafish model, one of the disadvantages of nano-formulations is that they do not achieve target cell specificity.<sup>115</sup> Therefore, Wang et al used cell-specific promoters to deliver specific retinal cell types, such as retinal pigment epithelium, rod cells, cone cells, and ganglion cells, using liposome-protamine-DNA complex (LPD)-mediated gene delivery loaded in lipid-based nanoparticles by a two-step packaging technology employing a multilayering method.<sup>116</sup> These findings indicate that peptide-modified LPD nanoparticles can be delivered for ocular gene therapy of retinal diseases including DR.

## Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a major cause of blindness in the developed world and choroidal neovascularization (CNV) and geographic atrophy are serious and potentially devastating complications of the disease.<sup>117</sup> Many studies have shown that nano-carrier DDSs have potential to treat AMD (Table 4). However, these studies are still in the preliminary stage. Therefore, further studies are needed to develop novel formulations. Unlike anterior segment drugs, posterior segment drugs must overcome several ocular barriers before reaching the target site. For example, anti-VEGF drugs are given through an intravitreal injection, and even though the delivery is of small therapeutic molecules, there is still poor permeability. Nano-carrier DDSs improve the

permeability of therapeutic agents across biological membranes and benefit therapeutics of CNV of the eye using both invasive and non-invasive techniques.<sup>118</sup> Nano-medicine targets delivery and binds with the CNV site, and prolongs the release time of the therapeutic agent.

Kringle 5 (K5) is a natural anti-angiogenic peptide and a proteolytic fragment of plasminogen with a length of 80 amino acids. However, its anti-angiogenic effect is short-lived due to the short half-life of the K5 peptide in the vitreous and retina. K5 nanoparticles containing the K5 plasmid mediate continuous expression of K5 in the retina for up to 4 weeks. Jin et al used K5-carrying PLGA nanoparticles (K5-NP) to observe their effect on laser-induced CNV in rats. The results showed that K5-NP mediated the continuous expression of K5 in the retina (primarily in the inner retina) for up to 2 weeks. Interestingly, there was also high expression of K5 in the outer retina at the laser photocoagulation site. Intravitreal injection of K5-NP reduced the area of CNV, reduced the permeability of retinal blood vessels and the high expression of VEGF, and downregulated the expression of inflammatory factors, such as TNF- $\alpha$  and ICAM-1, and even weakened  $\beta$ -catenin aggregation. These results suggest that K5 has anti-inflammatory activity, and that K5-NPs have a sustained inhibitory effect on CNV.<sup>119</sup>

Very few studies have been conducted on treating AMD with nanotechnology in the past 5 years, and this should inspire more attention from researchers in the future.

## Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a type of proliferative retinopathy that occurs in premature infants and low-weight infants. Premature birth can cause the retina to be exposed to a high partial pressure oxygen environment. The relative hypoxia generated in the body promotes the release of VEGF, which induces retinal angiogenesis, vitreous hemorrhage, and traction retinal detachment, leading to preventable causes of childhood blindness.<sup>120</sup> A nano-carrier DDS has been developed for ROP in the last decade. In the study by Kim et al, gold was loaded onto nanoparticles and exhibited anti-VEGF-induced angiogenesis through blocked autophosphorylation of VEGF receptor-2 to inhibit extracellular signal-regulated kinase (ERK) 1/2 activation in a ROP mouse model.<sup>121</sup>

## Retinoblastoma

Retinoblastoma (Rb) is one of the most common malignancies of children. Current therapeutic strategies for

Table 4 Nanocarriers to Deliver Anti-Age-Related Macular Degeneration Agents

Study	Experimental Models	Drug	Vehicle/Carriers	Production Method(s)	Results	Conclusion	Future Direction
Tang M, et al <sup>178</sup> 2018	An Alkali-Burn Corneal Neovascularization Model in the Mouse	Silicon	Nanoparticles	Photochemical method.	SINPs-RGD features efficacious antiangiogenic ability; SINPs-RGD can label angiogenic blood vessels and has neovascularization suppression effects.	the SINPs-RGD as a novel class of high-quality theranostic probe is suitable for simultaneous diagnosis and treatment in ocular neovascular diseases	Unspecified
Wang Y, et al <sup>116</sup> 2016	Balb/c mice and Sprague-Dawley rats	LPD-mediated gene delivery	Lipid-based nanoparticles	A two-step packaging technology employing a multilayering method	Cell-specific promoters enable lipid-based nanoparticles to deliver genes to specific retinal cells in vivo.	This work will inspire investigators in the field of lipid nanotechnology to couple cell-specific promoters to drive expression in a cell- and tissue-specific manner.	The formulated lipid nanoparticles may be appropriate for use with other tissues for the purposes of gene delivery with tissue-specific promoters.
Huu VA, et al <sup>179</sup> 2015	Sprague-Dawley rats	Nintedanib	Nanoparticle	Light-sensitive polymer	Stably retain encapsulated molecules in the vitreous; released cargo in response to UV exposure up to 30 weeks post-injection; light-triggered release of nintedanib 10 weeks post-injection suppresses CNV in vivo.	Light-sensitive nanoparticles are biocompatible and cause no adverse effects on the eye as assessed by electroretinograms (ERG), corneal and retinal tomography, and histology.	Whether light can trigger release of multiple therapeutic doses of BIBF 120.
Luo L, et al <sup>180</sup> 2013	C57BL/6j mice and cynomolgus macaque monkeys	RGD- targeted	PLGA nanoparticles	Emulsion solvent evaporation method	Improved with nearly 40% restoration of visual loss induced by CNV.	These findings offer a nanoparticle-based platform for targeted, vitreous-sparing, extended-release, nonviral gene therapy.	Further studies would be necessary before concluding this delivery system is completely safe.

Iwase T, et al <sup>181</sup> 2013	Pathogen-free C57BL/6 mice and Dutch belted rabbits	Doxorubicin	Poly(sebacic acid)- polyethylene glycol nanoparticles	Oil-in-water emulsion method	Reduced HIF-1-responsive gene products, strongly suppressed CNV, and no retinal toxicity; suppressed NV for at least 35 days in vivo; sustained release in vivo for at least 105 days.	A novel HIF-1-inhibitor- polymer conjugate formulated into controlled-release particles maximizes efficacy and duration of activity, minimizes toxicity, and provides a promising new chemical entity for treatment of ocular NV.	A single-agent that targets multiple pro-angiogenic effectors is expected to have substantial benefits from a clinical perspective and could provide a major step forward the treatment of highly prevalent neovascular diseases of the eye.
Kyosseva SV, et al <sup>182</sup> 2013	Mutant mice with targeted deletion of the Vldlr gene	Cerium oxide	Nanoparticles	Simple wet chemistry methods	Many cell signaling, cellular development, growth and proliferation, and tissue development were affected; inhibited the activation of ERK 1/2, JNK, p38 MAP kinase, and Akt.	Nanoceria may represent a novel therapeutic strategy to treat AMD, RAP, and other neurodegenerative diseases.	Unspecified
Yandrapu SK, et al <sup>183</sup> 2013	Rat model	Bevacizumab	PLGA nanoparticles	Emulsion solvent evaporation method	In vitro release of bevacizumab from NP in PMP was sustained for 4 months.	NP in PMP is a novel sustained release system for protein drugs to reduce frequency of protein injections in the therapy of back of the eye diseases.	NP in PMP will sustain drug levels much further in vivo, which will be assessed in future studies.
Jo DH, et al <sup>184</sup> 2012	C57BL/6 mice	Silicate	Nanoparticles	Reverse microemulsion method	No direct toxicity; reduced anomalous retinal angiogenesis in vivo; inhibited in vitro VEGF- induced angiogenesis via suppression of VEGF receptor-2 phosphorylation and blocking ERK 1/2 activation.	SiNPs could be an inhibitor of the potency and safety of retinal neovascularization that is mediated by VEGF	Biodegradation and biodistribution of NPs might be investigated before clinical application

(Continued)

Table 4 (Continued).

Study	Experimental Models	Drug	Vehicle/Carriers	Production Method(s)	Results	Conclusion	Future Direction
Iezzi R, et al <sup>185</sup> 2012	Royal College of Surgeons (RCS) rat retinal degeneration model	Hydroxyl-terminated polyamidoamine	Nanodevices	Unspecified	Sustained release effects over 90 days. One intravitreal injection of 1 mg of FA conjugated to 7 mg of the dendrimer was able to arrest retinal degeneration, preserve photoreceptor outer nuclear cell counts, and attenuate activated microglia, for an entire month.	PAMAM dendrimers (with no targeting ligands) have an intrinsic ability to selectively localize in activated microglia, and can deliver drugs inside these cells for a sustained period for the treatment of retinal neuro-inflammation.	This approach can have significant implications in the treatment of neuro-inflammation in other neurodegenerative diseases such as cerebral palsy, autism, and Alzheimer's disease.
Liu HA, et al <sup>186</sup> 2011	Brown-Norway rats	PEGylated liposome-protamine-hyaluronic acid nanoparticles (PEG-LPH-NP) loaded with siRNA (PEG-LPH-NP-S)	Liposome-polymer hybrid nanoparticles	Post-insertion method	Protected siRNA load and facilitated the intracellular delivery of siRNA, the expression inhibition of VEGFR1, and the reduction of CNV area in vivo.	PEG-LPH-NP may be a promising lipid nanoparticle system for the siRNA treatment of CNV.	Unspecified
Jin J, et al <sup>119</sup> 2011	Brown Norway rats	Plasminogen kringle	PLGA nanoparticle	Emulsion-diffusion-evaporation technique with some modifications	Intense K5 expression was detected in the retina 2 weeks after the injection of K5-NP. Areas of CNV were significantly decreased in the K5-NP treatment group compared with that in the control-NP group. The K5-NP injection also significantly reduced vascular permeability.	K5 has a novel anti-inflammatory activity. K5-NP mediates a sustained inhibitory effect on CNV	The receptor and signaling pathway mediating the anti-inflammatory activity of K5, however, remains to be defined.
Zhang C, et al <sup>187</sup> 2010	Brown Norway rats	PshHIF-1 $\alpha$	PLGA nanoparticle	Water-in-oil-in-water (W/O/W) multiple emulsion technique	Expression of GFP preferentially localized in the retinal pigment epithelium cell layer and lasted for 4 weeks; reduced the mean thickness of the CNV lesions in vivo.	pshHIF-1 $\alpha$ NPs may act as a novel therapeutic option to transfer specific pDNA and inhibit the formation of experimental CNV.	The efficacy of this method is not clear yet and needs further determination.

**Abbreviations:** IOP, intraocular pressure; AMD, age-related macular degeneration; RAP, retinal angiomatous proliferation; CNV, choroidal neovascularization.

advanced Rb include the use of chemotherapeutic agents, such as topotecan. Nevertheless, the efficacy of topotecan in the treatment of advanced Rb is unsatisfactory.<sup>122</sup> Additionally, the side-effects of long-term anticancer therapy on the health of children cannot be ignored. Consequently, preparing a novel sustained-release formulation of chemotherapeutic agents is of great importance. Qu et al produced topotecan-loaded mesoporous silica nanoparticles with folic acid conjugated on the surface to achieve superior anticancer efficacy (58%) in human retinoblastoma cells (Y79).<sup>123</sup> Further in-vivo experiments by Delrish proved this finding.<sup>124</sup> In that study, thiolated chitosan nanoparticles were used to encapsulate topotecan and develop an intraocular tumor chemotherapeutic drug carrier with improved biocompatibility, controlled release, targeted delivery, and enhanced physical stability.<sup>124</sup>

## Optic Neuropathy

Optic neuropathy is characterized by the loss of axons in the optic nerve and retina, followed by death of RGCs, resulting in irreversible blindness.<sup>125,126</sup> RGCs are responsible for signal transmission from the retina to the brain and their death through apoptosis causes visual impairment. The mechanistic target of rapamycin (mTOR) pathway plays a critical role in the health and disease status of the retina and optic nerve.<sup>127</sup> RGC damage is modulated by rapamycin through the mTOR pathway.<sup>128</sup> Therefore, combining mTOR pathway stimulating biologics to protect RGCs would provide better control over cell pathway modulator delivery, release, clearance, and residency time. Eriksen et al prepared two liposome formulations using the film hydration method. Liposome aqueous cores were loaded with ciliary neurotrophic factor (CNTF) and insulin-like growth factor-I (IGF), while liposome membranes were loaded with the lipid-conjugated osteopontin peptide (OPP) and either production of anthocyanin pigment 2 (PAP2) or production of anthocyanin pigment 4 (PAP4). Finally, Eriksen et al found that these liposomes promoted neuroprotection by stimulating the mTOR pathway after a single injection in an N-methyl-d-aspartic acid mouse model with extensive retinal damage. Their findings demonstrated significant experimental upregulation of mTOR signaling promoting RGC survival and axon regeneration after an optic nerve crush injury.<sup>129</sup>

## Uveitis

The uvea is composed of the iris, the ciliary body, and the choroid. Inflammation in any part of the uvea can be

defined as uveitis. According to the main anatomical sites of ocular inflammation, uveitis can be further divided into anterior, intermediate, posterior, and panuveitis. Anterior uveitis is the main site of inflammation in the anterior segment (iris and ciliary body). Intermediate uveitis is defined as inflammation of the vitreous cavity and serrated margin. Posterior uveitis involves the retina and choroid. Inflammation in panuveitis includes all layers. The main symptoms of uveitis are scleral hyperemia, pain, and visual impairments. Treatments for uveitis include the application of anti-inflammatory and corticosteroids alone or in combination with other immunosuppressive agents.<sup>130</sup>

There is increasing interest in inducing positively charged nanocarriers by coating PLGA nanoparticles, cubosomes/cubosomal gels, or PVCL-PVA-PEG nanomicrocellular and cationic nanostructured lipid carriers (Table 5). Most recently, the water-insoluble corticosteroid triamcinolone acetonide (TA) was loaded onto cationic, nanostructured lipid carriers to treat anterior uveitis. The outcomes indicated that encapsulation of TA in the cationic lipid nanocarriers increases corneal penetration without increasing toxicity and increases the drug's bioavailability within the eye.<sup>131</sup> Similar safety and efficiency were found in an evaluation of a topical nanomicrocellular formulation for the immunosuppressant drug everolimus. In that study, everolimus loaded positively charged Soluplus<sup>®</sup>, a grafted copolymer of polyvinyl caprolactam-polyvinyl alcohol-polyethylene glycol (PVCL-PVA-PEG) of 65.55 nm, was used to improve permeability through ocular epithelia with minimal or no irritation resulting in enhanced ocular bioavailability to treat posterior uveitis.<sup>132</sup>

Cubosomes are lipid-based nanoparticles in which the membranes are entangled into a complex array of pores arranged in a cubic lattice. Compared with liposome analogs, these complex nanoparticles encapsulate a large amount of drug.<sup>133</sup> The cubosomes were nanosized (100 to 278 nm) with high encapsulation efficiency ( $94 \pm 4.7\%$ ) of the lipophilic drug beclomethasone dipropionate. Transcorneal permeation and IOP measurement data suggested significant controlled release, enhanced corneal permeability, and greater relative bioavailability from cubosomes and the Cubo-gel in vitro. Furthermore, superior anti-inflammatory properties were recorded for the Cubo-gel to treat endotoxin-induced posterior uveitis in a rabbit model.<sup>134</sup>

Table 5 Nanocarriers to Deliver Anti-Uveitis Agents

Study	Experimental Models	Drug	Vehicle/Carriers	Production Method(s)	Results	Conclusion
Nikita, et al <sup>132</sup> 2021	Unspecified	Everolimus	PVCL-PVA-PEG nanomicellar	Unspecified	Have high encapsulation efficiency and sustained release of everolimus; have higher permeation across goat cornea than everolimus suspension.	Everolimus nanomicelles could be considered a promising topical drug delivery nanocarrier for treating uveitis.
Garg V, et al <sup>188</sup> 2021	Endotoxin-Induced Uveitis in Rabbit	Tacrolimus	Proglycosome nano-vesicles	Propylene glycol modified lipid vesicles	PNV treatment not only subsides clinical symptoms of uveitis but also prevents breakdown of blood aqueous barrier.	Tacrolimus loaded PNVs are a potential new topical treatment for uveitis.
Gaballa SA, et al <sup>134</sup> 2020	Rabbits' model	Beclomethasone Dipropionate	Cubosomes/Cubosomal Gels	Top-down technique	Transcorneal permeation parameters Papp, flux and AUC0-10h, were markedly enhanced up to 4-, 5.8- and 5.5-fold, respectively.	Cubosomes/Cubo-gel could be an auspicious ocular delivery system for BDP that was able to effectively treat uveitis.
Nirbhavane P, et al <sup>131</sup> 2020	LPS induced inflamed cells	Triamcinolone acetonide	Cationic nanostructured lipid carriers	Hot microemulsion method	Sustained release effects in vitro; no cytotoxicity; retained inside the cells for 24 h; reduced the TNF- $\alpha$ level in LPS induced inflamed cells.	cTA-NLC could be a promising option for the topical treatment of uveitis.
Coburn PS, et al <sup>189</sup> 2019	A murine sterile endophthalmitis model	Gatifloxacin	Rabbit nanosponges	Biomimetic erythrocyte-derived nanosponge	Reduced the hemolytic activity of a diverse array of PFTs; human nanosponges alone protected mouse retinas following intraocular infection with <i>E. faecalis</i> and <i>S. pneumoniae</i> but not <i>B. cereus</i> or <i>MSSA</i> .	Clinical improvements in intraocular infections following nanosponge treatment were dependent on the complexity and types of toxins produced. Nanosponges might serve as an adjunctive therapy for the treatment of ocular infections.
Chemmaneni SR, et al <sup>190</sup> 2013	New Zealand White (NZW) rabbits	Dexamethasone	PLGA nanoparticles	Standard oil-in-water (o/w) emulsion-solvent extraction method	DXM flow was bidirectional in the endocapsular space and it was found in the anterior and posterior chambers after up to 6 weeks after WHAT?	The feasibility of drug delivery from the capsular bag to the anterior and posterior segments effectively compared to topical alternatives.
Elibialy NS, et al <sup>191</sup> 2013	Male New Zealand white rabbits	Prednisolone acetate	Liposomes	Film hydration method	Have higher entrapment efficiency and slower release rate; higher concentration of PSA in aqueous humor.	pSUV and pMLV are effective carriers for PSA and have a good potential as drug delivery systems in the ocular therapy

## Vitreous Opacities

Myopia and aging are the main causes of progressive aggregation of vitreous collagen, leading to vitreous opacity and severely affecting vision. The main complaint of vitreous opacity is the visual phenomenon of “floating view”.<sup>135</sup> As nanomedicine-based therapeutic solution can locally ablate “floaters” and highly reduce light energy, compared with traditional YAG laser therapy. Sauvage et al proposed hyaluronic acid (HA)-coated gold nanoparticles to localize them with greatly reduced light energy. In that study, the collagen aggregates were destroyed with approximately 1000 times less light energy after applying nanosecond laser pulses than typically used for YAG laser therapy, indicating that applying the laser to ablate the plasmonic nanoparticles conjugated with the vitreous opacity was a safer, faster, and more reliable treatment for eye diseases.<sup>136</sup>

## Anti-VEGF Agents and Novel Strategies Based on Nanotechnology

Biopharmaceuticals and biotechnological therapeutics for treating angiogenesis in ocular disease are mainly based on intravitreal injection of anti-VEGF agents.<sup>137,138</sup> The intravitreally injected anti-VEGF drugs improve visual acuity and macular morphology in most patients with pathological ocular angiogenesis, such as CNV, proliferative diabetic retinopathy, ROP, and neovascular glaucoma.<sup>139–142</sup> The VEGF inhibitors aflibercept, bevacizumab, conbercept, pegaptanib, and ranibizumab are approved treatments for certain eye diseases that occur particularly in the elderly,<sup>16</sup> and bevacizumab is usually used “off-label” in clinical practice.<sup>143</sup> Due to the limited residence time of anti-VEGF drugs in the vitreous body, monthly intravitreal injections of these agents are recommended with 3-monthly loading dose injections followed by individualized therapy with “pro re nata” (PRN) or “treat and extend” (T&E) regimens.<sup>144,145</sup> However, repeated intravitreal injections increase the risk for adverse systemic and ocular effects of the anti-VEGF drugs, including a hypertensive crisis, ischemic stroke, retinal detachment, hemorrhage, cataract, or endophthalmitis.<sup>146–148</sup> Therefore, strategies to reduce the frequency of intraocular injections of these anti-VEGF agents and extend their residence time in the vitreous body are still needed. The ocular residence time and release time of anti-VEGF medication is related to (1) the molecular size, (2) the formation of molecular conglomerates and (3) the presence of crystallizable fragments.<sup>147</sup> Several nano-

carriers have been used to load anti-VEGF drugs for sustained drug release, thereby minimizing the number of intravitreal injections required. To date, many efforts have been focused on the development of nano-carriers for bevacizumab and ranibizumab, which have demonstrated sustained release effects in vitro and a notably increased antiangiogenic efficacy of pathological ocular angiogenesis in vivo when both formulations are administered via intravitreal injection (Table 6). Furthermore, polymeric nanoparticles enhance permeation after surface modification with a cationic polymer.<sup>149,150</sup> Recent advances in nanotechnology have offered many promising opportunities as an ocular anti-VEGF delivery system for pathological angiogenic ocular diseases.

## Nanotechnology and Ophthalmic Drug Delivery System: Current Challenges

Ocular nano-carrier DDSs are particularly versatile, as there has been tremendous progress improving drug stability, solubility, corneal permeability, and retention time, as well as increasing bioavailability and efficacy, but the exact mechanism of action, quality control, and safety evaluation deserve further attention. Notably, the vehicles used for nano-carrier DDSs should be further evaluated. For example, the toxicity of excipients and pollutants has been evaluated in vitro, while the inflammatory reaction has been evaluated in vivo.<sup>151</sup> Additionally, the size of the mouse lens is quite different from that of humans; thus, drug permeability from the cornea to the target in the retina may be converse. Furthermore, the difficulty is to achieve efficient delivery of drugs to the posterior segment of the eye through non-invasive means. Moreover, the current research trend is to design and synthesize new carrier materials or use two or more methods to prepare composite systems.

## Liposomes

Many problems have developed when applying liposome preparations in ophthalmology, such as low drug loading, leakage of embedded drugs, poor long-term stability, high cost of industrialized large-scale production, difficulty with sterilization, and relatively low formulation targeting. Moreover, the retention time of simple liposomes in the eye is not ideal, so the development of new liposome preparations is necessary.

Table 6 Nanocarriers to Deliver Anti-VEGF Agents

Study	Disease	Experimental Models	Drug	Vehicle/Carriers	Production Method(s)	Results	Mean Particle Size (nm)	Future Direction
Formica ML, et al <sup>147</sup> 2021	Neovascular ocular pathologies	HUVEC	Bevacizumab and triamcinolone	Lipid mix and stabilizers	Phase inversion temperature	Enhanced antiangiogenic properties in HUVEC	113–182	Unspecified
Liu J, et al <sup>192</sup> 2019	CNV	Rabbit model	Bevacizumab and dexamethasone	PLGA-nanoparticles	Emulsion-solvent evaporation	Sustained release effects in vitro; enhanced efficacy inhibiting tube formation and VEGF secretion in HUVEC; increased antiangiogenic efficacy of CNV in a rabbit model.	190–222	Merit future investigation to validate and improve clinical use in treating AMD and other angiogenesis-dependent diseases.
Sun JG, et al <sup>149</sup> 2019	Corneal neovascularization and an oxygen-induced retinopathy	Mice model	Bevacizumab	Mesoporous silica nanoparticles	Nanocasting	Sustained release effects in vitro; enhanced antiangiogenic properties in HUVEC; enhanced antiangiogenic efficacy in vivo.	140	Unspecified
Savin CL, et al <sup>193</sup> 2019	DR	Rabbit model	Bevacizumab	Chitosan grafted polyethylene glycol methacrylate nanoparticles	Double crosslinking (ionic and covalent) process in reverse emulsion	Sustained release effects in vitro; enhanced efficacy as antiangiogenic in vivo.	200–900	Unspecified
Uğurlu N, et al <sup>194</sup> 2019	Eye posterior segment neovascularization	Rabbit model	Bevacizumab	Chitosan nanoparticles	Ionic gelation	Sustained release effects in vitro; high intravitreal drug concentration after subretinal injection in vivo.	188	Further studies are warranted to evaluate the stability of antibody-loaded nanoparticles and the anti-angiogenesis of bevacizumab loaded nanoparticles.



Luis de Redin I, et al <sup>150</sup> 2019	Corneal neovascularization	Rat model	Bevacizumab	Human serum albumin nanoparticles	Desolvation followed by freeze-drying	Sustained release effects in vivo; formulation remained in eye for more than 4 hours post-topical administration; improved antiangiogenic efficacy in vivo.	310	Unspecified
Juan M. Llabot, et al <sup>195</sup> 2019	Corneal neovascularization	Unspecified	Bevacizumab and suramin	Human serum albumin nanoparticles	Desolvation	Sustained release effects in vivo; bevacizumab released from Nps-Ga was characterized by a small burst effect followed by a sustained release rate.	158–210	Unspecified
Zhang XP, et al <sup>196</sup> 2018	Oxygen-induced retinopathy and corneal neovascularization	Mice model	Bevacizumab	PLGA-nanoparticles	Double-emulsion solvent evaporation	Sustained release effects in vitro; increased half-life of drug and enhanced antiangiogenic efficacy in vivo; enhanced antiangiogenic properties in HUVEC.	133	Unspecified
Yan J, et al <sup>197</sup> 2018	Neovascular age-related macular degeneration	Human umbilical vein endothelial cells	Ranibizumab	Ring opening polymerization, following addition of iron oxide nanoparticles	PLGA-PEGylated magnetic nanoparticles	Inhibition of the tube formation in HUVEC	5–10	Unspecified
D. K. Karumanchi, et al <sup>198</sup> 2018	Unspecified	Rabbit model	Bevacizumab	Phospholipids and lipids of different chain size	Lipid hydration and extrusion	Sustained release effects in vivo; slow release and retained antibody activity after intravitreal administration in vivo.	120–385	Unspecified
Mu H, et al <sup>199</sup> 2018	CNV	Rabbit model	Bevacizumab	Phospholipids and lipids of different chain size, albumin and PVA	Double emulsification	Sustained release effects in vivo; prolonged residency time in eye after intravitreal injection in vivo; enhanced antiangiogenic efficacy in a laser-induced CNV.	1190–4360	Unspecified

(Continued)

Table 6 (Continued).

Study	Disease	Experimental Models	Drug	Vehicle/Carriers	Production Method(s)	Results	Mean Particle Size (nm)	Future Direction
Pandit J, et al <sup>200</sup> 2017	VEGF related retinal disease	Goat and pig	Bevacizumab	Chitosan-coated PLGA nanoparticles	Emulsion-solvent evaporation	Increased drug transscleral permeation; enhanced bioadhesion in vivo.	222	Further studies concerning the cytotoxicity and concentration dependent reduction of the VEGF concentration in DR model were underway.
Sousa F, et al <sup>201</sup> 2017	VEGF related retinal disease	HUVEC	Bevacizumab	PLGA-nanoparticles	Double-emulsion solvent evaporation	Sustained pH-dependent bevacizumab release in vitro.	198	The mechanisms underlying bevacizumab delivery at the sub-cellular level are certainly needed.
Elsaid N, et al <sup>202</sup> 2016	Macular diseases	HUVEC	Ranibizumab	PLGA microparticles entrapping chitosan nanoparticles	Chitosan crosslinking – modified double emulsion method	Sustained release effects in vivo; enhanced antiangiogenic properties in HUVEC.	17–350	Unspecified
Varshochian R, et al <sup>48</sup> 2015	Eye posterior segment neovascularization	Rabbit mode	Bevacizumab	PLGA-albumin nanoparticles	Double-emulsion solvent evaporation	Sustained release bevacizumab for about 2 months after intravitreal injection and increased half-life of drug in vivo.	190	Unspecified
Lu Y, et al <sup>203</sup> 2014	Diabetic retinopathy	Rabbit model	Bevacizumab	Chitosan nanoparticles	Unspecified	Sustained release effects in vivo; inhibition of VEGF expression in vivo.	88.9	The preparation of nanoparticle should be optimized to achieve the goal of reducing intravitreal injection and the occurrence of complications in clinical practices.

## Nano-Suspensions

Nano-suspensions, particularly cationic suspensions, are suitable for ocular administration of poorly soluble and poorly absorbed drugs. However, most of the suspending agents for nano-suspensions are surfactants, which may be irritating and toxic to the eyes. Therefore, encapsulating the nano-suspension into a suitable gel matrix or bio-adhesive matrix, or even preparing an ophthalmic implant, may produce superior sustained release effects. In addition, the stability of a nano-suspension is insufficient compared with other colloidal particle systems, and storage time is shorter under the same conditions.

## Microemulsions/Nanoemulsions

Micro and nanoemulsions also used as ophthalmic preparation carriers, but droplet size, long-term stability, and the toxicity caused by the large number of surfactants and co-surfactants restrict their wide application. Therefore, it is necessary to focus on the irritation caused by nano-emulsions.

## Nanomicelles

PLGA nanomicelles have problems, such as relatively low drug loading, unsuitable release rate control, and difficulty in large-scale production, which have also become an important obstacle to their wide application in sustained drug release. In addition, PLGA nanomicelles contact or enter the eye as a foreign body, and their potential toxicity to eye tissues requires further study.

## Polymeric and Lipid Nanoparticles

Polymeric and lipid nanoparticles have a strong carrying capacity for fat-soluble substances, but insufficient carrying capacity for water-soluble substances. To achieve an optimal effect in the case of topical nano-formulations, it is highly desirable to engineer bioadhesive/mucoadhesive nano-systems to enhance the reactivity and bioavailability of nano-systems in the ocular cul-de-sac.<sup>152</sup>

## Anti-VEGF Agents

The main challenges for an anti-VEGF agent delivery system based on nanotechnology focus on loading molecules that maintain their biological activity after being released from the nanoparticle system, and studying formulation stability, pharmacokinetics, and efficacy in *in vivo* and *in vitro* models.<sup>153</sup>

## Future Prospects

Nanotechnology-based therapeutics have revolutionized the prevention of ocular disorders. Although there is a distinct advantage over commonly used ocular administration routes (intravitreal, topical, systemic, and periocular), all approaches are still limited to pre-clinical studies with several challenges need to be overcome, eg, large-scale manufacturing, and late phase clinical trials to enable scholars to achieve robust findings and evidence. Furthermore, future development of an ideal nanoscale clinical drug delivery vehicle should focus on the heterogeneous manifestations of the disease, such as the etiology and pathogenesis. The effects of particle size, surface charge, and composition and aggregation on the pharmacokinetic and pharmaco-toxic profiles need to be determined.

Using active targeting ligands to modify nano-formulations or incorporating penetration enhancers into composite systems may be an effective method for ocular nano-carrier DDSs to deliver drugs to the posterior segment of the eye, but studies concerning the uptake of targeted nano-carriers in the treatment of posterior-segment ocular diseases are scarce. Studies are needed to fill these gaps and overcome the problems associated with nano-carriers functionalized with multiple ligands of cells and tissues of the posterior eye as vehicles.

Many excellent nano-carrier DDS therapeutics require innovation to treat ocular disorders. For example, myopia also known as short-sightedness or near-sightedness, has become a serious public health problem worldwide. The number of individuals with myopia has reached nearly 2 billion worldwide, which includes 277 million individuals with high myopia.<sup>154</sup> Pharmacological strategies to control myopia include the non-specific anti-muscarinic agent atropine<sup>155</sup> and the M1 receptor-specific antagonist pirenzepine.<sup>156</sup> Atropine is the most widely studied agent for this indication, and once-daily topical low-concentration atropine eye drops effectively control the development of myopia.<sup>157,158</sup> However, there is little evidence on the ocular bioavailability of low-concentration eye drops. Due to the limited retention time of the drug in the conjunctival sac and low bioavailability, a nano-carrier DDS should be developed to load topical low-concentration atropine. The drug may achieve sustained release and improve the curative effect, which has potential value for the control of myopia.

## Conclusion

The penetration and delivery of drugs is particularly difficult under the complex and multiple physiological ocular barriers. Traditional drug preparations, such as eye drops, have a good therapeutic effect for anterior eye diseases, but there are some shortcomings, such as low bioavailability, frequent drug use, poor permeability. Intravitreal injection of drugs overcomes the ocular barrier for posterior eye diseases and achieves a therapeutic effect, but it has a high risk of various complications and adverse reactions which have brought great challenges to the treatment of diseases. Therefore, research and development of new DDSs are needed to better deliver drugs to the eyes and prolong the duration of drugs in the eyes.

Scientists have actively studied a variety of nanocarrier DDSs, such as liposomes, nanoemulsions, nanoparticles, nano-suspensions and nanomicelles, which show excellent delivery potential in in vitro and in vivo animal models, and prolong the retention time in the eye, suggesting that nano-carrier DDSs are a good application prospect in ocular drug therapy approaches and have potential value for further clinical development.

## Abbreviations

5-FU, fluorouracil; AMD, Age-related macular degeneration; AUC, area under the curve; BAB, blood-aqueous barrier; BRB, blood retinal barrier; CeCl<sub>3</sub>@mSiO<sub>2</sub>, prepared cerium (III) chloride (CeCl<sub>3</sub>)-loaded mesoporous silica; CeO<sub>2</sub>-NPs, synthesized cerium oxide nanoparticles; CH-MEs, chitosan-coated cationic microemulsions; CNTF, ciliary neurotrophic factor; CNV, choroidal neovascularization; CNV, corneal neovascularization; CsA, cyclosporine; CT, Nano-computed tomography; DDSs, drug delivery systems; DED, Dry eye disease; DM, diabetes mellitus; DR, Diabetic retinopathy; DSP, dexamethasone sodium phosphate; DSP-Zn-NP, dexamethasone sodium phosphate using zinc ion bridging; EAU, experimental autoimmune uveoretinitis; ERK1/2, extracellular signal-regulated kinase; HA, hyaluronic acid; IC<sub>50</sub>, the 50% inhibitory concentration; ICAM-1, intercellular adhesion molecule-1; IGF, insulin-like growth factor-I; IOL, intra ocular lens; IOP, intraocular pressure; K5, Kringle 5; K5-NP, K5-carrying PLGA nanoparticles; LECs, lens epithelial cells; LPD, liposome-protamine-DNA complex; MEs, microemulsions; mPEG-PCL, glycol-block-polycaprolactone; mTOR,

mechanistic target of rapamycin; NEs, nanoemulsion; NSAIDs, non-steroidal anti-inflammatory drugs; OPP, osteopontin peptide; PAP2, production of anthocyanin pigment 2; PAP4, production of anthocyanin pigment 4; PCNPs, synthesized cerium oxide nanoparticles (CeO<sub>2</sub>-NPs) coated with PEG-PLGA; PEG, poly (ethylene glycol); PLGA, poly lactic co-glycolic acid; PRN, “pro re nata”; PVCL-PVA-PEG, polyvinyl caprolactam-polyvinyl alcohol-polyethylene glycol; Rb, Retinoblastoma; RGC, retinal ganglion cell; ROP, Retinopathy of prematurity; ROS, reactive oxygen species; siRNA, small interfering RNA; STZ, streptozotocin; T&E, “treat and extend”; TA, triamcinolone acetonide; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

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## Disclosure

The authors declare no conflicts of interest in this work.

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