Nanomedicine for Ocular Drug Delivery

Xiaojie Xu and Yi Y. Zuo

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Abstract
The eyes are one of the most important and complex sensory organs of the body. They act as a gateway to collect external images and transmit them to the brain as signals through the optic nerve. Genetic or acquired disorders in different compartments of the eye lead to various ocular diseases that can cause mild to severe symptoms from burning and itching, to visual impairment or even blindness. So far, pharmaceutical interventions for ocular diseases have demonstrated rather limited efficacy, mostly due to difficulties for drugs to cross the physiological and biological barriers of the eye. Nanotechnology provides new opportunities for the development of drug delivery systems particularly adapted to overcoming the eye-associated barriers. To date, a number of nanomedicine formulations, such as nanomicelles, liposomes, nanoparticles, dendrimers, and nanogels, have demonstrated the capacity of reducing the degradation of labile drugs and increasing the residence time and bioavailability of drugs in various ocular tissues. This chapter introduces these commonly studied nanomedicine formulations for treating various ocular diseases, including dry eye, cataracts, glaucoma, age-related macular degeneration, and diabetic retinopathy. Emerging toxicological studies about nanoparticle interactions with the ocular surface and tissues are also briefly discussed.

Keywords
Nanoparticle · Nanomedicine · Nanotoxicology · Nano-bio interaction · Drug delivery · Eye · Ocular surface · Tear film · Dry eye · Age-related macular degeneration

Introduction
The eyes are one of the most important and complex sensory organs of the body. They act as a gateway to collect external images and transmit them to the brain as signals through the optic nerve. Genetic or acquired disorders in different compartments of the eye lead to various ocular diseases that can cause mild to severe symptoms from burning and itching, to visual impairment or even blindness. So far, pharmaceutical interventions for ocular diseases have demonstrated rather limited efficacy, mostly due to difficulties for drugs to cross the physiological and biological barriers of the eye. Nanotechnology provides new opportunities for the development of drug delivery systems particularly adapted to overcoming the eye-associated barriers. To date, a number of nanomedicine formulations, such as nanomicelles, liposomes, nanoparticles, dendrimers, and nanogels, have demonstrated the capacity of reducing the degradation of labile drugs and increasing the residence time and bioavailability of drugs in various ocular tissues. This chapter introduces these commonly studied nanomedicine formulations for treating various ocular diseases, including dry eye, cataracts, glaucoma, age-related macular degeneration, and diabetic retinopathy. Emerging toxicological studies about nanoparticle interactions with the ocular surface and tissues are also briefly discussed.
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Anatomy of the Eye

The eyes are one of the most important and complex sensory organs of the body. They act as a gateway to collect external images and transmit them to the brain as signals through the optic nerve. As shown in Fig. 1, the eye can be broadly divided into two segments: the anterior segment that occupies the front third of the eye, and the posterior segment that occupies the remaining two-thirds of the eye [1]. The anterior segment is composed of the cornea, conjunctiva, iris, lens, ciliary body, and aqueous humor. The posterior segment comprises the vitreous humor, retina, choroid, sclera, and optic nerve. This section introduces the detailed anatomy of the eye.
Anterior Segment

Cornea
Cornea is a transparent structure, with an average thickness of approximately 540 μm, which covers the front portion of the eye. It is made up of proteins and cells that do not rely on blood vessels to provide nutrients. The main function of cornea is to refract or bend light, thus focusing most of the light that enters the eye. The cornea comprises five layers: the epithelium, Bowman’s layer, the stroma, Descemet’s membrane, and the endothelium. The front layer, i.e., corneal epithelium, prevents foreign matters from entering the eye and absorbs nutrients and oxygen from tears and the aqueous humor in the anterior chamber. Bowman’s layer is a tough layer composed of collagen (mainly type I collagen fibrils), laminin, nidogen, and perlecan that protects the corneal stroma. The stroma is a thick, transparent middle layer, accounting for more than 90% thickness of the cornea. It consists of regularly arranged collagen fibers along with sparsely distributed interconnected keratocytes that are cells for general repair and maintenance. Descemet’s membrane is a dense and cell-free basement membrane that anchors the epithelium or endothelium to connective tissues. The corneal endothelium is a simple squamous monolayer responsible for regulating fluid and solute transport between the aqueous humor and the stromal compartment. Unlike the corneal epithelium, the endothelium cannot be regenerated if it were damaged.

Conjunctiva
Conjunctiva is a clear, thin membrane that covers a part of the front surface of the eye and the inner surface of the eyelids. Unlike the cornea, the conjunctiva has many small blood vessels that supply nutrients to the eye and eyelids. It also contains special cells that secrete a component of the tear film to help prevent dry eye. The conjunctiva has two continuous segments: the bulbar conjunctiva, covering the anterior part of the sclera, and the palpebral conjunctiva, also called tarsal conjunctiva, covering the inner surface of both upper and lower eyelids. The primary functions of the conjunctiva are to keep the front surface of the eye and the inner surface of the eyelids moist and lubricated, and to protect the eye from dust and pathogens.

Iris
Iris is a thin circular structure with an aperture in the center, i.e., the pupil, acting as a diaphragm that regulates the amount of light entering the eye. The iris, with a diameter in the general range of 11–13 mm, roughly consists of two layers: a pigmented fibrovascular layer known as the stroma and a second layer of pigmented epithelial cells. The color of iris is established genetically, and it depends on the pigments in the iris. The iris separates the space between the cornea and the lens into two chambers: the anterior chamber between the cornea and the iris, and the posterior chamber between the iris and the lens.
**Lens**
Lens is a transparent and biconvex structure that resides behind the iris with the support of the ciliary body’s zonular fibers. It is made up of unusual, elongated cells that have no blood supply but obtain nutrients from the surrounding fluids, mainly the aqueous humor that bathes the front of the lens. The lens of adult humans is approximately 10 mm in diameter and 4 mm in thickness. The main function of the lens is to focus light rays onto the retina. The shape of the lens can be altered by relaxation and contraction of the ciliary muscles surrounding it, thus enabling the eye to focus clearly on objects at widely varying distances.

**Ciliary Body**
Ciliary body is a heavily muscled ring of tissue with an extensive capillary bed that is anterior to the lens. The ciliary body includes two main functional areas: the ciliary muscle that controls the shape of the lens, and the ciliary epithelium that produces the aqueous humor. The ciliary body is part of the uvea, i.e., the layer of tissue that delivers oxygen and nutrients to the eye tissues. The ciliary body joins the ora serrata of the choroid to the root of the iris.

**Aqueous Humor**
Aqueous humor is a transparent water-like fluid similar to plasma, filling the space between the cornea and the lens. Total 99.9% of the aqueous humor is water, while the other 0.1% consists of sugars, vitamins, proteins, and other nutrients. The aqueous humor is produced in the nonpigmented portion of the ciliary body at a rate of about 2 μL/min. It nourishes the cornea and lens and gives the eye its shape by maintaining the intraocular pressure.

**Posterior Segment**

**Vitreous Humor**
Vitreous humor, also known as vitreous body, is a clear, avascular, and elastic colloidal gel that fills the space between the lens and the retina. It supports the retina and maintains the intraocular pressure. The vitreous humor is mainly composed of collagen fibers and acidic mucopolysaccharides, with its nutrients coming from the choroid and the aqueous humor. The volume of vitreous humor in adult humans is about 3–4 mL/eye, accounting for four-fifths of the eye’s volume. Different from the aqueous humor, the metabolism of the vitreous humor is so low that it has no ability to regenerate. Loss, liquefaction, or degeneration of the vitreous humor not only affects its transparency, but could also lead to retinal detachment.

**Retina**
Retina is a thin layer of tissue that lines the back of the eye. The main function of retina is to receive light that the lens has focused, convert the light into neural signals, and send these signals to the brain for visual recognition. The retina is
composed of ten distinct layers. From the vitreous humor to the choroid, these layers are the following: (1) Internal limiting membrane that represents the structural boundary between the vitreous and the retina; (2) nerve fiber layer that contains the axons of ganglion cells; (3) ganglion cell layer that contains nuclei of ganglion cells. The photosensitive ganglion cell is important for entrainment of circadian rhythms and reflexive responses such as the pupillary light reflex; (4) inner plexiform layer; (5) inner nuclear layer; (6) outer plexiform layer; (7) outer nuclear layer; (8) external limiting membrane that separates the inner photoreceptors from supporting cells; (9) photoreceptor layer that comprises two types of photoreceptors: rods and cones. Rods function mainly in dim light and provide the black-and-white vision. Cones function in well-lit conditions and are responsible for the perception of colors, as well as the high-acuity vision used for tasks such as reading. In each human retina, there are 110–125 million rods and 6.3–6.8 million cones. When light hits the photoreceptor, it is absorbed by the light-sensitive photopigment, transformed into electrical impulses, and further relayed to the brain via the optic nerve; and (10) retinal pigment epithelium that supplies the photoreceptors with nutrients. The retinal pigment epithelium contains granules of melanin pigment that enhance visual acuity by absorbing light not captured by the photoreceptor cells, thus reducing glare. Another important function of the retinal pigment epithelium is to store and synthesize vitamin A, which is essential for the production of visual pigments.

**Choroid**

Choroid lies between retina and sclera. It is primarily composed of a dense capillary plexus, as well as small arteries and veins. As it contains numerous blood vessels and cells, the choroid supplies most necessary nutrients and oxygen to the back of the eye.

**Sclera**

Sclera is the white part of the eye, which occupies about 80% of the external surface of the eye. It is an opaque and elastic layer that is mainly composed of collagen fibers. The sclera is avascular, with nutrients coming from anterior vessels and the choroid. The main function of sclera is to maintain the globe shape of the eye to resist external forces and injury.

**Physical Barriers for Ocular Drug Delivery**

Drugs administrated topically or systemically to the eye must cross several physiological and biological barriers. As shown in Fig. 2, the main barriers for ocular drug delivery include the tear film, the corneal barrier, the conjunctival barrier, the blood-aqueous barrier, and the blood-retina barrier [2].
Tear Film

Tear film is a multilayered biological barrier that protects our eyes from potential risks of the environment. It is rapidly reorganized and spread as a continuous layer over the ocular surface following the upward movement of the eyelid during a blink. The tear film of healthy adults has a thickness of 6–10 μm and should be able to maintain its integrity during the 6-s interblink period. As shown in Fig. 3, the tear film is composed of three consecutive layers: the inner mucin layer, the intermediate aqueous layer, and the outermost lipid layer. The mucin layer mainly consists of viscous, high molecular-weight sugar-rich glycosylated proteins that function as lubricants to facilitate spreading of the tear film on the ocular surface. The aqueous layer, representing the largest portion of the tear film with a thickness of approximately 4 μm, is made of solutions of electrolytes, peptides, and proteins, such as lipocalin, lysozyme, and lactoferrin. These proteins not only contribute to wound healing and anti-inflammatory processes, but also interact with the lipid layer to affect its stabilization and organization. The lipid layer, commonly known as the tear film lipid layer (TFLL), is approximately 40 nm thick. It is generally believed that the TFLL consists of two sublayers: a polar lipid layer adjacent to the aqueous layer, and a nonpolar lipid layer that resides upon the polar lipids and is directly exposed to
The polar lipids account for 20 mol% of the TFLL, with phospholipids being the most abundant lipid class (~12 mol%) in human tears, and a new class of polar lipids, (O-acyl)-ω-hydroxy fatty acids (OAHFAs), accounting for ~4 mol% of the TFLL [4]. The nonpolar lipids account for 80 mol% of the TFLL, with wax esters (WEs, i.e., esters of a fatty acid and a fatty alcohol, accounting for ~43 mol%) and cholesteryl esters (CEs, i.e., esters of a fatty acid and a cholesterol, accounting for ~39 mol%) being the most prevalent nonpolar lipid classes, and a small amount of triacylglycerol [5]. The TFLL plays a key biophysical role in stabilizing the tear film by decreasing surface tension, optimizing interfacial rheology, and retarding evaporation of the aqueous layer [6, 7]. The TFLL also provides antimicrobial activities and serves as a barrier against environmental particles and pathogens.

Being the outermost layer of the eye, the tear film represents the initial physical barrier for topically administrated drugs to the eye. Tears are characterized by a high turnover rate with a restoration time of 2–3 min, thus limiting the ocular residence time for a drug (usually 5–6 min before drugs being completely washed away) and consequently minimizing the time period during which the drug can penetrate the air [3].

**Fig. 3** Structure and composition of the tear film: (a) the tear film is composed of three layers: the inner mucin layer, the intermediate aqueous layer, and the outermost lipid layer that consists of two sublayers, i.e., the polar lipid layer and nonpolar lipid layer; (b) chemical composition of the tear film lipid layer: 20% polar lipids, including phospholipids (PLs) and (O-acyl)-ω-hydroxy fatty acids (OAHFAs), and 80% nonpolar lipids, including wax esters (WEs), cholesteryl esters (CEs), and a small amount of triacylglycerol (TAG); and (c) chemical structures of major tear film lipids. (Reproduced with permission from Ref. [3]. Copyright 2016 Elsevier)
ocular tissues. Reflex stimulation by some ophthalmic drugs with low pH may increase lachrymation by 100-fold, which would dramatically decrease the bioavailability of drugs. Another factor that makes tear film a barrier for ocular drug delivery is that tears contain proteins and mucins. With approximately 2–3 mL mucus secreted daily, mucin in the tear film has a protective role by forming a hydrophilic gel layer that moves over the glycocalyx of the ocular surface and clears cell debris, particles, and pathogens, as well as drugs. Mucin may bind with drug molecules, thereby reducing the effective concentration of drugs in contact with the cornea. Furthermore, tears contain buffering systems in the form of carbonic acid and weak organic acids. Due to their considerable volume compared to the volume of topically administrated drugs, tears may modify the degree of ionization (pKa) of a drug, and thus its bioavailability [8].

Corneal Barrier

As introduction in section “Cornea,” the cornea is composed of five layers of alternating polarities: the epithelium, Bowman’s layer, the stroma, Descemet’s membrane, and the endothelium. The sandwich-like structure of the cornea makes it an effective barrier not only to microorganisms but also to most hydrophilic and lipophilic drugs. On the one hand, the corneal epithelium consists of five to six layers of cells closely packed and connected with tight junctions. The high lipid contents of the epithelium and the endothelium make them crucial barriers to hydrophilic molecules. The presence of tight junctions between the corneal epithelial cells retards paracellular drug permeation, thus limiting corneal permeability to hydrophilic and ionized molecules. On the other hand, the corneal stroma, which is constituted by an extracellular matrix consisting of a lamellar arrangement of collagen fibrils, is characterized by a high water content that makes this layer impermeable to lipophilic molecules. Furthermore, both the corneal epithelium and stroma represent a barrier to macromolecules, only allowing molecules smaller than 50 kDa to diffuse into the stroma [9].

Conjunctival Barrier

Drugs can be absorbed into the anterior segment through the conjunctival/scleral route. As introduced in section “Conjunctiva,” the conjunctiva is a vascularized tissue that lines the inside of the eyelids and covers the sclera. The external epithelial cells of conjunctiva form junctions that limit paracellular drug penetration. Conjunctiva is a major rate-limiting barrier for hydrophilic drugs due to rapid drug elimination by the conjunctival blood and lymphatic flow. Therefore, only hydrophobic drugs with low molecular weights are able to cross the conjunctiva [10]. Once surviving conjunctival clearance, drugs can penetrate to the sclera, in which they have a higher permeability than in cornea.
**Blood-Aqueous Barrier**

The blood-aqueous barrier (BAB) is an anterior barrier of the eye for systemically administrated drugs. The BAB is composed of the nonpigmented cell layer of the ciliary body epithelium and endothelial cells of blood vessels in the iris. As introduced in section “Ciliary Body,” the ciliary body epithelium is responsible for secretion of aqueous humor into the posterior chamber of the eye. The ciliary body extends posteriorly from the iris root to the retina, forming a ring around the globe of the eye. The ciliary body is a bilayer comprised of two distinct cell layers: a pigmented cell layer and a nonpigmented cell layer. The pigmented and non-pigmented cells are coupled via gap junctions. The pigmented cells contact the choroidal blood supply, whereas the basolateral membrane of the nonpigmented epithelium contacts the aqueous humor. Tight junctions are present in the non-pigmented epithelial cells, but not in the pigmented cells. Thus, the physical barrier to drugs across the ciliary body is mostly due to the nonpigmented epithelium.

**Blood-Retinal Barrier**

The blood-retinal barrier (BRB) is an important posterior barrier of the eye for systemically administrated drugs. Presence of the BRB is essential for the structural and functional integrity of the retina. Functions of the BRB are to regulate fluids and molecular movement between the ocular vascular beds and retinal tissues, and to prevent leakage of macromolecules and other potentially harmful agents into the retina. Under disease conditions where BRB breakdown occurs, vision can be seriously compromised. The BRB consists of an inner barrier (iBRB) and an outer barrier (oBRB). The iBRB is established by the tight junctions, also known as zonulae occludentes, between neighboring retinal endothelial cells. These specialized junctions restrict the diffusional permeability of the retinal endothelial layer to values in the order of $0.14 \times 10^{-5}$ cm/s for sodium fluorescein that is used as a fluorescent tracer in ophthalmology and optometry. The oBRB is established by the tight junctions between neighboring retinal pigment epithelial cells. The retinal pigment epithelium separates the neural retina from the fenestrated choriocapillaris and plays a fundamental role in regulating nutrients from the blood to photoreceptors as well as eliminating waste products and maintaining retinal adhesion [11].

**Nanomedicine for Treating Ocular Diseases**

**Routes for Ocular Drug Delivery**

As demonstrated in Fig. 4, there are four general routes for administrating therapeutic agents to the anterior and posterior segments of the eye, i.e., topical, systemic, intravitreal, and transscleral administrations [12].
Topical Administration

Topical administration mostly refers to the use of eye drops, accounting for over 90% of ophthalmic products on the current market. In spite of their convenience to use, eye drops are very inefficient in delivering drugs, due to their limited administration volumes and fast clearance. In most cases, only 1% or less of a topically applied dose can enter the anterior segment of the eye, and less than 0.001% is expected to reach the posterior segment. Because of this restriction, eye drops are mostly used to treat dry eye and corneal diseases, but they have very limited success in treating posterior segment eye diseases.

Systemic Administration

Similar to the topical route, systemic administration also fails to achieve satisfactory ocular bioavailability since systemically administrated drugs need to overcome the BRB. Orally administrated drugs have to survive the harsh environment of the gastrointestinal tract and the first-pass metabolism. Although intravenous administration may be used to overcome these challenges, the dilution effect of the blood and the selective permeability of the BRB further limit drug entry into the eye. The poor delivery efficiency entails more frequent delivery with higher doses, thus increasing the risk of systemic side effects.

Intravitreal Administration

Intravitreal administration is an intervention of directly injecting drugs into the anterior chamber or the vitreous humor of the eye. It is a topical drug delivery method that can deliver a high dose of drugs to the target while avoiding the side effects of first-pass metabolism for systemically administrated drugs. Intravitreal injection is the main route of delivering macromolecules to the posterior segment of the eye. The drugs most commonly delivered via the intravitreal route are antibiotics,
corticosteroids, and antiangiogenic agents such as vascular endothelial growth factor (VEGF) inhibitors. Repeated intravitreal injections of anti-VEGF drugs have become the first-line treatment for age-related macular degeneration (see section “Age-Related Macular Degeneration” for details). However, being an invasive procedure, intravitreal injection could be associated with complications such as endophthalmitis, retinal detachment, and intraocular hemorrhage.

**Transscleral Administration**
The transscleral route includes subconjunctival, posterior juxta scleral, peribulbar, subtenon, and retrobulbar injections. Drugs delivered by this route can enter the posterior segment of the eye through the conjunctiva-sclera-choroid-retina pathway, achieving a superior ocular bioavailability (~0.01–0.1%), compared to the topical route (≤0.001%). However, it still fails to deliver sufficient drugs to the retina due to drug losses from the periocular space, the choroidal circulation, etc.

**Nanomedicine Formulations**
Nanotechnology provides new opportunities for the development of drug delivery systems particularly adapted to overcoming the eye-associated barriers. To date, a few nanomedicine formulations have demonstrated the capacity of targeted delivery and controlled release, reducing the degradation of labile drugs, and increasing the penetration, residence time, and bioavailability of drugs in various ocular tissues [13, 14]. This section will introduce some commonly studied nanomedicine formulations for treating ocular diseases. As shown in Fig. 5, these nanomedicine formulations include nanomicelle, liposome, nanoparticle, dendrimer, and nanogel [15, 16]. Table 1 summarizes representative nanomedicine formations that have been studied for ocular drug delivery [17].

**Nanomicelle**
Nanomicelles are made of self-assembled amphiphilic molecules that form nanosized colloidal structures with a hydrophobic core shielded by a hydrophilic shell. Nanomicelles have a common size range of 10–100 nm. Nanomicelles are one of the most studied nanomedicine formulations for ocular drug delivery. For instance, Civiale et al. developed dexamethasone-loaded nanomicelles made of copolymers of polyhydroxyethylaspartamide (PHEA) and PEGylated PHEA for anterior segment delivery [18]. In vivo dexamethasone concentration profiles were determined in rabbits with aqueous humor sampling. Results showed that dexamethasone-loaded PHEA nanomicelles produced a higher ocular bioavailability in comparison to dexamethasone suspensions. There were also studies using nanomicelles for posterior segment delivery. All studies suggested that formulations based on nanomicelles help penetrate ocular barriers and deliver more drugs to the posterior segment [19].
Liposomes are lipid vesicles with one or more phospholipid bilayers enclosing an aqueous core. Liposomes include small unilamellar vesicles (20–100 nm) made of a single bilayer, large unilamellar vesicles (200–800 nm), and multilamellar vesicles (500–5000 nm) that contain multiple concentric bilayers. Liposomes have several advantages that make them ideal for drug delivery. Because liposomes are non-covalent aggregates, their size, lipid composition, and electric charge can be easily designed and engineered. Liposomes are capable of carrying both hydrophobic (when embedding drugs in the lipid bilayers) and hydrophilic (when encapsulating drugs in the aqueous core) drugs. The surface of liposomes can be easily modified with polymers, carbohydrates, and antibodies, thus realizing stealth and targeting functions for drug delivery. Liposomes are made of biodegradable materials and, hence, in general have a high-membrane permeability and low cytotoxicity. All these advantages make liposomes a promising nanomedicine formation for ocular drug delivery.

Liposomes have demonstrated a good effectiveness for both anterior and posterior segment delivery [16]. For drug delivery to the anterior segment of the eye, efforts are mainly put toward improving precorneal residence time by incorporating positively charged lipids or mucoadhesive polymers in liposomes. Positively charged liposomes have exhibited a better efficacy for ocular delivery than negatively charged and neutral liposomes due to their capacity in binding with the
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negatively charged corneal surface. For posterior segment delivery, liposome development is more focused toward improving the half-life of drugs by reducing clearance from the vitreous humor, protecting labile molecules such as peptides and oligonucleotides from degradation, and providing a sustained and controlled release. Drugs bound to liposomes can increase their bioavailability and prolong their half-life in the ocular environment. For instance, it was found that the vitreous half-life of fluconazole in rabbit eyes increased from 3.08 to 23.40 h after formulating into liposomes [20].

### Nanoparticle

Nanoparticles, also known as nanospheres or nanocapsules, are solid drug carriers with a particle size of 10–1000 nm. Nanoparticles for ocular drug delivery are generally made of proteins, such as human serum albumin, or polymers, such as sodium alginate, chitosan, poly(lactide-co-glycolide) (PLGA), polylactic acid, and polycaprolactone. Drugs can be loaded either on the surface and inside the shell of the nanoparticles. Because topically administrated nanoparticles can be rapidly eliminated from the precorneal pocket, it is a common practice to modify the nanoparticles with mucoadhesive polymers, thus improving their precorneal residence time. Polyethylene glycol, chitosan, and hyaluronic acid are most commonly used molecules to modify nanoparticles for ocular drug delivery. Among these molecules, chitosan is positively charged and hence can help bind to the negatively charged corneal surface, thereby improving the precorneal residence time and

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decreasing clearance of the drug [21]. Once administrated, deposition and retention of nanoparticles depend on their size and surface properties. It was found that after transscleral administration, nanoparticles in the range of 200–2000 nm retained for more than 2 months, while smaller nanoparticles were rapidly cleared from periocular tissues [22].

**Dendrimer**

Dendrimers are nanosized, highly ordered, branched polymeric molecules. Dendrimers are available in different molecular weights with their terminals ended with various (amino, hydroxyl, carboxyl, etc.) functional groups. Drugs can be either entrapped in the dendrimer network through hydrogen bonds, hydrophobic interactions, and ionic interactions, or conjugated through covalent bonds. The highly branched structure of dendrimers allows incorporation of both hydrophobic and hydrophilic drugs. Molecular weight, size, surface charge, molecular geometry, and functional group are all important factors to design dendrimer formulations for drug delivery [23]. However, there are relevantly less results reported with dendrimer formulations for ocular drug delivery, likely due to their poor ability in loading the same amount of drugs as other nanocarriers.

**Nanogel**

Nanogels are nanoscale hydrogel particles composed of highly cross-linked hydrophilic polymers. Nanogels can be directly loaded with drugs by equilibration or swelling in water, followed by reduction in solvent volume and gel collapse, leading to the formation of tightly packed nanoparticles. Nanogels can be used for controlled release of both hydrophilic and hydrophobic drugs by varying the composition and conformation of polymers, and the degree of crosslinking [24].

**Treatments of Anterior Segment Eye Diseases**

Anterior segment eye diseases (ASED) refer to a range of disorders that affect the front of the eye, i.e., the anterior segment, which includes the cornea, conjunctiva, iris, lens, and ciliary body (see section “Anterior Segment” for details). ASED can be congenital, hereditary, or acquired. Typical disorders in this category include the dry eye disease, blepharitis, contact lens-related disorders, corneal ulcers, cataract, conjunctivitis, refractive errors, and so on. This section will be focused on two most common ASED, i.e., the dry eye disease and the cataract, and their treatments with nanomedicine formulations. Table 2 gives a comprehensive summary of nanomedicine formulations currently studied in clinical trials for treating both anterior and posterior segment eye diseases [17].

**Dry Eye Disease**

Dry eye is a multifactorial disease, characterized by an irritation of the eye due to deficiencies in producing enough tears or maintaining the stability of tear film on the ocular surface. Dry eye could result in damage of the corneal epithelium,
<table>
<thead>
<tr>
<th>Products/nanoformulations (cargos)</th>
<th>Conditions/disease</th>
<th>Administrations</th>
<th>Number enrolled</th>
<th>Status</th>
<th>Phase</th>
<th>ClinicalTrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticles (urea)</td>
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<td>Eye drops</td>
<td>50</td>
<td>Completed</td>
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<tr>
<td>Albumin (paclitaxel)</td>
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<td>NCT00738361</td>
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<tr>
<td>Cyclodextrin (dexamethasone)</td>
<td>Diabetic macular edema</td>
<td>Eye drops</td>
<td>40</td>
<td>Unknown</td>
<td>II/III</td>
<td>NCT01523314</td>
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<td>Lecithin/glycerin (coenzyme Q10)</td>
<td>Ataxia with ocular apraxia type 1</td>
<td>Oral</td>
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<tr>
<td>Liposome (latanoprost)</td>
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<td>Liposomes (latanoprost)</td>
<td>Ocular hypertension and open-angle glaucoma</td>
<td>Subconjunctival injection</td>
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<td>NCT02466399</td>
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<td>Liposomes (vincristine)</td>
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<td>Unknown</td>
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<td>NCT00335738</td>
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<td>Intravitreal injection</td>
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<td>Active, not recruiting</td>
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<td>NCT03093701</td>
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<tr>
<td>Lipid (TLC399)</td>
<td>Central/branch retinal vein occlusion with macula edema</td>
<td>Intravitreal injection</td>
<td>30</td>
<td>Recruiting</td>
<td>I/II</td>
<td>NCT02006147</td>
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<td>INVELTYS/mucus penetrating particles (Loteprednol etabonate)</td>
<td>Postoperative inflammation and pain following ocular surgery</td>
<td>Topical administration</td>
<td>900</td>
<td>Completed</td>
<td>FDA approved</td>
<td>NCT02163824 and NCT02793817</td>
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<td>Bromfenac DuraSite/synthetic polymer of cross-linked polyacrylic acid (bromfenac)</td>
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<td>Topical administration</td>
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<td>Completed</td>
<td>FDA approved</td>
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(continued)
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<th>Conditions/disease</th>
<th>Administrations</th>
<th>Number enrolled</th>
<th>Status</th>
<th>Phase</th>
<th>ClinicalTrials.gov identifier</th>
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</thead>
<tbody>
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<td>DexaSite/synthetic polymer of crosslinked polyacrylic acid and chitosan (dexamethasone)</td>
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<td>Completed</td>
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<td>Eye drops</td>
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<td>Completed</td>
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<td>NCT02845674</td>
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<td>Eye drops</td>
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<td>NCT02688556</td>
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<tr>
<td>Mesenchymal stem cells-derived exosomes</td>
<td>Macular holes</td>
<td>Intravitreal injection</td>
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<td>Recruiting</td>
<td>Early phase I</td>
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<td>Serum exosomal miRNA</td>
<td>Diabetic retinopathy</td>
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<td>200</td>
<td>Not yet recruiting</td>
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inflammation of the ocular surface, ocular fatigue, and impaired vision. Dry eye disease (DED) is the most prevalent eye disease that affects 10–30% of the world population. The current treatment of dry eye is mostly palliative rather than curative. It mainly relies on the use of drug-free artificial tears and over-the-counter eye drops and lubricants to hydrate the ocular surface. Effective therapeutic interventions in treating DED are still lacking. It is estimated that the DED directly and indirectly causes a $55 billion annual economic burden in the United States alone. Therefore, there is an urgent need to develop translational solutions to effectively manage the DED.

Topical administration of immunosuppressive drugs such as cyclosporine A (CyA) helps control ocular surface inflammation so that it increases tear secretion and the stability of tear film. Topical CyA also effectively restores epithelial damage and reduces disease recurrences in the long term, thus alleviating dry eye symptoms [25]. As shown in Fig. 6a, a number of nanomedicine formulations, such as nanomicelles, liposomes, and nanoparticles, have been developed to deliver CyA in the preclinical stage [26]. For example, it has been shown that CyA-loaded poly-ε-caprolactone (PECL) nanocapsules were able to increase CyA concentration in cornea five-times higher than that of the traditional oily formulation of CyA [27]. The increased bioavailability was attributed to internalization of the PECL nanocapsules in the corneal epithelium. Similar enhancement in bioavailability can be achieved by encapsulating CyA in a variety of nanoscale polymer shells, such as a double shell of hyaluronic acid and PECL, cysteine polyethylene glycol monostearate, or mixtures of surfactants and propylene glycol. Figure 6b shows the synthesis of cysteine-functionalized nanostructured lipid carrier (Cys-NLC) for the topical administration of CyA [28]. It was found that after topical administration to
rabbits, the CyA concentration in tear fluids of the Cys-NLC treated group was significantly higher than the group treated with the traditional oil solutions of CyA (Fig. 6c) [28]. In general, these novel nanomedicine formulations led to higher drug concentrations and longer-lasting periods (up to 24 h) in a broad range of ocular tissues including the cornea, conjunctiva, iris, ciliary body, and aqueous humor, in comparison to the traditional oily formulation of CyA. More recently, it has been reported that topical administration of CyA-loaded polymeric nanomicelles based on polyoxyl 40 stearate and methoxy poly(ethylene glycol) hexylsubstituted poly(lactide) led to a 28.5-fold increase of drug concentration in comparison to the traditional oily CyA solution [29].

Cataract
A cataract is a cloudy area of the lens of the eye that leads to a decrease in vision. Cataracts are a leading cause of blindness globally. According to the World Health Organization (WHO), cataracts affect approximately 65.2 million people worldwide and cause moderate to severe vision loss in over 80% cases. Cataracts are a leading cause of age-related vision loss in the United States. More than half of all Americans of 80 years older have cataracts. Symptoms of cataracts include blurry vision, abnormal color perception, monocular diplopia, glare, and impaired vision. Cataracts are mostly caused by electrolyte disturbances and oxidative damage. Transparency and refractive properties of the lens are regulated by the concentration of lens proteins in lens fibers. Mutations of these proteins can increase the oxidative stress, thus leading to the formation of cataracts. To date, the only available treatment for cataracts is surgical removal of the opacified lens and replacement with an artificial one. However, surgical treatments suffer from side effects such as implant disintegration, corneal wounds, postsurgical inflammation, and posterior capsular cataract formation. Hence, there is a general need for nonsurgical preventative and treatment interventions for cataracts.

Anticataract agents have been investigated in two distinct categories: chemical agents and antioxidants [30]. Some nonsteroid anti-inflammatory drugs such as aspirin, paracetamol, ibuprofen, and bendazac were found to delay cataract formation by effectively increasing blood pressure or inhibiting posttranslational protein modifications. Antioxidants are reducing agents that accept electrons from free radicals and reactive oxygen species, and therefore can protect tissues from oxidative stress and damage. Many antioxidant molecules have been found to be effective anticataract agents, such as glutathione, cysteine, cysteine prodrug L-2-oxothiazolidine-4-carboxylic acid, N-acetyl carnosine, N-acetylcysteine, and N-acetylcysteine amide. Some flavonoids, such as curcumin and quercetin, and β-carotenes, such as lutein and lycopene, have also demonstrated anticataract properties [31]. However, most of these drugs have very low delivery efficiencies due to their inability to overcome physical barriers of the eye (see section “Physical Barriers for Ocular Drug Delivery” for details).

Nanomedicine formulations have been studied to improve the bioavailability, biocompatibility, and biodegradability of anticataract drugs. Curcumin was encapsulated in PLGA nanoparticles for systemic administration, which increased the oral
bioavailability of the drug by ninefold compared to free curcumin. Lutein can be loaded with Labrasol® (a nonionic surfactant excipient) to form a nanoemulsion, which demonstrated a shorter lag time and two times more cellular accumulation compared with free lutein. Liposomes have also been reported as an efficient formulation for preventing cataracts. For example, it was found that vitamin E-containing liposomes made of dipalmitoyl phosphatidylcholine and dioleoyl phosphatidylcholine delayed cataract progression in a rat model [32]. Cytochrome C-loaded freeze-dried liposomes also exhibited significant efficacy in retarding the onset and progression of cataracts in rats [33].

**Treatments of Posterior Segment Eye Diseases**

Posterior segment eye diseases (PSED) refer to a spectrum of disorders that affect the back of the eye, i.e., the posterior segment, which includes the retina, choroid, and optic nerve (see section “Posterior Segment” for details). The most prevalent PSED include glaucoma, age-related macular degeneration, and diabetic retinopathy. These PSED are now recognized as a major cause of visual impairment worldwide and are more prevalent than infectious causes of visual impairment such as trachoma and corneal ulcers. Novel nanomedicine formulations to treat these PSED will be introduced in this section.

**Glaucoma**

Glaucoma is a group of eye conditions characterized by damage of the optic nerve. The symptoms of glaucoma include vision loss, eye pain, mild-dilated pupil, redness of the eye, and nausea. It was estimated that about 80 million people had glaucoma worldwide in 2020, and this number is expected to increase to over 111 million by 2040. The WHO estimated that 4.5 million people worldwide are blind due to glaucoma. Although most of the genetic bases of glaucoma are still not completely understood, increased intraocular pressure (IOP), ischemia of the optic nerve, and the activation of oxidative stress-related pathways are found in the progression of this disease. At present, the major aim in controlling glaucoma is to prevent or delay the loss of visual field. This is because neuronal cell death is irreversible. Once the visual field is lost, there is no cure available. It was found that an effective IOP reduction resulted in a delay of onset and progression of glaucoma in 80–90% patients in clinical trials.

Drugs to treat glaucoma are classified by their active ingredients, including prostaglandin analogs, beta blockers, alpha agonists, carbonic anhydrase inhibitors, and Rho-kinase inhibitors. Most of these drugs are lipophilic and hard to penetrate physical barriers of the eye. Nanomedicine formulations are able to increase the drug concentration in target tissues and result in improved and long-lasting therapeutic effects. The first study of using nanomedicine formulations to treat glaucoma was reported in 1986 [34]. The study showed a more prolonged myosis after administration of pilocarpine-containing poly(butylcyanoacrylate) nanospheres, compared to traditional pilocarpine solutions. Liao et al. synthesized pilocarpine-loaded
gelatin-covered mesoporous silica nanoparticles (p/GM) [35]. The gelatin coating was controlled by varying its thickness on the mesoporous silica nanoparticles, thereby realizing a sustained drug release. It was found that p/GM0.05, i.e., with 0.05 mg gelatin coating per mg of nanoparticles, was able to release pilocarpine in a long-lasting (up to 36 days) and high-concentration (~50%) fashion, thus maintaining a normal IOP for a period up to 21 days [35].

More recently, antiglaucoma drugs, such as beta blockers (betaxolol) or carbonic anhydrase inhibitors (dorzolamide), have been encapsulated in chitosan nanoparticles. It was found that betaxolol-loaded chitosan nanoparticles led to a significant decrease in IOP compared to traditional formulations [36]. Hyaluronic acid-modified chitosan nanoparticles codelivered with timolol maleate and dorzolamide hydrochloride showed a high efficacy in reducing IOP. Other examples of antiglaucoma drug-loaded nanoparticles include Eudragit® RL100 and RS100-based nanoparticles, PLGA nanoparticles, and cationic solid lipid nanoparticles [13]. Nanoemulsions have also been studied to deliver antiglaucoma drugs. Topical administration of nanoemulsions to hypertensive rabbits was able to reduce IOP up to 8 h [37]. Liposomes have also been tested for delivering antiglaucoma drugs. In general, it was found that cationic liposomes were more effective than neutral and negatively charged liposomes, likely due to stronger interactions of these liposomes with the ocular mucosa. For example, Natarajan et al. reported a long-lasting unilamellar liposome formulation for delivering a prostaglandin derivative, latanoprost (Xalatan®) [38]. It was found that a single subconjunctival injection of latanoprost-loaded liposomes led to IOP reduction for up to 120 days (Fig. 7). The IOP was further reduced over another 180 days after a second injection was administered [38].

**Age-Related Macular Degeneration**

Age-related macular degeneration (AMD) is a complex eye disease characterized by a progressive loss of central vision due to degenerative and neovascular changes at the macular area, which is responsible for central and sharp vision at the posterior segment of the eye. AMD can be divided into the slowly developing dry (~80%) and the rapidly blinding wet (~20%) forms. The disease impairs abilities to read and to recognize faces, thus severely compromising the patients’ independency. AMD is the leading cause of blindness in the elderly population in developed countries. Its prevalence increases with age. It is estimated that the incidence of AMD in people of age 65–75 is 1%, and the incidence increases to 13% in people of age 85 and above. With improved mortality conditions at advanced ages, it is projected that in 2050, 20% of the world population will be older than 65. As a consequence, the prevalence of AMD is expected to double during the next two decades. In general, patients with AMD incur twice the annual costs per patient compared with individuals without AMD. The economic burden of AMD is estimated to be above $35 billion/year in the United States alone.

Currently, AMD is treated with the photodynamic therapy, transpupillary thermotherapy, macular surgery, radiation, retinal translocation, and most commonly, anti-vascular endothelial growth factor (anti-VEGF) agents. The three most widely used
anti-VEGF drugs at present are Avastin® (bevacizumab), Lucentis® (ranibizumab), and Eylea® (afibercept). Bevacizumab is a whole anti-VEGF-A immunoglobulin, while ranibizumab is a fab fragment of an antibody against VEGF-A. Afibercept is a new recombinant fusion protein that is composed of two main components, i.e., the VEGF-binding portions from the extracellular domains of human vascular endothelial growth factor receptor-1 (VEGFR-1) and VEGFR-2. Afibercept has the ability to bind VEGF-A, VEGF-B, or placental growth factor and to inhibit angiogenesis.

To deliver drugs directly to retina, anti-VEGF agents are administered intravitreally, which reduces the dosage required and avoids the side effects associated with systemic administration. However, intravitreal injections are associated with various complications, such as endophthalmitis, a sight-threatening infection with reported incidences of 0.019–0.09%. Multiple monthly to bimonthly injections
are required for long periods of time for the treatment of AMD, thus increasing the risk of infection. Apart from the endophthalmitis risk, the need for frequent intravitreal injections poses a significant burden to the patients and healthcare providers. Hence, there is an urgent need and a great interest of developing a noninvasive topical ocular formulation, ideally in the form of eye drops, to deliver anti-VEGF drugs to patients with retinal vascular diseases such as AMD.

Liposomes have been studied for the treatment of AMD. The biodegradable and biocompatible nature of phospholipids makes liposomes attractive for ocular delivery. There are several lipidosome formulations currently under study for the treatment of AMD, such as peptide-modified PEGylated liposomes, vector-mediated liposomes, and PEGylated cationic liposomes [39, 40]. Tavakoli et al. synthesized sunitinib-loaded liposomes to block the neovascularization signaling pathway through inhibition of the tyrosine kinase of vascular endothelial growth factor receptors (VEGFRs). By comparing the encapsulation efficiency, loading capacity, and drug release profile in buffer and vitreous, they showed that liposomes with the mean size of 104 nm could effectively carry sunitinib and release it up to 3 days (Fig. 8) [41]. de Cogan et al. reported that therapeutic levels of bevacizumab in the posterior segment were achieved in rats following topical administration when this anti-VEGF drug was conjugated with a cell-penetrating peptide, i.e., short cationic sequences (less than 30 amino acids) with a remarkable capacity for biomembrane translocation [42]. Although being tested only in rodents, this research demonstrated the feasibility of a potentially promising noninvasive formulation for topical administration of anti-VEGF drugs to treat patients with AMD.

Diabetic Retinopathy

Diabetic retinopathy (DR) is a diabetes complication that affects the eye. It can be defined as a microvascular disease that leads to capillary occlusion, and damage of blood vessels and light-sensitive tissues in the retina. In its early stage, the patient might not have symptoms. As the condition progresses, patients with DR may have blurred vision, impaired color vision, and even blindness. DR can be divided into two broad categories: the nonproliferative DR (NPDR) and the proliferative DR (PDR). NPDR is further subdivided into mild, moderate, and severe [43]. In the mild and moderate NPDR stages, the walls of blood vessels in retina weaken. Tiny bulges (microaneurysms) protrude from the walls of smaller vessels, sometimes leaking fluid and blood into the retina. Larger retinal vessels then begin to dilate and become irregular in diameter. When it reaches the severe stage, too much sugar can lead to severe block of the blood vessels. PDR is the result of further development from severe NPDR. In this stage, due to the damage of blood vessels, capillary endothelial cells begin to proliferate, and hypoxic retinal tissue releases vascular proliferation substances to promote the growth of abnormal retinal blood vessels, i.e., neovascularization, which grow in an attempt to supply oxygen to the hypoxic retina. This could result in retinal detachment and blindness.

The mechanisms by which hyperglycemia results in retinal pathology remain inconclusive. The main biochemical pathways that influence DR include protein kinase C activation, advanced glycation end product (AGE) pathway, oxidative
stress, and expression of growth factors, such as VEGFs. Typical drugs to treat DR include corticosteroids, AGE inhibitors such as carnosine, and antioxidants. Polymeric nanospheres have been studied to deliver these drugs to treat DR. PLGA, chitosan, polyvinyl alcohol, and poly(methyl methacrylate) nanospheres all have a high drug encapsulation rate to prolong the resident time of the free drugs. Liposome formulations are mainly based on biodegradable lipids, such as phospholipids, ceramides, and glycerides. Dendrimers, such as polyamidoamine, are also studied. Drugs can be entrapped in the dendrimer network composed of the functional groups to promote a sustained drug delivery to the retina.

**Ocular Nanotoxicology**

The ocular surface serves as a potential biological portal for environmental particulate matters and pathogens to enter the human body. Hence it is important to understand the nano-bio interactions at the ocular surface, and the health impact of natural, incidental, and engineered nanoparticles that enter the body via the eye [44]. This section briefly introduces emerging toxicological studies about

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**Fig. 8** Nanomedicine formulations for treating age-related macular degeneration: (a) cumulative release of sunitinib (%) from a liposomal formulation. The insert shows a magnified view of the release profile over 5 days; (b) representative late-phase fluorescein angiograms in control mice and in aflibercept, liposomal sunitinib, and sunitinib-cyclodextrin treated mice, 3 days after photocoagulation; and (c) vascular leakage measured by fluorescein angiography. (Reproduced with permission from Ref. [41]. Copyright 2022 Elsevier)
nanoparticle interactions with the ocular surface and tissues. Table 3 summarizes a few representative ocular nanotoxicological studies [44].

**Impact on the Ocular Surface**

Nanoparticles mostly affect the ocular surface, which is composed of the corneal epithelium in the center and the surrounding conjunctival epithelium (see section “Anterior Segment”). It was found that nanoparticles could induce a series of inflammatory events at the ocular surface, featured by symptoms such as dryness, burning, itching, gritty eyes, conjunctival chemosis, limbitis, redness, and swelling of eyelids. Ocular surface inflammation may cause tear film dysfunction. Dry eye is one of the most common ocular surface disorders directly associated with exposure to particles. Han et al. found that exposure to titanium dioxide nanoparticles worsened dry eye symptoms [45]. Researchers have also showed that exposure to PM2.5 induced allergic conjunctivitis [46].

**Impact on the Lens**

It has been reported that cigarette smoke, diesel exhaust, and aerosols of iron nanoparticles all have an adverse impact on the lens [47]. Exposure to these metal-containing particles and aerosols leads to accumulation of metals, such as cadmium, in the lens, which could induce oxidative stress and trigger cataractogenesis [48]. In addition to direct exposure to metal-containing particles, inhaled metal nanoparticles may also enter the blood and then accumulate in the aqueous humor by penetrating the blood-aqueous barrier (see section “Blood-Aqueous Barrier”), thus increasing the toxic metal concentration in the eye. Increasing metal ions in the eye may promote cataract formation by inducing oxidative stress, inhibiting antioxidant pathways, and modifying the structure/formation of the lens extracellular matrix. It was proposed that iron nanoparticles could cause oxidative damage to lens through the metal-catalyzed Fenton reaction [49].

**Impact on the Retina**

Nanoparticles may cause retinal vascular layer damage and cell degeneration by inducing oxidative stress. Söderstjerna et al. studied the effects of 20 and 80 nm silver and gold nanoparticles on an in vitro cell culture model of the mouse retina [50]. It was found that exposure to these nanoparticles by 72 h, even at low particle concentrations, caused significant oxidative stress and apoptosis of the retinal cells (Fig. 9), which could lead to visual impairment or even blindness. Cytotoxicity of these nanoparticles was attributed to their neurotoxic effects especially on the sensory neurons of the retina, i.e., the photoreceptors, which are the most vulnerable neurons of the retina and the key for a proper vision [50]. In addition, it has been
<table>
<thead>
<tr>
<th>Compound</th>
<th>Biological model</th>
<th>Mechanism</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Au NP</td>
<td>Zebrafish eye</td>
<td>Disrupt eye development and pigmentation</td>
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<tr>
<td>Ag/Au NP</td>
<td>Cell and tissue culture of mouse retina</td>
<td>Oxidative stress</td>
<td>Apoptosis, neurotoxic effect, and even visual impairment</td>
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<tr>
<td>Ag NP</td>
<td>Bovine retinal endothelial cells</td>
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<td>Cytotoxicity and apoptosis</td>
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<td>Ag NP</td>
<td>New Zealand white rabbits</td>
<td></td>
<td>Conjunctival redness, edema, and discharge</td>
</tr>
<tr>
<td>Ag NP</td>
<td>Guinea pigs</td>
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<td>Grade 1 conjunctivae irritation</td>
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<tr>
<td>Fe NP</td>
<td>Human corneal epithelial cells</td>
<td>Elevated inflammatory response, cell death-related pathway indicators, and generated mistranscribed RNA</td>
<td>Cell death</td>
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<td>CeO₂ NP</td>
<td>Rat retina primary cells, tubby mutant mice, and very low-density lipoprotein receptor knockout mouse</td>
<td>Antioxidative effect</td>
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<tr>
<td>SiO₂ NP</td>
<td>Human corneal epithelial cells and Sprague–Dawley rats</td>
<td>Cell membrane damage, cell death, and mitochondrial dysfunction</td>
<td>Corneal injury</td>
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<td>TiO₂ NP</td>
<td>Rabbits</td>
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<td>Reversible ocular conjunctival redness</td>
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<td>New Zealand white rabbits</td>
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<td>Ocular surface damage</td>
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<tr>
<td>ZnO NP</td>
<td>Rat retinal ganglion cells</td>
<td>Overproducing ROS, caspase 12, decreasing plasma membrane calcium ATPase and bcl 2/caspase 9, and disrupting intracellular calcium homeostasis</td>
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<tr>
<td>ZnO NP</td>
<td>Sprague–Dawley rats</td>
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<td>Retinopathy</td>
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<tr>
<td>Fullerene</td>
<td>Rabbit</td>
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<td>Conjunctival redness and corneal epithelial defects</td>
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(continued)
reported that nanoparticles can increase serum homocysteine levels, which in turn reduces the retinal blood flow velocity. Moreover, dissolution of excess metal ions in the eye was found to be associated with retinal detachment, age-related macular degeneration, and intraocular bleeding.

Table 3 (continued)

<table>
<thead>
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<th>Mechanism</th>
<th>Outcome</th>
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<td>Rabbits</td>
<td></td>
<td>Conjunctiva redness and blood vessel hyperemia</td>
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<td>SWCNT</td>
<td>ARPE-19</td>
<td>Changes in SOD levels, membrane integrity, and cell apoptosis increase in LDH release, ROS generation, and apoptosis</td>
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<td>Human retinal pigment epithelium cells</td>
<td>Decrease in cell survival rate</td>
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<tr>
<td>MWCNT</td>
<td>Rabbit</td>
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<td>Conjunctival redness/discharge and vessel hyperemia</td>
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<td>GO NP</td>
<td>Primary human corneal epithelium cells and human conjunctiva epithelium cells; Sprague–Dawley rats</td>
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<tr>
<td>GO NP</td>
<td>Kunming mice and corneal epidermal cells</td>
<td>Inflammation and apoptosis</td>
<td>Incrassated corneal stromal layer and iris neovascularization</td>
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NP nanoparticle, SWCNT single-walled carbon nanotubes, MWCNT multiwalled carbon nanotubes, GO graphene oxide, ROS reactive oxygen species, SOD superoxide dismutase, LDH lactate dehydrogenase

reported that nanoparticles can increase serum homocysteine levels, which in turn reduces the retinal blood flow velocity. Moreover, dissolution of excess metal ions in the eye was found to be associated with retinal detachment, age-related macular degeneration, and intraocular bleeding.

**Conclusion**

Nanotechnology provides new opportunities for the development of drug delivery systems particularly adapted to overcoming the eye-associated barriers. A number of nanomedicine formulations, such as nanomicelles, liposomes, nanoparticles, dendrimers, and nanogels, have demonstrated the capacity of increasing the residence time and bioavailability of drugs in the treatments of various ocular diseases, including dry eye, cataracts, glaucoma, age-related macular degeneration, and diabetic retinopathy. Despite the preliminary success achieved by these novel drug delivery systems, it should be noted that development of nanomedicine formations for preventing and treating ocular diseases is still in its infancy. Potential toxicity of nanoparticles due to interactions with the ocular surface and tissues should be further investigated.
References


Fig. 9  Adverse effects of silver (Ag) and gold (Au) nanoparticles (NPs) on mouse retina: (a) TEM images demonstrating uptake of Ag and Au NPs found in all three retinal nuclear neuronal layers, i.e., the ganglion cell layer (GCL), the inner nuclear layer (INL), and the outer nuclear layer (ONL). Arrowheads show NPs that have been taken up by the retinal cells. Scale bars equal to 0.2 mm for images (A–D); 1 mm for (E, F), (I, J), and (M, N); and 0.5 mm for (G, H), (K, L), and (O, P); (b) retinal cell apoptosis was detected with the TUNEL assay. Apoptosis was detected in the ONL, INL, and GCL after exposure to 20 and 80 nm Ag and Au NPs; (c) oxidative stressed cells were detected using AvidinD as a marker. AvidinD-positive cells were detected after exposure to 20 and 80 nm Ag and Au NPs. (Reproduced with permission from Ref. [50]. Copyright 2014 PLOS)


