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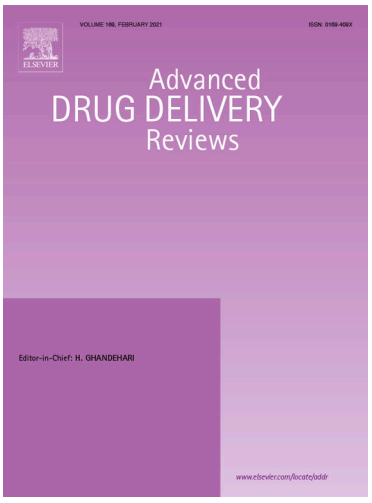

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Polymer- and Lipid-Based Nanocarriers for Ocular Drug Delivery: Current Status and Future Perspectives

Haijie Han[1,2,#], Su Li[1,#], Mingyu Xu[1,#], Yueyang Zhong[1,2], Wenjie Fan[1], Jingwei Xu[1,2], Tinglian Zhou[1], Jian Ji[3], Juan Ye[1,2,*], and Ke Yao[1,2,*]

1 Eye Center, the Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Road, Hangzhou 310009, People's Republic of China

2 Zhejiang Provincial Key Lab of Ophthalmology, the Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Road, Hangzhou 310009, People's Republic of China

3 MOE Key Laboratory of Macromolecule Synthesis and Functionalization of Ministry of Education, Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, People's Republic of China

* Corresponding author: xlren@zju.edu.cn (Ke Yao); yejuan@zju.edu.cn (Juan Ye)

# Authors contributed equally to this work.

Abstract:

Ocular diseases seriously affect patients' vision and life quality, with a global morbidity of over 43 million blindness. However, efficient drug delivery to treat ocular diseases, particularly intraocular disorders, remains a huge challenge due to multiple ocular barriers that significantly affect the ultimate therapeutic efficacy of drugs. Recent advances in nanocarrier technology offer a promising opportunity to overcome these barriers by providing enhanced penetration, increased retention, improved solubility, reduced toxicity, prolonged release, and targeted delivery of the loaded drug to the eyes. This review primarily provides an overview of the progress and contemporary applications of nanocarriers, mainly polymer- and lipid-based nanocarriers, in treating various eye diseases, highlighting their value in achieving efficient ocular drug delivery. Additionally, the review covers the ocular barriers and

administration routes, as well as the prospective future developments and challenges in the field of nanocarriers for treating ocular diseases.

Keywords: Polymer-based nanocarrier; Lipid-based nanocarrier; Ocular drug delivery; Ocular diseases; Ocular barriers

Abbreviations:

AMD, age-related macular degeneration; AMP, antimicrobial peptide; ATP, adenosine triphosphate; BAB, blood-aqueous barrier; BOB, blood-ocular barrier; BRB, blood-retinal barrier; CIP, ciprofloxacin; CNV, choroidal neovascularization; CsA, Cyclosporine A; DED, dry eye disease; DME, diabetic macular edema; DOX, doxorubicin; DR, diabetic retinopathy; DSP, dexamethasone sodium phosphate; ERK, extracellular regulated protein kinase; FDA, Food and Drug Administration; FGF, fibroblast growth factor; Flt, Fms-like tyrosine kinase; GDNF, glial cell line-derived neurotrophic factor; HCE, human corneal epithelial; HIF, hypoxia inducible factor; HSP, heat shock protein; KTZ, ketoconazole; LCA, Leber congenital amaurosis; ICAM-1, intercellular adhesion molecule-1; LEC, lens epithelial cell; LFA, lymphocyte function-associated antigen; LNC, lipid-based nanocarrier; HA, hyaluronic acid; IL-6, interleukin-6; IL-12, interleukin-12; ILM, inner limiting membrane; IOL, intra-ocular lens; ION, ischemic optic neuropathy; IOP, intraocular pressure; IRD, inherited retinal disease; MAPK, mitogen-activated protein kinases; miRNA, microRNA; MMP, matrix metalloproteinase; MOX, moxifloxacin; MRSA, methicillin-resistant *Staphylococcus aureus*; mTOR, mammalian target of the rapamycin; Nd: YAG, neodymium-doped yttrium aluminum garnet; NF-κB, nuclear factor kappa-B; NLC, nanostructured lipid carrier; NSAIDs, nonsteroidal anti-inflammatory drugs; PAMAM, polyamindoamine; PCL, polycaprolactone; PCO, posterior capsular opacification; PDA, polydopamine; PDGF, platelet-derived growth factor; PDR, proliferative retinopathy; PDT, photodynamic therapy; PEG, poly(ethylene glycol); PEI, polyethyleneimine; PLA,

polylactic acid; PLGA, poly(lactic-co-glycolic acid); PNC, polymer-based nanocarrier; PTA, photothermal transduction agent; PTT, photothermal therapy; PVR, proliferative vitreoretinopathy; RBC, red blood cell; RCE, retinal capillary endothelial; RGC, retinal ganglion cell; RGD, arginine-glycine-aspartic acid; RNAi, RNA interference; RNV, retinal neovascularization; ROS, reactive oxygen species; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; shRNA, short-hairpin RNA; siRNA, small interfering RNA; SLN, solid lipid nanoparticle; SOD, superoxide dismutase; TAC, tacrolimus; TKI, tyrosine kinase inhibitor; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TON, traumatic optic neuropathy; VEGF, vascular endothelial growth factor; VEGF-A, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor.

1. Introduction

Ocular diseases seriously affect the vision and life quality of patients today. More than 250 million people are affected by visual impairment globally, and the morbidity prediction is still not optimistic [1]. It is projected that by 2050, around 115 million people will be blind if treatment is not improved from 2020's statistic of approximately 43.3 million worldwide, contributing to the high population growth in undeveloped areas and the global population ages [2, 3]. There are multiple treatment options currently available for the management of ocular diseases, including surgery, laser, and medication administrations. Among them, medication administration is the most common therapeutic method, but still has nonnegligible disadvantages, including short ocular retention time, reduced drug accumulation, and insufficient bioavailability, which ultimately result in limited ocular therapeutic benefits [4]. These drawbacks reinforce the need to bring innovative drug delivery strategies to the forefront for effectively combating eye diseases [5-7].

The application of nanocarriers represents a promising means to selectively deliver and concentrate drugs in ocular lesions. Among all the nanocarriers, polymer-based

nanocarriers (PNCs) and lipid-based nanocarriers (LNCs) are particularly attractive. Specifically, both PNCs and LNCs have been shown to enhance penetration, retention and solubility, reduce toxicity, prolong release, and enable targeted delivery of the drug [8-10]. In addition to these common characteristics, uniquely, the PNCs are provided with versatility by precise control of particle characteristics and the ease of surface modification, while LNCs are offered with advantages such as formulation simplicity with a range of physicochemical properties, use of physiological lipids and GRAS excipients, and the industrial scale production facility at low cost [11, 12]. These delicate features make PNCs and LNCs promising candidates for pharmaceutical therapy in clinical ophthalmology.

Based on the above, this review aims to introduce the recent progress and application of nanocarriers majorly incorporating PNCs and LNCs in ocular disease treatment. Specifically, the eye anatomy, drug delivery barriers, and administration routes will be presented first. Then, the development of ocular PNCs and LNCs for various eye diseases will be introduced in detail. Finally, their potential prospects and challenges in the clinical application of ophthalmology will be discussed. In this approach, we believe that this review can serve as a valuable reference for the rational design of PNCs and LNCs for ocular diseases, as well as for the advancement of drug delivery systems for ophthalmic applications.

2. Eye Anatomy and the Ocular Barriers Affecting Drug Delivery

Despite being one of the most easily accessible organs in the body, medication delivery to eye tissues is extremely difficult. Similar to the brain, the eye is referred to as being "immune privileged" since it is one of the central nervous systems, which is shielded from circulation. The precise eye anatomy with its complex ocular barriers makes it a highly separated organ isolated from systemic circulation. Thus, the treatment of ocular diseases faces multiple challenges, especially in the posterior segment.

2.1 Eye Anatomy

The eye is a complex organ made up of sensitive tissue structures arranged as compactly adjoined layers, whose cross-sectional diagram is shown in Fig. 1. The ciliary body and lens anatomically separate the eyeball into the anterior and posterior eye. To be specific, the anterior segment mainly contains the cornea, conjunctiva, iris, ciliary body, and lens, while the posterior segment includes the sclera, vitreous humor, retina, choroid, and optic nerve [13].

2.2 The Ocular Barriers Affecting Drug Delivery

The eye has complex but precise anatomy and structure. However, due to the presence of those unique characteristics, drugs may encounter multiple barriers, resulting in poor concentrations in the targeted locations (Fig. 1).

2.2.1 Tear Film Barrier

Tear film, a precorneal film that covers three layers, including an outer thin lipid layer, a middle aqueous layer, and an innermost mucous layer, forms the first permeability barrier that limits ocular drug delivery [14]. Anatomically, the outer oil layer prevents water from evaporating and simultaneously reduces medication absorption into the cornea and sclera [15]. In the middle aqueous layer, some endogenous proteins such as globulin, albumin, and lactoferrin can bind and metabolize the administered medication, resulting in decreased bioavailability [16]. The inner layer, the mucus layer, is a complex mixture of water, mucins, lipids, salts, enzymes, etc. [17] The mucus layer is the densest at the epithelial apex and gets more dilute as it extends outward into the tear fluid, and plays a significant role as a barrier in drug delivery since its pore structure with negatively charged glycans and hydrophobic regions traps and adheres to foreign particulates, followed by being washed by mucus turnover before reaching the corneal surface [18, 19].

Apart from the above structural barriers, the nasolacrimal duct drainage and the constant rapid flow of tears dynamically constitute significant barriers. The average tear volume is roughly 7 μL but dramatically increases to 30 μL after topical administration,

causing immediate drainage of extra fluid through the nasolacrimal duct with over 85% of administered drug dose lost before reaching the corneal surface. Moreover, the retained drug could be further diluted by rapid tear turnover, which lowers the concentration gradient and diffusion rate, resulting in low bioavailability of intraocular drugs in aqueous humor, usually ranging from 0.1% to 5% [7, 20].

2.2.2 The Corneal Barrier and Anterior Segment Barrier

The cornea is the most apparent mechanical and chemical barrier to both hydrophobic and hydrophilic molecules. Five regular and ordered layers, namely epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium, make up the optically clear avascular structure of the cornea [21, 22]. Epithelium and stroma are the rate-limiting layers for the trans-corneal permeation of drugs. The external corneal stratified multilayer epithelium is a hydrophobic layer with tight junctions between epithelial cells, which creates a dense barrier for the hydrophilic drugs that primarily diffuse through paracellular channels [23]. Besides, the existence of drug efflux pumps and drug-degrading enzymes such as cytochrome P450 in the epithelium contributes to another reason for low topical drug bioavailability [4]. Different from the epithelium, the stroma is a hydrophilic fibrous layer, limiting the penetration of hydrophobic molecules that are passively transported *via* the transcellular pathway. Therefore, the molecular size and hydrophobicity/hydrophilicity of the drug play a crucial role in its cornea's permeability properties.

The ciliary body locates posterior to the iris and secretes aqueous humor that nourishes interior ocular tissues. The secreted aqueous humor flows towards the cornea, gathers in the Schlemm's canal, and ultimately drains into the episcleral blood vessels. Therefore, aqueous humor presents a dynamic barrier to eliminating therapeutic drugs from the ocular tissues. The concentration of those drugs will be further reduced by the rapid aqueous humor turnover (approximately 2-3 $\mu L\ min^{-1}$), deteriorated by the resistance to the aqueous humor flow direction [7, 24].

When drugs progressively move from the aqueous humor towards the posterior segment, they encounter the iris and lens. There is a lack of sufficient available data to assess the barrier nature of these structures. However, there is proof that the ciliary body and the iris express relevant active drug transporters, which further impedes drug permeation [25]. Besides, the melanin pigment in the ciliary body binds to the drug, and the iris can hamper the drug to the posterior segment [26]. As for the lens, the cortex and nucleus formed by intact and compact lens fibers limit drug diffusion in the lens [27].

In addition to the corneal pathway, topically administrated drugs can reach the conjunctiva and enter the eye *via* the conjunctiva-sclera-choroid pathway [28]. The conjunctiva is a transparent mucous membrane that covers the eye's surface around the cornea, consisting of the upper epithelium and lower stromal layer that contains vascularized tissues with extensive blood and lymphatic flow [29]. The conjunctiva is 25 times more absorbent than the cornea due to its 17-time wider surface area, fewer layers of epithelial cells, and 250-time larger paracellular spaces, which makes it more permeable, particularly for large hydrophilic molecules [30, 31]. However, due to its high blood vessel density, drugs that penetrate the conjunctiva may enter the general blood circulation *via* the conjunctival sac or the nasal cavity rather than into the ocular segments [4]. Therefore, it can bring considerable drug loss, particularly for smaller hydrophilic molecules, thereby lowering their ocular bioavailability [32].

2.2.3 Sclera and Bruch's-Choroid Complex

The sclera is another substantial barrier to drug delivery to the eye with limited permeability in addition to the cornea. It is a dense, hydrophilic, collagenous connective tissue that makes up the major eyeball's outer shell, consisting of intersecting and stacking scleral collagen matrix with negatively charged proteoglycan matrix in the inter-fibril space [33]. The thickness of the sclera appears to be a critical factor in transscleral drug delivery [34].

The choroid resides between the sclera and the retina and is a prominent dynamic barrier because of its high vascularization and innervation for supplying blood to the retina. The choroid can be divided into five layers from the outside to the inside: the suprachoroidal cavity, the two vascular layers, the choroid capillary layer, and Bruch's membrane. Bruch's membrane, the basement membrane of the retinal pigment epithelium (RPE), is a thin collagenous membrane (2 to 4 μm) that is sandwiched between the choriocapillaris from the outside and the RPE from the inside. Since RPE expresses a wide range of enzymes (esterases, peptidases, dehydrogenases, cytochrome P-450 enzymes) and efflux proteins (P-gp), it also serves as a metabolic barrier against drug permeability [35]. Bruch's-choroid complex presents a more significant barrier to drug delivery *via* the transscleral pathway than the sclera itself. It can bind the solute, especially positively lipophilic drugs, thereby forming a slow-release drug depot in the Bruch's-choroid complex [36]. Furthermore, the molecular size also affects Bruch's-choroid complex permeability with hydrophilic carboxyfluorescein and dextrans, showing an exponential decrease with increasing molecular radius in bovine tissues [37].

2.2.4 Vitreal Barrier

The vitreous humor acts as the first barrier against drug permeation to the underlying retinal and choroidal tissues after intravitreal administration, a most widely applied intraocular administration that can achieve drug concentrations in the posterior segment of the eye. The viscosity of vitreous fluid impedes the diffusion of more extensive and heavier therapeutic cargoes like proteins, with no significant retardation of smaller molecules [38]. Besides, the net anionic charge of the vitreous humor regulates the diffusion of drug molecules. To be specific, negatively charged particles diffuse freely, while positively charged particles get trapped in the vitreous body [39]. Consequently, the molecular weight and charge of the administered drug have a huge impact on its vitreous distribution and retinal bioavailability. The following structural barrier for molecular diffusion to the retina after the vitreous fluid is the inner limiting

membrane (ILM), a membrane formed by the footplates of the Müller glial cell [40]. With an average pore size of 10-25 nm, the ILM forms a strict physical barrier against most nanoparticles; however, uptake and transcellular permeation *via* Müller cells may be an alternative mechanism of getting into the inner retina from the vitreous chamber [41].

2.2.5 Blood-Ocular Barrier (BOB)

The BOB system includes the anterior blood-aqueous barrier (BAB) and the posterior blood-ocular barrier (BRB). The BAB that presents in the anterior segment of the eye is made up of non-fenestrated vascular endothelium covering the iris blood vessels and tight junctions (zonula occludens) linking the apical portions of neighboring epithelial cells of the non-pigmented ciliary body epithelium and prevents drug entry from the plasma into the aqueous humor [42]. However, the BAB is still not a complete barrier on account of the fenestrated capillaries in the ciliary body stroma. These fenestrated capillaries, as the secondary source of plasma protein leakage to the iris, also enable the entry of small molecules into the iridial circulation [25]. The BRB primarily impedes drug diffusion into the retina after systemic circulation [43]. The BRB present in the posterior segment can be further divided into inner and outer BRB. The inner BRB consisting of retinal capillary endothelial (RCE) cells possesses tight intercellular junctions and selectively defends the retina against foreign substances in the blood circulation, particularly hydrophilic compounds and macromolecules [44]. The intercellular junctions of retinal microvasculature are robust structural barriers against molecular diffusion to and from the retina due to the retinal microvascular endothelium's characteristics, including its lack of fenestrations and the expression of specialized intercellular junction proteins [30]. The outer BRB separating the choroid and Bruch's membrane from the inner retina is constituted by the tight junctions between RPE cells and allows only 1-2% of an administrated drug to reach the retina and vitreous region [14, 30].

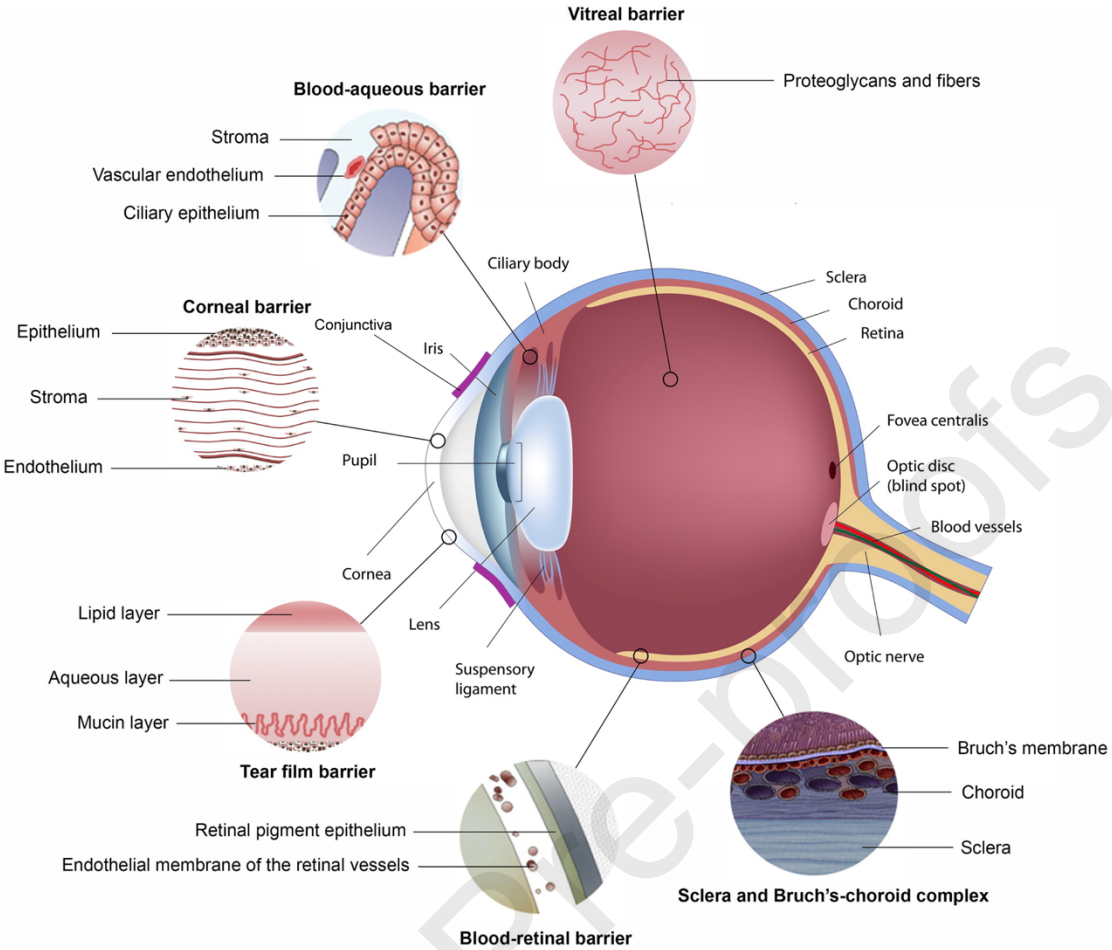

Fig. 1. The ocular barriers against drug delivery, reproduced with slight modification from literature [43]. Drugs may encounter multiple obstacles during delivery, such as the tear film barrier, the corneal barrier, the sclera and Bruch's-choroid complex, the vitreal barrier, the BAB, and the BRB.

3 The Ocular Administration Routes and Drug Kinetics

3.1 The Ocular Administration Routes

Effective drug concentration in lesion location is the key to managing ocular diseases. To achieve effective drug concentration in target positions with avoidance of the existing ocular barriers, various administration routes including systemic, topical, intraocular, and periocular administration, have been developed accordingly, and their injection areas, benefits, and challenges are summarized in Table 1.

3.1.1 Systemic Administration

Systemic administration, including intravenous and oral dosing, remains a huge challenge to deliver drugs into the ocular tissues, mainly due to the following three reasons. First, orally administrated drugs must survive the harsh environment of the gastrointestinal tract and first-pass metabolism. Second, the eye has a much less blood supply than the whole body, consequently with little drug accumulation. More importantly, the BOB restricts the drugs from reaching the ocular tissues. As mentioned previously, BAB restricts drug penetration into the eye's anterior segment from the systemic circulation, while both inner and outer BRB allow very limited drug administration in the posterior segment of the eye [13, 45]. Thus, it requires a high dose and frequent drug administration to achieve the desired therapeutic efficacy, which may result in systemic adverse effects and poor therapy compliance.

3.1.2 Topical Administration

Topical application is still the preferred way to manage ophthalmic disorders due to its non-invasive administration method. It accounts for over 90% of the ophthalmic product on the market today [2]. However, limited drug delivery efficiency remains a crucial problem. Pre-corneal drug loss is still the main issue for topical administration because of the high tear turnover rate, blinking, lacrimation, and nasolacrimal drainage. Consequently, eye drops must be frequently instilled to keep the required drug concentration on the ocular surface, which may lead to poor compliance and complications. In addition, topical application is less effective for treating posterior eye disorders even with repeated dosages due to the obstinate existence of the anatomical corneal barrier [46]. Meanwhile, the impact of side effects, such as preservative damage, ocular irritation, complications caused by steroids, etc., should not be disregarded [46].

3.1.3 Intraocular Administrations

Intraocular administrations mainly involve intracameral, intravitreal, subretinal, intrastromal, suprachoroidal, and intrastromal routes. Intracameral injection directly injects the drug into the anterior chamber, which is usually used after cataract surgery and for treating anterior segment diseases such as fungal and bacterial keratitis.

However, this method fails to deliver drugs to the posterior segment attributing to the penetration of the drug against the aqueous humor flow in the eye [47]. On this account, intravitreal injection is adopted to attain drug concentrations in the posterior area of the eye. It comprises direct intravitreal injection and intravitreal implantable devices and has become the dominant method in treating vitreoretinal diseases in recent decades [48]. It facilitates the delivery of therapeutics, for instance, anti-vascular endothelial growth factor (VEGF) [49], steroids [50], genes [51], and stem cells [52] and increases the drug concentration in the vitreous and the retina. However, it exists a high-level risk of ocular complications such as bleeding, retinal holes, cataracts, vitreous hemorrhage, high intraocular eye pressure, secondary glaucoma, optic nerve damage, endophthalmitis as well as retinal toxicity [53]. The subretinal injection is applied to access and deliver agents to the subretinal space that is located between RPE cells and photoreceptors, to cure better vision diseases caused by mutations in photoreceptors and, or RPE genes and retinal degenerative diseases. The suprachoroidal administration is utilized for implants, microneedles, and other formulations, with the drug administered between the sclera and choroid, minimizing the systemic side effects [54, 55]. The intrastromal injection is known as a minimally invasive administration that can enhance the drugs in the diseased corneal stroma without damaging compromised tissue structures [56].

3.1.4 Periocular Administrations

Periocular administrations can provide a longer duration of action than intravitreal injections owing to the possibility of injecting larger volumes (up to 1 mL in comparison to 100 μL intravitreally) but a relatively low risk of ocular pain, infection, endophthalmitis, or bleeding [15]. Subconjunctival injection, as the most common periocular administration, is placed between the bulbar conjunctiva and sclera and utilized in clinical practice to deliver drugs, such as local anesthetics and anti-inflammatory medications, to the anterior segment of the eye. However, the bioavailability of subconjunctival medications is often limited due to their significant

absorption by the lymphatic and blood circulatory systems, rather than intraocular distribution. As a result, frequent injections are required, which can carry operational risks such as conjunctival edema and subconjunctival hemorrhage [32, 57]. The rest of the periocular administrations including posterior juxtascleral, retrobulbar, peribulbar and sub-tenon administrations are mainly used in the anesthesia during ocular surgery. Of particular note is that periocular administration still fails to deliver sufficient drugs in the retina owing to drug loss from the periocular space, the BRB, the choroidal circulation, etc. [26, 58-60].

Table 1 Classifications of ocular administration routes and injection areas.

Type	Method	Area	Benefits	Challenges
Systemic	Intravenous	-	High patient compliance	BOB, low bioavailability, and systemic toxicity caused by high dosing
	Oral	-		
Topical	-	On the surface of the cornea	High patient compliance, self-administration, non-invasiveness	Low bioavailability, high dosing
Intraocular	Intracameral	Into the anterior chamber	Direct delivery to the vitreous humor and retina, acute dosing, BRB avoidance, high therapeutic effects	Poor patient compliance, invasiveness, drug toxicity, postoperative complications, including pain, bleeding, vitreous hemorrhage, high intraocular eye pressure, retinal detachment, endophthalmitis, lens and optic nerve damage
	Intravitreal	Into the vitreal body		
	Subretinal	Under the retina		
	Intrastromal	Into the corneal stroma		
	Suprachoroidal	Between the sclera and choroid		
	Subconjunctival	Into the space between the conjunctiva and sclera		
Periocular	Posterior juxtascleral	Posterior to the supertemporal limbus down to the sclera	Selective delivery to both anterior and posterior segments, avoidance of corneal and conjunctival barriers, long duration of action, a site for depot formulations	Poor patient compliance, invasiveness, drug deposition, compliance including pain, bleeding, infection, scarring, eyeball or optic nerve damage
	Retrobulbar	Between the four rectus muscles and their intermuscular septa		
	Peribulbar	Outside the four rectus muscles and their		

	intramuscular septum
Sub-tenon	Space posteriorly between the Tenon's capsule and sclera

3.2 Ocular Drug Kinetics

Based on the ocular barriers and the drug administration summarized above, ocular drug kinetics, including penetration and elimination, is illustrated in Fig. 2 [61]. In brief, drug penetration strategies mainly include topical delivery by trans-corneal and non-corneal penetration (Route **1** and **2**), systemic administration through the BAB (Route **3**) and the BRB (Route **4**), and direct injection through vitreous administration (Route **7**). The drug elimination strategies primarily involve the passage of trabecular meshwork and Schelemm's canal (Route **5**), the systemic circulation across the BAB (Route **6**), the BRB (Route **8**), and the passage of the anterior route to the posterior chamber (Route **9**).

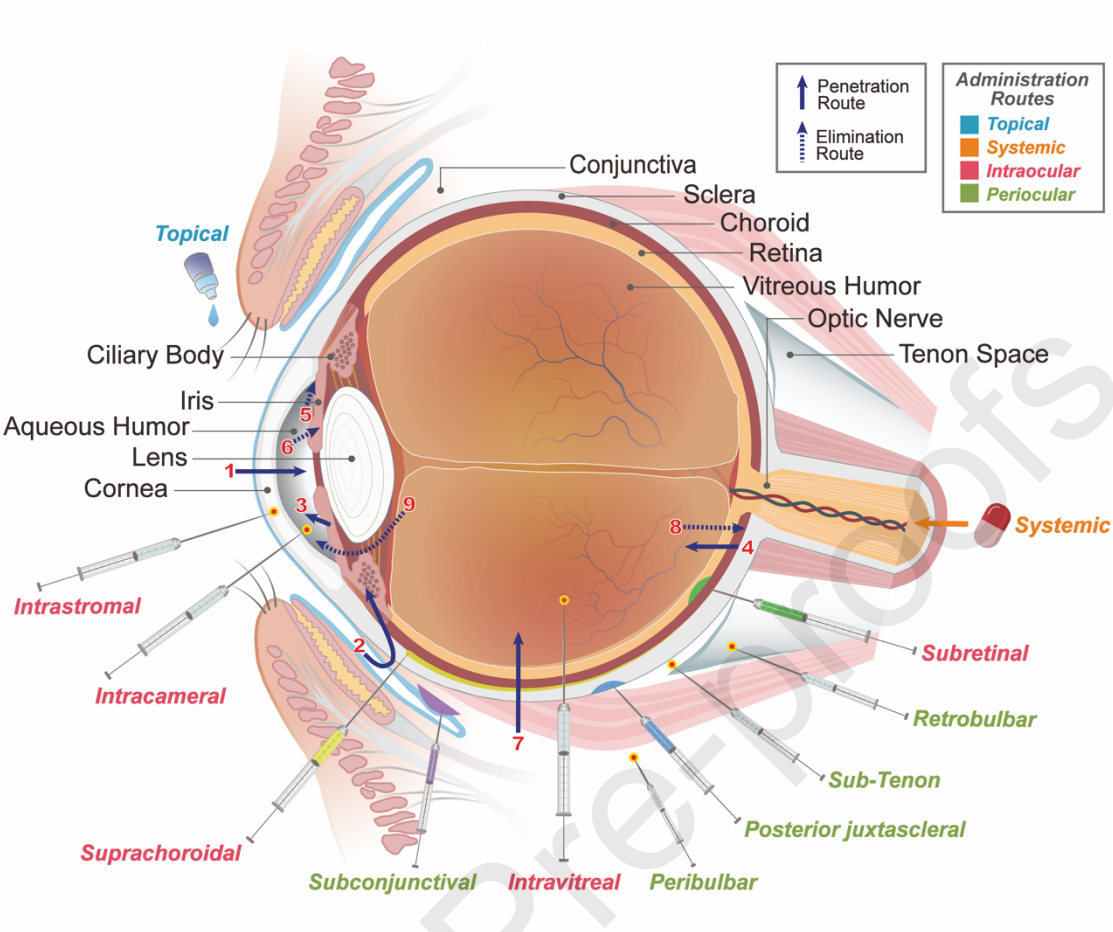

Fig. 2. The scheme of the approach of ocular administrations, including topical, systemic, intraocular, and periocular administrations, and the ocular drug kinetics illustrating the penetration and elimination during drug delivery. The number refers to different delivery routes: **1)** trans-corneal permeation into the anterior chamber from the tear and cornea, **2)** non-corneal permeation into the anterior uvea through the conjunctiva and sclera, **3)** drug distribution into the anterior chamber across BAB from the bloodstream, **4)** drug distribution into the ocular posterior segment across BRB from the circulation, **5)** elimination from the anterior chamber through the aqueous humor turnover to the trabecular meshwork and Sclemm's canal, **6)** elimination from the aqueous humor into the systemic circulation across the BAB, **7)** intravitreal drug administration, **8)** elimination from the vitreous through posterior route across the BRB, and **9)** elimination from the vitreous through the anterior route to the posterior chamber.

4 Factors Affecting Nanocarriers for Managing Ocular Diseases

This review will focus on the studies of PNCs and LNCs for ocular drug delivery. The PNCs here mainly refer to polymeric nanoparticles, micelles, nanogels, and dendrimers. Polymeric nanoparticles, composed of various polymers, can be further classified into nanospheres and nanocapsules depending on the core-shell structures. Micelles are self-assembled from amphiphilic molecules or block copolymers [15]. Nanogels are three-dimensional cross-linked networks of hydrophilic polymers with small sizes on the nanometer [62]. Dendrimers are spherical tree-like branched nanostructured polymers with a central core and side-chain moieties [63]. The LNCs here mainly encompass liposomes, lipid nanoparticles, and nanoemulsions. Liposomes are self-assembled vesicles that have one or more layers of phospholipid that enclose the aqueous phase [64]. Lipid nanoparticles can be further divided into two species, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Nanoemulsions are colloidal particulate delivery systems formed by dispersing two immiscible liquids using an emulsifying agent along with the physical share-induced rupturing [65].

Physicochemical properties such as particle size, surface property, and targeting moieties greatly influence the determination of the administration route and the efficiency of drug delivery as well as subsequent therapeutics in ocular diseases [66]. Therefore, we will then introduce what physicochemical properties of nanocarriers may be focused on for better drug delivery to corresponding ocular disease.

4.1 Size

The size of nanocarriers has a great influence on the drug loading efficacy and the delivery mechanism during ocular drug delivery. To ensure effective medication delivery, drug carriers must be small enough to penetrate the ocular barriers, while also being well-tolerated by the human eye [67]. Nanoparticles with smaller sizes can offer better stability and biodistribution profile. Thereinto, drug-loaded nanoparticles with 50-400 nm are the preferred size for ocular drug delivery, providing more effective mucoadhesion and highly passing through ocular barriers to the target site, with less

ocular irritation [3, 68]. In the pre-corneal region, nanocarriers <200 nm can be easily absorbed by the cornea and conjunctiva through topical administration [69, 70]. In the sclera, the transport of macromolecules is constrained by the interlacing and stacking structure of collagen fibrils [71]. Given that the scleral water channels/pores are 30-350 nm in size, hydrophilic nanoparticles (20-80 nm) can diffuse into the vitreous humor after passing through the sclera pores [72, 73]. As for the posterior segment, the vitreous fluid mainly hinders the movement of heavy therapeutic agents, and through intravitreal injection, smaller particles (<350 nm) could reach the retina [72, 73]. The Bruch's membrane is considered to be permeable to large molecules up to 150 kDa, with permeability declining with age [38].

4.2 Surface Property

The surface property of nanocarriers, including surface charge and hydrophobicity/hydrophilicity, also plays a critical role in their distribution concentration in ocular tissues [74].

Both the cornea and the conjunctiva have negative surface charges. The cornea shows a net-negative surface charge as a result of high sialic acid and sulfate content in most mucins in the mucous layer [75]. On this account, mucins can attract or repulse nanocarriers through electrostatic interactions depending on their surface charge [76]. The retention time of cationic nanocarriers can be enhanced more evidently on negatively charged ocular tissues than the anionic ones, providing an increased opportunity for the drug to enter the eye [41, 77, 78]. The lens capsule comprises laminins, collagens, and proteoglycans with a negative charge, impeding the advance of positively charged nanocarriers, and neutral molecules or nanocarriers were observed to diffuse more quickly across the lens capsule than anionic ones [79]. In the sclera, positively charged molecules appear to be permeate-hindered, presumably because of their electrostatic binding with the negatively charged proteoglycans in the scleral matrix [80]. In the posterior segment, the charge of the nanocarriers affects the vitreal dispersion and retinal bioavailability of loaded cargo [41, 77, 78]. The net

negative charge of the vitreous humor modulates the diffusion of nanocarriers. Positively charged nanocarriers get trapped in the vitreous humor, whereas negatively charged ones diffuse freely [39].

The hydrophobicity/hydrophilicity property of nanocarriers also impacts their penetration and distribution. The cornea is with both hydrophobic and hydrophilic characteristics in different layers. Therein, the external corneal stratified epithelium with multiple layers is hydrophobic while it is, on the opposite, hydrophilic in the stroma layer, therefore limiting the penetration of hydrophobic molecules that are passively transported *via* the transcellular pathway. Similar to the corneal stroma, hydrophilic molecules permeate through hydrophilic collagen-based scleral matrix pores more readily than lipophilic molecules. The epithelium of the lens forms a barrier to hydrophilic molecules. In the BRB, small lipophilic molecules can achieve higher permeation across RPE than hydrophilic ones due to their capacity to diffuse across the intracellular pathway [81]. It is concluded that the nanocarrier charge effect dominates their distribution when <350 nm; as it becomes larger, the size may play a major role [82].

4.3 Targeting Moieties

Surface decoration of nanocarriers with targeting moieties could enhance the specific accumulation of cargo in target cells and tissues while reducing unnecessary side effects [83, 84]. Currently, surface modification of nanoparticles has been widely applied in the treatment of ocular diseases. Since VEGF plays an essential role in ocular neovascularization, anti-VEGF antibodies, such as bevacizumab and ranibizumab, have been modified onto nanocarriers to enhance ocular delivery and therapeutic effects on corneal neovascularization [85] and choroidal neovascularization (CNV) [86]. Moreover, αVβ3-high affinity arginine-glycine-aspartic acid (RGD) peptide-modified nanoparticles have been developed to target RPE that over-expresses integrin receptor αVβ3 for the treatment of CNV [87]. Dry eye disease (DED) is a common ocular surface disease disorder, and targeted treatments for DED can be focused on multiple

aspects, including membrane molecules such as sialic acid and intercellular adhesion molecule-1 (ICAM-1). Specifically, nanoparticles with polymer-peptide moieties are utilized to target sialic acid-containing glycosylated transmembrane molecules on the ocular surface epithelium to cure DED [88], while nanocarriers modified with targeting peptide ICAM-1 can interact with lymphocytes for treating Sjögren's syndrome (SS), a chronic autoimmune disease that affects lacrimal glands and can cause DED [89]. Additionally, the use of mannose [90-93] and aptamers [94] in nanocarriers is receiving widespread attention. Developing ocular nanocarriers based on mannose and aptamers may possess bright application prospects in the treatment of ocular diseases.

5. Ocular Disease

5.1 Corneal Neovascularization

The cornea is an avascular and transparent eye tissue with no capillary or vessel permeation. The "angiogenic privilege" is maintained by the balance between angiogenic and anti-angiogenic factors [95, 96]. A wide range of external and internal factors can affect the homeostasis of "angiogenic privilege". For instance, infection, inflammation, hypoxia, trauma, corneal transplantation, and systemic or genetic diseases can lead to corneal opacity, edema, scarring, and corneal neovascularization [96, 97]. Current treatments for corneal neovascularization include topical steroids, anti-VEGF medications, non-steroid anti-inflammatory agents, surgical interventions, photodynamic therapy (PDT), and gene therapy [98]. Despite confirmed efficacy, the current treatments are restricted by inevitable adverse effects and low bioavailability, calling for more advanced and well-designed therapeutic approaches. In the following sections, the PNCs and LNCs designed for treating corneal neovascularization are reviewed based on the pathophysiology of corneal angiogenesis.

VEGFs, critical mediators of vasculogenesis and angiogenesis, have been reported to be the primary drivers of several eye-blinding diseases and tumor genesis [99]. Targeting VEGF signaling pathways and their related molecules is an important

therapeutic strategy to suppress aberrant angiogenesis [100]. Anti-VEGF treatments using monoclonal antibodies, including bevacizumab, aflibercept, and ranibizumab, have been clinically approved by Food and Drug Administration (FDA) [101]. Aside from anti-VEGF antibody, small-molecule tyrosine kinase inhibitor (TKI) is another group of anti-angiogenic strategy *via* blocking adenosine triphosphate (ATP) binding and inhibiting phosphorylation, and eventually suppressing the downstream pro-angiogenic signaling pathways, such as VEGF/VEGFR (vascular endothelial growth factor receptor) and platelet-derived growth factor (PDGF) pathways [100, 102]. The evidence in animal models and clinical trials has confirmed topical treatment of TKIs such as sunitinib, apatinib, dasatinib, and cabozantinib can alleviate corneal neovascularization [103]. Aside from that, herbs and plant-derived compounds, including celastrol, flavonoids, and curcumin, have been abundantly used to modulate angiogenesis, whose function can be substantially improved by PNCs [100].

To improve bioavailability and prolong drug release, PLGA, one of the most popular biodegradable polymers, was used to encapsulate bevacizumab and exhibited significant anti-VEGF properties [85]. Despite being used as drug carriers, some PNCs such as chitosan possess the intrinsic anti-VEGF ability. Zahir-Jouzdani *et al.* designed a thiolated derivative of chitosan nanoparticles, presenting longer retention time and more evident therapeutic effects with the high mucoadhesion ability of the thiol group [104]. Furthermore, RGD peptides that can specifically bind αvβ3 integrins receptors were adopted for targeting ocular angiogenesis [105]. Chang *et al.* synthesized RGD-modified and HA-conjugated polymeric nanoparticles for site-specific corneal neovascularization treatment [106].

Micelles are also abundantly studied in treating corneal neovascularization. Previous studies have synthesized micelles based on amphiphilic block polymer poly(ethylene glycol)-poly(ε-caprolactone) (PEG-PCL), which facilitated higher drug loading and increased the aqueous phase stability than free drug [107, 108]. Although the micelles showed significant therapeutic effects with diminished corneal edema and

neovascularization, the drug loading capacity was only 1.68% [108]. Subsequently, Li *et al*. developed the triblock copolymer PEG-PCL-polyethyleneimine (PEG-PCL-PEI) micelles, which significantly increased drug loading, prolonged the retention time, and improved penetration into the cornea *via* opening the tight junction [109]. To improve drug bioavailability, cationic polypeptide carriers with mucoadhesive ability were developed for cabozantinib delivery *via* N-carboxy anhydride ring-opening polymerization [110]. The positively charged amino groups of the nanoparticles can bind with the anionic mucosal sialic acid residues on the cornea with high affinity, exhibiting prolonged retention time. It is noteworthy that nanocarriers can also facilitate a combination of several anti-angiogenic approaches. Kim *et al.* developed genistein-loaded Fms-like tyrosine kinase-1 (Flt-1) peptide-hyaluronate conjugate micelles with Flt-1 peptide for antagonizing VEGFR1 or Flt1 and genistein for inhibiting tyrosine protein kinases, achieving angiogenesis inhibition and corneal neovascularization treatment [111].

As the first nanoparticles approved by FDA, LNCs have been substantially studied for treating corneal neovascularization. Among various LNCs, NLC formulations have been preferred due to their ability to increase penetration through the ocular epithelial layer and prolong the residence on the cornea [112]. Furthermore, compared with other LNCs, NLC production usually does not include organic solvent residues, allowing large-scale manufacturing [112]. To increase the drug solubility, Li *et al.* synthesized NLC with soy lecithin encapsulated dasatinib to manage corneal neovascularization, which increased the drug solubility by more than 1220 times [113]. The nanoparticles also exhibited a sustainable release profile of around 25% within 24 h and reduced the ocular toxicity compared with the free drug.

Inflammation is another essential contributor to the pathogenesis of corneal angiogenesis due to chemical and mechanical injury, infection, and immune disorder [95, 98]. Inflammatory cells like macrophages produce pro-angiogenic factors and pro-inflammatory cytokines, which are important mediators of corneal angiogenesis [95,

114]. Corticosteroids, despite the inevitable side effects, are potent anti-inflammatory medications that can inhibit VEGF, matrix metalloproteinases (MMPs), and tumor necrosis factor-α (TNF-α) [115]. In clinical practice, corticosteroids such as dexamethasone and dexamethasone sodium phosphate (DSP) are considered the first-line treatments for corneal neovascularization [115-117]. To achieve sustainable drug release and higher biocompatibility, DSP was encapsulated with carboxyl terminated PLGA containing zinc ion [118, 119]. The zinc acts as an ionic bridge between the terminal carboxyl groups on PLGA and the phosphate groups on DSP. To enhance cellular uptake, Zhang *et al.* developed phenylboronic acid (PBA)-based glycopolymer nanoparticles for trans-cornea delivery of dexamethasone [120]. Owing to the modification of boric acid motifs, the nanoparticles managed to permeate into the corneal epithelial cells and infiltrate into the corneal stroma layer, thereby presenting a significantly smaller neovascular area.

Cyclosporine A (CsA) is another popular anti-inflammatory and immunomodulatory agent of interest among studies. It has been proven to suppress VEGF-induced endothelial cell migration and angiogenesis [121-123]. To enhance the solubility and bioavailability of CsA, copolymers mPEG-hexylsubstituted poly(lactides) (MPEG-hexPLA)-based micelles were constructed [124]. Another potent immunosuppressant, tacrolimus (TAC) was encapsulated in liposomes and exhibited reduced neovascularization by around 50% through the regulation of VEGFs, MMPs, and interleukin-6 (IL-6) [125].

Small molecular inhibitors for various pathways have become one of the most extensively pursued areas for inhibiting aberrant angiogenesis [102]. Drugs encapsulated with LNCs have been developed for higher solubility and biocompatibility [126-128]. For instance, cationic-NLCs composed of solid lipid precirol ATO5 and liquid lipid capryol PGMC were synthesized, which showed an enhanced cellular uptake by 1.5 fold [129]. Wang *et al.* developed liposomes loading ferrostatin-1, a specific inhibitor of ferroptosis. Significant curative effects were

observed for corneal opacity and corneal neovascularization, possibly owing to the inhibition of reactive oxygen species (ROS), inflammation, and neovascularization [128] (Fig. 3).

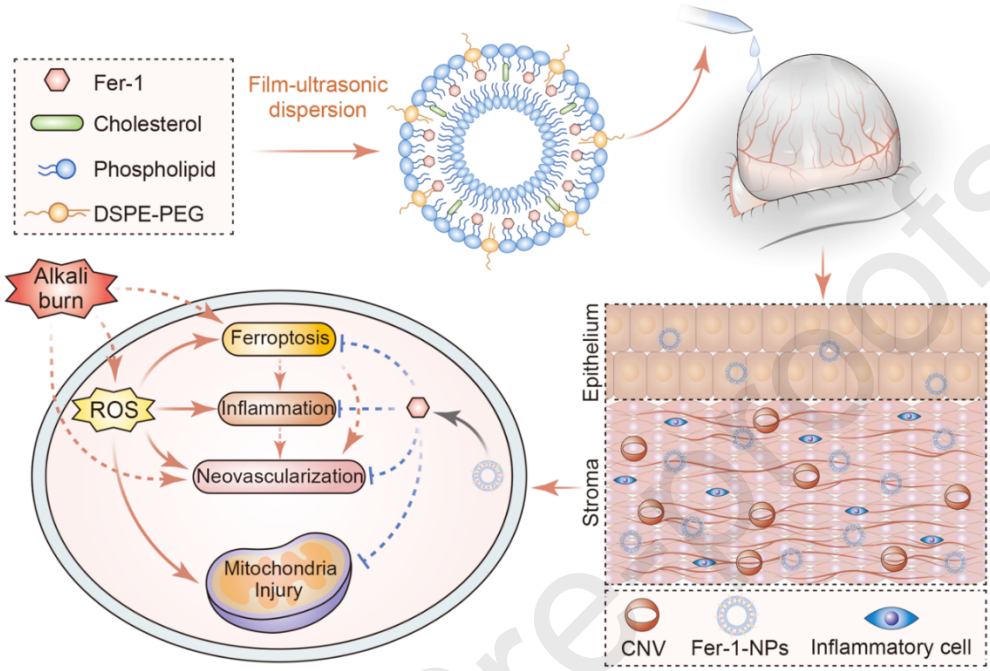

Fig. 3. Preparation of ferrostatin-1-loaded liposomes for corneal alkali burn injury through inhibition of ferroptosis [128].

Gene therapy, as a rapidly advancing area of treatment, uses exogenous genetic materials, including DNA, RNA, microRNA (miRNA), small interfering RNA (siRNA), short-hairpin RNA (shRNA), and antisense oligonucleotides (ASOs), to regulate, modulate, and compensate specific gene functions [130]. Numerous studies have demonstrated promising results of gene therapy in treating ocular diseases. While viral vectors have the problems of immunogenicity, mutagenesis, insufficient capacity, and expensive production, several non-viral vectors, including PNCs and LNCs have been introduced to protect the genes from degradation and enhance their cellular uptake [131]. Compared with conventional gene delivery approaches, PNCs and LNCs can improve the pharmacokinetics of genes, facilitate targeted delivery across various biological barriers, and offer multiple functions by loading various genes [130].

Gene silencing by siRNA is one of the most common approaches, which can selectively degrade the targeted mRNA through an RNA-induced silencing complex [130]. Several attempts have been made to achieve efficient siRNA delivery for corneal neovascularization treatment. For example, siRNA has been incorporated into PEI to target inflammation and suppress corneal neovascularization [132, 133]. As a positively charged polymer, PEI forms ionic conjugates with the negatively charged siRNA for efficient delivery. To overcome the potent toxicity of PEI with high molecular weight, another study developed a reducible branched PEI which can be cleaved to a nontoxic low-molecular-weight PEI as a safe and effective siRNA carrier [132]. More recently, Liu *et al.* designed a novel ROS-responsive lipid nanoparticle for VEGF siRNA delivery [134] (Fig. 4). The thioketal bond in the hydrophobic tail of the ROS-responsive cationic lipids can facilitate the delivery of siRNA into the cytoplasm effectively. Triggered by the elevated ROS during corneal angiogenesis, the lipid nanoparticles efficiently delivered and released siRNA and significantly downregulated VEGF expression, leading to the suppression of corneal neovascularization.

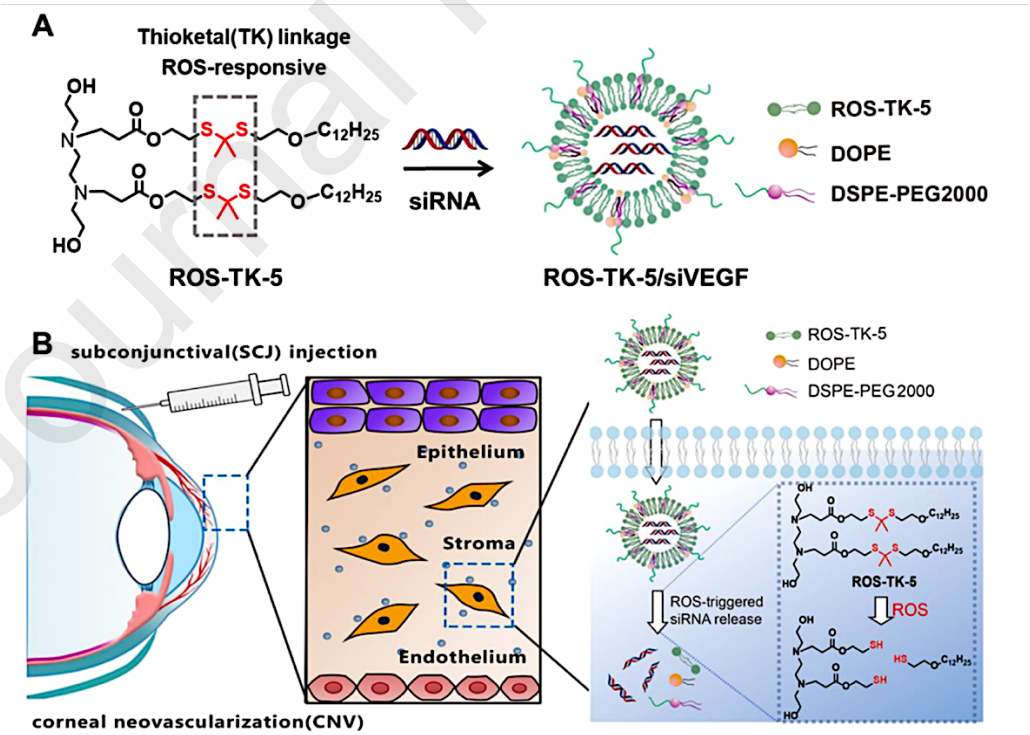

Fig. 4. Schematic depiction of ROS-responsive lipid nanoparticles for effective RNAi delivery and corneal neovascularization treatment [134].

Compared with siRNAs, shRNAs are more attractive genes due to their ability to be continuously produced by the host cell and avoid nonspecific off-target effects, making them a nonimmunogenic and long-lasting gene-silencing strategy [135, 136]. Cho *et al.* prepared PLGA nanoparticles with a plasmid containing shRNA targeting vascular endothelial growth factor-A (VEGF-A), which down-regulated the VEGF-A protein expression by 79.9% and provided sustained gene silencing effects over the 7-week course of the study [137]. Targeted RGD-modified PLGA nanoparticles loading Flt23k (a recombinant anti-VEGF interceptor contract of VEGFR) plasmid was further utilized to target VEGF intracellularly [138]. Additionally, Iriyama *et al.* reported a polyplex micelle, PEG-polycation carrying ethylenediamine units in the side chain (PEG-b-P[Asp(DET)]) complex formation with VEGFR-targeting Flt-1 plasmid DNA, for improved transfection efficiency and reduced toxicity, corroborating the prolonged gene therapy provided by the PNCs [139].

PDT is based on an exogenous photosensitizer and light exposure to generate singlet oxygen or ROS [140, 141]. For years, photosensitizer-loaded nanocarriers have emerged as a more efficient alternative to conventional PDT, which increases the specificity, bioavailability, and accumulation of photosensitizer at the targeted pathological site [142]. Dendrimer porphyrin, with fascinating characteristics such as well-defined structure, high flexibility, and photodynamic efficacy, has been developed as a novel photosensitizer for anti-angiogenic treatment [143]. Encapsulation of dendrimer porphyrin into PEG-based polyion complex micelles has shown high stability and selective accumulation at the corneal neovascularization site [144]. Jiang *et al.* further developed a novel photosensitizer, amphiphilic boron dipyromethene derivative with extended conjugation structure by Knoevenagel condensation, to self-assemble to form spherical nanoaggregates in an aqueous solution [145]. The extension

of conjugation extent makes it possible to shift absorption wavelength to red or near-infrared region. Upon red light irradiation, the nanoaggregates generated singlet oxygen, thus dramatically decreasing corneal neovascularization [145]. Although PDT has shown satisfactory therapeutic efficacy in treating corneal neovascularization, further *in vivo* studies and more advanced PNCs are required for clinical application.

5.2. Keratitis

As a sight-threatening corneal infection, keratitis may lead to corneal opacity, conjunctival scar, and even eyeball atrophy without proper and prompt treatments. Currently, the first-line regimens mainly involve the topical application of antibiotic eye drops. However, the therapeutic efficiency of conventional antibiotic eye drops-based pathogen eradication regimens is hindered due to limited antimicrobial activities of broad-spectrum antibiotics, drug resistance to antibiotics, time-consuming laboratory tests to screen the sensitive antibiotics, and low bioavailability of eye drop [146]. To effectively reduce the pathogen burden, PNCs and LNCs can be applied to extend the residence time on the cornea and enhance the penetration of antibiotics.

Owing to their nano-size and lipophilic nature, SLNs are effective in penetrating physiological barriers [147]. Khames *et al.* prepared natamycin SLNs (NAT-SLNs) using the emulsification-ultrasonication technique [148]. The NAT-SLNs formula optimized by a Box-Behnken statistical design had a small size (25 nm), positive surface charge (25 mV), and high entrapment efficiency (84%). The antifungal evaluation revealed the superiority of NAT-SLN formulation with decreased minimum inhibitory concentration (MIC) values by 2.5 times relative to the unformulated natamycin. Compared to the unformulated drug, the higher calculated apparent permeability (11.59×10^{-2} cm h^{-1} *v.s.* 7.28×10^{-2} cm h^{-1}) and steady-state flux (3.94 mol h^{-1} *v.s.* 2.48 mol h^{-1}) of NAT-SLN formulation confirmed the increased ocular absorption in deep corneal layers. SLNs are frequently used to deliver water-insoluble antifungal agents. Liang *et al*. also prepared SLN-based econazole eye drops (E-SLNs)

for controlled econazole release and elevated its anti-fungal activity without irritation [149].

Compared to the drugs in solution, ophthalmic nanogel formulation can significantly extend the corneal retention time and improve the bioavailability of loaded drugs [150]. In the past years, the application of nanogel formulation in ocular drug delivery has aroused huge interest, and various nanogels were designed and manufactured to improve the therapeutic performance of voriconazole, itraconazole, natamycin, etc. in the management of fungal keratitis [151-154].

Despite conventional antibiotics, antimicrobial peptides (AMP) combined with nanogels have been explored to manage keratitis. As promising antibiotics alternatives, AMP and analogs possess broad-spectrum antimicrobial activity and low susceptibility to antimicrobial resistance [155, 156]. However, due to their low stability in the presence of protease, the clinical application of AMP was largely restricted. Hereby, Obuobi *et al.* reported AMP encapsulated DNA nanogels platform that features three monomers terminated by complementary "sticky end" units [157]. Then, a novel α-helical peptide L12 was entrapped in the nanogel by adopting a post-loading and pre-loading method [158]. Rapid release of L12 (45.59% of L12 can be released from the L12 nanogels within 2 h) can ensure the availability of lethal antibacterial concentrations. *In vitro* evaluation showed that the pre-loaded L12 nanogels can reduce bacterial inoculum by 89.2% at 4× MIC within 2 h of treatment. In addition, in the *Staphylococcus aureus (S. aureus)* infected bacterial keratitis model, a progressive decrease in corneal thickness can be observed, indicating that L12 nanogels can reduce bacterial bioburden and alleviate clinical symptoms.

Apart from controlled drug release, well-designed nanocarriers could enhance trans-corneal penetration for increasing drug concentration in the cornea and aqueous humor, thus improving the therapeutic efficiency of loaded drugs. Mucus-penetrating particles (MPP) are nanoparticles formulated with mucoinert surface coatings, which can enhance the delivery efficiency of small-molecule drugs and nucleic acids alike

[19]. FDA has approved two loteprednol etabonate-based products (Eysuvis® and Inveltys™) for treating ocular inflammation and pain since MPP can provide rapid and enhanced intraocular drug absorption [159]. Josyula *et al.* constructed insoluble moxifloxacin-pamoate (MOX-PAM) complex for formulation into mucus-penetrating nanosuspension eye drops to treat ocular infection [160]. MOX-PAM ion pairs were first prepared by simple mixing of anionic disodium pamoate and cationic MOX *via* electrostatic interaction and then formulated using a wet bead-milling method to obtain MOX-PAM NS [146]. Compared to the commercial formulation Vigamox®, mucoinert MOX-PAM NS displayed a ~1.6-fold increase in C_{max} (peak concentration of drug) in the aqueous humor, indicating an enhanced intraocular drug absorption. Besides, MOX-PAM NS displayed a significantly increased cumulative drug exposure as $AUC_{0\text{-}24h}$ (area under the curve) was ~1.7-fold and ~4.4-fold higher in the aqueous humor and cornea in animal models.

The active targeting of bacteria enables improved drug transport to the infected cornea, promoting therapeutic efficiency and reducing drug dosages. Recently, Zhang *et al.* designed and prepared glycopolymers-based, boron dipyrromethene (BODIPY), and boronic acid-modified pathogen-driven micelles for enhanced antibiotic internalization to combat bacterial keratitis [161]. The high affinity between the boric acid groups and the diol-containing bacterial cell wall enabled efficient cellular internalization, which promotes the cellular internalization of antibiotics and performs bioadhesive functions (Fig. 5). Under bacteria-free conditions, the micelles showed slow ciprofloxacin (CIP) release, whereas the release was enhanced (57.8% *v.s.* 75.5% in 48 h) in the presence of *S. aureus*. When applied to *S. aureus*-infected rat cornea, the micelles significantly reduced bacteria burden, suppressed the release of proinflammatory cytokines, and decreased the signals attracting neutrophils to the corneas. In addition, the bacteria-targeting micelles can further relieve inflammation and promote wound healing by introducing ROS-scavenging agents [162]. Despite the interaction between boric acid groups and diol-structure, specific receptor-ligand

interactions also inspired the designing of active targeting drug delivery platforms. Zhang *et al.* reported condition-responsive anti-toll-like receptor 4 (TLR4) antibodies surface-conjugated ketoconazole encapsulated gelatin nanoparticles (anti-TLR4-GNPs) [163]. By binding the over-expressed TLR4 in human corneal epithelial (HCE) cells, anti-TLR4-GNPs can efficiently increase corneal adhesion to extend retention time on the corneal surface. The more severe the infection, the higher TLR4 expression and proteolytic activity. The binding of anti-TLR4-GNPs to the cornea and micelles degradation and drug release can be determined by the severity of infection and inflammation. Therefore, anti-TLR4-GNPs enable a stimuli-responsive and site-specific drug release. *In vivo* rat model studies have confirmed the therapeutic benefit of anti-TLR4-GNPs.

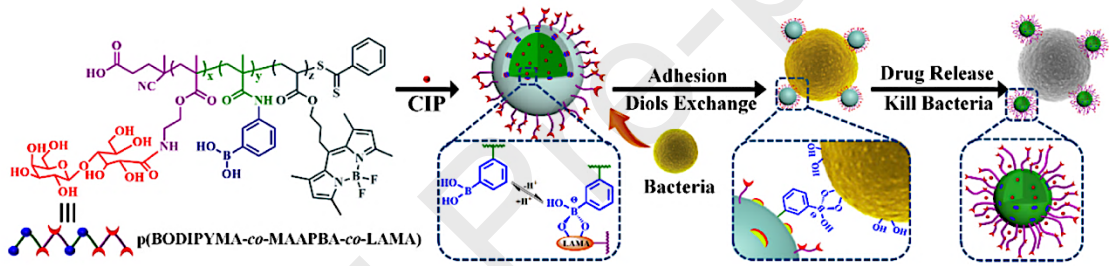

Fig. 5. Self-assembly of the glycopolymer into nanotherapeutics and a schematic illustration of drug release and bacterial mortality [161].

Since antibiotics can suffer from shortcomings such as poor efficiency and the emergence of antibiotic-resistant pathogens, efforts have been made to explore alternative antibiotics, for instance, photosensitizers-based PDT [164]. Recently, Zhu *et al.* reported targeting photodynamic bactericidal nanoparticles PαGal$_{20}$-b-PGRB$_n$ for specifically eliminating *P. aeruginosa*. It was synthesized by reversible addition-fragmentation chain transfer (RAFT) polymerization and exerted its function by α-D-galactose species for specifically binding to Lec A of *P. aeruginosa* and rose bengal as a photosensitizer to generate ROS to damage DNA, RNA, protein, and biomembrane[165]. This PDT platform also displayed excellent performance in

eliminating multidrug-resistant *P. aeruginosa* biofilm and improving the recovery of *P. aeruginosa*-infected keratitis.

Another prospective approach to manage antibiotic-resistant pathogens infection is photothermal therapy (PTT), which utilizes the photothermal conversion effect of photothermal transduction agents (PTAs) to convert light energy into heat and kill target pathogens. Conventional PTAs, such as metallic and polymeric nanoparticles have been reported to display high therapeutic efficiency in the treatments of methicillin-resistant *Staphylococcus aureus* (MRSA) induced keratitis [166, 167]. Recently, Zhu *et al*. reported pH-activatable organic nanoparticles through the self-assembly of a pH-responsive phenothiazinium dye for efficient low-temperature PTT of ocular bacterial infection [168]. With photothermal conversion efficiency up to 84.5%, these organic nanoparticles just need an ultralow light dose of 36 J cm^{-2} to achieve efficient low-temperature photothermal sterilization at pH 5.5. Meanwhile, they exhibited good penetration and highly efficient elimination of drug-resistant bacterial biofilms through negative to positive charge reversion in acid biofilms.

5.3 DED

DED is a multifactorial ocular surface disease characterized by an imbalance of homeostasis in the tear film and the persistence of a vicious cycle of ocular surface inflammation, tear film instability, and hyperosmolarity, eventually leading to visual surface damage and self-perpetuation of the disease [169, 170]. At present, there is an increasing tendency to the morbidity of DED due to the increase in the frequency of use of electronic products, the aggravation of environmental pollution, and the wearing rate of contact lenses, affecting approximately 350 million people worldwide, with an estimated global prevalence of 5% to 50% according to 2017 statistics [171, 172]. The DED will cause not only severe problems to the quality of life of patients, leading to eye discomfort, visual impairment, and even blindness but also psychological depression, which adds a substantial economic burden to society [173, 174]. However,

the pathogenesis of DED has not been fully elucidated. Most studies suggest that inflammation is the core of its pathogenesis [175]. A rapid but nonspecific congenital immunity and a slower but more specific acquired immunity constitute the inflammatory response in DED [176]. The main goal of DED treatment is to restore tear film homeostasis and break the persistence of the DED vicious cycle. Common treatments include artificial tears, topical secretagogues, corticosteroids, and immunosuppressants for DED treatment, but they are accompanied by disadvantages, including patient compliance, increased intraocular pressure, side effects such as cataract and glaucoma, and ocular discomfort [177]. To overcome ocular drug delivery barriers and improve drug bioavailability, the development of ocular drug delivery systems, especially PNCs, has made significant progress, and PNCs turn out to be very attractive and promising strategies in the advanced treatment of DED.

The lack and the instability of tears are the main characterizations of DED. Thus, nanotherapies for tear imitation are also in the spotlight. Phosphatidylcholine-based liposome artificial tears were reported to serve as a tear substitute by adding components similar to those found in natural tears [178], while another phosphocholine liposomal formulation reduced the DED by helping to restore the lipid layer, the outmost layer of the tear film with high biodegradability and biocompatibility [179].

Since inflammation is the core pathogenesis of DED, treatments aiming at different sites in the progression of inflammation development receive the most attention. Azithromycin (AZM) is the second generation of broad-spectrum synthetic macrolide antibiotics. Novel AZM-loaded liposomes named ACIP-Lip were designed using AZM-cholesteryl hemisuccinate ion pair (ACIP) to increase the drug loading efficiency to treat DED [180]. Lin *et al.* reported that subconjunctivally injecting hydroxyl-terminated polyamindoamine (PAMAM) dendrimer-dexamethasone conjugate nanoparticles could selectively localize in the inflamed lacrimal glands and been uptaken by the infiltrating cells, showing an enhanced therapeutic effect for DED in a rabbit autoimmune dacryoadenitis model [181]. Except for glucocorticoids, non-

steroidal anti-inflammatory drugs (NSAIDs) can be also employed topically to target the inflammatory component of DED. However, NSAIDs like ibuprofen have very limited aqueous solubility. Dukovski's group proposed a functional cationic ibuprofen-loaded nanoemulsion with chitosan as the cationic agent and lecithin as the anionic surfactant enabling chitosan incorporation, achieving enhanced drug solubility, prolonged ocular surface residence, and stabilizing the tear film for effective mild-to-moderate DED treatment [182]. Other anti-inflammation treatments based on dipotassium glycyrrhizinate, catechin, and tetrandrine exhibited preferable therapeutic effects on the DED animal model [183-186]. For instance, by utilizing the characteristic that glycyrrhizin can act as a novel multifunctional nanocarrier as it has an amphiphilic structure and can self-assemble into micelles, Li *et al.* prepared novel ophthalmic solutions based on glycyrrhizin as the nanocarrier and loading phytochemical naringenin against experimental DED [183].

The secondary immune response is also an essential part of the pathogenesis of DED, where most commercial immunosuppressants take place. Topical CsA is the first FDA-approved drug that inhibits T cell-mediated immune responses and controls DED by improving tear production affected by ocular inflammation through immunosuppression. However, due to its hydrophobic structure, poor solubility, and poor permeability, it is not easy to directly administrate. Therefore, many CsA-based nanocarriers have been developed accordingly [187]. CsA-loaded mPEG-PLA micelles showed an enhanced ocular retention time and a promoted uptake [123, 188], while Liu *et al*. developed cationized HA-coated spanlastics for ocular CsA delivery to prolong ocular retention, improve corneal permeation, and increase tear production [189].

In addition to CsA, TAC, one of the commonly used immunosuppressors in clinics, is also popular as a standard treatment for "nano-modification". TAC-loaded liposomes, micelles, polymeric nanoparticles, and nanovesicles were reported to have promoted bioavailability, improved ocular retention time, increased ocular penetration, and enhanced DED therapeutic effects [190-192]. Besides, another immunomodifier,

pimecrolimus, was utilized for manufacturing pimecrolimus-loaded PEG-PCL micelles (PNM), proving the distinguished therapeutic outcomes for keratoconjunctivitis sicca [193]. Apart from the immunological preparations mentioned above, a multivalent biopolymeric nanoparticle assembled from a diblock elastin-like polypeptide using the S48I48 ELP scaffold fused with a ICAM-1 targeting peptide was manufactured to disrupt ICAM-1 and lymphocyte function-associated antigen (LFA) interactions in the development of the secondary immune response *in vitro*, indicating further utility potential therapeutic *in vivo* [89].

However, beyond inflammation, its upstream factor, over-produced ROS, plays a significant role in DED development. We developed cationic polypeptide micelles named MTem/Los to safely and efficiently treat DED. The micelles were loaded with p38 mitogen-activated protein kinases (MAPK) inhibitor Losmapimod to inhibit inflammation, and conjugated with ROS scavenger Tempo to decrease excess oxidative stress, thus reducing the proinflammatory cytokines and chemokines expression, restraining macrophage proinflammatory phenotypic transformation, and inhibiting cell apoptosis. These cationic micelles effectively enhanced ocular retention time, reversed corneal epithelial defect, saved goblet cell dysfunction, recovered tear secretion, and ultimately alleviated DED [194] (Fig. 6).

In addition to the techniques mentioned above, other therapeutic applications such as autophagy regulation and anti-fibrosis have been brought recently. Melatonin-loaded polymer polyvinyl caprolactam-polyvinyl acetate-polyethyleneglycol graft copolymer micelles (Mel-Mic) were introduced to treat DED by increasing autophagosome number [195]. Antifibrotic topical vitamin A-coupled liposomes consisting of heat shock protein-47 (HSP47) siRNA against HSP47 (VA-lip HSP47) was developed to defend the DED after the transplantation of allogeneic hematopoietic stem cell [196].

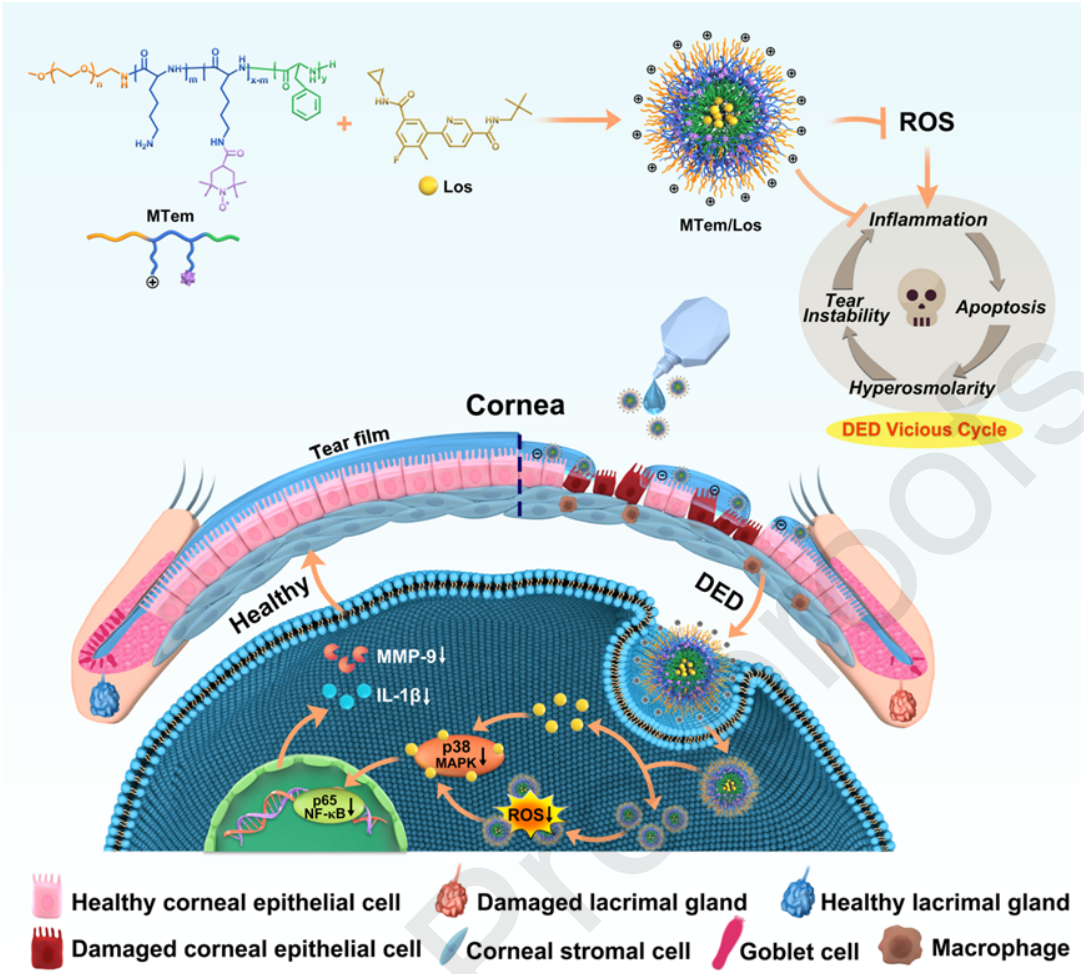

Fig. 6. Schematic diagram of the preparation, therapeutic effects, and mechanism of anti-oxidant and anti-inflammatory MTem/Los to treat DED by breaking the vicious cycle [194].

5.4 Cataract and its Postoperative Complications

As the top leading cause of blindness worldwide, cataract is affecting an increasingly aging population [2]. Various causes can lead to cataract formation, including aging, congenital abnormalities, systemic diseases, trauma, and drug-related changes [197]. To date, the most effective cataract treatment is a surgical intervention to remove the opacified lens and replace it with an artificial intraocular lens [198]. However, there are also many attempts to develop less invasive therapeutics, advanced-designed intraocular lens, and tissue-specific drug delivery systems, warranting more

updated investigation into the prevention and treatment of cataract and their complications.

Although surgical intervention is recommended as the most effective treatment for cataracts, medical therapeutics to delay the onset and progression of cataracts have long been an active topic. Many natural and synthesized anti-oxidative agents, including coenzyme Q10, curcumin, resveratrol, and lutein have the ability to alleviate oxidative stress to rescue lens damage [199]. Chitosan-modified liposomes that load coenzyme Q10 extended the precorneal drug residence time by 4.8 fold [200]. Vora *et al.* developed lipid-cyclodextrin-based nanoparticles with high polyphenols loading and mucoadhesive properties for cataract treatment [201]. Yogaraj *et al.* further investigated the anti-cataract effect of curcumin-based polyaminoamine dendrimer in rat pups' cataract models [202]. The solubility of curcumin increased 345 fold and the release pattern was prolonged by 17 fold, and *in vivo* study confirmed significantly attenuated cataract formation through regulation of pro-inflammatory gene expression.

Diabetic cataract, a common diabetic ocular complication, is characterized by increased oxidative stress and accumulation of advanced glycation end products (AGEs) [203]. Katti's group reported that topical administration of corticosteroids or pyrrolidine dithiocarbamate-loaded nanocarriers composed of PCL core and pluronic® F-68 shell could exhibit suppressed oxidative stress in lens tissues and decrease cataract progression, as evidenced by inhibited protein carbonyls and malondialdehyde in diabetic rat models [204, 205].

Posterior capsular opacification (PCO), one of the most common complications following cataract surgery, is one of the primary causes of secondary visual impairment. The incidence of PCO is reported to be around 20-40% in adults and 100% in children [206]. The residual lens epithelial cells (LECs) may either proliferate, trans-differentiate, or form Soemmerring's ring and Elschnig's pearls and eventually contribute to reduced visual quality [206, 207]. In clinical settings, PCO is generally

treated by neodymium-doped yttrium aluminum garnet (Nd: YAG) laser capsulotomy, while some other safer, more effective, and advanced therapeutics are being explored.

The fundamental strategy to prevent or postpone PCO is inhibiting residual LECs' proliferation. Therefore, the anti-proliferative drug doxorubicin (DOX) has been abundantly studied as a potential therapeutic for PCO. Guha *et al.* designed mPEG-PCL nanoparticles for DOX loading to minimize the toxicity without compromising its autophagy effectiveness [208]. To enhance the biocompatibility and efficacy of drug-loaded intra-ocular lens (IOLs), another study prepared polysaccharide multilayer modified IOL with DOX-loaded chitosan nanoparticles, which exhibited significant anti-adhesion and anti-proliferation properties [209]. Qin *et al.* later investigated the electrostatic adsorption of positively charged PAMAM and negatively charged heparin sodium and synthesized a multilayer-modified DOX-PAMAM IOL [210]. Owing to the cell-penetrating cationic features, increased cellular uptake and improved anti-proliferative efficacy were observed.

Other anti-proliferative approaches targeting PCO were also studied. For example, Zhang *et al.* designed NLCs encapsulating genistein, a potent TKI and verified their ability to inhibit the proliferation, migration, and transformation of LECs [211]. With high drug loading, sustainable drug release, and enhanced cellular uptake, the nanoparticles have become the preliminarily successful polymeric carrier for PCO prevention. Another anti-metabolite drug, 5-fluorouracil, was encapsulated into chitosan nanoparticles to develop a sustained and controlled release system and further modified the intra-ocular lens [212]. The results have confirmed the nanoparticles could suppress LECs proliferation and nanoparticles-modified IOL could significantly inhibit the incidence of PCO.

5.5 Glaucoma

Glaucoma is a chronic progressive optic neuropathy characterized by the irreversible degeneration of retinal ganglion cells (RGCs) and their axons, resulting in

loss of peripheral and occasionally central vision [213]. It has been recognized as the most significant contributor to irreversible blindness worldwide, affecting more than 76 million individuals worldwide, and the prevalence is estimated to reach 111.8 million by 2040 [214]. Though caused by heterogeneous pathological processes, intraocular pressure is the primary and only known modifiable risk factor, which may alter the biomechanical aspects of the posterior globe, leading to increased pressure on the RGC axons and RGC apoptosis subsequently [215]. Therefore, the reduction of intraocular pressure is the generally accepted therapeutic strategy. Conventional medication includes parasympathomimetics, prostaglandin analogues, β-blockers, α-agonists, and carbonic anhydrase inhibitors, exerting their effects *via* decreasing aqueous humor production or increasing aqueous humor outflow [216]. Recently, cell softening therapy, as a causative therapy to promote aqueous humor outflow by addressing dysfunction of pressure-regulating Schlemm's canal endothelial cells, has brought forth two new potent agents, rho-kinase inhibitors and actin depolymerizers. However, the physiochemical characteristics and the adverse effects limited their clinical application. Neuroprotection is another appealing field to explore and will be discussed in the "Retinal Ganglion Cell Disease" section.

For conventional agents, low solubility and limited corneal permeation are major obstacles. Liposomes were widely used for their excellent corneal penetration ability and affinity while suffering from physical instability, aggregation, and loss of the entrapped drug followed by a burst release. Liposomes with gelatinized core were an alternative for increased entrapment of hydrophilic drugs, reported to reach 50% entrapment efficiency of timolol maleate [217]. Niosomes are non-ionic surfactant-based vesicles and showed the advantages of enhanced drug entrapment efficiency, better stability, and lower cost than liposomes [218]. Niosomal formulations have been used for the delivery of latanoprost, betaxolol, and pilocarpine, displaying excellent encapsulation efficiency and sustained release [219, 220]. However, certain drawbacks of niosomes, such as the aggregation, leakage, and hydrolysis of the encapsulated drug,

limited the shelf life of the dispersion. Thus, proniosomes which are the inactive form of niosomes and can be transformed into an active form by hydration were prepared to overcome the problem of instability. The brimonidine tartrate proniosomal formulation achieved improved bioavailability and longer residence time [221]. Furthermore, coupling conventional niosomes with bile salts created more stabilized vesicular carrier systems with enhanced permeation, bliosomes, which were explored in acetazolamide delivery [222]. In addition, apart from altering the physiochemical compositions, nanoparticles with exotic membrane phases attracted extensive attention recently, and among those, cubosomes were considered to be the next generation of smart LNCs for the higher membrane surface area to volume ratios, capability to solubilize agents with different hydrophilic-hydrophobic nature, and equilibrium structure [223]. Cubosomes have been investigated to deliver acetazolamide and latanoprost [224, 225]. Especially, phytantriol (biocompatible surfactant)-based cubosomes provided greater structural stability and maintained a slow but sustained release profile of latanoprost [225]. Apart from LNCs, the unique features of PAMAM dendrimers contributed to enhanced cornea penetration and slower drainage *via* their appropriate size and mucoadhesive nature [226]. Lancina *et al.* creatively complexed timolol into the backbone of PAMAM dendrimers to form polymeric drugs [227]. Nanogels are promising candidates to adhere to the mucous layer and achieve sustained release of loading agents and have been investigated to deliver pilocarpine and timolol maleate [228, 229]. Instead of altering composing material, the nanostructure is of vital importance. For instance, hollow PLA nanoparticles were developed and the shell thickness can regulate the release of pilocarpine. The results suggested that the formulation with the optimal shell thickness(~40 nm) sustainably relieves intraocular pressure (IOP) for more than 56 days after one intracameral injection [230]. Intriguingly, Kim *et al.* offered a novel strategy to prolong preocular retention time by iontophoresis through skin-attached electrodes, allowing latanoprost-loaded PLGA nanoparticles to permeate and deposit into the eye,

and prolonged (more than 7 days) and marked increase (23 times than commercial products) in drug efficacy were detected [231].

Apart from conventional medications, nitric oxide (NO)-donating compounds, calcium channel blockers, adenylyl cyclase agonists, melatonin receptors agonists, rho-kinase inhibitors, actin depolymerizers, etc. were recognized as promising candidates for IOP reduction, and PNCs and LNCs were developed to increase their delivery efficacy [232-240]. For example, the therapeutic effects of NO largely depend on the concentration at a specific location. Thus, Chandrawati *et al.* fabricated an NO delivery platform that releases NO with controlled dosage *via* enzyme biocatalysis in the trabecular meshwork, where the resistance existed. Specifically, β-gal-NONOate (NO donors) were slowly released as the degradation of its vector, liposomes, and catalyzed by β-galactosidase (the enzyme) encapsulated in PNCs enmeshed in the trabecular meshwork [241]. Additionally, micelles modified with Flt-4/VEGFR-3 for targeting Schlemm's canal endothelial cells and delivering latrunculin A for softening the cells were explored for glaucoma nanotherapy [240, 242].

Gene therapy against glaucoma has attracted extensive attention. To alleviate high ocular pressure, connective tissue growth factor (CTGF) is a promising target for modulating pathological processes in the trabecular meshwork and Schlemm's canal. Based on that, Dillinger *et al.* developed CTGF siRNA nanoparticles coated by layer-by-layer PEI and final layer HA, where the HA coating avoided adhesive retention in the outflow pathway and precisely delivered siRNA to the targeted area by selectively binding to CD44 [243].

5.6. Endophthalmitis

Endophthalmitis is a severe vitreous and/or aqueous infection caused by bacteria or fungi that could lead to permanent vision loss in the affected eye. The main treatment options are primarily intravitreal antimicrobials injection; some cases can also benefit from vitrectomy (surgical debridement of the vitreous) [244]. In addition, systemic and

topical antibiotics, intravitreal steroids, and silicone oil are effective adjunctive therapies [245]. Frequent intravitreal administration is necessary to achieve an effective therapeutic concentration of antibiotics in the eye. However, as an invasive approach, the intravitreal injection may result in subconjunctival hemorrhage, corneal abrasion, traumatic cataracts, retinal detachment, etc. Besides, the production of biofilms by many of the most common causative organisms can also pose a significant barrier to intravitreal antibiotics [246]. To improve drug bioavailability and reduce the administration frequency, various nanocarriers, including PNCs and LNCs, have been designed and fabricated accordingly. Presently, liposomal amphotericin B agents have been thoroughly researched, and corresponding products (AmBisome®, Abelcet®, and Amphotec®) have also been marketed and used in the treatment of endophthalmitis.

Owing to their ability to penetrate physiological barriers, SLNs are also widely reported in topical ocular therapy to cope with intraocular infection [247]. In the past years, the ocular SLNs have also been further optimized, to better elevate bioavailability, improve solubility and minimize toxicity [248]. Kakkar *et al.* have developed a lipid-PEG-based ketoconazole formulation (KTZ-SLNs), which is composed of Compritol® 888 ATO and PEG 600 matrix, to address the toxicity, photodegradation, and bioavailability issues of local use of KTZ [249]. *Ex vivo*/corneal permeability studies displayed that KTZ-SLNs significantly improved the apparent permeation coefficient (P_{app}) compared to free KTZ aqueous suspension ($14.31\times10^{-6} \pm 1.25\times10^{-6}$ cm s^{-1} *v.s.* $8.68\times10^{-6} \pm 0.84\times10^{-6}$ cm s^{-1}). Similar lipid-PEG matrix SLNs were also described to encapsulate hydrophilic fluconazole and to reach the posterior eye segment [250].

As second-generation LNCs, NLCs have been designed to address the problems of SLNs, such as low entrapment efficiency and drug expulsion during storage [251]. Gade *et al*. creatively evaluated the *ex vivo* permeation of moxifloxacin NLCs (MOX-NLCs) loaded *in situ* gel, and found that the permeation of MOX-NLCs was 2-fold higher (208.7 ± 17.6 μg) than pure MOX *in situ* gel [252]. Their work suggested that

NLCs can be a promising candidate to prevent and treat endophthalmitis. Youssef *et al*. prepared CIP-containing NLCs loaded *in situ* gel (CIP-NLC-IG) for topical ocular administration in bacterial endophthalmitis treatment [253]. The trans-corneal permeability of CIP from CIP-NLC-IG formulations was 1.9-fold higher than that achieved with commercial CIP ophthalmic solution. Therefore, by extending drug residence time on the ocular surface and ensuring sustained drug release, CIP-NLC-IG could enhance the ocular bioavailability and improve therapeutic performance.

5.7 Uveitis

Uveitis refers to inflammation in the uvea, the retina and its vessels, and the papilla [254]. As a major cause of visual impairment, uveitis accounts for 10-15% of blindness in developed countries and is the fifth or sixth leading cause of blindness worldwide [255, 256]. Unlike other vision-threatening diseases, such as cataracts and age-related macular degeneration (AMD), uveitis tends to affect younger people, as 60-80% of patients are 20 to 50 years old [257]. Early-age visual impairment can lead to long-term disability and pose a much greater impact on life quality. Therefore, the significance of developing the proper treatment to restore vision and prevent blindness is self-evident. Currently, topical and systemic administrations of corticosteroids (dexamethasone, triamcinolone acetonide, etc.), are still the first-line clinical treatment of uveitis. For systemic therapy, the significant side effects of corticosteroids on target organs should not be ignored. While topical ophthalmic medications, such as eye drops, suspensions, gels, and ointments, are still restricted by low bioavailability and poor patient compliance. Despite these drawbacks, topical therapy is still broadly accepted owing to its noninvasiveness, ease of administration, and low cost. Therefore, developing superior delivery methods to enhance bioavailability, and reduce administration frequency is crucial for the uveitis therapy [258].

Improving drug payload is still urgently required for ocular steroid delivery. As a novel class of prodrugs, peptide-drug conjugates (PDCs) are formed by cleavable

covalent links of specific peptide sequences to drugs [259]. Yu *et al*. designed dexamethasone-peptide conjugate (Dex-SA-FFFE) self-assembled nanoparticles, which were formed *via* a biodegradable ester bond linkage to act as a "self-drug" delivery system and treat anterior uveitis [260]. In PBS containing 20 U mL^{-1} esterases, Dex-SA-FFFE nanoparticles sustainably released both dexamethasone and Dex-SA-FFFE. Dex-SA-FFFE nanoparticles can downregulate the TNF-α and IL-6 levels in aqueous humor, and the anti-inflammatory efficacy was nearly identical to DSP aqueous solution. Therefore, the bioactivity of dexamethasone *in vivo* was not compromised by the conjugation of dexamethasone to the peptide.

PLGA is also an optional carrier with excellent biocompatibility and degradability for drug delivery. Rebibo *et al*. fabricated nonirritant and stable TAC-loaded PLGA nanocapsules for ocular inflammation management [261]. TAC-loaded PLGA nanocapsules displayed excellent performance in increasing drug retention and improving penetration to deeper ocular compartments. However, for PLGA, it is difficult to load highly water-soluble drugs, such as DSP, and achieve sustained drug release using conventional encapsulation methods. Therefore, Luo *et al*. developed biodegradable DSP-loaded nanoparticles (DSP-Zn-NP) using divalent cationic zinc ions as an ionic "bridge" between the anionic carboxyl-terminated PLGA and DSP with a high DSP loading (6% w/w) [262]. When DSP-Zn-NP was administered by subconjunctival injection, the DSP levels in the anterior and vitreous chamber can be detached for at least 3 weeks. DSP-Zn-NP can effectively diminish ocular inflammation and protect retinal function in the experimental autoimmune uveitis rat model, showing that DSP-Zn-NP can be a prospective candidate for managing noninfectious uveitis.

Another problem that hampers therapeutic efficiency is the poor permeability of drugs across biological barriers. Ghezzi *et al*. investigated a polymeric micelle formulation that is prepared with non-ionic amphiphilic polymers, tocopherol polyethylene glycol succinate (TPGS), and Solutol® HS15, to promote cyclosporine retention in eye tissues [263]. The interaction of the micelles with the fibers and with

the interfibrillar material together with the enzymatic hydrolysis of the TPGS determines the release of cyclosporine and its transscleral diffusion. Apart from micelles disassembling and cyclosporin release, water-based TPGS micelles formulation can undergo transscleral diffusion and form a drug reservoir in the tissue to achieve sustained release. Besides, vitamin E and vitamin E succinate can be released owing to TPGS hydrolysis, further improving the recovery of oxidation-mediated diseases.

Although corticosteroids remain the first-line treatment of uveitis, their association with long-term systemic and topical side effects, such as glaucoma and cataract, can exert a nonnegligible impact on the patients [264]. Therefore, researchers have made efforts to develop novel alternative drugs, for instance, biologics with fewer side effects, to cope with inflammation. Liu *et al*. constructed a novel programmed cell death protein 1 (PD-1) antibody and pyruvate kinase M2 (PKM2) activator TEPP-46-integrated, PEG-modified PLGA nanoparticles for targeted inhibition of early activation and proliferation of effector T cells, which effectively alleviated the experimental autoimmune uveitis mice model by systemic administration [265].

5.8 Retinal Vascular Diseases

The unique feature of the retina receiving dual blood supply gives rise to two types of neovascular diseases in the ocular posterior segment, CNV and retinal neovascularization (RNV). CNV refers to a nonspecific wound repair response that the abnormal growth of choroidal vessels extends through Bruch's membrane into the sub-RPE or subretinal space, while RNV refers to the abnormal growth of existing retinal blood vessels, which is an end-stage pathological process shared by ischemic retinal disease, existing as the typical clinical manifestations of AMD and diabetic retinopathy (DR) respectively [266].

AMD is the third leading cause of blindness worldwide and the primary cause of irreversible vision loss among the elderly population in developed countries [267],

which is traditionally divided into two phases: early AMD and late AMD. Early AMD refers to large drusen or retinal pseudodrusen, or pigmentary abnormalities, while late AMD commonly develops into two types: dry AMD (also termed "geographic atrophy" or "non-neovascular AMD") and wet AMD (also termed "exudative" or "neovascular AMD"). Dry AMD refers to the presence of sharply demarcated atrophic lesions of the outer retina, resulting from the loss of photoreceptors, RPE, and underlying choriocapillaris, while wet AMD manifests as CNV, resulting in hemorrhages, intraretinal oedema, and ultimately fibrosis [268]. Among those two types, wet AMD accounts for 10-15% of the total prevalence of AMD but is responsible for more than 80% of blindness, so current research was generally focused on wet AMD [269].

DR is the leading cause of legal blindness in working-age individuals (20-74 years) worldwide [270], and about one-third of people with diabetes mellitus were identified with DR [271]. As the prevalence of diabetes mellitus continues to increase, more people are facing the risk of retinopathy. DR can develop into several aberrant processes; among these, diabetic macular edema (DME) and proliferative retinopathy (PDR) are notable changes. DME refers to the accumulation of fluid intraretinally or subretinally caused by increased vascular permeability, while PDR is symbolized by neovascularization of the disk and elsewhere [272].

For retinal vascular homeostasis, the balance between angiogenic stimulators (VEGF, PDGF, fibroblast growth factor (FGF), etc.) and angiogenic inhibitors is necessary [273]. Variable conditions, like hypoxia, inflammation, and oxidative stress can break the delicate balance and cause neovascularization [266]. Current ocular treatments for CNV and RNV mainly focused on anti-VEGF drugs, laser photocoagulation, and corticosteroids. Among these therapies, the limited efficacy of laser photocoagulation and the potential risk of cataracts and glaucoma of corticosteroids restrain their clinical use, and intravitreal injection of VEGF antagonist gradually replaced them as the principal strategy [274]. Pegaptanib is the first anti-VEGF drug approved by FDA, which is an aptamer that specifically binds to $VEGF_{165}$

and larger isoforms [275]. Recently, ranibizumab and aflibercept have been commonly adopted for clinical treatment. Ranibizumab is a humanized antigen-binding fragment (Fab) that specifically binds all isoforms of human VEGF, and bevacizumab is a monoclonal antibody to VEGF. However, anti-VEGF treatments require repeated and life-lasting intravitreal injections, which may lead to hemorrhage, retinal detachment, endophthalmitis, etc. Meanwhile, as the most efficacious agents for neovascular diseases, long-term use of VEGF antagonists will cause macular dysfunction and only 25-40% of the patients showed obvious visual improvement [276]. Thus, the limitations further necessitate the development of PNCs for various therapeutic agents and their clinical applications.

As illustrated above, the pathogenesis of different retinal vascular diseases shared several common agents, including anti-VEGF drugs, corticosteroids, and photosensitizers. Additionally, other promising agents (such as other anti-growth factors, anti-inflammatory agents, anti-proliferative agents, etc.), combined therapies, and gene therapies have been reported while not yet applied to clinical practice. However, the insufficient retinal delivery, repeated dosage, instability of these agents, etc. remain a significant challenge for an ideal therapy, for which nanocarriers provide an appealing alternative.

Growth factors play crucial roles in retinal vascular disease, including VEGF, hypoxia-inducible factor-1 (HIF-1, regulating most of the genes coding for proteins related to angiogenesis), placenta growth factor (PLGF, selectively activating VEGFR-1), angiopoietin-1 receptor 2 (binds to Tie-2 stimulating phosphorylation of endothelial nitric oxide synthase (eNOS)), protein kinase B (PKB/Akt), extracellular regulated protein kinase (ERK), and PDGF (induced by hypoxia, then stimulating pericytes, accelerates vessel leakage and neovascularization) [277]. Among these factors, VEGF makes a vital contribution to CNV, thus making VEGFR the most efficacious target and VEGFR-related drugs the commonest choice of loading agents, especially those already applied in the clinic, including bevacizumab [49, 278, 279], ranibizumab [280,

281], and aflibercept [86, 282]. Notably, TKIs are widely explored in neovascular disease for their ability to inhibit VEGF/VEGFR, PDGF/PDGFR, etc., and several TKIs were successfully delivered and functioned in the posterior segment by PNCs and LNCs, including apatinib [283], axitinib [284], rivoceranib [285], cediranib [286], nintedanib [287], pazopanib [288], imatinib [289], sorafenib [290] and etc. Apart from growth factors, the signals from the extracellular matrix (ECM) are indispensable for the survival and stabilization of endothelial cells. Integrin takes responsibility for much of the communication between endothelial cells and ECM. Extensive evidence revealed that integrin, especially RGD-binding integrin played a critical role in retinal vascular disease for participating inflammation, leakage, angiogenesis, and fibrosis [291]. Besides, pigment epithelial derived factor (PEDF), Flt-1, angiostatin/plasminogen, endostatin/collagen XVIII, collagen IV, and serpin from ECM are endogenous inhibitors of angiogenesis [277].

LNCs have been widely applied in the treatment of retinal vascular diseases for their biocompatibility, easily tunable properties, and drug-loading capacity irrespective of polarity [292]. Mu *et al*. reported bevacizumab-loaded multivesicular liposomes (MVLs) for extended retention and a lower frequency of injection [293]. Compared with regular liposomes of a single compartment, MVLs are composed of multiple discontinuous internal aqueous compartments divided by nonconcentric lipid bilayers to achieve higher encapsulation efficiency for hydrophilic drugs [294]. The polarity of posterior segments can prevent the effective delivery of liposomes: the highly cationic liposomes can be easily immobilized by the negatively charged vitreous humor, while PEGylated liposomes with low positive surface charge can be easily cleared out. To remove the obstacle, Lee *et al*. created a delicate liposomal formulation with optimal surface charge and good dispersal in vitreous humor by balancing these two components [281].

Polymeric nanoparticles are widely recognized powerful delivery platforms as well. PLGA nanoparticles are promising candidates for the excellent biocompatibility,

safety profile, and tunable biodegradation rate [295], but several inherent defects, including protein instability, an initial burst release, nonuniform particle sizes, and inflammation response, limit the delivery efficacy and biocompatibility [296]. To enhance the delivery efficacy and prolong release profile, chitosan, a hydrophilic polysaccharide with cationic properties, has been used to improve drug payload and achieve prolonged drug release and surface retention [297]. Chitosan-coated PLGA nanoparticles achieved subconjunctival administration of bevacizumab for improved permeability via the electrostatic interaction between positively charged chitosan and negatively charged ocular surface [279]. Moreover, chitosan-N-acetyl-l-cysteine (CNAC), a derivative of chitosan, showed stronger mucoadhesive properties by forming strong disulfide bonds with cysteine-rich domains of the mucus glycoproteins with extra N-acetyl-l-cysteine (NAC), leading to improved mucoadhesive properties. To avoid exposing proteins to organic solvents or sonication, supercritical infusion and pressure quench technology were adopted to construct porous PLGA microparticles to encapsulate bevacizumab-coated PLA nanoparticles for the stable release of bevacizumab for 4 months [298]. Since the degradation of PLGA to lactic acid and glycolic acid during drug release will result in acidic environments, leading to acceleration of drug release and degradation of protein drugs, blending poly (cyclohexane-1,4-diyl acetone dimethylene ketal) (PCADK), a type of polyketal synthesized by two neutral compounds (1,4-cyclohexanedimethanol and 2,2-dimethoxypropane), with PLGA contributed to avoid the rapid decrease in pH and stabilize protein drugs [299]. Additionally, the incorporation of albumin into the delivery system is also an alternative to stabilizing protein drugs [300]. Apart from PLGA, other polymers exhibited their potential in retinal delivery. Jiang *et al*. reported polydopamine (PDA) nanoparticles, which have the inherent property of redox-responding, thus providing a synergic effect of anti-oxidative stress and VEGF inhibition [301]. PLA/PLA-polyethylene oxide (PEO) nanoparticles were manufactured for integrin-antagonist peptide, C16Y delivery, and surprisingly, the

nanoparticles exhibited excellent barrier penetration after intravitreal injection and were observed to penetrate the ILM. Protein/peptide is also an appealing platform for retinal delivery due to its excellent biocompatibility. Suda *et al*. reported a pazopanib - loaded high-density lipoprotein (HDL) mutant prepared by the fusion of apoA-I proteins with cell-penetrating peptides (CPPs) and phospholipids, presenting the capability of treating CNV in mice *via* topical instillation [288].

Micelles are another potent PNCs in retinal drug delivery. Zhao *et al*. developed a micelle-based delivery system assembled by copolymer EPC (nEPCs) composed of PEG, PCL, and poly (propylene glycol) (PPG) segments to carry aflibercept to treat retinal neovascular disease, and surprisingly, nEPCs exhibited intrinsic antiangiogenic properties, providing synergistic effects with VEGF agonists [86]. Besides, a conjugate of GGNQWFI (an anti-Flt1 peptide) and tetra-n-butyl ammonium-modified hyaluronate *via* amide bond with the presence of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate was reported to self-assemble to form micelle-like nanoparticles in aqueous solution, displaying the dose-dependent effect of VEGF blocking [302].

Intriguingly, Li *et al*. developed a unique hybrid cell membrane of red blood cells (RBC) and retinal endotheliocyte (REC)-cloaked PLGA nanoparticles for VEGF blocking [303] (Fig. 7). The major therapeutic effect was attributed to REC membrane coating, which acted as a decoy to attract VEGF and prevented its binding with VEGFR, thus leading to reduced CNV area and leakage, while the homotypic targeting capability of REC and the immune evasion property of RBC accounted for the enhanced accumulation in the retina.

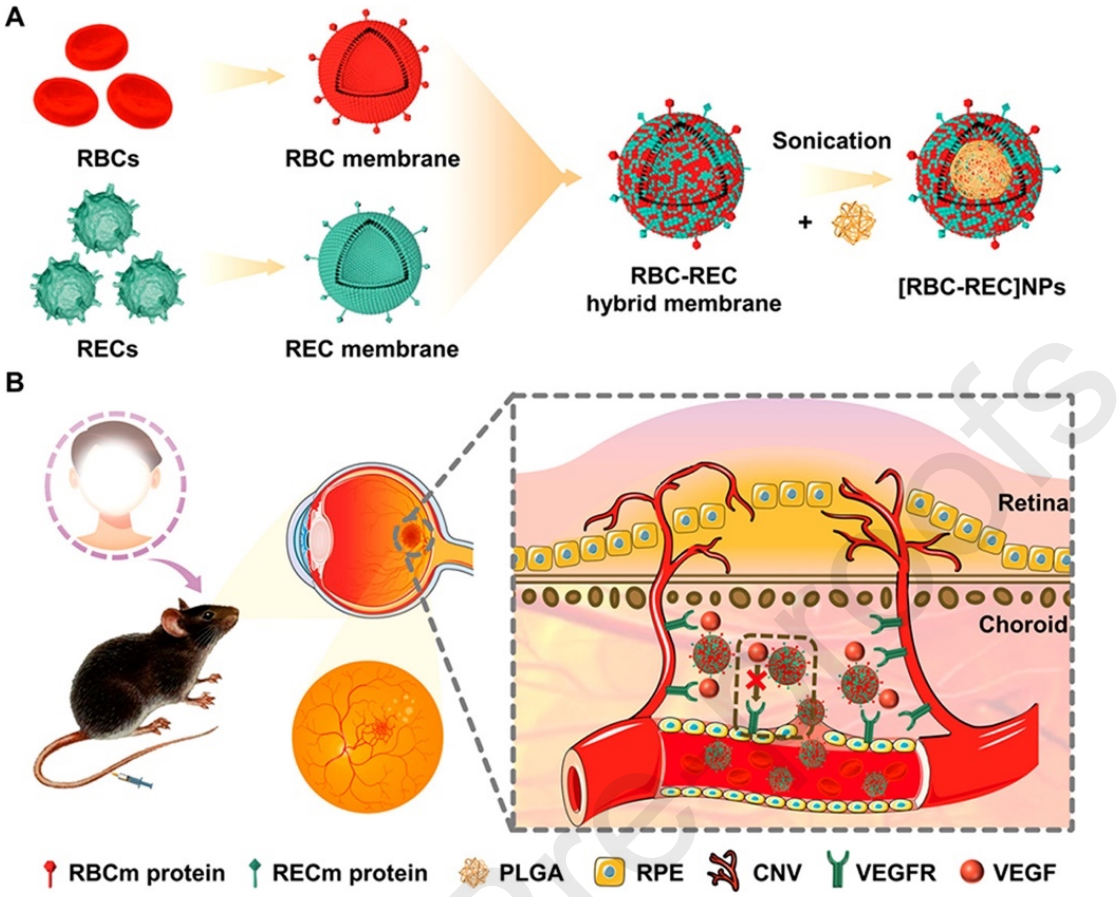

Fig. 7. A hybrid cell membrane cloaked biomimetic nanoparticles exploiting the targeting capability of REC and the immune evasion property of RBC for CNV treatment [303].

Surface engineering nanocarriers can provide unique properties to improve retinal drug delivery efficacy, including enhanced penetration, targeted release, etc. Externally triggered drug release allows the high spatial and temporal resolution of drug delivery, such as light-responsive drug release, which can achieve ocular targeting for the light-absorbing characteristics of the eye and is well explored in retinal delivery [304]. Huu *et al*. developed a far ultraviolet (UV) light-degradable polymer with an o-nitrobenzyl moiety in each monomer, which can degrade into fragments when absorbing UV, for the on-demand delivery of nintedanib [287]. CPP is also widely used for surface modification to enhance ocular penetration for topical applications [305]. Annexin A5 was conjugated to liposomes in bevacizumab topical delivery system, as annexin A5-

mediated endocytosis significantly enhanced the ability of corneal permeability to achieve a physiologically significant concentration of bevacizumab in the posterior segment [278].

Inflammation was identified to contribute to neovascularization and RPE damage, which is a crucial pathological change for both AMD (dry and wet AMD) and DR [306, 307]. Corticosteroids present a powerful anti-inflammatory effect, and triamcinolone acetonide, dexamethasone, and budesonide are the loading drugs of choice. Various drug delivery systems, including NLCs [308], polymeric nanoparticles [309, 310], and dendrimers [311], were developed. Among these, dendrimers, especially hydroxyl-terminated generation four PAMAM dendrimers (D4-OH), have great potential as ocular nanocarriers. The small size and near-neutral charge of hydroxyl-terminated PAMAM-triamcinolone acetonide conjugate allow unhindered tissue diffusion and effective phagocytosis by microglia/macrophages (mi/ma) and RPE [311] (Fig. 8). To enhance cellular uptake, folate-functionalized PEG-PCL nanoparticles were manufactured and resulted in enhanced internalization into ARPE-19 (human RPE cell line) *via* receptor-mediated endocytosis and reduced toxicity [309]. Since hydrophobic and hydrophilic properties contribute to the stability of the system and effective interaction with target sites, Mahaling *et al*. reported core-shell nanoparticles consisting of a hydrophobic PCL core and a hydrophilic Pluronic® F68 shell, where the hydrophobic core and the hydrophilic mucoadhesive shell interacted differentially with ocular tissues, resulting in barrier penetrating and retina concentration [312]. Besides, Ryu *et al*. reported amphiphilic polymeric nanoparticles formed by hydrophilic poly (γ-glutamic acid) and hydrophobic L-phenylalanine, exhibiting resistance to proteases[50].

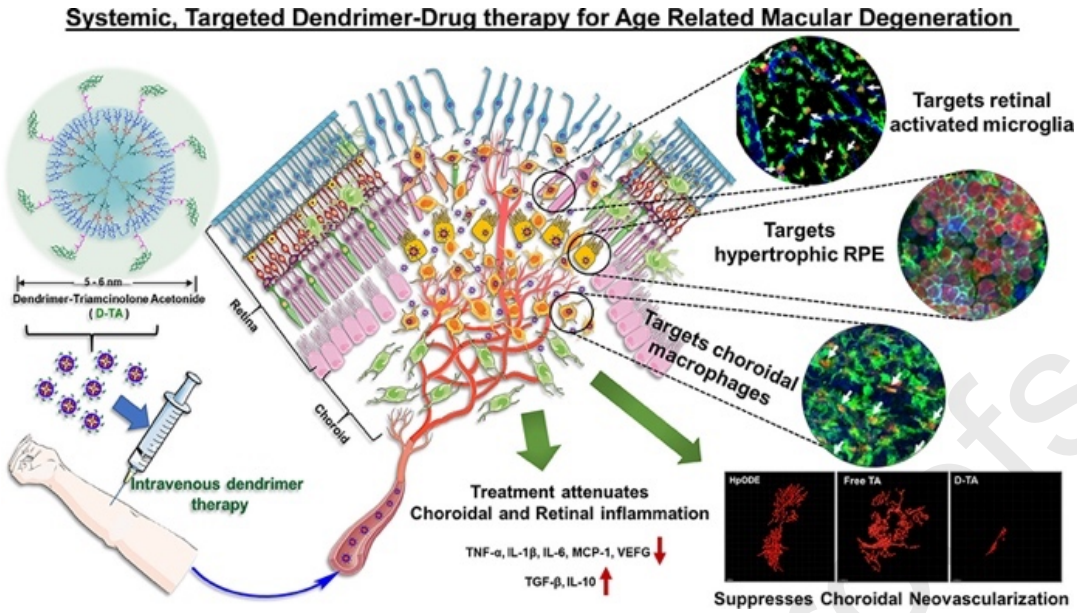

Fig. 8. Dendrimer-triamcinolone acetonide (D-TA) conjugate shows the potential of ameliorating CNV by the unique feature of macrophages/RPE targeting and anti-inflammation [311].

Apart from corticosteroids, clodronate produces a marked effect through macrophage depletion, and its liposome formulations could efficiently diminish CNV lesions [313]. Cytokines are promising anti-inflammatory agents, and PLGA nanoparticles carrying interleukin-12 (IL-12) for down-regulating MMP-9 and VEGF-A were reported [314]. Besides, self-assembling TAC micelles [315] and rapamycin-loaded chitosan-modified PLGA nanoparticles [316] were prepared for the anti-oxidative and anti-inflammatory effects.

Plant-derived natural medicines showed multiple benefits, especially anti-inflammatory properties, and several agents, including lutein [317], curcumin [318], triptolide [319], honokiol, epigallocatechin gallate (EGCG), quercetin [320], etc. were investigated as potential drugs for antiangiogenesis. Chitosan-based nanocarriers are alternative delivery platforms for delivering plant drugs, owing to their biocompatibility and capability of enhancing drugs' solubility. For instance, Buosi *et al*. reported high molecular weight chitosan-based nanogels for resveratrol delivery, which surprisingly showed the additional property of endolysosomal escape [321].

Additionally, chitosan-sodium alginate (CS-SA) nanoparticles were manufactured for lutein delivery, which showed prolonged retention of lutein and prevented RPE cells from oxidative stress [317]. Vitamin B12-modified amphiphilic deoxycholic acid conjugated chitosan nanoparticles made it possible for intragastrical administration to treat type II diabetes induced-retinopathy [322]. Notably, Ala-Pro-Arg-Pro-Gly (APRPG), as a vessel-homing peptide specifically targeting VEGFR-1, can act as a targeting component, and APRPG peptide-modified liposomes were efficacious for triptolide delivery [319]. Another research reported PAMAM-coated compound liposomes with berberine hydrochloride and chrysophanol loaded, possessing enhanced cellular permeability and bioadhesion [323].

Hypocrellin B is a widely used photosensitizer and liposomes were confirmed as an efficacious nanocarrier [324, 325]. Especially, Chen *et al*. reported that hypocrellin B-loaded triphenyl phosphonium-modified cationic liposomes (TPP cationic LHB) with the property of mitochondria targeting could cause the death of vascular endothelial cells, whereas did negligible harm to RPE [324]. Other photosensitizers, such as dendritic photosensitizers [326], BPD-MA [327], and m-THPP [327] were investigated as well. Micelles [326], liposomes [327], and polymeric nanoparticles [327] were alternatives for photosensitizer delivery. However, due to the limited efficacy of PDT for choroidal and retinal neovascularization, the related therapies were less explored, especially in recent years.

Antiproliferative agents, such as DOX [304, 328] and acriflavine [329], showed the properties of diminishing fundus neovascularization. Li *et al*. designed co-assembled glycopeptide nanotransforrs (GPNTs) named MRP@DOX, which was composed of three components: glycopeptide, cationic peptide, and DOX [330] (Fig. 9). The system exhibited the following advantages: (1) electrostatic interaction between positively charged MRP@DOX and negatively charged mucin layer could prolong the retention time; (2) the mannose ligand of MRP@DOX was to mediate phagocytosis by M2 macrophages; (3) the enzyme-response motif to be cleaved by lysosomes resulted

in the self-assembly of the hydrophobic peptide to form nanofibers, and nanofibers significantly prolonged the retention time than nanoparticles. Wang *et al*. reported another delicate light-responsive delivery system, a DEACM-CPP functionalized PEG-PLA block copolymer self-assembled to nanoparticles with photo-responsive properties [304]. DEACM is a photocleavable caging group, and CPP can enhance cellular uptake when the covalent bond with DEACM cleaved after light triggering, thus resulting in the accumulation of DOX in the retina and reduced systemic toxicity. Besides, cytotoxica criflavine was also a potent inhibitor of HIF-1 and HIF-2, and PLGA nanoparticles were used to deliver this water-soluble agent with sustained drug-release properties [329].

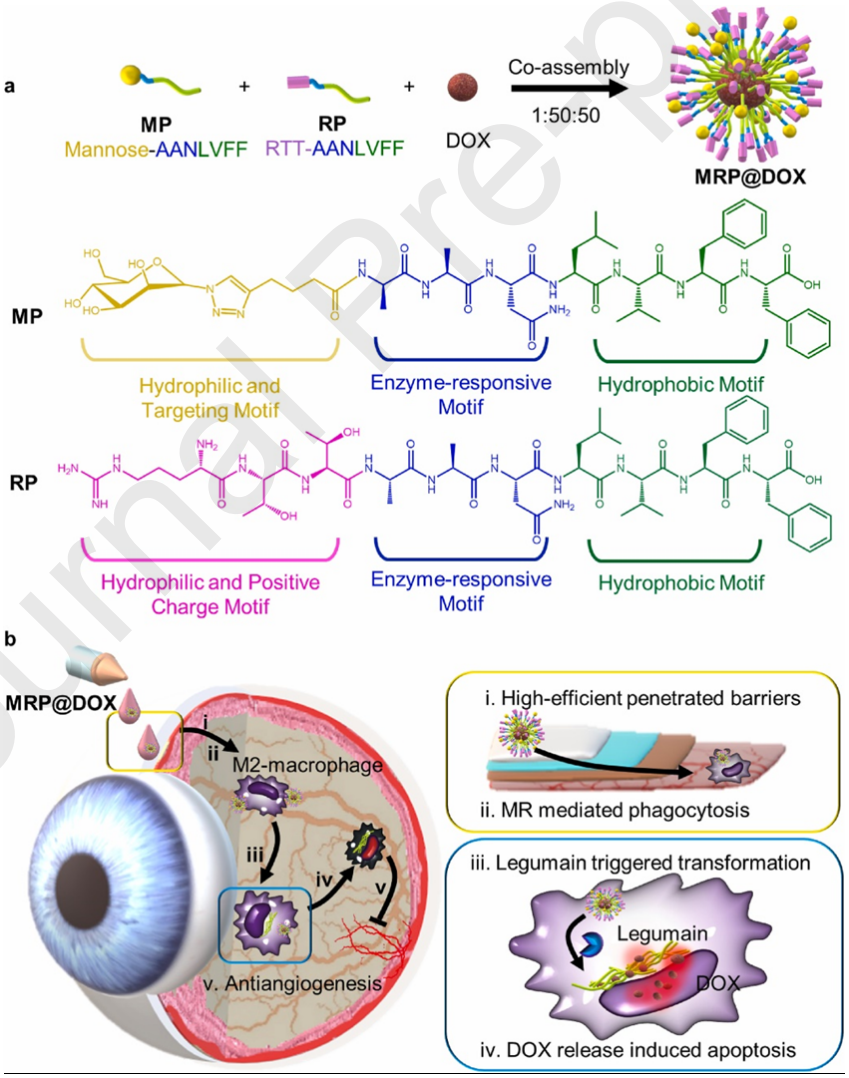

Fig. 9. GPNTs eyedrops comprised of glycopeptide and cationic peptide with enhanced permeability and retention for inhibiting CNV [330].

As aging diseases, AMD and DR share pathogenic processes with other age-related diseases, such as atherosclerosis, hypertension, and diabetes mellitus. Metabolic dysfunction is well recognized as a major contributor to aging diseases, so it is anticipated that lipid-regulating agents are promising therapeutics for AMD and DR. Fenofibrate [331] and pioglitazone [332] loaded PLGA nanoparticles were confirmed effective for AMD and DR treatment. Moreover, it was reported that a very low-density lipoprotein receptor (VLDLR), a membrane receptor mediating lipid transport, was associated with Wnt signaling-mediated RNV, thus the soluble very low-density lipoprotein receptor extracellular domain (VLN) encapsulated PLGA nanoparticles (VLN-NP) were prepared and confirmed effective to treat ocular neovascularization [333].

Gene therapy is gaining popularity in the treatment of retinal vascular disease *via* introducing exogenous nucleic acids that express or silence the target gene [334]. An ideal gene delivery system is supposed to display the following properties: (1) effective gene complexation; (2) efficient cellular internalization; (3) efficient endosomal escape; (4) precise transportation into the nucleus [51]. To specifically deliver the target gene, Singh *et al*. reported an intravenous anti-VEGF intraceptor gene delivery system attaching dual-targeting components: transferrin, which can be actively taken into retinal cells, and RGD peptide, which can bind with integrin receptors upregulated in neovascular segments [87]. Besides, a multifunctional core-shell system was manufactured to deliver Flt23k (the VEGF-binding domains of the Flt-1 receptor) encoded plasmid with precise intracellular localization, which was composed of 1) amino acid-functionalized dendrimer and nuclear localization signal (NLS) core for enhanced nucleic acid complexation, internalization, and nuclear localization, 2) lipid bilayer inner shell composed of pH-sensitive lipid DOPE/cholesteryl hemisuccinate (CHEMS) for improved endosomal escape, and 3) HA-1,2-dioleoylphosphatidylethanolamine (DOPE) outermost shell for increased cellular

uptake [51] (Fig. 10). To silence target genes, RNA interference (RNAi) is a process of specifically recognizing target genes with a base pairing complementary sequence and then degrading the target genes by intracellular nuclease. siRNA is a powerful strategy to down-regulate gene expression based on RNAi [335]. Liu *et al*. reported VEGFR-1-targeting-siRNA-loaded PEGylated liposome-protamine-hyaluronic acid (HA) nanoparticles (PEG-LPH-NP-S) by a simple mixture of siRNA, HA, and protamine to form a stable negatively charged complex via charge-charge interaction, which was further encapsulated by cationic liposomes [336]. Trimethyl chitosan-HA nanopolyplexes are another potential platform for VEGFR siRNA delivery, where HA contributed to improve transfection and decrease degradation rate, while chitosan accounted for the good biocompatibility [337]. Additionally, amphiphilic polypeptides were reported to present effective nucleic acid complexation and internalization, where the oppositely charged hydrophilic amino acids are capable of controlling siRNA binding and release, while hydrophobic amino acids provide the property of self-assembly and cell membrane penetration [338]. Besides, hyperbranched cationic polysaccharide derivatives could efficiently deliver nuclear factor kappa-B (NF-κB), a classic pro-inflammatory factor [339]. Compared with siRNA, shRNA has the advantages of high potency and sustainable effects using low copy numbers resulting in few off-target effects [135]. Zhang *et al*. reported a HIF-1a shRNA plasmid encapsulated PLGA nanoparticles, displaying clinical prospects for CNV treatment [340]. miRNA can cause translational repression and mRNA destabilization *via* partial binding of target mRNA [341]. miR200-b is a promising anti-angiogenic agent by down-regulating VEGFR-2, and therefore a plasmid with miR200-b amplified and cloned into a pCAG-eGFP vector directed by the ubiquitous CAG was constructed as the therapeutic agent, which was further compacted by CK30PEG10K into DNA nanoparticles, showing encouraging delivery efficacy *in vivo* [341]. As is known that chemokine is a kind of cytokine that recruits bone marrow-derived cells, especially macrophages, resulting in neovascularization. MicroRNA-539-5p, identified to

overexpress in the CNV area, is a regulator of CXCR-7 (CXC chemokine receptor 7), which can be specifically delivered by PLGA nanoparticles grafted with RGD to pathological tissues [342].

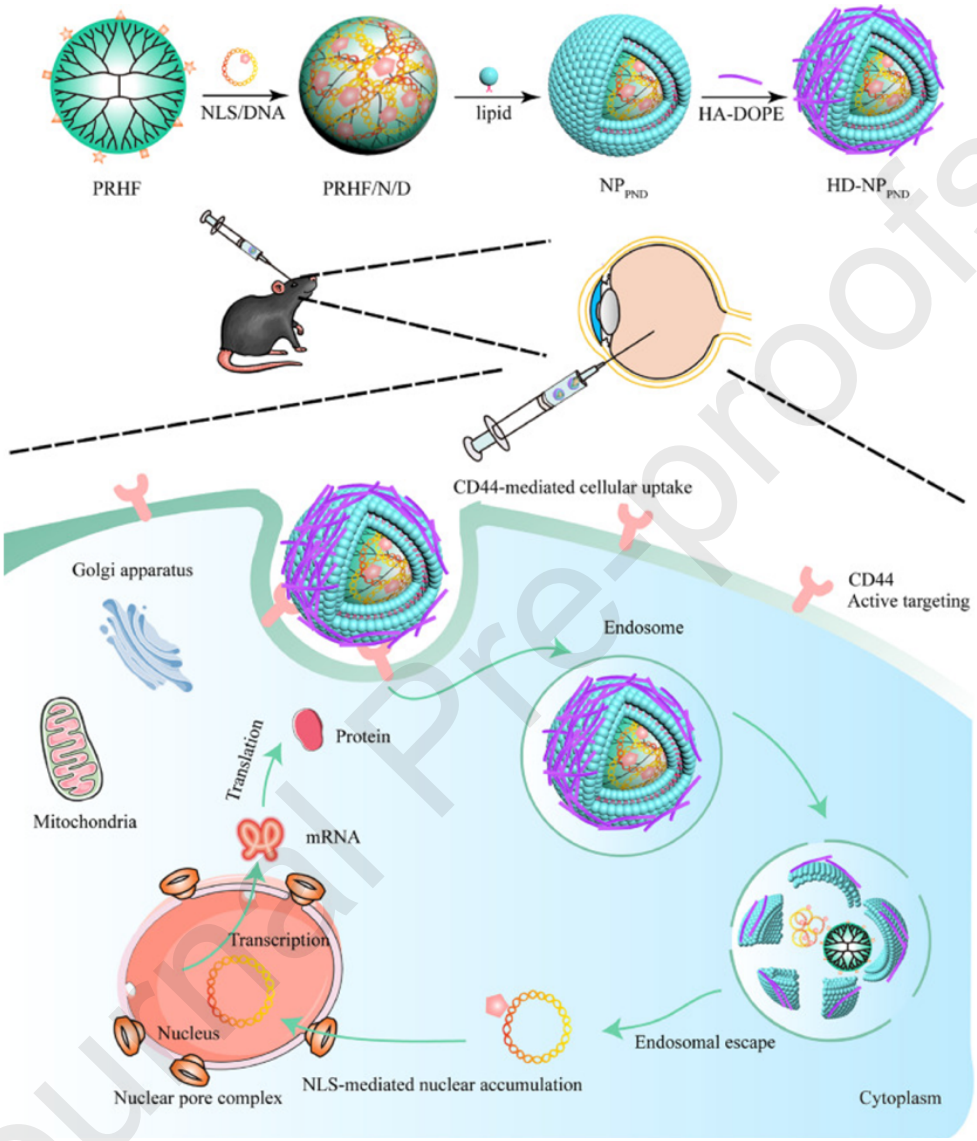

Fig. 10. A core-shell delivery system with dendrimers and NLS as the inner core, lipid bilayer as the inner shell, and DOPE as the outer shell, presented the merits of targeted retina gene delivery, endosomal escape, and nuclear accumulation [51].

As is known, the simultaneous delivery of multiple drugs targeting different pathogenesis may provide more benefits than monotherapy due to the multifactorial pathogenesis. Bevacizumab-adsorbed and dexamethasone-loaded RGD-PEG-

PLGA/PLGA/PEI nanoparticles (aBev/cRGD-DPPNs) were manufactured with PEI regulating the bevacizumab absorption and RGD targeting CNV, showing inspiring therapeutic effects both *in vitro* and *in vivo* [343, 344]. Intriguingly, as anti-Flt-1 peptide-HA conjugate has been confirmed effective in CNV and RNV [302], Kim *et al.* further attempted to package genistein, an antioxidant and anti-inflammatory agent, to achieve a synergic effect for reducing vessel leakage in DR [111]. Chittasupho *et al.* reported an R5K peptide-itraconazole dual loading system with R5K peptide preventing the binding of VEGF/VEGFR and itraconazole blocking the VEGF signaling pathway, demonstrating a synergistic effect on the anti-VEGF process [345]. The co-delivery of PDTC (an antioxidant) and triamcinolone acetonide with polymeric nanoparticles consisting of pluronic® F-68 shell and PCL core also provided an alternative for enhanced therapeutic effects [205]. Notably, Behroozi *et al*. reported that N-acetyl cysteine (an antioxidant)-loaded and diselenide-incorporated liposomes with the ability to be disrupted in oxidative stress and release its payload, thus achieving disease-triggered drug release [346]. Besides, though PDT showed limited effects, the combined therapy of PDT with other agents was explored, such as photosensitizer and TKI (photocyanine and sorafenib), which demonstrated encouraging results [347].

5.9 Proliferative Vitreoretinopathy (PVR)

PVR refers to a complication that can follow rhegmatogenous retinal detachments (RD), which is estimated to occur in 5-10% of all RD cases and is the major cause of failure after RD surgery. Over 50% of PVR cases result in severe uncorrectable vision loss. PVR is characterized by the growth of membranes on both surfaces of the detached retina and on the posterior hyaloid [348]. The pathogenesis includes several sequential processes: (1) cells migration, mainly RPE and glial cells; (2) migrating cells proliferation; (3) membrane development; (4) cellular membrane contraction; (5) extracellular collagen production; and finally (6) the presence of fixed folds in the retina [349]. Among these steps, cellular proliferation is the emphasized one.

The pharmaceutical agents that attempted to prevent PVR were mainly anti-inflammatory, anti-proliferative, anti-neoplastic, anti-growth factor, and antioxidant drugs. However, none of them showed satisfying results in clinical trials or have been approved for the treatment of PVR [349]. The unexpected outcome could be partly explained by the improper administration time and insufficient concentration in the retina [350], into which nanocarriers may provide new insights. Meanwhile, novel targets have been discovered and investigated with drug delivery strategies as well.

Corticosteroids are theoretically feasible agents as inflammation plays a key role in PVR pathogenesis. A promising dexamethasone implant (Ozurdex; Allergan Inc, Irvine, CA) was designed to sustainably release comparable concentration for as long as 6 months after a single injection, and it has been explored for the treatment of PVR.

VEGF agonist is one of the latest approaches for PVR treatment. Recently, PEG-PCL micelles and PLGA nanoparticles were reported to carry hydrophobic TKI dasatinib to inhibit RPE cell proliferation, adhesion, and migration [351, 352]. Flt23k is another potential target, and a sophisticated delivery system was constructed with Flt23k intraceptor encoded plasmids core, biodegradable PLGA shell, and RGD modification, demonstrating both anti-CNV and anti-fibrosis effects after administration [353, 354].

Encouragingly, the polymer itself can act as the therapeutic component as well as the delivery component. Parikh *et al*. designed an elaborate multiblock thermo-responsive polymer composed of PEG, PCL, and PPG, named poly(CEP), with an inherent therapeutic effect for PVR, which underwent reversible phase changes, from unimers to polymeric micelles as the concentration increased and from a solution to gel state as the temperature increased [355]. *In vivo* results confirmed the ability to prevent PVR through clathrin-dependent internalization, suppression of canonical EMT transcription factors, and subsequent reduction of RPE cell hyper-proliferation and migration.

5.10 Inherited Retinal Disease

Inherited retinal diseases (IRD), such as retinitis pigmentosa (RP), Stargardt disease, and Leber congenital amaurosis (LCA), are a group of disorders with clinical and genetic diversity that account for a marked proportion of blindness worldwide. They are typically caused by mutations of genes that express proteins essential for the development, structure, function, and survival of retinal cells [356].

RP is hereditary retinopathy that affects about 2.5 million individuals worldwide. More than 3,000 genetic mutations from nearly 70 genes are related [357]. It is characterized by bone spicules (pigmented deposits) caused by the loss of photoreceptors, and patients may suffer from nyctalopia initially, then progressive deterioration of the peripheral visual field, and eventually tunnel vision [358]. RP can be classified into three categories: autosomal dominant RP (adRP), autosomal recessive RP (arRP), and X-linked form of RP (XLRP). For adRP, the mutation of RHO (encoding Rhodopsin) is the primary cause. Rhodopsin is a photo-excitable G Protein-Coupled Receptor (GPCR) composed of protein (rhodopsin) and chromophore (11-cis-retinal), and it can operate the phototransduction cascade by absorbing light energy into the retina and activating transducin (Guanosine diphosphate binding protein). For arRP, Retinal RPE 65 kDa protein (RPE65) is the representative gene but only accounts for about 2% of arRP. RPE65, also known as retinoid isomerohydrolase, is a key enzyme for the restoration of visual pigment, thus the defect of RPE65 can cause the loss of chromophore production, thereby leading to progressive photoreceptor degeneration [359]. Mutations of RPE65 also contribute to the pathogenesis of Leber Congenital Amaurosis. XLRP, accounting for 10-15% of RP, is mainly caused by Retinitis Pigmentosa GTPase Regulator and Retinitis Pigmentosa 2 [357].

Stargardt disease is characterized by central vision loss, and the prevalence is 1:6,578 worldwide [360]. The fundus manifestation of Stargardt disease is the accumulation of lipofuscin and bis-retinoid compounds within the RPE cell layer. Among those deposits, A2E is a main component of lipofuscin, and the accumulation

of A2E is a commonly acknowledged indicator of Stargardt disease progression [361]. All Stargardt disease is associated with ABCA4, an ATP-binding cassette transporter, which plays a crucial part in preventing the accumulation of toxic retinoid compounds by clearing all-trans-retinal and excess 11-cis-retinal from photoreceptor cells [356].

LCA is rare hereditary retinopathy that affects 1:80,000 people worldwide. LCA is characterized by severe and early visual loss, sensory nystagmus, amaurotic pupils, and absent electrical signals on electroretinogram (ERG) as the consequence of gene mutation [362]. Among these pathogenic genes, RPE65 is the most representative one and accounts for 6% of all LCA cases [359].

Although several therapeutic strategies are being evaluated, including drug discovery and gene therapy, no pharmacological agents have been incorporated into clinical practice to prevent the progression of RP, Stargardt disease, and LCA. Most attempts have been made on slowing the progression of the disease through neuroprotection [363]. For Stargardt disease, the primary neuroprotective strategy is inhibiting the deposition of toxic metabolites *via* visual cycle modulators and inhibitors of retinol transport or bis-retinoid production, but no clinical trials have reported the safety and efficacy of related compounds. Several agents display neuroprotective properties, including neurotrophic, anti-apoptotic, anti-inflammatory, and antioxidant drugs. Though the effectiveness of these therapies is not confirmed, they are used clinically with no other treatment available. Due to the increasing knowledge of causal genes, gene therapy may be a promising approach. Several viral vector-based therapies have entered clinical trials, but non-viral delivery systems are under exploration.

Several attempts have been made to bridge the gap between the largely unmet medical needs and the low efficacy of conventional drugs. Mutations in rhodopsin lead to the misfolding and therefore cause adRP, so ATP-driven chaperone valosin-containing protein (VCP), as a molecular checkpoint for protein quality control, may be beneficial for adRP treatment, but the poor water-solubility of the VCP inhibitor remains to be solved. Sen *et al.* reported that mPEG-cholane nanoparticles remarkably

increased the water-solubility of ML240 (VCP inhibitor) by two orders of magnitude and prolonged the drug released over ten days ML240 [364]. Additionally, myriocin inhibits serine palmitoyl-CoA transferase (a rate-limiting enzyme of ceramide biosynthesis), and thus lowers retinal ceramide concentration and prevents photoreceptors from apoptosis subsequently. SLNs were manufactured for myriocin delivery, achieving prolonged treatment and effective photoreceptor rescue [365]. Moreover, proinsulin was also a potential target for RP, and PLGA nanoparticles were used as vectors [366]. Interestingly, P3HT, as a semiconductor, can serve as a light-responsive component for mediating light-evoked stimulation of retinal neurons and persistently rescuing visual functions, which achieved excellent therapeutic effect in RP rats for as long as 8 months [367]. Additionally, the efficacy of P3HT was further confirmed in fully degenerated retinas [368].

To prohibit the deposition of toxic metabolites, retinylamine, as a primary amine, was used for its capability of lowering the concentration of all-trans-retinal by sequestering it as a Schiff base and inhibiting retinoid isomerase (RPE65) as well. Puntel *et al*. reported retinylamine-loaded PLA nanoparticles, and the system showed promising therapeutic effects for both Stargardt disease and AMD [369]. 5-ASA contains a primary amines group as well, making it a potential agent for Stargardt disease. Wu *et al*. manufactured nanoglobular dendrimer 5-ASA conjugate with a hydrolyzable schiff base spacer (AGFB-ASA) that outperformed free 5-ASA as well as achieved prolonged release for treating retinal degeneration [370]. Additionally, chromophore 11-cis-retinal deficiency causes photoreceptor degeneration in LCA patients, while 9-cis-retinal is an alternative for 11-cis-retinal and thus can prevent vision loss, so a chitosan-9-cis-retinal conjugate was developed, and showed the capability of preventing the vision loss in Rpe65(-/-) animal model [371].

Gene therapy is an essential part of IRD treatment, but polymer-based gene delivery systems have not yet been well developed. CK30PEG10K and span poly-L-arginine nanoparticles were reported to be suitable vectors for rhodopsin (RP) and

RPE65 (LCA) [372, 373], and cell-penetrating peptide TAT modification could improve the therapeutic efficacy by enhancing cell permeability and improving gene delivery [373] (Fig. 11). Notably, a pH-sensitive lipid (1-aminoethyl) iminobis [N-(oleoylcysteinyl-1-amino-ethyl) propionamide] (ECO)/pDNA formulation was designed and extensively confirmed as an efficacious vector for promoting pH-sensitive endosomal escape and lowering the cytosolic release of nucleic acids in target tissues [374]. The system was further modified by including the all-trans-retinylamine modification, acting as a targeting component by binding to interphotoreceptor retinoid-binding protein and then being transferred to the RPE layer [375]. Furthermore, Sun *et al*. manufactured and optimized the (ECO)/pDNA formulation for ABCA4 delivery as follows. Firstly, an ABCA4 plasmid containing rhodopsin promoter (pRHO-ABCA4) was constructed and modified by the simian virus 40 enhancer to enhance gene expression. Secondly, it was encapsulated by self-assembled pH-sensitive ECO nanoparticles. Thirdly, sucrose was used as a stabilizer for the consistency and stability of ECO/pDNA formulation. After administration, ECO/pRHO-ABCA4 treated Abca4 (-/-) mice showed a significant reduction in A2E accumulation by 36% [374, 376].

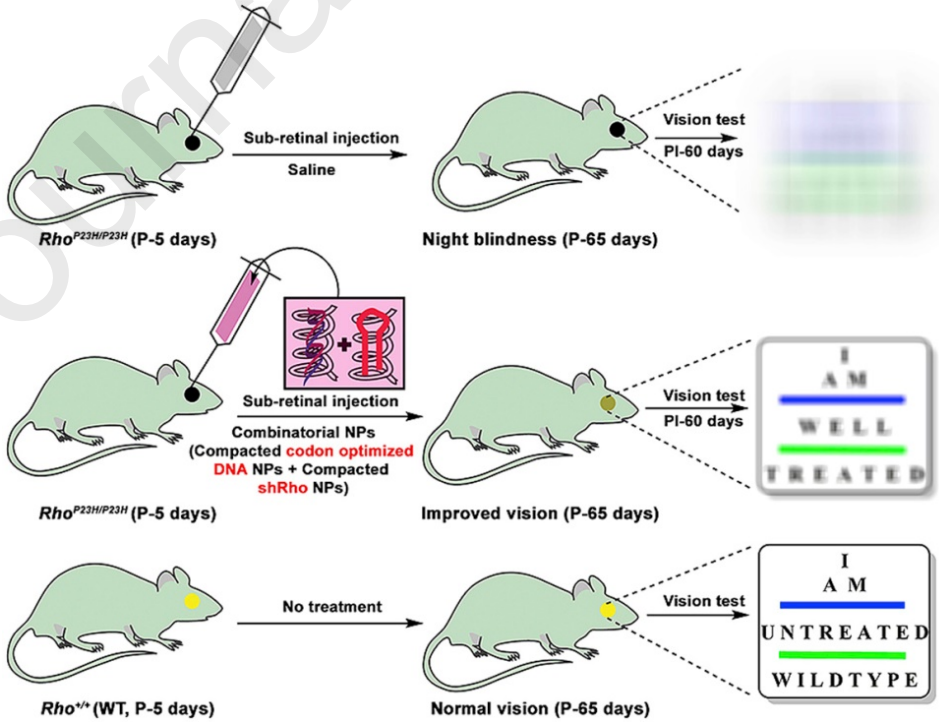

Fig. 11. The effective vision rescue properties of rhodopsin DNA compacted CK30PEG diblock copolymer with TAT modification [373].

5.11 Retinal Ganglion Cell Disease

RGC damage is generally caused by glaucoma, ischemic optic neuropathy (ION), and posterior segment trauma. ION refers to all optic neuropathy caused by ischemia and is a common acute optic neuropathy in the elderly, with an annual incidence projected at 2.3 to 10.2 cases per 100,000 persons 50 years of age or older [377]. Traumatic optic neuropathy (TON) is commonly caused by falls, road traffic accidents, and assaults, which can happen by sharp trauma (direct injury) damaging the optic nerve directly or damage from transmitted forces following a concussive blow to the head or orbit (indirect injury), and indirect TON is the most common form of TON and happens in roughly 2.3% of all head trauma patients [378]. Pharmaceutical agents mainly include neurotrophic factors, growth factors, antioxidants, and anti-inflammatory agents [379]. For glaucoma, the leading strategy is to reduce IOP, as reviewed in the “Glaucoma” section, which is certainly a very successful "neuroprotectant" in itself. However, considering the existence of normal tension glaucoma and the unmet need for optic nerve protection, complementary neuroprotective therapy has received extensive attention, and several drugs, such as neurotrophic factors and memantine, are therefore investigated [380]. For ION, corticosteroids are the primary clinical treatment and can improve visual outcomes [377]. For TON, corticosteroids, erythropoietin (EPO), and levodopa plus carbidopa [381] have been applied in clinical practice. However, the low efficacy of retinal delivery, short half-life, poor bioavailability, etc. limits their therapeutic effects, whereas well-designed nanocarriers might provide optional formulation.

Neurotrophic factors, such as glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), etc., are an integral part of RGC protection, but their short half-life remains a significant challenge. To address these problems,

cubosomes were applied to avoid the repeated dosage of BDNF [382]. Compared with liposomes, cubosomes display higher membrane surface area, the ability to solubilize molecules with different hydrophilic/hydrophobic characteristics, and the equilibrium nanostructure [223]. Apart from neurotrophic factors, brimonidine, a conventional agent for lowering intraocular pressure, was reported to have a neuroprotective effect and has been identified to be a promising agent for TON treatment, which could be carried by albumin nanoparticles and PDA nanoparticles [383, 384]. Notably, brimonidine-loaded PDA nanoparticles presented both anti-inflammatory and anti-oxidative effects, which may explain the underlying mechanism of increased RGC survival. Superoxide dismutase (SOD) is a widely explored antioxidant enzyme, but the membrane-impermeable property constrains its clinical use of it in the posterior segment, and a peculiar boronic acid-rich dendrimer was prepared for enhanced retinal delivery of SOD [385]. Besides, the boronic acid-rich dendrimer displayed an efficacious and robust protein delivery approach, where the phenylboronic acid (PBA), as an electron-deficient group, can bind with the cationic groups of proteins through the combination of nitrogen-boronate complexation and cation-π and ionic interactions, while the cationic dendrimer can interact with the anionic groups of proteins, hence the combined efforts explaining the extraordinary delivery efficacy [386].

Variable novel pharmaceutical agents have been investigated for RGC protection. The rapamycin signaling pathway is confirmed to be associated with RGC protection. Eriksen *et al.* reported liposomes with multiple mammalian targets of the rapamycin (mTOR) pathway stimulating biologics loaded, including ciliary neurotrophic factor, insulin-like growth factor 1, a lipopeptide N-fragment osteopontin mimic, and lipopeptide phosphatase tension homologue inhibitors for either the ATP domain or the c-terminal tail, presenting RGC rescue and retina electrophysiological dysfunction inhibition after intravitreal injection [387]. Sigma-1 receptor (S1R) has neuroprotective properties as well, and dehydroepiandrosterone is an FDA-approved endogenous S1R agonist. Amphiphilic core-shell micelle nanoparticles were designed for the delivery of

dehydroepiandrosterone with excellent stability, versatile bioconjugation, and prolonged drug release, which composed of single/individual multi-arm star block copolymer PAMAM-PVL-PEG with the hydrophobic PAMAM-PVL core and the hydrophilic PEG shell [388]. Additionally, Cx43 mimetic peptide ameliorates vessel leakage and inflammation by inhibiting uncontrolled hemichannel opening. Two nanocarriers, PLGA nanoparticles and HA-coated albumin nanoparticles, were investigated for Cx43 delivery [389, 390], and human serum albumin seemed to be preferable with no inflammatory response detected.

Gene therapy contributes to RGC protection as well. Caspase-3 siRNA loaded polybutylcyanoacrylate nanoparticles [391] and miRNA-124 loaded PEG-PSA nanoparticles [392] were reported to prevent RGC apoptosis.

5.12 Eye Tumor

There could be a variety of tumors that form in the eye, which usually metastases from other parts of the body. Here, we will only discuss studies related to two types of common intraocular primary tumors, retinoblastoma (RB) and uveal melanoma (UM) [393].

RB is an aggressive ophthalmic tumor that may occur in infants and children. It has a worldwide prevalence of 1/15,000 to 1/20,000 live births. The possible prognosis for RB includes loss of vision, secondary monocular tumors, and even death [394]. Although current chemotherapy has shown some success in RB management, there still exists notable shortcomings, including inadequate pharmacokinetic parameters, multidrug resistance, low therapeutic efficiency, nonspecific targeting, and the need for adjuvant therapy, etc. [395]

Various nanocarriers were used to achieve controlled release of anti-cancer drugs. Ahmed *et al*. prepared carboplatin-loaded apotransferrin (Apo-nano-carbo) and lactoferrin (Lacto-nano-carbo) nanoparticles by sol-oil technique [396]. Possibly releasing drugs through receptor-mediated endocytosis, the nanoparticles showed

significant intracellular uptake, sustained retention, and high anti-proliferative activity against RB cells. Hardy *et al*. co-delivered melphalan and miR-181a by switchable LNCs, which presented excellent endosomal escape ability [397]. These two agents could complementarily reduce the RB cell viability *in vitro* and RB cell counts *in vivo*. Dinarvand *et al*. loaded thiolated chitosan nanoparticles with topotecan (TPH-TCs-NPs) and observed a remarkable difference between the tumor control group and TPH-TCs-NPs treated group in a xenograft rat model [398]. Their investigations revealed enhanced potency and correlation of TPH-TCs-NPs compared to free TPH in RB cells and tumors, both *in vitro* and *in vivo*. Vemuganti *et al*. mounted lactoferrin nanoparticles (Lf-Nps) with carboplatin and etoposide and applied them onto CD133-depleted (cancer stem cells, CSC) and CD133-enriched (non-CSC) and RB Y79 cell populations [399]. In both *in vitro* cellular models, these Lf-Nps encapsulating anti-cancer drugs exhibited superior absorbability, retention, and cytotoxicity relative to the standard drug alone.

Some studies have further integrated other therapy effects in addition to the drug effect for better treatment of RB. Rosilio *et al*. encapsulated an anticancer drug, beta-lapachone, and a photosensitizer, m-THPC, into a poly(D,L)-lactide (PDLLA) nanoparticle which was coated with a phospholipid bilayer [400]. It was observed that the PDLLA nanoparticles were tightly bound to the surface of RB cells and rapidly internalized. This dual chemotherapy/phototherapy treatment is able to provide the same cytotoxicity at a lower dose than monotherapy of both compounds. Rengan *et al*. developed multifunctional PLGA and PCL nanoparticles (PNPs) carrying a CDK 4/6 inhibitor, Palbociclib, and a near-infrared dye, IR820, as chemo/photothermal agents (PCB/IR PNPs) [401]. Upon exposure to NIR light, the PCB/IR PNPs displayed a significant cytotoxic effect (86.5 ± 2.3%) in RB Y79 cell lines in comparison to the control groups. It is believed that the synergistic effect of PCB/IR PNPs induced by NIR light leads to DNA damage and thereafter to apoptosis. Zhou *et al*. fabricated multifunctional liposomes packing DOX, indocyanine green (ICG), and liquid

perfluoropentane [402]. The photoacoustic properties of ICG and the phase transition ability of perfluoropentane endow liposomes with promising photoacoustic/ultrasound imaging capabilities. Furthermore, the laser-activated photothermal conversion of the liposomes could destruct tumor cells, while simultaneously initiating perfluoropentane phase transformation to release DOX, resulting in synergistic antitumor effects.

UM is the most prevalent primary intraocular malignancy. In approximately 50% of UM cases, the tumor metastasizes, ultimately leading to the death of the patient [403]. Despite advances in the diagnosis and local treatment of UM over the past decades, there is still a demand for effective therapies.

The phthalocyanine photosensitizer, IR 700, was conjugated to the drug carrier, a recombinant papillomavirus-like particle, to construct AU-011 for treating primary UM [404]. AU-011 binds to UM cells *via* the modification of heparan sulfate on the surface of the carcinomas. Upon a 589 nm laser activation, AU-011 causes acute cellular necrosis, membrane destruction, and immunological cell death through the release of damage-associated molecular patterns. In 2020, a phase 2 trial was announced to evaluate the safety and efficacy of AU-011 *via* suprachoroidal administration in subjects with primary indeterminate lesions and small choroidal melanoma. No relevant results have been published to date. Shen *et al*. prepared curcumin-loaded PEG-PLGA nanoparticles that are further incorporated in collagen II and HA hydrogel (CO-HA Gel) matrix [405]. The nanoparticle/hydrogel composite could maintain an effective release of curcumin for up to four weeks and showed efficient proliferation inhibition of human UM cells. Carbone *et al*. encapsulated Sorafenib, a tyrosine protein kinases inhibitor that was proven to suppress tumor growth and metastases, with two solid lipids (Softisan or Suppocire) at different concentrations [406]. They achieved a sustained and prolonged drug release, demonstrating the potential of this approach to facilitate topical administration of Sorafenib for UM treatment, as opposed to systemic dosing.

Another approach is to inhibit the proliferation and differentiation of cancer cells at the genetic level. In different cancers, including UM, certain microRNA signatures

would appear different from healthy cells. Therefore, restoring regular levels of microRNAs can resume the normal behavior of cells. Shi *et al*. constructed recombinant DNA plasmids (early growth response-1 tumor necrosis factor-α and pEgr1 thymidine kinase, pEgr1-TNFα-TK) according to the Egr1 promoter sequence. Dendrimer nanoparticles were employed to deliver the genes into the human choroidal melanoma OCM-1 cell line [407]. Their results demonstrated that the recombinant plasmid pEgr-1-TNFα-TK could effectively inhibit the proliferation of the OCM-1 cell line and cause apoptosis as well as necrosis.

6. Potential Ocular PNCs and LNCs in Clinical Trials and on the Market

According to the latest reports on MarketResearch, the market of global ophthalmic pharmaceutical drugs is projected at 40.5 billion dollars in 2020 and anticipated to reach 65.6 billion dollars by 2030 [408, 409], where polymer- and lipid-based formulation plays a vital part and is supposed to accelerate the future growth of the market. Recent decades have witnessed several promising ocular nanoformulations reaching the market, and extensive nanoformulations for various eye disorders are now in clinical trials (Phases 2 and 3), as listed in Table 2 and Table 3, respectively.

The most abundant ophthalmic nanoformulations and clinical trials are in the field of DED and ocular fundus neovascularization-related diseases. As previously discussed in 5.3, CsA is popular in DED but with various limitations and challenges. As the first micellar formulation and the highest concentration of CsA approved by the FDA in DED, Cequa®(formerly Seciera™), has been recently put on the market, showing good biocompatibility and high therapeutic efficacy and offering advantages of improved stability, less manufacturing deadlock, therefore greater cost-effectiveness compared to most other colloidal CsA formulations [410]. Xelpros™, developed by Lipixelle® technology, is announced as the first and only preservative benzalkonium chloride-free micellar formulation of latanoprost, which guarantees its excellent biosafety. For CNV,

Visudyne® is a liposomal verteporfin formulation was approved by the FDA in 1999 for PDT. Macugen, a PEG anti-VEGF aptamer, was also developed for combating CNV.

Table 2 Approved ophthalmic PNCs and LNCs products for ocular diseases.

Product	Drug	Nanoformulation	Indication	Year to the market	Reference
Kenalog®	0.1% Triamcinolone acetonide	Polymeric nanoparticles	DED	Prior to 1982	[411-413]
Restasis®	0.05% Cyclosporine	Nanoemulsion	DED	2002	[414]
Triesence®	40mg mL^{-1} Triamcinolone acetonide	Polymeric nanoparticles	DED	2007	[411-413]
Ikervis®	0.1% Cyclosporine	Nanoemulsion	DED	2015	[415]
Cequa®	0.09% Cyclosporine	Micelles	DED	2018	[410, 416]
Eysuvis®	0.25% Loteprednol etabonate	Polymeric nanoparticles	DED	2020	[417]
Lacrisek®	Vitamin E and Vitamin A-palmitate	Liposomes	DED	NA	[413]
Cyclokat®	0.1% Cyclosporine	Nanoemulsion	DED	NA	[413, 418]
Cyporin-N®	0.05% Cyclosporine	Nanoemulsion	DED	NA	[419]
Lacrinmune®	Cyclosporine	Nanoemulsion	DED	NA	[419]
AzaSite®	1% Azithromycin	Micelles	DED; keratitis; eye inflammation	2007	[420]
Ozodrop®	0.5% Ozonized oil	Liposomes	Post cataract surgery inflammation	NA	[421]
Durezol®	0.05% Difluprednate	Nanoemulsion	Eye inflammation	2008	[422]
Inveltys™	1% Loteprednol etabonate	Polymeric nanoparticles	Eye inflammation	2018	[423]
Xelpros™	0.005% Latanoprost	Micelles	Glaucoma	2018	[424]
AmBisome®	50 mg vial Amphotericin B	Liposomes	Endophthalmitis	1997	[425]
Abelcet®	5 mg mL^{-1} Amphotericin B	Liposomes	Endophthalmitis	1995	[425]
Amphotec®	50 and 100 mg vial	Liposomes	Endophthalmitis	1996	[425]
Trivaris™	80 mg mL^{-1} Triamcinolone acetonide	Polymeric nanoparticles	Uveitis	2008	[413]
Visudyne®	15mg Verteporfin	Liposomes	CNV	1999	[426]
Macugen®	0.3mg 90μL^{-1} Pegaptanib	Aptamer-nanoparticles	CNV	2004	[427]

Table 3 Under clinical trial PNCs and LNCs for ocular diseases.

Product	Drug	Nanoformulation	Indication	Clinical Trials	Phase	Reference
TJO-087	0.05% Cyclosporine	Nanoemulsion	DED	NCT05245604	Phase 3	[428]
Brimonidine tartrate nanoemulsion eye drop	0.2% Brimonidine tartrate	Nanoemulsion	DED	NCT03785340	Phase 3	[429]
ISV-303	Bromfenac	Micelles	Post cataract surgery inflammation	NCT01576952	Phase 3	[430]
ISV-305	dexamethasone	Micelles	Post cataract surgery inflammation	NCT03192137	Phase 3	[431]
Urea-loaded nanoparticles eye drops	Urea	Polymeric nanoparticles	Cataract	NCT03001466	Phase 2	[432]
POLAT-001	Latanoprost	Liposomes	Glaucoma	NCT02466399	Phase 2	[433]
Catioprost	0.005% Latanoprost	Nanoemulsion	Glaucoma	NCT01254370	Phase 2	[434]
KSI-301	VEGF antibody	Antibody biopolymer conjugate	wet AMD	NCT04964089	Phase 3	[435]
			DME	NCT04611152	Phase 3	[436]
				NCT04603937	Phase 3	[437]
			NPDR	NCT05066230	Phase 3	[438]
			RVO	NCT04592419	Phase 3	[439]
GB-102	Sunitinib	Polymeric nanoparticles	wet AMD	NCT03953079	Phase 2	[440]
			DME; Retinal vein occlusion	NCT04085341	Phase 2	[441]
D-4517.2	TKI	Dendrimers	wet AMD; DME	NCT05387837	Phase 2	[442]
OCS-01	1.5% mg mL^{-1} Dexamethasone	Polymeric nanoparticles	Inflammation and pain of the post cataract surgery	NCT05147233	Phase 3	[443]
			DME	NCT05066997	Phase 2	[444]
Triamcinolone acetonide liposomes	0.2% Triamcinolone acetonide	Liposomes	wet AMD	NA	Phase 2	[445, 446]
TLC399 (ProDex)	Dexamethasone	Liposomes	Retinal vein occlusion	NCT03093701	Phase 2	[447]
				NCT02006147	Phase 2	[448]
Marqibo	Vincristine sulfate	Liposomes	RB	NCT00335738	Phase 3	[449]
				NCT00072384	Phase 3	[450]
			UM	NCT00506142	Phase 2	[451]
Taxol	Paclitaxel	Albumin-stabilized nanoparticles	UM	NCT01200342	Phase 2	[452]

6. Conclusion and Outlook

Ocular diseases pose a huge threat to vision and adversely affect the life quality of a big population worldwide. However, the unique anatomy of the eye poses a significant challenge to effective drug delivery since ocular barriers dramatically reduce drug accumulation and bioavailability. Conventional therapy often requires repeated dosages with low efficacy, which cannot fully meet the patients' expectations. Nanocarriers, especially PNCs and LNCs offer a promising strategy for effective ocular drug delivery, possessing a variety of merits in terms of enhanced permeability, increased retention, improved solubility, reduced toxicity, prolonged release, and targeted delivery, and ultimately bringing higher bioavailability of the drug and offering a novel and appealing paradigm for patients. This review summarizes the recent and ongoing efforts to fabricate PNCs and LNCs for ocular drug delivery, providing a comprehensive overview of the promising application of nanocarriers for ocular diseases.

Advances in the theory and technology of material synthesis and nanocarrier preparation allow the precise engineering of nanocarriers to address the unmet need for treating ocular diseases. Various materials with different physiochemical characteristics have been designed and synthesized to construct PNCs and LNCs. The use of biodegradable materials has reduced the toxicity of these nanocarriers and enabled specific adjustments to the release profile, while the use of natural materials has enhanced their biocompatibility, biodegradation, biosafety, permeation, surface retention, and even intrinsic targeting properties [453]. Efforts have also been made to modify the nanostructure of PNCs and LNCs to improve their ocular delivery efficacy by designing their internal and external morphology for better stability, adjustable release rate, and increased surface area. Surface modification further enables precise delivery *via* specific interaction with tissue, cell, and organelle. Moreover, by adding biologically responsive components to the nanocarriers, PNCs and LNCs, can be modified to be responsive to light, magnetic fields, ultrasound, thermal, pH variations, redox potential, enzymatic activation, and even dual or multi-stimuli responsiveness,

achieving more precise therapies with controlled site-specific drug release and better therapeutic outcomes [454].

PNCs and LNCs in ophthalmic formulations showed great promise due to the advancement of nanotechnology and the huge market potential. Despite numerous successful laboratory studies, there still exist challenges to the clinical application of these nanocarriers, with some attempts, such as KSI-301, failing to show encouraging results. One of the key challenges is the heterogeneity of these nanocarriers, which can result in therapeutic instability. Therefore, it is crucial to explore robust manufacturing processes and standardize analytical tools and methodologies for better clinical translation [455]. Additionally, the toxicity and immune response are also significant concerns that need to be addressed. Overall, the use of PNCs and LNCs in ophthalmic formulations holds significant promise, but more work needs to be done to overcome the challenges associated with their clinical application. With continued research and development, these nanocarriers have huge potential to revolutionize the treatment of ocular diseases.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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