Chinese Chemical Letters 37 (2026) 112062

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Nanomaterial-based drug delivery systems for ocular diseases: A review

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ARTICLE INFO

Article history:
Received 27 August 2025
Revised 2 November 2025
Accepted 3 November 2025
Available online 4 November 2025

Keywords:
Nanomaterials
Nanocarriers
Drug delivery
Ocular diseases
Ophthalmic treatment

ABSTRACT

Ocular diseases are the main cause of vision loss and even blindness, with treatments including topical medications (such as eye drops), intravitreal injections, and surgery. However, the eye's complex anatomical structure and physiological barriers significantly limit drug bioavailability, affecting therapeutic efficacy. Nanomaterials have shown promise in ophthalmic drug delivery due to their unique properties. Nanomaterials can effectively penetrate ocular barriers to enhance drug permeability and bioavailability. Their ocular penetration can be further optimized by regulating nanoparticle (NP) size and surface properties, thereby prolonging drug residence time on the ocular surface and reducing administration frequency. Additionally, as controlled-release carriers, they enable sustained drug release to extend therapeutic duration and improve treatment efficacy. In addition, some nanomaterials also possess biological activities such as antioxidant, antibacterial and anti-inflammatory, making them a promising therapeutic strategy. This review focuses on the advances in nanomaterials application for ocular diseases, summarizes the mechanisms underlying nanomaterial-based drug delivery, and discusses the current challenges and future research directions, with the aim of providing new insights into the clinical application and translation of nanomaterials in ophthalmology.

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1. Introduction

Ocular diseases are leading causes of vision impairment and blindness, encompassing conditions such as keratitis, cataracts, uveitis, glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR) [1]. These diseases not only severely impact patients' quality of life but also impose a significant economic burden on society. With the aging population, lifestyle changes, and environmental factors, the prevalence of ocular diseases has increased notably. Currently, the treatment of ocular diseases primarily relies on drug therapy and surgery. Drug therapy, particularly in the early and middle stages of ocular diseases, remains the most common approach. The most frequently used form of drug therapy is local administration, which includes eye drops and intravitreal injections [2]. However, the eye's complex structure presents multiple physical and physiological barriers, such as the aqueous humor barrier, tear film, cornea, and blood-retinal barrier (BRB). While these barriers protect the eye from harmful substances, they also hinder drugs from reaching the target site, resulting in low bioavailability and reduced therapeutic effectiveness [3]. Furthermore, since drugs often cannot achieve their full therapeutic effects, patients are required to use medication more frequently. This not only increases the economic burden on patients but also reduces treatment adherence, while heightening the risk of side effects and complications, such as allergic reactions, bleeding, and infection [4]. Therefore, developing more effective drug delivery systems to enhance drug bioavailability, improve therapeutic outcomes, and minimize side effects is crucial for the treatment of ocular diseases.

In recent years, with the rapid development of nanomaterials, the application of nanomaterials in the diagnosis and treatment of ocular diseases has gradually become a research hotspot. Drug delivery through nanomaterials is expected to become a new method for the treatment of ocular diseases. Owing to their nanoscale size (typically 1–100 nm), controllable surface properties, excellent bio-

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https://doi.org/10.1016/j.cclet.2025.112062
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compatibility, and stability, nanomaterials possess unique advantages in drug delivery and are promising for wide application in ocular disease treatment [5]. Altering their size, composition, and surface characteristics, nanomaterials can effectively break through various physical and physiological barriers of the eye, enhancing drug bioavailability [6]. By modifying their size, composition, and surface characteristics, nanocarriers can penetrate various ocular barriers to enhance drug bioavailability and enable site-specific targeting, thereby increasing drug concentration at the lesion site and improving therapeutic efficacy [7]. Furthermore, they protect drugs from degradation, achieve controlled release to prolong therapeutic duration and reduce administration frequency, minimize side effects [8], and support the loading of diverse therapeutic agents, making them ideal for multiple treatment modalities [9].

Research has made significant strides in utilizing nanomaterials for ocular disease diagnosis and treatment. These materials not only address the limitations of traditional drug delivery systems but also enable targeted drug delivery and long-term sustained release. For example, in retinal diseases like DR and AMD, modifying the physical and chemical properties of nanomaterials allows for targeted drug delivery and sustained release, thereby improving therapeutic efficacy [10]. Additionally, nanomaterials show great promise in the diagnosis of ocular diseases. They can serve as imaging agents to enhance image resolution, improving the accuracy of early disease detection [11]. Despite their potential, the practical application of nanomaterials in ophthalmology faces several challenges. The eye's complex structure still limits their delivery efficiency, which remains a key barrier to their widespread clinical adoption. Biocompatibility and long-term safety, particularly in the sensitive environment of the eye, are also concerns that require further investigation to avoid immune and toxic reactions. To promote the further development and application of nanomaterials in ocular disease diagnosis and treatment, we have conducted an in-depth review of relevant high-quality research published over the past five years. This review analyzes the limitations of traditional drug delivery methods, highlights the latest advancements in nanomaterials for ocular applications, summarized the mechanism of nanomaterials in drug delivery, and discusses the challenges and future development directions for nanomaterials in ophthalmology. We hope this review will contribute to the continued development and application of nanomaterials in the field of ocular diseases.

2. Classification of nanomaterials

Nanomaterials are materials with dimensions smaller than 100 nm [12]. Due to their distinctive physical, chemical, and biological properties, they have found widespread applications in drug delivery, biomedical engineering, and various other fields. Depending on their composition, nanomaterials are typically categorized into several types, including metal nanomaterials, metal oxide nanomaterials, polymer nanomaterials, carbon-based nanomaterials, and composite nanomaterials. Detailed content is provided in the "Classification of nanomaterials" section of the Supporting information.

3. Ocular anatomy, disease classification and treatment

3.1. Ocular anatomy and disease classification

The human eye is a highly complex and sophisticated biological structure, composed mainly of two parts: The eyeball wall and the contents of the eyeball (Fig. S1 in Supporting information). Detailed content is provided in the "Ocular anatomy, disease classification and treatment" section of the Supporting information.

3.2. Conventional drug treatments and limitations

The effective delivery of drugs is crucial for treating eye diseases. Current methods of drug administration for eye diseases include local ocular surface delivery, vitreous cavity injection, periocular injection, and systemic administration. While these methods are commonly used and have demonstrated some therapeutic efficacy, they still present limitations that cannot be ignored. Detailed content is provided in the "Ocular anatomy, disease classification and treatment" section of the Supporting information.

4. Mechanisms of ocular drug delivery by nanomaterials

The application of nanomaterials in the treatment of ocular diseases represents a significant advancement in ophthalmic therapeutics, offering innovative strategies to overcome the inherent limitations of conventional drug delivery systems. The eye's complex anatomical and physiological barriers severely restrict drug penetration and bioavailability. Nanomaterials, by virtue of their unique physicochemical properties, provide a versatile platform to enhance drug delivery efficiency, improve targeting precision, and enable multifunctional therapeutic effects. The mechanisms through which nanomaterials facilitate the treatment of ocular diseases can be summarized as follows: (1) Ocular barrier penetration; (2) Prolonging drug residence time; (3) Controlling drug release; (4) Targeted drug delivery; (5) Inhibiting oxidative stress; (6) Antibacterial and anti-inflammatory effects; (7) Anti-angiogenesis; (8) Multifunctional drug delivery systems; (9) Gene therapy delivery. Detailed content is provided in the "Mechanisms of ocular drug delivery by nanomaterials" section of the Supporting information.

5. Advances in the application of nanomaterials in ocular diseases

5.1. Ocular surface diseases

5.1.1. Dry eye disease

The tear film is a thin, transparent layer of tears that covers the surface of the eyeball, playing a crucial role in maintaining clear vision [13]. It consists of three layers: The lipid layer, the aqueous layer, and the mucus layer, from outermost to innermost. The lipid layer, primarily secreted by the meibomian glands, helps reduce tear evaporation and stabilizes the tear film. The aqueous layer, secreted by the lacrimal glands and accessory lacrimal glands, forms the bulk of the tear film, providing essential nutrients to the cornea and maintaining the moisture of the ocular surface. The mucus layer, composed mainly of mucin secreted by conjunctival goblet cells, contributes to the formation and stability of the tear film. The tear film has multiple physiological functions and is of great significance for maintaining the normal structure and function of the ocular surface [14].

Dry eye disease, marked by tear film instability and ocular surface damage due to abnormal tear quantity, quality, or dynamics, leads to discomfort and visual impairment [15]. Despite its high prevalence, diagnosis remains difficult due to diverse symptoms and methods. Tear biomarkers such as proteins and lipid metabolites offer promising diagnostic potential [16]. Detecting and quantifying changes in these biomarkers is crucial for accurate diagnosis. Ye *et al.* [17] created a rapid detection system using metal nanomaterials that identify biomarkers *via* light scattering, showing high consistency with clinical diagnoses. Wechsler *et al.* [18] developed a biosensor with hydrogel-coated gold nanoshells (AuNSs), enhancing protein recognition through covalent bonds for improved dry eye diagnosis.

Oxidative stress plays a key role in dry eye, with excess reactive oxygen species (ROS) disrupting metabolism and redox balance [19]. Clearing ROS and controlling inflammation are critical treatment strategies. Nanoantioxidants, including nanozymes, nanomaterials with enzyme-like activity, offer advantages such as cost-effectiveness and stability over traditional antioxidants [20]. Cui *et al.* [21] designed CsA-loaded ceria nanozyme eye drops that sustainably release the drug while exerting antioxidant effects to reduce ROS and inflammation (Fig. S2A in Supporting information). Zhang *et al.* [22] developed PBnZ nanozyme eye drops using n-FeZIF-8 and PVA, extending corneal contact time and mitigating oxidative damage (Fig. S2B in Supporting information). Ou *et al.* [23] encapsulated Cu2-$_x$Se NPs in a hydrogel for adhesive, ROS-scavenging eye drops. Similarly, Wang *et al.* [24] formulated biocompatible nanoparticles from grape seed polyphenols that neutralize ROS and protect the ocular surface, offering a natural antioxidant option for dry eye treatment.

The onset of dry eye disease is influenced by multiple factors, with insufficient tear secretion or rapid evaporation being key contributors. Traditional treatment often involves topical eye drops, but their short residence time on the ocular surface necessitates frequent application, which limits their effectiveness and may lead to significant side effects. Thus, extending the residence time of the drug on the ocular surface is crucial for improving dry eye treatment. Eye drops based on multifunctional nanomaterials hold great promise as an ideal therapeutic option for dry eye. Lin *et al.* [25] prepared carbonized nanogels from lysine hydrochloride by thermal decomposition to make eye drops for the treatment of dry eye. The eye drops exhibited high biocompatibility and enhanced residence time on the ocular surface by interacting with the mucin layer, helping to alleviate dry eye symptoms. In animal models of dry eye, the eye drops were found to effectively relieve the condition. Zhou *et al.* [26] introduced a novel drug delivery system utilizing nanogels loaded with diquafosol sodium. This system not only inhibited ROS production and reduced inflammation but also extended the residence time of the drug on the ocular surface. Additionally, it promoted mucin secretion and restored tear film stability, further improving the treatment of dry eye.

5.1.2. Keratitis

The cornea, situated at the front of the eyeball, forms the outermost fibrous layer of the eye together with the sclera, accounting for about one-sixth of this membrane [27]. It is a transparent, avascular, and elastic tissue composed of five distinct layers from front to back: The epithelial cell layer, the anterior elastic layer, the stromal layer, the posterior elastic layer, and the endothelial cell layer. The epithelium, comprising about 10% of the cornea, consists of 4–6 layers of squamous epithelial cells. Beneath it, the anterior elastic layer is an acellular collagen membrane. The stromal layer, making up roughly 90% of the cornea, is composed of regularly arranged collagen fibers that ensure transparency. The posterior elastic layer is a regenerable, elastic membrane secreted by endothelial cells, and the innermost endothelial layer consists of tightly joined hexagonal cells providing a strong barrier function. Beyond its structural role, the cornea is a critical refractive medium, contributing approximately 43.25 D of the eye's total refractive power [28]. Changes in its refractive power can significantly alter the eye's overall refractive state. When its defenses are compromised, pathogenic factors can cause corneal inflammation, known as keratitis, which is classifiable into infectious, endogenous, and localized spreading types based on etiology [29]. Despite differing causes, keratitis commonly features stromal edema, turbidity, scarring, and neovascularization [30].

Infectious keratitis, a major cause of vision loss, is categorized into bacterial, fungal, and viral types. Bacterial keratitis is particularly common and is associated with risk factors like contact lens misuse, antibiotic/steroid overuse, microbial resistance, and ocular trauma [31]. It typically has an acute onset and requires prompt treatment. Current diagnosis relies on corneal scraping and culture, which are invasive, time-consuming, and have low positive rates, creating a need for faster, more sensitive methods. Fluorescence imaging offers a promising alternative. For instance, Xiang *et al.* [32] developed copper-based nanoparticles (NPs) with nitroreductase probes that enable bacterial fluorescence imaging for non-invasive diagnosis (Fig. S2C in Supporting information). Under laser irradiation, these NPs also release antibacterial copper ions, providing a theranostic platform.

Clinical treatment primarily uses broad-spectrum antibiotics like moxifloxacin and levofloxacin. However, their efficacy is limited by poor corneal penetration and bioavailability, compounded by the short residence time of eye drops, which can foster resistance and adverse reactions [33]. Advanced drug delivery systems are being developed to overcome these barriers. Padaga *et al.* [34] created ciprofloxacin-loaded NPs from ethylene glycol chitosan and polylactic acid, which extended corneal residence time, enhanced penetration, and disrupted biofilms. Similarly, mucoadhesive polymers that interact with mucins can improve drug retention. Ch *et al.* [35] developed mucoadhesive polyelectrolyte complex NPs for moxifloxacin, increasing its residence time and permeability while demonstrating strong bactericidal effects.

Nitric oxide (NO), an endogenous free radical with potent bactericidal and anti-inflammatory properties, is another promising therapeutic [36]. NO-based antibacterial therapies have been explored as effective treatments for bacterial keratitis due to their ability to modulate bacterial metabolism and the immune response. In one study, Hyejoong *et al.* [37] developed a silica NP-based NO delivery system that showed excellent antibacterial and anti-inflammatory effects. Photodynamic therapy (PDT) is another emerging treatment that generates reactive oxygen species (ROS) under light to kill bacteria. Zhang *et al.* [38] combined NO therapy with PDT using an upconversion NP (UCNP) core coated with mesoporous silica (Fig. S2D in Supporting information). The platform used upconversion NPs (UCNPs) as the photoreactive core, coated with mesoporous silica to carry both PDT photosensitizers and NO donors. Under 808 nm NIR light, the platform released NO and generated ROS, with the resulting superoxide radicals interacting with NO to produce potent bactericidal agents, achieving synergistic effects. PTT is another promising antibacterial treatment that uses photothermal agents to release heat, killing bacteria by raising tissue temperature [39]. PTT offers deeper tissue penetration compared to PDT, making it particularly useful for treating infections in deeper tissues. MXenes, especially V2C MXenes, are photothermal agents with high photothermal conversion efficiency and good biocompatibility. He *et al.* [40] developed a V2C MXene-based nanoplatform decorated with platinum NPs, enhancing photothermal conversion efficiency *via* surface plasmon resonance and effectively inhibiting biofilms.

Fungal keratitis, often caused by plant trauma, steroid abuse, or contact lenses, can lead to severe complications like corneal perforation and blindness. Topical antifungals are the mainstay, but their efficacy is limited by the corneal stromal barrier [33] Nanomaterials show promise in enhancing antifungal drug delivery and efficacy to address these limitations. For example, Sathe *et al.* [41] developed a natamycin-loaded nanomicelle system for sustained 24-hour release and improved corneal penetration. Sha *et al.* [42] created a NP-gel complex for natamycin that provided better penetration, biocompatibility, and residence time. The scarcity of effective antifungals remains a challenge. AgNPs have been widely studied for their antifungal properties, as they can exert antibacterial and antifungal effects by interacting with silver ions [43]. While AgNPs show promising antibacterial efficacy, their biological toxicity limits their application in the body. To overcome this,

Shi *et al.* [44] developed silver microspheres (AgMPs) using fetal bovine serum albumin, which gradually release silver ions, offering sustained antifungal activity without damaging corneal cells. Further improving the treatment of fungal keratitis, Ye *et al.* [45] created AgCu2O NPs that inhibited and destroyed fungal biofilms. To combat drug resistance from protective fungal cell walls, Ju *et al.* [46] designed a peptide conjugate nano-assembly that, upon contact with fungi, exposes α-helical peptides to disrupt cell walls, outperforming natamycin eye drops in a rabbit model.

5.1.3. Corneal repair and regeneration

The cornea is a transparent, avascular tissue crucial for clear vision. Damage from trauma or infection can cause stromal thinning, opacity, scarring, and neovascularization, potentially leading to blindness [47]. P Rapid repair of this tissue is therefore essential for vision restoration. Recent advances in nanomaterial-based therapies, particularly transparent hydrogels, show great promise. These hydrogels possess pre-gel fluidity and strong tissue adhesion, allowing them to flow into corneal defects, solidify, and support regeneration without the need for sutures, thereby avoiding further surgical trauma. Shen *et al.* [48] developed a hybrid hydrogel from porcine decellularized corneal stroma and methacrylated hyaluronic acid, which adhered closely to the stroma, promoted epithelial repair, and accelerated healing while maintaining transparency. Zhou *et al.* [49] created a suture-free PEG-Lysozyme hydrogel that encapsulated lysozyme to promote corneal epithelial cell migration and act as an active substitute, enhancing epithelial repair and protecting the stroma (Fig. S2E in Supporting information). The lysozyme in the hydrogel promoted corneal epithelial cell migration and repair. Additionally, the hydrogel serves as an active corneal substitute, helping to maintain the integrity of the corneal tissue during the repair process. While corneal transplantation is effective for severe damage, donor scarcity and immune rejection are limitations. Hydrogel patches offer a potential alternative. Li *et al.* [50] designed a light-curable hydrogel that forms a transparent, adhesive patch upon UV irradiation, promoting epithelial and stromal repair in rabbit models. Zhao *et al.* [51] developed a patch from recombinant human collagen and methacrylate gelatin that aided repair, prevented scarring, and maintained corneal transparency.

Oxidative stress and inflammatory reactions are major contributors to corneal stromal scarring, neovascularization, and decreased corneal transparency after corneal tissue damage [52]. Conventional drug therapies are often hindered by the corneal barrier and poor bioavailability. Advanced nanomaterial-based delivery systems, such as NPs, nanofibers, and hydrogels, improve drug efficacy through enhanced bioavailability and prolonged release. Ge *et al.* [53] developed NPs loaded with anti-inflammatory drugs and incorporated them into an injectable hydrogel system for the treatment of corneal damage. The hydrogel in this system not only prolonged the residence time of the drug on the ocular surface but also improved the bioavailability of the anti-inflammatory drugs. Farasatkia *et al.* [54] used a nanofibril double-layer membrane to gradually release antioxidant ascorbic acid, alleviating oxidative stress. Tang *et al.* [55] encapsulated mesenchymal stem cell exosomes in a thermosensitive hydrogel. The slow release of exosomes containing miR-432–5p accelerated epithelial repair and minimized scarring by inhibiting extracellular matrix deposition, thus preserving corneal transparency and function.

5.2. Lens diseases

The lens is a transparent biconvex structure situated behind the iris and in front of the vitreous body. Its primary role is to adjust the eye's refractive power by altering its curvature, ensuring light focuses precisely on the retina to form a clear image [56]. Cataract,

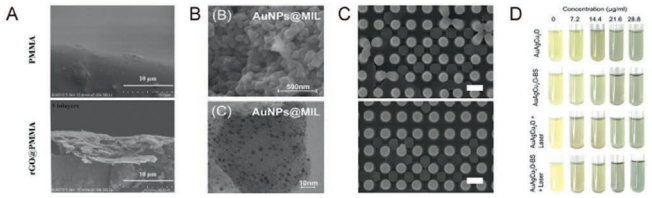


Fig. 1. Representative application of nanomaterials in lens diseases. (A) Scanning electron microscope (SEM) images of PMMA and rGO@PMMA. Copied with permission [65]. Copyright 2022, Elsevier. (B) SEM and transmission electron microscope (TEM) images of AuNPs@MIL. Copied with permission [67]. Copyright 2023, the Author(s). (C) SEM images of the NPA after exposure to *S. aureu*. Copied with permission [70]. Copyright 2020, Wiley-VCH GmbH. (D) The antibacterial effect of new metal NPs against methicillin-resistant Staphylococcus aureus. Copied with permission [72]. Copyright 2020, the Author(s).

characterized by lens opacity, is the leading global cause of blindness [57]. The pathogenesis of cataract is complex and is related to many factors, such as age, environment, metabolism, and genetics [58]. Among these, oxidative damage to the lens plays a crucial role in the onset and progression of cataracts. For example, Li *et al.* [59] synthesized chitosan-based NPs loaded with baicalin, which helped prolong the residence time of baicalin on the ocular surface, thereby continuously exerting its antioxidant effects and improving cataract symptoms. Cerium oxide NPs, recognized for their strong antioxidant properties, are also explored for treating cataracts [60]. Hanafy *et al.* [60] found that nano-cerium dioxide could delay cataract progression, potentially by acting as a catalase mimetic, thus reducing the glutathione-to-oxidized glutathione ratio. This suggests that cerium oxide NPs may offer a potential therapeutic strategy for cataract.

Surgery remains the most commonly used treatment for cataracts. Currently, IOLs are made from two main types of optical materials: Rigid materials such as polymethylmethacrylate (PMMA), and foldable materials made of hydrogel, silicone, and both hydrophilic and hydrophobic substances [61]. While cataract surgery is highly effective, posterior capsular opacification (PCO) is a frequent complication that significantly impacts postoperative vision [62]. Especially for young patients, the incidence of PCO is very high. Nd:YAG laser posterior capsulotomy is the main method for treating PCO, but it can cause complications such as iritis, glaucoma, retinal detachment, and macular edema. Consequently, it is necessary to explore new methods for the prevention and treatment of PCO. PCO occurs primarily due to the excessive proliferation, differentiation, and migration of residual lens epithelial cells within the capsular bag toward the visual axis [63]. Therefore, the complete removal of these epithelial cells is key to preventing PCO. Photothermal therapy (PTT) using near-infrared light offers a non-invasive alternative [64]. Zhang *et al.* [65] developed an innovative IOL by assembling graphene oxide and polyethyleneimine (Fig. 1A). After the graphene oxide was reduced to rGO, a multilayer film with good photothermal conversion ability and stability was formed. This film exhibited high photothermal conversion efficiency. Under infrared laser irradiation, the film induced apoptosis in lens epithelial cells, effectively preventing PCO. Gold nanomaterials are another effective option for PTT due to their excellent photothermal conversion efficiency and biocompatibility, and have been widely used as photosensitizers in PTT. Liu *et al.* [66] incorporated porous GNPs into IOLs to develop a novel IOL with photothermal properties. The porous structure of the GNPs enabled efficient photothermal conversion. Under infrared laser irradiation, the NPs induced apoptosis in lens epithelial cells, preventing PCO. Similarly, Hong *et al.* [67] mixed GNPs with glycidyl methacrylate and 2-ethyl acrylate to form a polymer mixed with GNPs, which was used as a material for making IOLs (Fig. 1B). This functionalized IOL material could not only effectively remove residual lens epithelial cells

in a short period of time, but also play a long-term role in preventing PCO under infrared laser irradiation, and had a synergistic therapeutic effect.

Endophthalmitis is a serious complication that can arise after cataract surgery, severely impacting a patient's vision and potentially leading to blindness [68]. Although the prolonged use of anti-inflammatory eye drops post-surgery can help prevent the onset of endophthalmitis, frequent administration not only increases the patient's burden but also may lead to adverse reactions such as drug resistance and allergies. Therefore, delivering drugs directly through the IOL or incorporating an antibacterial coating on the IOL surface presents a promising strategy to prevent postoperative endophthalmitis. Topete *et al.* [69] explored the potential of IOLs as anti-inflammatory drug delivery systems by developing drug-loaded IOLs that could sustainably release anti-inflammatory drugs. This approach effectively prevented postoperative inflammation and reduced the frequency of drug administration compared to traditional eye drops, providing a more convenient and efficient treatment alternative. In a similar vein, Choi *et al.* [70] designed a nanopillar array (NPA) coating using anionic polymers, which was integrated into the IOL (Fig. 1C). This NPA coating demonstrated antibacterial properties by disrupting bacterial cell membranes, inhibiting the adhesion of lens epithelial cells, and delaying PCO. Intraocular injection of antibiotics remains the primary treatment for endophthalmitis. However, frequent injections increase the risk of drug resistance, reduce the effectiveness of treatment, and may cause multiple complications [71]. In recent years, nanomaterials with inherent antibacterial properties have gained attention as a promising alternative treatment. Ye *et al.* [72] developed a novel drug delivery system based on metal NPs loaded with anti-inflammatory drugs (Fig. 1D). Leveraging the photothermal effect of the metal NPs, this system could kill bacteria by releasing metal ions, while simultaneously releasing anti-inflammatory drugs to reduce inflammation. In a rabbit model of endophthalmitis following cataract surgery, the dual antibacterial and anti-inflammatory effects of the metal NPs drug were highly effective, offering a promising approach for preventing and treating postoperative endophthalmitis.

5.3. Uveal disease

5.3.1. Uveitis

The uvea is the eye's middle layer, located between the sclera and retina, and consists of the iris, ciliary body, and choroid. It is highly vascularized and pigment-rich, which makes it a common site for ocular immune diseases. Harmful substances from the systemic circulation can accumulate here, and the tissue's antigenicity predisposes it to autoimmune reactions [73]. athological damage to the uvea includes inflammation, tumors, and degeneration. Uveal inflammation can disrupt lens and vitreous metabolism, cause turbidity, lead to iris adhesions, impair aqueous humor circulation, and result in secondary glaucoma or vision loss [74].

Uveitis, the most prevalent uveal disease, involves intraocular inflammation and can cause severe complications like cataracts, glaucoma, and retinal detachment [75]. It is categorized as infectious or non-infectious, with autoimmune dysregulation being a primary cause. The uvea's abundance of immune components makes it susceptible to inflammatory triggers [76]. When immune function is dysregulated, these substances activate immune cells and release inflammatory mediators, contributing to the onset or recurrence of uveitis. Currently, the most commonly used treatments for uveitis are steroid hormones and immunosuppressants. However, the bioavailability of drugs administered *via* eye drops is limited, necessitating frequent applications and often resulting in adverse reactions such as red eyes, eye pain, and blurred vision. Thus, alternative drug delivery methods are being explored. For instance, Bengani *et al.* [77] developed a contact lens encapsulating a hydrogel loaded with dexamethasone. This lens could release dexamethasone continuously for up to seven days, offering effective treatment for uveitis, reducing the frequency of drug use, and minimizing adverse drug reactions.

Although steroids can manage uveitis, long-term use is problematic, especially for vulnerable groups. Adalimumab (ADA), an anti-TNF-α antibody, is effective but systemic use risks immunosuppression [78]. However, systemic administration of ADA can cause immunosuppression, increasing the risk of infections and tumors. To mitigate these risks, alternative routes of administration are necessary. Eye drops are a commonly used non-invasive treatment method, but the eye has multiple biological barriers that limit drug penetration and bioavailability [79]. Chen *et al.* [80] used chitosan and glycerophosphate to construct ADA-loaded hydrogel eye drops as a treatment for uveitis (Fig. S3A in Supporting information). Compared with ordinary eye drops, this hydrogel eye drops showed excellent corneal penetration and sustained release of ADA. Minocycline, a semi-synthetic antibiotic with strong anti-inflammatory properties, had been used to treat various conditions [81]. However, long-term systemic use of minocycline could lead to serious adverse effects. To reduce these risks, Zhu *et al.* [82] created a minocycline-loaded nanomaterial hydrogel that controlled inflammation for up to 21 days while reducing adverse effects.

In addition to immune factors, oxidative stress significantly contributes to uveitis pathogenesis by generating ROS, causing lipid peroxidation and retinal damage [83]. Combining antioxidant and anti-inflammatory strategies is promising. Antioxidant NPs that can scavenge peroxides, ROS, and free radicals are emerging as a promising therapeutic approach [84]. They offer distinct advantages over traditional antioxidants, such as a larger surface area, greater stability, and prolonged persistence. Cerium NPs, in particular, show potential for ocular disease treatment due to efficient ROS-scavenging properties. Liu *et al.* [85] used thermosensitive copolymer nanomaterials and cerium NPs to develop a multifunctional hydrogel eye drop (Fig. S3B in Supporting information). The eye drop loaded with dexamethasone for the synergistic anti-inflammatory and antioxidant treatment of uveitis. Furthermore, the sustained release of the drug enhanced the therapeutic duration, improving treatment efficacy. Jin *et al.* [86] designed a nanogel loaded with antioxidant NPs that delivered cerium oxide NPs to the vitreous cavity, alleviating oxidative stress and treating uveitis. Cao *et al.* [87] created an antioxidant NP using curcumin and polyvinylpyrrolidone, demonstrating excellent biocompatibility and ROS-scavenging ability.

5.3.2. Choroidal neovascularization (CNV)

CNV involves the growth of new blood vessels beneath the retinal pigment epithelium (RPE), occurring either between the RPE and retina or between the RPE and choroid [88]. It is commonly associated with wet age-related macular degeneration, central exudative chorioretinopathy, and high myopia. The process begins with abnormal choroidal capillaries breaking through the choroidal capillary basement membrane and Bruch's membrane, proliferating and migrating under the retinal neuroepithelium [89]. These fragile, permeable vessels lead to exudation, hemorrhage, and eventual scarring, significantly impairing vision.

Common diagnostic techniques include indocyanine green angiography (ICGA), fluorescein fundus angiography (FFA), optical coherence tomography (OCT), and OCT angiography (OCTA). However, limited penetration depth of FFA and ICGA, restricts imaging of deep CNV. Nguyen *et al.* [90] used RGD peptide-conjugated GNP clusters to enhance CNV visualization, achieving a 17-fold signal increase. In another study, gold nanorods (GNRs) conjugated with RGD peptides (GNR-RGD) improved CNV resolution and dis-

tinguished normal from pathological vessels, providing a potential method for CNV visualization [91].

Vascular endothelial growth factor (VEGF) plays a crucial role in CNV formation [92]. Intravitreal anti-VEGF injections are the primary treatment, though repeated administration risks resistance, endophthalmitis, hemorrhage, and retinal detachment. Alternative strategies are thus needed. Gao *et al.* [93] developed a supramolecular nanofiber hydrogel with anti-VEGF drugs and $CaCl_2$ for sustained intravitreal release, reducing injection frequency. Li *et al.* [94] created biomimetic nanoparticles from retinal endothelial and red blood cell membranes that bind VEGF, inhibiting CNV with improved safety. Angiopoietin-1, a cytokine involved in angiogenesis, helps maintain vascular stability and protects endothelial cells from VEGF-induced damage [95]. Under pathological conditions, angiopoietin-2 antagonizes angiopoietin-1, leading to the breakdown of vascular integrity and promoting the formation of new blood vessels and leakage. Supplementing angiopoietin-1 can restore vascular instability caused by angiopoietin-2 [96]. However, angiopoietin-1 is chemically unstable and prone to hydrolysis. Yao *et al.* [97] encapsulated it in nanoparticles for targeted, sustained release at CNV sites, inhibiting vessel formation and leakage. Chen *et al.* [98] designed a biomimetic lipoprotein nanocarrier for topical eye drop delivery, effectively reaching the posterior eye and showing efficacy comparable to intravitreal aflibercept.

Inflammation and disrupted retinal homeostasis also drive CNV. Ischemia and hypoxia cause mitochondrial damage and excessive reactive oxygen species (ROS), amplifying inflammation. Macrophages and microglia release growth factors and inflammatory mediators, sustaining a destructive cycle [99]. Graphene oxide quantum dots are natural antioxidants that scavenge ROS and reduce inflammation, while minocycline inhibits macrophage/microglia activation. Huang *et al.* [100] developed a nano-delivery system combining both, enabling sustained release and demonstrating anti-inflammatory, antioxidant, and anti-angiogenic effects (Fig. S3C in Supporting information). Oxidative stress not only aggravated inflammation but also promoted VEGF expression in endothelial cells, contributing to angiogenesis. Zhang *et al.* [101] used RGD-modified nanoparticles loaded with salvianolic acid A, an antioxidant, to inhibit CNV in mice. Shen *et al.* [102] combined antioxidants and angiogenesis inhibitors in a NP formulation, demonstrating synergistic effects in inhibiting CNV progression.

Photodynamic therapy (PDT) is another CNV treatment that induces vessel occlusion *via* light activation. However, PDT consumes oxygen and generates ROS, worsening hypoxia and inflammation [103]. Metal NPs can mitigate these issues by consuming oxidative stress intermediates and alleviating hypoxia, inflammation, and oxidative damage. Jin *et al.* [104] designed a ZIF-8 platform with Pt and Au nanoparticles: Pt NPs catalyze hydrogen peroxide decomposition to relieve hypoxia and enhance PDT, while Au NPs exert anti-inflammatory and anti-angiogenic effects, offering a comprehensive CNV treatment strategy (Fig. S3D in Supporting information).

5.3.3. Uveal melanoma (UM)

UM is the most common intraocular malignancy in adults [105]. Its clinical manifestations are related to the location and volume of the tumor, which seriously affects the patient's visual function. UM is highly malignant, with high mortality, easy metastasis, and easy recurrence, resulting in great challenges in its clinical treatment [106].

Radiotherapy is a key treatment for UM by generating ROS to kill tumor cells [107]. However, the hypoxic tumor microenvironment limits ROS production and reduces radiotherapy efficacy. To address this, Yao *et al.* [108] developed a nanozyme that catalyzes hydrogen peroxide into oxygen, alleviating hypoxia and enhancing radiotherapy sensitivity. In UM, ROS accumulation can activate the mTOR pathway, leading to glutamine production and the maintenance of the tumor cells' redox state [109]. Disruption of this pathway increases ROS levels, inducing tumor cell pyroptosis, a proinflammatory form of cell death. Ren *et al.* [110] designed ROS-responsive nanoparticles loaded with MS-275 and V-9302, which decompose in the tumor site, release drugs, increase ROS, and trigger pyroptosis, effectively inhibiting UM progression in mouse models (Fig. S3E in Supporting information). Research has shown that lncRNA OUM1 is overexpressed in UM, promoting tumor cell proliferation, metastasis, and drug resistance. Targeting lncRNA OUM1 with RNA interference (siOUM1) could inhibit tumor cell proliferation and increase sensitivity to therapy [111]. However, effective delivery systems for RNA interference have been a challenge. Li *et al.* [111] utilized NPs to deliver siOUM1 and successfully achieved RNA interference therapy with promising anti-tumor effects.

PDT, which uses photosensitizers to produce ROS under light, is another common UM treatment [112]. Tumor hypoxia and abnormal vasculature hinder PDT efficacy. Studies have found that Lenvatinib can normalize tumor blood vessels and improve PDT outcomes [113]. Zheng *et al.* [114] developed composite nanoparticles that degrade under light, release ROS-sensitive polymers, generate ROS, and induce tumor cell death, while the co-delivered Lenvatinib promotes vascular normalization. Similarly, Li *et al.* [115] developed nanomicelles with tumor-targeting properties, designed to deliver oxygen to hypoxic regions within the tumor, further enhancing the therapeutic effect of PDT.

5.4. Glaucoma

Glaucoma is a neurodegenerative eye disease and a leading cause of irreversible blindness, primarily characterized by elevated intraocular pressure (IOP) that results in optic nerve damage and vision loss [116]. It is categorized into primary, secondary, and developmental types. Current treatments focus on lowering IOP to slow nerve damage and protect retinal ganglion cells [117]. Topical hypotensive medications are first-line therapies, reducing IOP by enhancing aqueous humor outflow or decreasing its production. However, drug delivery is limited by ocular barriers, reducing bioavailability and duration of action [118]. Chitosan, a biopolymer known for its excellent mucosal adhesion, permeability, and sustained-release properties, is frequently used in sustained drug delivery systems [119]. Kumara *et al.* [120] created a chitosan and graphene quantum dot nanocomposite that improved mucosal adhesion and prolonged drug action. Mesoporous NPs also enhance drug delivery. Luo *et al.* [121] used chitosan to modify hollow mesoporous ceria NPs (HMCNs) for the delivery of IOP-lowering drugs (Fig. 2A). The modified NPs demonstrated sustained drug release over a period of up to 10 days, effectively penetrating corneal tissue, extending drug action time, and improving therapeutic outcomes. Radwan *et al.* [122] developed a chitosan-coated bovine serum albumin NP for the sustained release of IOP-lowering drugs. These NPs showed good penetration through the cornea and sustained IOP-lowering effects in glaucoma models. Similarly, Cuggino *et al.* [123] used acrylic acid and *N*-isopropylacrylamide NPs to develop a nanogel that can carry IOP-lowering drugs, achieving sustained release of the drug, and has the potential to continuously deliver glaucoma drugs.

In addition, other delivery methods include drug-eluting contact lenses, which increase drug duration and bioavailability [124]. Drug delivery through contact lenses can not only increase the duration of drug action, but also improve the bioavailability of drugs. It is a promising drug delivery route. Kumara *et al.* [125] embedded chitosan encapsulated with ocular hypotensive drugs into contact lenses to develop a drug-loaded contact lens, which increased

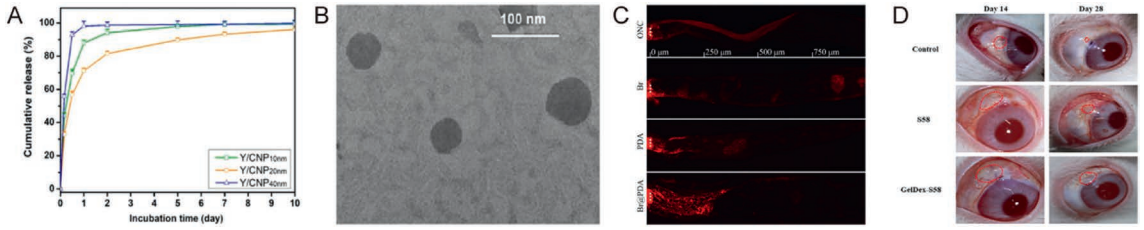


Fig. 2. Representative application of nanomaterials in glaucoma. (A) Cumulative drug release profiles from various types of HMCNs. Copied with permission [121]. Copyright 2021, the Author(s). (B) TEM images of novel NPs. Copied with permission [129]. Copyright 2022, American chemical society. (C) The effects of PDA NPs on axon regeneration 30 days after ONC. Copied with permission [131]. Copyright 2021, the Author(s). (D) Morphology of filter bubbles in animals in different groups at different time points. Copied with permission [134]. Copyright 2023, the Author(s).

the duration of drug action and bioavailability. Iontophoresis is a non-invasive method for delivering drugs to the inside of the eye. Under the action of appropriate current, it can better deliver drug molecules to the inside of the eye without causing eye damage [126]. To this end, Kim *et al.* [127] combined drug-loaded NPs with iontophoresis to develop a new drug delivery route. They placed drug-loaded NPs locally in the eye and then used iontophoresis to penetrate the drug into the eye, thereby increasing the duration of drug action.

Oxidative stress plays a central role in retinal ganglion cells death in glaucoma [128]. Elevated IOP impairs mitochondrial function in retinal ganglion cells, triggering excessive production of ROS. This ROS accumulation activates a series of cell death signaling pathways, ultimately leading to retinal ganglion cell degeneration. Therefore, strategies aimed at reducing oxidative stress and ROS production in retinal ganglion cells are crucial for enhancing cell survival. Rong *et al.* [129] developed a novel NP (NP1) loaded with a necroptosis inhibitor (Fig. 2B). The results showed that NP1 not only scavenged excess ROS in retinal ganglion cells but also inhibited the necroptosis pathway through the release of the encapsulated necroinhibitor-1. Polydopamine (PDA), a melanin-like polymer, exhibits strong antioxidant properties due to its phenolic groups and has been widely applied in the treatment of oxidative damage [130]. Lou *et al.* [131] constructed a multifunctional therapeutic platform to protect retinal ganglion cells using PDA NPs (Fig. 2C). These NPs effectively reduced ROS levels, thereby mitigating oxidative stress-induced damage and safeguarding retinal ganglion cells. Natural polymer-based hydrogel has good biocompatibility and biodegradability, which makes it a promising candidate for drug delivery platform. Liu *et al.* [132] developed a novel natural polymer hydrogel containing PDA NPs encapsulating curcumin, a natural antioxidant compound. This nano-hydrogel complex not only demonstrated excellent antioxidant properties but was also injectable, offering a non-toxic solution for alleviating oxidative stress, reducing ROS production, and preserving retinal ganglion cell function. These findings suggested that such nano-hydrogel systems might offer a promising treatment for glaucoma.

Trabeculectomy remains one of the most common surgical interventions for glaucoma, but the formation of scar tissue in the filtration area often compromises surgical success [133]. Although anti-fibrotic drugs can help reduce scar tissue formation, their short duration of action limits their effectiveness. To address this, Lin *et al.* [134] developed a photocurable bio-adhesive hydrogel, GelDex-S58, which is loaded with anti-fibrotic drugs (Fig. 2D). GelDex features a porous structure with high drug-loading capacity and controlled release and degradation properties. The results showed that compared to anti-fibrotic drugs alone, GelDex significantly prolongs the retention time of the filtration bleb and reduces collagen deposition in the conjunctival tissue. This approach effectively minimizes scar tissue formation, thereby enhancing the success rate of trabeculectomy.

5.5. Retinal diseases

The retina is a transparent membrane consisting of an inner neuroepithelium and an outer pigment epithelium, with a total of 10 layers. There are two important parts on the retina, namely the optic disc and the macula [135]. The optic disc, also known as the optic papilla, is the part where the optic nerve exits the eyeball. The macula is the area between the upper and lower vascular arches at the posterior pole of the retina, and is named for its rich content of lutein. In the center of the macula is a blood-free depression called the fovea, which is the area where vision is sharpest [136]. The retina is the initial site of vision formation and is also the site of lesions for many blinding eye diseases.

5.5.1. AMD

AMD is a leading cause of vision loss in the elderly and is categorized into dry AMD and wet AMD [137]. Dry AMD, accounting for 80%–90% of cases, involves progressive retinal pigment epithelium (RPE) atrophy, leading to photoreceptor degeneration [138]. Wet AMD is characterized by CNV, where leaky, hypoxic blood vessels cause severe retinal damage [139].

Oxidative stress plays a critical role in the pathogenesis of AMD, particularly in dry AMD [140]. The high metabolic activity of the retina generates significant ROS. When ROS exceed the retina's antioxidant capacity, they damage cellular components, accelerating AMD. Antioxidants are thus a key therapeutic strategy. Astragaloside-IV, a compound with antioxidant and anti-inflammatory properties, can protect RPE cells but has poor solubility [141]. To improve its bioavailability, alternative delivery technologies are necessary. Lipid nanocapsules (LNCs) are an ideal carrier for hydrophobic drugs with the characteristics of large drug loading and low cytotoxicity and have been widely used as a carrier for drug delivery. Sun *et al.* [142] encapsulated astragaloside-IV in LNCs to develop an eye drop for AMD treatment. These LNCs could penetrate ocular barriers to reach the retina, reduce ROS production, inhibit oxidative stress, and protect retinal morphology and function in AMD mouse models. Metal NPs, known for their potent antioxidant effects, have been explored as potential therapeutic agents for AMD. These NPs are easy to synthesize, highly stable, and exhibit excellent diffusion properties, making them suitable for antioxidant therapy. For instance, cerium dioxide NPs have been used in antioxidant treatments for various ocular diseases [143]. Platinum NPs also exhibit strong antioxidant effects. Cupini *et al.* [144] explored whether platinum NPs could protect retinal cells from oxidative stress damage. The study found that in AMD mouse models, injection of platinum NPs could inhibit retinal oxidative stress and inflammatory responses, protect retinal function, and have good therapeutic effects. Melanin, a natural antioxidant, is crucial for protecting retinal cells from oxidative damage. However, in RPE cells, melanin levels and antioxidant activity decrease with age, and regeneration within these cells is not possible. Thus, supplementing melanin could provide a thera-

peutic strategy for AMD. Melanin-like NPs (MNPs), which exhibit strong bio-similarity to natural retinal melanin, have been identified as effective antioxidants [145]. Kwon *et al.* [146] used melanin-like NPs (MNPs), which reduced oxidative stress and protected retinal function in a mouse model. Studies have shown iron dysregulation contributes to AMD, with elevated ferrous ions found in AMD patients' maculae and aqueous humor [147]. Excess iron promotes oxidative stress and inflammation. Tang *et al.* [148] developed a Prussian blue analogue, KCa [FeIII(CN)6] (CaPB), which binds ferrous ions. CaPB NPs reduced iron levels, mitigated oxidative stress, and prevented RPE and photoreceptor damage (Fig. S4A in Supporting information).

Chronic inflammation is another key driver of AMD, interacting with oxidative stress in a destructive cycle [149]. Targeting inflammation is therefore a viable treatment approach. Rapamycin (Rap), an immunosuppressant, inhibits inflammation but has poor water solubility, limiting its ocular delivery [150]. To overcome this issue, Mei *et al.* [151] utilized synthetic high-density lipoprotein NPs to deliver Rap. By encapsulating Rap within NPs, they improved its solubility, enabling higher drug concentrations. Compared to simple Rap injection, this NP-based delivery system demonstrated minimal cytotoxicity, effectively scavenged ROS, inhibited inflammation, and slowed the progression of AMD. Polymer NPs, particularly those made from poly(lactic-*co*-glycolic acid) (PLGA), have gained significant attention due to their stability, ability to enhance drug bioavailability, and provide sustained drug release. PLGA is a polymer approved by the U.S. Food and Drug Administration (FDA) with good biodegradability and compatibility, and is widely used as a drug delivery carrier. Suri *et al.* [152] utilized chitosan-modified PLGA NPs for the delivery of Rap. Compared with PLGA NPs, chitosan-modified PLGA NPs showed stronger stability and sustained drug release. In addition, chitosan-modified PLGA NPs also increased the residence time of the drug on the surface of the eyeball, promoted drug penetration and accumulation in the lesion site, and improved the drug treatment effect.

CNV is the primary pathological feature of wet AMD and a major cause of blindness. In addition to the previously mentioned nanomaterial applications in CNV, Xu *et al.* [153] developed a light-activated NP system loaded with anti-VEGF drugs and vascular disrupting agents. Upon exposure to 690 nm light, the NPs simultaneously release both anti-VEGF drugs and vascular-damaging agents, providing a combined approach to inhibiting angiogenesis and disrupting abnormal blood vessels in CNV. In CNV mouse models, this system significantly reduced vascular leakage, strongly inhibited CNV formation and had no obvious systemic toxic and side effects. Importantly, unlike traditional intravitreal drug delivery, these NPs are administered intravenously, overcoming the limitations of intravitreal injections while achieving effective therapeutic outcomes. This novel approach holds promise as a potential treatment for wet AMD.

5.5.2. DR

DR is a severe complication of diabetes, primarily characterized by retinal microvascular abnormalities, retinal leakage, and neovascularization. These changes lead to disrupted retinal blood circulation, visual impairment, and, in severe cases, vision loss [154]. The risk of DR is closely linked to the duration of diabetes and the level of blood glucose control, with a higher incidence observed in patients with longer disease duration. According to whether there is neovascularization, DR is classified into two types: Nonproliferative DR and proliferative DR. Proliferative DR is marked by increased retinal neovascularization, elevated vascular permeability, retinal ischemia and hypoxia, and retinal leakage, which significantly damage retinal structure and function. Early detection and treatment are critical in managing DR, as timely intervention can delay disease progression, improve treatment outcomes, and protect vision. 8-Hydroxy-2′-deoxyguanosine (8-OHdG) is a sensitive biomarker for DR, useful for early screening and monitoring disease progression [155]. Hainsworth *et al.* [156] developed a urine sensor based on nanotechnology capable of detecting 8-OHdG levels, providing a non-invasive method for screening DR and detecting the transition from early to late stages.

Increased levels of VEGF play a central role in retinal neovascularization in DR [157]. Targeted anti-VEGF therapy is a common and effective strategy to inhibit retinal neovascularization. Clinically, intravitreal injection of anti-VEGF agents is a main treatment for DR. However, this treatment method requires patients to frequent intravitreal injections, which not only leads to poor patient compliance, but also causes multiple complications such as endophthalmitis and intraocular hemorrhage. Therefore, it is necessary to develop alternative drug delivery methods. Nano drug delivery systems offer several advantages, including break through ocular barriers, protect drugs from degradation, and sustain drug release, making them ideal for ocular drug delivery. Radwan *et al.* [158] developed NPs using hyaluronic acid and bovine serum albumin to deliver anti-VEGF drugs to the posterior pole of the eye. In rat DR models, the NPs alleviated pathological changes and provided retinal protection. Pandit *et al.* [159] designed polymer NPs made from chitosan, which were loaded with anti-VEGF drugs. These NPs demonstrated improved permeability, more efficient drug delivery to the posterior eye, and a greater reduction in VEGF levels compared to traditional methods. Additionally, GNPs have been shown to inhibit VEGF-induced endothelial cell proliferation, thus reducing retinal neovascularization. Dave *et al.* [160] used GNPs to construct a drug delivery system for targeted delivery of anti-VEGF drugs. The NPs not only enabled targeted drug delivery to the retina but also exhibited excellent biocompatibility and sustained drug release characteristics, making them an effective method for treating DR.

The formation of new blood vessels in DR is not solely regulated by VEGF but is also influenced by various inflammatory factors. In DR, the retina experiences significant inflammation, which exacerbates retinal damage and accelerates disease progression. Anti-inflammatory therapy has thus emerged as an important treatment approach for DR. The retinal microenvironment, which involves complex interactions between different retinal cells, is crucial for maintaining retinal homeostasis. Disruption of this environment contributes to DR development [161]. Increased ROS in the retinal microenvironment damage RPE cells, triggering an inflammatory response through the activation of immune cells and microglia. To address this, Zhou *et al.* [162] developed a glucose-responsive hydrogel to deliver Cu-PEI/siMyD88 NPs to RPE cells (Fig. S4B in Supporting information). This hydrogel exerts anti-inflammatory and antioxidant effects, protecting RPE cells and reshaping the retinal microenvironment. In mouse DR models, the hydrogel reduced retinal inflammation and oxidative stress, delayed disease progression, and offered a new strategy for DR treatment. Lipid metabolism disturbances, which lead to lipid peroxidation, are another significant factor in DR pathogenesis [163]. Lipid peroxidation damages cell integrity, aggravates retinal inflammation, and contributes to vascular abnormalities [164]. Selenium (Se), an essential trace element, has antioxidant and anti-inflammatory properties and has been used in treating various diseases [165]. Se NPs, due to their superior biocompatibility compared to traditional Se compounds, have been explored as a therapeutic agent for DR. Niu *et al.* [166] used Se NPs to develop a porous Se nanosphere. It could inhibit ROS production and inflammatory responses, protect retinal vascular endothelial cells, reduce retinal neovascularization, and alleviate vascular lesions, offering a dual action of anti-inflammatory and anti-lipid peroxidation effects.

5.5.3. Retinopathy of premature (ROP)

ROP is a proliferative retinopathy that occurs in low-birth-weight or premature infants. It is a leading cause of blindness in this population, primarily characterized by the abnormal proliferation of retinal blood vessels [167]. The main risk factors for ROP include premature birth, low birth weight, and exposure to high concentrations of oxygen after birth. Retinal neovascularization is the key pathological feature of ROP, leading to retinal ischemia, hypoxia, leakage, and a persistent inflammatory response. Over time, this damages retinal function, resulting in severe vision loss or even blindness. Although intravitreal injections of anti-VEGF drugs are commonly used to inhibit retinal neovascularization in ROP patients, this method could cause various postoperative complications and pose risks to the development of the retina, brain, and other organs in infants [168]. Therefore, alternative routes of administration are urgently needed for effective treatment. In this regard, Bohley *et al.* [169] developed LNCs loaded with both anti-inflammatory and anti-VEGF drugs (Fig. S4C in Supporting information). They evaluated the therapeutic effects of these nanocapsules through intravenous administration. Cyclodextrin was embedded within the LNCs, enhancing their ability to pass through cellular barriers and improving their affinity and specificity for retinal cells. The results demonstrated that intravenous injection of LNCs effectively inhibited retinal neovascularization, reduced retinal inflammation, and had a therapeutic effect on ROP without impairing retinal development. EXOs are naturally occurring NPs secreted by various cell types. Due to their non-toxic, biodegradable, and highly biocompatible nature, EXOs are considered ideal carriers for drug delivery. They can efficiently penetrate biological barriers within the eye, offering strong drug delivery capabilities. Dong *et al.* [170] engineered EXOs loaded with anti-angiogenic peptides and assessed their delivery efficiency and therapeutic effects *via* retroorbital and intravitreal injections. The EXOs were able to efficiently deliver the peptides to the retina, inhibiting retinal neovascularization and vascular leakage. Notably, retroorbital injection provided the same drug delivery efficiency and therapeutic effect as intravitreal injection, offering a less invasive alternative for ROP treatment. Moreover, some studies have indicated that graphene quantum dots possess anti-tumor properties [171]. Given the similarities between retinal neovascularization and tumor growth, Zhao *et al.* [172] investigated the potential anti-angiogenic effects of graphene quantum dots. Their results showed that graphene quantum dots not only inhibited the proliferation and sprouting of retinal vascular endothelial cells *in vitro* but also reduced retinal neovascularization *in vivo*, suggesting their potential as a new treatment for retinal neovascularization in ROP. Additionally, Jian *et al.* [173] synthesized a novel carbon nanomaterial using sodium alginate and 1,8-diaminooctane *via* mild pyrolysis. This material demonstrated effective ROS scavenging, VEGF inhibition, and anti-inflammatory effects in a rabbit eye model, highlighting its potential as an effective therapeutic for retinal neovascularization. Xue *et al.* [174] developed a noninvasive fluorinated and RGD-modified ruthenium polymer nanozyme (FR-PolyRu) eye drop by encapsulating antioxidant PolyRu nanozyme within fluoridated liposomes. These eye drops can penetrate the ocular barrier through enhanced membrane permeability *via* fluorination, RGD-mediated targeting, and nanoenzyme-catalyzed oxygen-driven active transport after local administration. This combined action effectively inhibits pathological retinal neovascularization in oxygen-induced retinopathy (OIR) mice, offering a safe and effective non-invasive strategy for treating related diseases.

5.5.4. Retinitis pigmentosa (RP)

RP is a group of inherited retinal degenerative diseases, characterized by the progressive degeneration and apoptosis of retinal photoreceptor cells and dysfunction of retinal pigment epithelial cells, which ultimately lead to gradual vision loss or blindness [175]. RP is caused by a variety of gene mutations, and its genetic heterogeneity is high, involving hundreds of different genes. Gene therapy, which aims to replace or repair mutated genes, has emerged as a promising treatment for genetic disorders. In RP, mutations in the rhodopsin gene are a common cause, and this mutation is frequently targeted in gene therapy approaches. Zheng *et al.* [176] developed a NP containing the full-length rhodopsin genomic DNA, which effectively alleviated RP progression in a rhodopsin gene mutation model. This NP successfully delivered the genomic DNA to the retina and maintained high levels of transgene expression for up to five months, delaying the progression of RP. Similarly, SP *et al.* [177] investigated the therapeutic potential of NPs loaded with the full-length rhodopsin gene. Their findings demonstrated that the NPs enhanced rhodopsin expression, restored the structure and function of retinal photoreceptor cells, and suggested that gene enhancement therapy using full-length rhodopsin genomes holds promise for treating RP.

The degeneration and apoptosis of retinal photoreceptor cells are the hallmark pathological features of RP. In the advanced stages of RP, retinal photoreceptor cells almost entirely degenerate, impairing the retina's ability to detect external light stimuli. As a result, retinal neurons cannot be stimulated to generate visual signals, ultimately leading to blindness. In recent years, retinal prostheses have been developed to stimulate retinal neurons and potentially restore visual function [178]. Francia *et al.* [179] explored the use of conjugated polymer NPs injected into the subretina to restore visual activity in rats with late-stage RP. Their study found that the polymer NPs not only restored visually evoked cortical potentials and physiological pupil light reflexes but also partially restored vision, demonstrating the potential of subretinal prosthetic intervention as a promising treatment for late-stage RP. Similarly, Maya-Vetencourt *et al.* [180] designed conjugated polymer NPs capable of rescuing visual function in RP rats. Their results indicated that subretinal injection of these NPs did not induce any inflammatory response and successfully restored retinal light sensitivity and visual function, providing a novel therapeutic approach for RP.

5.5.5. Retinoblastoma (RB)

RB is a malignant retinal tumor and the most common intraocular cancer in children [181]. It often presents unilaterally or bilaterally and can metastasize to the orbit, intracranial region, or distant sites, potentially causing blindness or death if untreated. RB pathogenesis is strongly associated with mutations in the RB gene, making it a key target for diagnosis and therapy [182]. Hu *et al.* [182] developed artificial vesicle composite NPs loaded with DNA enzymes, based on MnO_2 nanosponges and artificial vesicles derived from human red blood cells (Fig. S4D in Supporting information). These NPs could target RB cell membranes, enter the cells *via* endocytosis, and release fluorescently modified DNA enzymes, acting as both an imaging agent for magnetic resonance imaging and a gene silencing therapy for two specific mRNAs in RB cells. This dual function of diagnostic imaging and gene therapy offered a novel approach for diagnosing and treating RB.

Chemotherapy is widely used for RB; however, the blood–retinal barrier (BRB) restricts drug delivery, reducing efficacy with systemic administration. Intravitreal injections improve delivery but require repeated dosing, increasing risks of adverse effects and complications. Therefore, advanced drug delivery systems are needed. Injectable hydrogels offer high drug loading, easy administration, and sustained release, making them attractive carriers [183]. Cooper *et al.* [184] developed an injectable dendrimer hydrogel for melphalan delivery, which maintained flowability post-gelation and slowly released the drug, delaying tumor progression. Similarly, Tabatabaei *et al.* [185] encapsulated melphalan in lipid nanoparticles, enhancing efficacy while reducing dosage and tox-

icity. Gold nanoparticles (GNPs) are also utilized for their anti-angiogenic properties and ability to cross ocular barriers. Haase *et al.* [186] constructed hyaluronic acid-coated GNPs functionalized with atrial natriuretic peptide (ANP), demonstrating effective anti-tumor activity *in vivo*.

PTT which uses photosensitizers to convert light into heat and kill cancer cells, has emerged as a promising RB treatment [187]. Advances in nanotechnology now allow combining PTT with chemotherapy *via* multifunctional nanomaterials. Mudigunda *et al.* [188] developed polymer NPs (PLGA/polycaprolactone) co-loaded with anti-tumor drugs and NIR dyes. Under infrared light, these NPs generate heat, causing DNA damage and cell death. Li *et al.* [189] designed liposomes co-loaded with anti-tumor drugs and indocyanine green. Upon laser irradiation, the liposomes produce heat and release drugs, yielding a dual therapeutic effect. Similarly, Jin *et al.* [190] also constructed a polydopamine (PDA)-based nanoplatform for synergistic chemo-photothermal therapy.

To systematically summarize the unique advantages and inherent limitations of different types of nanomaterials in intraocular drug delivery, Table S1 (Supporting information) provides a comprehensive comparative overview.

6. Challenges and limitations

Although nanomaterials have exhibited remarkable potential in addressing the unmet therapeutic needs of ocular diseases, their translation from preclinical laboratory research to routine clinical practice remains hindered by several interrelated and significant challenges. Critical hurdles in biocompatibility, scalable manufacturing, translational research, and targeted delivery require systematic solutions. Addressing these issues is imperative to secure the long-term safety, reliable efficacy, and industrial scalability essential for integrating nanomaterial-based therapies into clinical ophthalmology.

6.1. Biocompatibility and toxicity

The long-term biocompatibility and potential toxicity of nanomaterials remain primary concerns for intraocular applications, with risks varying significantly across material classes due to inherent differences in physical structure, chemical reactivity, and biological interaction patterns. The eye is an immune-privileged but highly sensitive organ with delicate tissues, limited regenerative capacity, and strict physiological barriers, where even mild toxicity can lead to irreversible vision impairment. For metal and metal oxide nanomaterials, such as AgNPs that exhibit strong antibacterial activity against pathogens causing keratitis, uncontrolled release of silver ions can damage corneal epithelial cells [43]. Shi *et al.* found uncoated AgNPs induced dose-dependent cytotoxicity in rabbit corneal epithelial cells, with 50 μg/mL AgNPs reducing cell viability by 40% *via* oxidative stress and mitochondrial dysfunction [44]. Cerium oxide NPs (CeO_2 NPs) possess ROS-scavenging ability, making them promising for treating conditions like dry eye and AMD [21,143]. However, studies show that high doses (*e.g.*, 100 μg/mL) can lead to their accumulation in RPE cells, causing lysosomal overload and impaired phagocytic function [60]. Polymer nanomaterials like PLGA, though widely used for sustained drug release in retinal diseases [152], but they degrade into lactic acid and glycolic acid that can alter the local microenvironment. Sun *et al.* [142] observed rapid degradation of PLGA-based LNCs in the anterior chamber lowered pH from 7.4 to 6.8, causing mild conjunctival hyperemia in rabbits. Chitosan NPs with cationic surface charge enhancing mucoadhesion in glaucoma can disrupt corneal epithelial cell membranes if molecular weight exceeds 200 kDa. Kumara *et al.* [120] reported chitosan-graphene quantum dot composites with +30 mV zeta potential increased corneal permeability by 25% but induced 15% cell lysis. PVA-based hydrogels for uveitis treatment with >5% residual PVA monomers can trigger uveal inflammation, increasing IL-6 and TNF-α expression in the choroid [82]. Graphene oxide used in PCO PTT generates 2-fold more ROS under 808 nm laser irradiation, leading to mild retinal inflammation [65]. Carbon quantum dots (CQDs) with high biocompatibility can cross the BRB and accumulate in the optic nerve, interfering with nerve signal transmission by inhibiting sodium-potassium ATPase activity. Thus, rigorous long-term toxicological studies are imperative and future research focusing on standardizing ocular-specific toxicity assessment protocols, investigating nanomaterial clearance pathways, and enhancing biocompatibility *via* surface modifications like PEGylation.

6.2. Scalability, stability, and sterilization

The transition from laboratory-scale synthesis to nanomedicine industrial-scale production presents significant challenges in maintaining batch consistency, physicochemical stability, and sterility. These challenges are crucial for ensuring predictable pharmacokinetics and reliable therapeutic effects in ocular applications. Laboratory-scale processes often rely on small-volume, precise control over reaction conditions (such as temperature, stirring speed, and reagent addition sequences) to produce nanomaterials with well-defined properties. However, scaling these processes to industrial levels often disrupts this precision, as minor variations in process parameters can propagate into significant differences across production batches. For ocular nanomedicines, even small deviations in particle size or surface charge can alter their ability to overcome ocular barriers (such as the cornea or BRB) or interact with target cells, leading to unpredictable therapeutic effects and potential safety risks. Scalability often compromises structural uniformity. For instance, while lab-scale microemulsion produced uniform LNCs for astragaloside-IV delivery in AMD, scaling up with high-shear mixing resulted in significant particle size variations (50–200 nm). Those larger than 150 nm exhibited a 40% reduction in corneal penetration [142]. Chitosan-modified PLGA NPs exhibit ± 5 mV surface charge variations across batches, with +20 mV batches having 20% higher mucoadhesion [152]. Long-term stability over 6–12 months at 4–25 °C (protected from light) remains a significant challenge. GNRs used for CNV imaging were found to aggregate upon light exposure, resulting in a 30% increase in hydrodynamic size after three months and a 50% reduction in photoacoustic signal intensity [91]. Thermosensitive chitosan hydrogels for glaucoma lose gelation ability after 6 months, with storage modulus decreasing from 1000 Pa to 500 Pa due to chitosan chain degradation [121]. Liposomes loaded with anti-VEGF drugs for DR undergo lipid oxidation, with 25% increased MDA levels after 4 months and 30% lower drug encapsulation efficiency [158]. Terminal sterilization is critical yet challenging for polymer nanomaterials. Autoclaving (121 °C, high pressure) degrades polymer nanomaterials, with CIP-loaded ethylene glycol chitosan-PLGA NPs losing 40% drug content and increasing 30% in particle size [34]. Gamma irradiation (25 kGy) reduces fluorescent intensity of copper-based NPs by 50%, compromising bacterial keratitis imaging [32]. Thus, developing robust scalable manufacturing and standardized quality control is essential to address these interconnected challenges and facilitate the clinical translation of ocular nanomedicines.

6.3. Limitations in clinical translation

Nanomaterial-based ocular therapies have shown encouraging efficacy and safety in cell and animal experiments. However, their transition from preclinical research to real-world clinical application is still hindered, mainly due to two interrelated obstacles: Preclinical models' limitations in reflecting human ocular bi-

ology and the uncertainties of evolving regulatory pathways for nanomedicines. Despite promising preclinical results, clinical translation of nanomaterial-based ocular therapies is hampered by preclinical model limitations and regulatory hurdles. Animal models (mice, rabbits) do not fully replicate human ocular physiology: Rabbit corneas (~400 μm) are thinner than human corneas (~550 μm), so CIP NPs penetrating 80% of rabbit corneas only penetrate 50% of human corneas *ex vivo* [34]. Mouse BRB is more permeable than human BRB, with cell membrane-cloaked NPs accumulating 3-fold more in mouse retinas than human retinal explants [97]. Most preclinical studies last <6 months, but human ocular nanomedicines require 10–15 years of safety data. Cerium oxide NPs showed no toxicity in 3-month rabbit studies but induced RPE cell dysfunction after 12 months [60]. Current detection methods (fundus photography, OCT) cannot identify early nanomaterial-induced damage, though Wechsler *et al.* developed a gold nanoshell biosensor for retinal stress biomarkers (*e.g.*, 8-OHdG) that lacks clinical validation [18]. Regulatory pathways for nanomedicines are evolving, requiring extensive characterization to define critical quality attributes (CQAs) and batch equivalence. Collaboration among scientists, clinicians, and regulatory agencies is needed to establish clear safety, efficacy, and quality control guidelines.

6.4. Targeted delivery and barrier penetration efficiency

While nanomaterials are designed to overcome ocular barriers, their delivery efficiency to specific intraocular targets, particularly the posterior segment (retina, choroid), is often suboptimal. The complex and multi-layered nature of barriers like the cornea and BRB continues to limit the penetration of even nanoscale systems [191]. Performance can be highly variable under different disease conditions. For example, inflammation may enhance permeability in some cases but increase nonspecific trapping in others [74]. Although surface modifications (*e.g.*, with cell-penetrating peptides, mucoadhesive polymers) have improved residence time and penetration to some extent, achieving truly specific targeting to diseased cells (*e.g.*, retinal ganglion cells in glaucoma, RPE cells in AMD) without off-target effects remains a challenge [91,101,121]. Future efforts should focus on designing smarter nanomaterials that can respond to specific pathological stimuli (*e.g.*, pH, enzymes) for triggered drug release, and on leveraging active targeting motifs with high affinity for ocular cell receptors to improve specificity and reduce required doses.

7. Future perspectives

Despite their substantial therapeutic potential, the clinical translation of nanomaterial-based interventions for ocular diseases remains contingent upon addressing long-standing challenges in biocompatibility, scalable manufacturing, and targeted delivery. Future advancements will hinge on a multi-pronged strategy that embraces next-generation materials, innovative technologies, and robust translational frameworks. A key direction involves the development of smarter, responsive nanomaterials engineered to react to specific pathological cues, on-demand drug release at the disease site. Complementing this, the exploration of natural nanocarriers, particularly exosome-based nanoplatforms, is highly promising. Leveraging their innate biocompatibility, low immunogenicity, and exceptional ability to cross biological barriers, EXOs can serve as ideal vehicles for targeted drug and gene delivery to challenging posterior segment tissues. Furthermore, the integration of artificial intelligence and machine learning is poised to revolutionize the entire design and optimization pipeline. These tools can analyze complex datasets to predict the optimal physicochemical properties for maximizing ocular penetration and cell-specific targeting, thereby accelerating the rational design of novel nanomaterials. This computational power will be particularly valuable for advancing nanomaterial-mediated gene therapy. Innovations in non-viral vectors, including lipid NPs and polymers designed for clustered regularly interspaced short palindromic repeats/-associated protein 9 (CRISPR/Cas9) delivery, hold immense potential for addressing the root causes of inherited retinal diseases, moving beyond symptomatic treatment. Bridging the translational gap also demands more predictive human-relevant models. Traditional animal models often fail to recapitulate human ocular physiology. Thus, the adoption of advanced systems such as three-dimensional (3D) retinal organoids and eye-on-a-chip microphysiological systems is crucial for more accurately evaluating biodistribution, safety, and efficacy prior to clinical trials. Simultaneously, advancing scalable and reproducible manufacturing processes is essential to ensure batch-to-batch consistency, long-term stability, and sterility. Ultimately, through sustained interdisciplinary collaboration among material scientists, ophthalmologists, computational biologists, and regulatory experts, these converging strategies can accelerate the realization of a new generation of targeted, effective, and personalized nanotherapies, transforming the treatment landscape for a wide range of currently difficult-to-treat ocular conditions.

8. Conclusion

In summary, nanomaterials have emerged as a revolutionary platform for diagnosing and treating ocular diseases, offering innovative solutions to overcome the inherent limitations of conventional therapies. Their unique physicochemical properties enable enhanced ocular barrier penetration, prolonged drug retention, controlled release, and targeted delivery. These advantages have been successfully demonstrated across a spectrum of ocular studies. While the majority of current applications remain at the preclinical stage, the rapid evolution of nanomaterial design underscores their significant translational potential. However, the path to clinical adoption is not without challenges. Key issues including long-term biocompatibility, batch-to-batch reproducibility, scalable manufacturing, and sterilization efficacy must be systematically addressed through interdisciplinary collaboration. Future efforts should prioritize the development of standardized safety evaluation protocols, disease-microenvironment-responsive nanomaterials, and more predictive ocular disease models. With continued advances in biomaterial science and a deeper mechanistic understanding of nanomaterial-ocular tissue interactions, nanotechnology is poised to fundamentally transform ophthalmic care. By integrating diagnostic and therapeutic functions into single platforms, next-generation nanomedicines hold the promise of enabling personalized, minimally invasive, and highly effective strategies for managing ocular diseases, ultimately preserving vision and improving patient quality of life worldwide.

CRediT authorship contribution statement

Yuke Ji: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Jia Liang:** Writing – original draft, Investigation, Conceptualization. **Xiangqing Hei:** Investigation, Conceptualization. **Lu Chen:** Investigation, Conceptualization. **Shudong Yu:** Writing – review & editing. **Dong Fang:** Writing – review & editing, Writing – original draft. **Hui Tan:** Writing – review & editing. **Shaochong Zhang:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (No. 82301223), the National Natural Science Foundation of China (No. 82271102), the Key Project Fund of National Natural Science Foundation (No. 82230031), the National Natural Science Foundation of China (No. 82571229), the Sanming Project of Medicine in Shenzhen (No. SZSM202411007), the Shenzhen Medical Research Fund (No. C2401007), the China Postdoctoral Science Foundation (No. 2025M772110).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.112062.

References

[1] J.M. Kang, A.P. Tanna, Med. Clin. North. Am. 105 (2021) 493–510.
[2] G. Xie, S. Lin, F. Wu, J. Liu, Adv. Drug Deliv. Rev. 200 (2023) 115004.
[3] S. Li, L. Chen, Y. Fu, J. Nanobiotechnol. 21 (2023) 232.
[4] D. Patel, S.N. Patel, V. Chaudhary, S.J. Garg, Curr. Opin. Ophthalmol. 33 (2022) 137–146.
[5] X. Zhu, S. Li, Mol. Cancer 22 (2023) 94.
[6] D.R. Janagam, L. Wu, T.L. Lowe, Adv. Drug Deliv. Rev. 122 (2017) 31–64.
[7] A. Mandal, R. Bisht, I.D. Rupenthal, A.K. Mitra, J. Control. Release 248 (2017) 96–116.
[8] L.X. Ling, Y. Ouyang, Y. Hu, J. Nanobiotechnol. 21 (2023) 248.
[9] S. Zha, H. Liu, H. Li, et al., ACS Nano 18 (2024) 1820–1845.
[10] X. Liu, K. Huang, F. Zhang, et al., J. Nanobiotechnology 22 (2024) 354.
[11] N. Liu, Q. Wu, Y. Liu, et al., Curr. Stem Cell Res. Ther. 16 (2021) 95–103.
[12] Z. Zhang, C. Ding, T. Sun, et al., Adv Healthc. Mater. 12 (2023) e2300153.
[13] S. Masoudi, Exp. Eye Res. 220 (2022) 109101.
[14] J. Sheppard, B. Shen Lee, L.M. Periman, Ann. Med. 55 (2023) 241–252.
[15] M. Rolando, J. Merayo-Lloves, Curr. Eye Res. 47 (2022) 813–823.
[16] J.R. Sempionatto, J.A. Lasalde-Ramirez, K. Mahato, et al., Nat. Rev. Chem. 6 (2022) 899–915.
[17] X. Ye, J. Yang, C. Hu, et al., Biosens. Bioelectron. 248 (2024) 115933.
[18] M.E. Wechsler, H.K.H. Jocelyn Dang, S.P. Simmonds, et al., Nano Lett. 21 (2021) 8734–8740.
[19] F. Yu, M. Zheng, A.Y. Zhang, Z. Han, J. Control. Release 315 (2019) 40–54.
[20] Q. Yang, W. Pu, K. Hu, et al., ACS Nano 17 (2023) 4813–4833.
[21] W. Cui, S. Chen, T. Hu, et al., ACS Nano 18 (2024) 11084–11102.
[22] W. Zhang, M. Zhao, D. Chu, et al., J. Nanobiotechnology 22 (2024) 229.
[23] L. Ou, Z. Wu, X. Hu, et al., Acta Biomater. 175 (2024) 353–368.
[24] T. Wang, Q. Fan, J. Hong, et al., Small 17 (2021) e2102485.
[25] P.H. Lin, H.J. Jian, Y.J. Li, et al., Acta Biomater. 141 (2022) 140–150.
[26] T. Zhou, S. Li, J. Zhu, et al., J. Control. Release 373 (2024) 306–318.
[27] M.A. Al-Aqaba, V.K. Dhillon, I. Mohammed, et al., Prog. Retin. Eye Res. 73 (2019) 100762.
[28] S.E. Wilson, A.A.M. Torricelli, G.K. Marino, Exp. Eye Res. 194 (2020) 108002.
[29] A. Austin, T. Lietman, J. Rose-Nussbaumer, Ophthalmology 124 (2017) 1678–1689.
[30] F. Stapleton, Ocul. Surf. 28 (2023) 351–363.
[31] K.K.W. Cheng, L. Fingerhut, S. Duncan, et al., Prog. Retin. Eye Res. 102 (2024) 101287.
[32] J. Xiang, R. Zou, P. Wang, et al., Biomaterials 308 (2024) 122565.
[33] S. Ch, P. Mishra, H. Bhatt, et al., Colloids Surf. B: Biointerfaces 208 (2021) 112113.
[34] S.G. Padaga, H. Bhatt, S. Ch, et al., ACS Appl. Mater. Interfaces 16 (2024) 18360–18385.
[35] S. Ch, M. Paul, S.G. Padaga, et al., Int. J. Biol. Macromol. 264 (2024) 130457.
[36] S.B. Wiegand, L. Traeger, H.K. Nguyen, et al., Redox Biol. 39 (2021) 101826.
[37] H. Jeong, J.H. Park, J.H. Shin, et al., Chem. Mater. 30 (2018) 8528–8537.
[38] H. Zhang, W. Jiang, Y. Peng, et al., Biomaterials 286 (2022) 121577.
[39] Q. Wang, J. Zhao, T. Huang, et al., Acta Biomater. 182 (2024) 275–287.
[40] X. He, Y. Lv, Y. Lin, et al., Adv. Mater. 36 (2024) e2400366.
[41] P. Sathe, V. Kailasam, V. Nagarjuna, et al., Int. J. Pharm. 656 (2024) 124118.
[42] X. Sha, L. Chan, X. Fan, et al., Int. J. Nanomedicine 17 (2022) 1463–1478.
[43] L. Liu, C. Ge, Y. Zhang, et al., Biomater. Sci. 8 (2020) 4852–4860.
[44] H. Shi, J. Ding, C. Chen, et al., ACS Biomater. Sci. Eng. 7 (2021) 5090–5098.
[45] Y. Ye, J. He, H. Wang, et al., ACS Nano 16 (2022) 18729–18745.
[46] X. Ju, L. Wu, N. Gao, et al., Adv. Healthc. Mater. 12 (2023) e2202409.
[47] M.E. Bhend, D. Kempuraj, N.R. Sinha, et al., Exp. Eye Res. 228 (2023) 109390.
[48] X. Shen, S. Li, X. Zhao, et al., Bioact. Mater. 20 (2023) 434–448.
[49] H. Zhou, S. Zhang, M. Lei, et al., Bioact. Mater. 29 (2023) 1–15.
[50] M. Li, R. Wei, C. Liu, et al., Bioact. Mater. 25 (2023) 333–346.
[51] L. Zhao, Z. Shi, X. Qi, et al., Biomaterials 313 (2025) 122754.
[52] M.S. Razavi, P. Ebrahimnejad, H.A. Javar, et al., Biomater. Adv. 154 (2023) 213648.
[53] Z. Ge, L. Long, F. Zhang, et al., Int. J. Biol. Macromol. 273 (2024) 132740.
[54] A. Farasatkia, M. Kharaziha, Int. J. Biol. Macromol. 183 (2021) 1013–1025.
[55] Q. Tang, B. Lu, J. He, et al., Biomaterials 280 (2022) 121320.
[56] Q. Yang, L. Ye, J. Liu, et al., Int. J. Med. Sci. 20 (2023) 542–550.
[57] R. Ganugula, M. Arora, S. Dwivedi, et al., ACS Nano 17 (2023) 6857–6874.
[58] C. Yang, A. Miao, C. Yang, et al., Adv. Sci. 9 (2022) e2105905.
[59] N. Li, Z. Zhao, H. Ma, et al., Mol. Pharm. 19 (2022) 3831–3845.
[60] B.I. Hanafy, G.W.V. Cave, Y. Barnett, B.K. Pierscionek, Nanomaterials 11 (2021) 1473.
[61] T. Lapp, K. Wacker, C. Heinz, et al., Dtsch. Arztebl. Int. 120 (2023) 377–386.
[62] I.M. Wormstone, Y.M. Wormstone, A.J.O. Smith, J.A. Eldred, Prog. Retin. Eye Res. 82 (2021) 100905.
[63] I.M. Wormstone, J.A. Eldred, Exp. Eye Res. 142 (2016) 2–12.
[64] J.W. Xu, H.N. Li, D.F. Hu, et al., ACS Appl. Bio Mater. 4 (2021) 3579–3586.
[65] C. Zhang, Q. Guo, Z. Tong, et al., J. Colloid. Interface Sci. 619 (2022) 348–358.
[66] D. Liu, Q. Wu, W. Chen, et al., Small 18 (2022) e2201098.
[67] Y. Hong, Q. Fang, T. Bai, et al., J. Nanobiotechnol. 21 (2023) 134.
[68] X. Zhang, Z. Chen, X. Li, et al., Antibiotics 12 (2023) 1670.
[69] A. Topete, J. Tang, X. Ding, et al., J. Control. Release 326 (2020) 245–255.
[70] G. Choi, Y. Song, H. Lim, et al., Adv. Healthc. Mater. 9 (2020) e2000447.
[71] T.J. Peck, S.N. Patel, A.C. Ho, Curr. Opin. Ophthalmol. 32 (2021) 62–68.
[72] Y. Ye, J. He, Y. Qiao, et al., Theranostics 10 (2020) 8541–8557.
[73] J. Gueudry, M. Muraine, J. Fr. Ophtalmol. 41 (2018) e11–e21.
[74] A.A. Bonfioli, F.M. Damico, A.L. Curi, F. Orefice, Semin. Ophthalmol. 20 (2005) 147–154.
[75] R. Amer, Y. Sharon, Ocul. Immunol. Inflamm. 33 (2025) 548–555.
[76] Z. Zhong, G. Su, A. Kijlstra, P. Yang, Prog. Retin. Eye Res. 80 (2021) 100866.
[77] L.C. Bengani, H. Kobashi, A.E. Ross, et al., Acta Biomater. 116 (2020) 149–161.
[78] F. Raad, P. Luque, S. Garcia Ledo, et al., Ocul. Immunol. Inflamm. 33 (2025) 340–346.
[79] E. Ramsay, E.M. Del Amo, E. Toropainen, et al., Eur. J. Pharm. Sci. 119 (2018) 83–89.
[80] Z. Chen, M. Yang, Q. Wang, et al., Carbohydr. Polym. 253 (2021) 117216.
[81] B. Shihmani, A. Rassouli, J. Mehrzad, S. Shokrpoor, Inflammopharmacology 31 (2023) 1913–1928.
[82] Y. Zhu, J. Zhou, Y. Hu, et al., Int. J. Pharm. 622 (2022) 121836.
[83] E.W. Bohm, F. Buonfiglio, A.M. Voigt, et al., Redox Biol. 68 (2023) 102967.
[84] X. Li, Z. Han, T. Wang, et al., Biomaterials 291 (2022) 121904.
[85] X. Liu, Z. Chen, J. Bai, et al., ACS Nano 17 (2023) 25377–25390.
[86] Y. Jin, D. Cai, L. Mo, et al., Biomaterials 309 (2024) 122617.
[87] F. Cao, K. Liang, W.W. Tang, et al., J. Control. Release 372 (2024) 551–570.
[88] R. Sacconi, S. Fragiotta, D. Sarraf, et al., Prog. Retin. Eye Res. 92 (2023) 101113.
[89] X.J. Zhang, X.N. Chen, F.Y. Tang, et al., Surv. Ophthalmol. 68 (2023) 1011–1026.
[90] V.P. Nguyen, Y. Li, J. Henry, et al., ACS Appl. Mater. Interfaces 13 (2021) 40214–40228.
[91] V.P. Nguyen, W. Qian, Y. Li, et al., Nat. Commun. 12 (2021) 34.
[92] T. Sunaga, M. Maeda, R. Saulle, et al., Cochrane Database Syst. Rev. 6 (2024) CD015804.
[93] H. Gao, M. Chen, Y. Liu, et al., Adv. Mater. 35 (2023) e2204994.
[94] L. Manjing, X. Zhaojian, Z. Lu, et al., ACS Nano 15 (2021) 9808–9819.
[95] M. Whitehead, A. Osborne, P.S. Widdowson, et al., J. Diabetes Res. 2019 (2019) 5140521.
[96] G. Elayat, A. Selim, Clin. Exp. Med. 24 (2024) 178.
[97] H. Yao, H. Xu, M. Wu, et al., Acta Biomater 166 (2023) 536–551.
[98] L. Chen, C. Fan, A. Wang, et al., Adv. Mater. (2025), doi:10.1002/adma.202508104.
[99] Y. Tian, F. Zhang, Y. Qiu, et al., Nat. Biomed. Eng. 5 (2021) 968–982.
[100] K. Huang, X. Liu, Z. Lv, et al., Small 19 (2023) e2207335.
[101] J. Zhang, J. Zhu, L. Zhao, et al., J. Nanobiotechnol. 19 (2021) 196.
[102] J. Shen, L. Chen, X. Lv, et al., Adv. Mater. 36 (2024) e2314095.
[103] K. Zhu, S. Qian, H. Guo, et al., ACS Nano 16 (2022) 11136–11151.
[104] Y. Jin, Y. Guo, J. Yang, et al., Adv. Mater. 35 (2023) e2209690.
[105] H. Tao, J. Tan, H. Zhang, et al., Adv. Sci. 10 (2023) e2302895.
[106] T. Huang, X. Xu, C. Cheng, et al., J. Nanobiotechnology 21 (2023) 146.
[107] A. Maurer, G. Clerici, J.A. Schaab, et al., Clin. Exp. Med 24 (2024) 234.
[108] Y. Yao, R. Xu, W. Shao, et al., Adv. Sci. 11 (2024) e2403107.
[109] Y. Ding, J. Yu, X. Chen, et al., Adv. Sci. 8 (2021) 2002404.
[110] H. Ren, Z. Wu, J. Tan, et al., Adv. Sci. 11 (2024) e2404375.
[111] Y. Li, F. Li, H. Pan, et al., J. Nanobiotechnol. 20 (2022) 472.
[112] D. Wei, Y. Huang, B. Wang, et al., Angew. Chem. Int. Ed. 61 (2022) e202201486.
[113] H. Deng, A. Kan, N. Lyu, et al., Liver Cancer 9 (2020) 338–357.
[114] X. Zheng, Y. Shi, D. Tang, et al., Adv. Sci. 10 (2023) e2206932.
[115] J. Li, Y. Xue, J. Tian, et al., Carbohydr. Polym. 237 (2020) 116119.
[116] R. Baghban, M.R. Talebnejad, A. Meshksar, et al., J. Nanobiotechnology 21 (2023) 402.
[117] B.N. Kumara, R. Shambhu, A. Prabhu, K.S. Prasad, Carbohydr. Polym. 289 (2022) 119426.
[118] A. Yu, H. Shi, H. Liu, et al., Int. J. Pharm. 575 (2020) 118943.

[119] B.N. Kumara, R. Shambhu, K.S. Prasad, Int. J. Biol. Macromol. 176 (2021) 47–65.
[120] B.N. Kumara, R. Shambhu, Y.B. Shim, et al., Int. J. Biol. Macromol. 253 (2023) 126917.
[121] L.J. Luo, D.D. Nguyen, J.Y. Lai, Theranostics 11 (2021) 5447–5463.
[122] S.E. Radwan, R.M. El-Moslemany, R.A. Mehanna, et al., Drug Deliv. 29 (2022) 1150–1163.
[123] J.C. Cuggino, L.I. Tartara, L.M. Gugliotta, et al., Mater. Sci. Eng. C: Mater. Biol.Appl. 118 (2021) 111383.
[124] H.J. Kim, K. Zhang, L. Moore, D. Ho, ACS Nano 8 (2014) 2998–3005.
[125] B.N. Kumara, K. Velmurugan, M.V. Ghate, et al., J. Mater. Chem. B 12 (2024) 2394–2412.
[126] E. Eljarrat-Binstock, F. Orucov, Y. Aldouby, et al., J. Control. Release 126 (2008) 156–161.
[127] S.N. Kim, C.H. Min, Y.K. Kim, et al., Acta Biomater. 144 (2022) 32–41.
[128] W.K. Ju, G.A. Perkins, K.Y. Kim, et al., Prog. Retin. Eye Res. 95 (2023) 101136.
[129] R. Rong, X. Zhou, G. Liang, et al., ACS Nano 16 (2022) 21225–21239.
[130] X. Yang, Y. Chen, J. Guo, et al., Adv. Sci. 10 (2023) e2207216.
[131] X. Lou, Y. Hu, H. Zhang, et al., J. Nanobiotechnology 19 (2021) 436.
[132] Y.C. Liu, Y.K. Lin, Y.T. Lin, et al., Adv. Sci. 11 (2024) e2308635.
[133] R. Lim, Clin. Exp. Ophthalmol. 50 (2022) 213–231.
[134] Y. Lin, W. Luo, B. Jiang, et al., iScience 26 (2023) 107633.
[135] M.P. Gupta, A.A. Herzlich, T. Sauer, C.C. Chan, Dev. Ophthalmol. 55 (2016) 7–17.
[136] J.M. Provis, P.L. Penfold, E.E. Cornish, et al., Clin. Exp. Optom. 88 (2005) 269–281.
[137] L. Su, X. Gong, R. Fan, et al., Redox Biol. 65 (2023) 102836.
[138] E. Buschini, A.M. Fea, C.A. Lavia, et al., Clin. Ophthalmol. 9 (2015) 563–574.
[139] S.P. Kambhampati, I.A. Bhutto, T. Wu, et al., J. Control. Release 335 (2021) 527–540.
[140] D. Chiras, G. Kitsos, M.B. Petersen, et al., Crit. Rev. Clin. Lab Sci. 52 (2015) 12–27.
[141] B. Leng, Y. Zhang, X. Liu, et al., Mediators Inflamm. 2019 (2019) 1082497.
[142] R. Sun, A. Zhang, Y. Ge, et al., Expert Opin. Drug Deliv. 17 (2020) 1305–1320.
[143] A. Tisi, M. Passacantando, L. Lozzi, et al., Exp. Eye Res. 182 (2019) 30–38.
[144] S. Cupini, S. Di Marco, L. Boselli, et al., ACS Nano 17 (2023) 22800–22820.
[145] H. Liu, Y. Yang, Y. Liu, et al., Adv. Sci. 7 (2020) 1903129.
[146] Y.S. Kwon, M. Zheng, A.Y. Zhang, Z. Han, ACS Nano 16 (2022) 19412–19422.
[147] D. Song, G.S. Ying, J.L. Dunaief, et al., Retina 39 (2019) 1965–1972.
[148] Z. Tang, M. Huo, Y. Ju, et al., Small Methods 5 (2021) e2100848.
[149] F.G. Holz, S. Schmitz-Valckenberg, M. Fleckenstein, J. Clin. Invest. 124 (2014) 1430–1438.
[150] J. Li, S.G. Kim, J. Blenis, Cell Metab. 19 (2014) 373–379.
[151] L. Mei, M. Yu, Y. Liu, et al., Nanomedicine 44 (2022) 102571.
[152] R. Suri, Y.R. Neupane, N. Mehra, et al., Int. J. Biol. Macromol. 191 (2021) 548–559.
[153] S. Xu, J. Li, K. Long, et al., Adv. Sci. 11 (2024) e2404218.
[154] Y.N. Li, H.W. Liang, C.L. Zhang, et al., Adv. Sci. 10 (2023) e2203351.
[155] Q.Y. Dong, Y. Cui, L. Chen, et al., Eur. J. Ophthalmol. 18 (2008) 94–98.
[156] D.P. Hainsworth, A. Gangula, S. Ghoshdastidar, et al., Am. J. Ophthalmol. 213 (2020) 306–319.
[157] N. Cheung, I.Y. Wong, T.Y. Wong, Diabetes Care 37 (2014) 900–905.
[158] S.E. Radwan, A. El-Kamel, E.I. Zaki, et al., Int. J. Nanomedicine 16 (2021) 4481–4494.
[159] J. Pandit, Y. Sultana, M. Aqil, Carbohydr. Polym. 267 (2021) 118217.
[160] V. Dave, R. Sharma, C. Gupta, S. Sur, Colloids Surf. B: Biointerfaces 194 (2020) 111151.
[161] Y. Murakami, K. Ishikawa, S. Nakao, K.H. Sonoda, Prog. Retin. Eye Res. 74 (2020) 100778.
[162] Y. Zhou, C. Zhao, Z. Shi, et al., Adv. Sci. 11 (2024) e2402368.
[163] J.V. Busik, J. Lipid Res. 62 (2021) 100017.
[164] Q. Kang, C. Yang, Redox Biol. 37 (2020) 101799.
[165] H. Daldal, M. Naziroglu, Biol. Trace Elem. Res. 200 (2022) 2283–2297.
[166] T. Niu, X. Shi, X. Liu, et al., Mol. Med. 30 (2024) 24.
[167] J.P. Vogel, S. Chawanpaiboon, A.B. Moller, et al., Best Pract. Res. Clin. Obstet. Gynaecol. 52 (2018) 3–12.
[168] K.D. Tran, L.A. Cernichiaro-Espinosa, A.M. Berrocal, Asia Pac. J. Ophthalmol. 7 (2018) 56–62.
[169] M. Bohley, A.E. Dillinger, F. Schweda, et al., Sci. Adv. 8 (2022) eabo6638.
[170] X. Dong, Y. Lei, Z. Yu, et al., Theranostics 11 (2021) 5107–5126.
[171] M. Yousaf, H. Huang, P. Li, et al., ACS Chem. Neurosci. 8 (2017) 1368–1377.
[172] N. Zhao, X. Gui, Q. Fang, et al., J. Nanobiotechnol. 20 (2022) 174.
[173] H.J. Jian, A. Anand, J.Y. Lai, et al., Adv. Healthc. Mater. 13 (2024) e2302881.
[174] B. Xue, S. Wang, T. Wu, et al., Sci. Adv. 11 (2025) eadu5571.
[175] M. Sen, M. Al-Amin, E. Kickova, et al., J. Control. Release 339 (2021) 307–320.
[176] M. Zheng, R.N. Mitra, E.R. Weiss, Z. Han, Mol. Ther. 28 (2020) 523–535.
[177] S. Sp, R.N. Mitra, M. Zheng, et al., Gene Ther. 30 (2023) 628–640.
[178] F. Benfenati, G. Lanzani, Lab. Anim. 47 (2018) 71–75.
[179] S. Francia, D. Shmal, S. Di Marco, et al., Nat. Commun. 13 (2022) 3677.
[180] J.F. Maya-Vetencourt, G. Manfredi, M. Mete, et al., Nat. Nanotechnol. 15 (2020) 698–708.
[181] S.R. Roy, S. Kaliki, Mymensingh Med. J. 30 (2021) 881–895.
[182] X. Hu, D. Zhang, L. Huang, et al., ACS Biomater. Sci. Eng. 10 (2024) 1830–1842.
[183] N. Duan, L. Mei, L. Hu, et al., ACS Appl. Mater. Interfaces 15 (2023) 6371–6384.
[184] R.C. Cooper, J. Wang, H. Yang, Biomacromolecules 25 (2024) 5928–5937.
[185] S.N. Tabatabaei, R.M. Derbali, C. Yang, et al., J. Control. Release 298 (2019) 177–185.
[186] A. Haase, N. Miroschnikov, S. Klein, et al., Mol. Oncol. 18 (2024) 832–849.
[187] S.B. Alvi, T. Appidi, B.P. Deepak, et al., Biomater. Sci. 7 (2019) 3866–3875.
[188] S.V. Mudigunda, D.B. Pemmaraju, S. Paradkar, et al., ACS Biomater. Sci. Eng. 8 (2022) 151–160.
[189] M. Li, X. Bian, X. Chen, et al., Drug Deliv. 29 (2022) 519–533.
[190] B. Jin, K. Lu, W. Gao, et al., Int. J. Nanomed. 19 (2024) 7799–7816.
[191] N.D. Sheybani, H. Yang, Chin. Chem. Lett. 28 (2017) 1817–1821.