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Emerging drug delivery strategies for glaucoma therapy: focus on nanoparticles and stimuli-responsive systems

Sourabh Kundu, Gitika Kumari and Dadi A. Srinivasarao *

Glaucoma is a progressive and chronic eye complication characterized by elevated intraocular pressure (IOP) and consequential optic nerve damage, ultimately leading to blindness. Current therapeutic interventions mainly focus on frequent topical administration of IOP-lowering agents. However, ocular tissues cause prompt clearance of the administered drugs, thereby leading to low bioavailability and reduced patient compliance. This necessitates the development of advanced delivery systems that not only enhance the ocular residence of therapeutic agents but also govern drug release at the site of interest in a spatiotemporally controlled manner. The emergence of nanomedicine and stimuli-responsive delivery systems partially helped to achieve these objectives. These systems show improved permeability, longer ocular retention, or stimuli-responsive drug release (against specific triggers like temperature, pH, ion or enzymes), thereby offering on-demand drug release at the site of interest. This review discusses the anatomy and physiology of ocular tissues, emphasizing their barrier properties for drug delivery in glaucoma therapy. The challenges associated with conventional drug delivery approaches, routes of drug administration, and the need for the development of advanced drug delivery systems have also been emphasized. Furthermore, recent advances in the development of polymeric ophthalmic drug delivery systems and formulation strategies are mentioned with a special emphasis on nanoparticles, *in situ* gels, and stimuli-responsive systems. Finally, we present our perspectives on scale-up issues, regulatory hurdles, and clinical translation of advanced drug delivery systems.

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1. Introduction

Glaucoma is a progressive and chronic neurodegenerative eye disease characterized by elevated intraocular pressure (IOP) and consequential optic nerve damage, ultimately leading to irreversible vision loss. According to the World Health Organization (WHO) report, more than 2.2 billion people have vision impairment; of these ~50% of cases could have been avoided or are yet to be addressed. The prominent causes of vision impairment include refractive errors, cataract, diabetic retinopathy, age-related macular degeneration and glaucoma.[1] These chronic eye diseases demand frequent administration of therapeutic agents that may diffuse across the ocular tissues to elicit therapeutic effects at the site of interest. However, the complex structures (anatomical) and barriers of the eye cause hindrance to drug diffusion and/or permeation, limiting the bioavailability and aggravating the pathological condition. These ocular tissues (that disallow the permeation of therapeutic agents) can be broadly classified into the anterior (or anterior segment) and the posterior (or posterior segment) eye tissues.[2] Current therapeutic strategies often rely on the frequent administration of eye drops, which are associated with limited drug bioavailability, rapid clearance, and poor patient adherence. These challenges emphasize the need for efficient drug delivery systems (DDS) for glaucoma therapy.[3] In recent years, advanced DDS have shown the potential to overcome the aforementioned limitations. Among these, nanoparticulate systems and stimuli-responsive DDS have garnered special attention as these systems offer controlled, targeted, and/or sustained release of entrapped drugs. Such systems can potentially improve bioavailability and therapeutic efficacy and minimize adverse effects while showing biocompatibility, biodegradability, and versatility for chemical modification. Furthermore, stimuli-responsive carrier systems can specifically respond to changes such as temperature, pH, enzymatic activity, light, or magnetic field *etc.* to release entrapped drugs.[4] Therefore, these carriers can be engineered to enable the release of anti-glaucoma drugs selectively at the local microenvironment of the eye for more efficient and patient-friendly treatment modalities. Such drug delivery approaches not only improve patient compliance but also minimize systemic exposure and potential side effects, thereby enhan-

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Balanagar, Hyderabad, Telangana, 500037, India.
E-mail: srinivasarao.ananda@niperhyd.ac.in

cing the overall therapeutic outcome. This review will delve into the recent advancements of nanoparticulate delivery systems and stimuli-responsive DDS for glaucoma therapy, along with fundamental aspects of ophthalmic drug delivery for managing glaucoma.

2. Anatomy of the eye and ocular diseases

The eye globe has complex and intricate anatomy and physiology. Tissues such as the cornea, conjunctiva, sclera, ciliary body, iris, and lens comprise the anterior segment, whereas the optic nerve, vitreous humor, retina, sclera, and choroid constitute the posterior segment. These unique and intrinsic anatomical barriers have evolved to protect the eye while performing coordinated physiological processes for visual perception. Therefore, these anatomical structures enable the eye to function as a precise optical system by translating the light into visual images.[5] These ocular tissues are briefly described below and are depicted in Fig. 1.

2.1 Ocular tissues

2.1.1 Cornea. The cornea is a transparent and avascular layered tissue composed of the endothelium, Descemet's membrane, stroma, Bowman's layer, and epithelium. The cornea covers the iris, pupil, and anterior chamber and functions as the primary refractive surface. Corneal clarity is crucial for vision, and opacity can impair sight.[2]

2.1.2 Sclera. The sclera is a tough outer layer that provides structural support and protection. The scleral thickness and durability help to maintain the eye shape.[2]

2.1.3 Iris. The iris is the colored part located between the cornea and lens. Iris muscles help to adjust the pupil size, which in turn controls the amount of light entering the eye.[2]

2.1.4 Pupil. The pupil is the aperture at the centre of the iris that enables entry of light. The pupil size changes in response to the intensity of light (dilating in dim light and constricting in bright light), thereby controlling the amount of light reaching the retina.[5]

2.1.5 Lens. The lens is a flexible and transparent structure that helps in focusing the light onto the retina. The lens's elasticity decreases with age, leading to presbyopia, wherein focusing on close objects becomes difficult.[5]

2.1.6 Vitreous humor. The vitreous humor is a gel-like material that fills the space between the retina and lens.[5]

2.1.7 Retina. This light-sensitive layer captures light and converts it into electrical signals. The optic nerve transmits these signals to the brain. The retina contains retinal pigmented epithelial cells (that form the outer blood–retinal barrier), amacrine cells, bipolar cells, horizontal cells, photoreceptor cells (rods and cones), Müller cells, and ganglionic cells. The retina's central portion is known as the macula and is responsible for sharp and detailed central vision.[5]

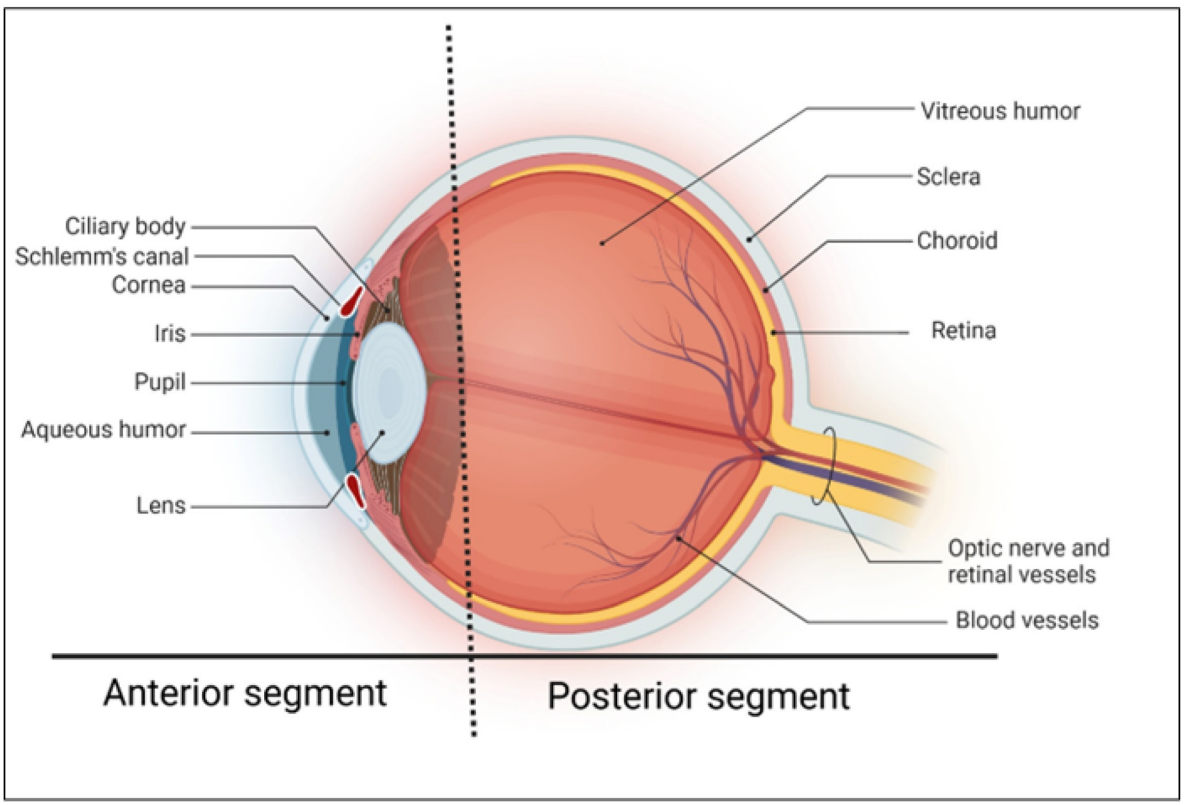

Fig. 1 Anatomy of the human eye showing anterior and posterior segments.

2.1.8 Optic nerve. The optic nerve is composed of retinal ganglion cell (RGC) axons that transmit visual information to the brain.[2]

2.2 Diseases affecting the eye

These complex and sensitive tissues are susceptible to various diseases that can affect the anatomical and physiological processes of the eye, ultimately leading to vision impairment. The most common eye diseases that affect vision are noted below.

2.2.1 Cataract. Cataracts are characterized by opacification of the lens that causes blurred vision, eventually leading to vision loss. This pathological condition is commonly associated with aging. Furthermore, cataract can be progressed during trauma, radiation, or diabetes. Current therapeutic interventions for cataract include surgical methods wherein the clouded lens is replaced with a clear artificial lens. The emerging therapeutic interventions include drug-based therapies wherein therapeutic agents are administered to reverse or halt the opacification of the lens.[6]

2.2.2 Age-related macular degeneration (AMD). AMD affects the macula of the retina. AMD can be classified into two forms: dry AMD and wet AMD (characterized by abnormal blood vessel growth) under the retina.[7] AMD can be treated *via* administration of vitamin-based supplements or anti-VEGF injections.[8]

2.2.3 Diabetic retinopathy. Diabetic retinopathy is characterized by pathological neovascularization in the retina. During diabetes, hyperglycemia causes loss of blood vessel integrity, leading to edema (macular edema) during the early stage and neovascularization during the late stage. The most common symptoms of diabetic retinopathy include blurred vision and dark areas in the visual field. Current therapeutic interventions include diabetes management by controlling blood sugar levels, LASER photocoagulation, and intravitreal administration of anti-VEGF drugs.[9]

2.2.4 Dry eye syndrome. Dry eye syndrome is observed when the tears produced by the eyes are not sufficient or evaporate too quickly. This condition can cause discomfort, a gritty sensation, redness, or blurred vision. It is often exacerbated by prolonged screen use, environmental factors, or underlying conditions like Sjögren's syndrome.[10] The available therapeutic interventions include lifestyle changes, topical administration of artificial tears, and/or medications or procedures to increase tear production or decrease tear drainage.[11]

2.2.5 Retinal detachment. Retinal detachment occurs when the retina separates from its underlying structures, which can lead to permanent vision loss. Symptoms include sudden flashes of light, floaters, and a shadow or curtain over part of the visual field. Treatment typically involves surgery to reattach the retina.[12]

2.2.6 Glaucoma. Glaucoma is a group of eye diseases that cause progressive damage to the optic nerve, often due to elevated IOP. The optic nerve damage impairs the transmission of visual impulses to the brain, ultimately leading to vision loss. Glaucoma can be classified into two types: (i) open-angle glaucoma (OAG, also known as wide-angle glaucoma), the most common form, and (ii) angle-closure glaucoma (ACG, also known as narrow-angle glaucoma), which is less common but more severe. During early stages, glaucoma often presents no symptoms; as the disease progresses, peripheral vision is lost first, followed by central vision.[13,14]

3. Glaucoma – pathophysiology and therapeutic interventions

3.1 Pathophysiology

Glaucoma is a group of eye conditions characterized by increased IOP and consequential damage to the optic nerve. Glaucoma affects approximately 80 million people globally, and this figure is projected to increase to 111 million by 2040. Glaucoma contributes ~15% of blindness cases worldwide and is the leading cause of irreversible blindness in the United States of America, affecting approximately 2.7 million Americans aged over 40 years.[15] Advanced cataracts, hyperthyroidism, myopia, diabetes, optic tumors, inflammation, or elevated blood pressure may cause abnormal IOP. Prolonged use of corticosteroids can also lead to glaucoma.[16] As discussed in the previous section, the eye consists of highly sensitive and coordinated structures that maintain its shape and physiological functions. In healthy individuals, the ciliary body produces aqueous humor, which flows *via* the pupil and drains through the Schlemm's canal (SC) and trabecular meshwork (TM). Any obstruction in the outflow can result in its accumulation, ultimately leading to elevated IOP, as seen in ACG.[17] In this condition, the peripheral iris comes in contact with the TM intermittently (appositional closure) or permanently (synechial closure), resulting in the angle closure. Meanwhile, in OAG, an increased resistance for aqueous humor drainage can be seen while the drainage angle between the cornea and iris remains open. As a result, the pressure in the eye gradually increases, resulting in mechanical stress on the optic nerve head, leading to optic nerve damage. Primary open-angle glaucoma (POAG) is the standard form characterized by a gradual and insidious rise in IOP with no apparent secondary cause. In contrast, secondary glaucoma results from other conditions or factors such as trauma, inflammation, or medication-induced changes, which lead to elevated IOP.[18] Anatomical changes that occur during glaucoma progression have been depicted in Fig. 2.

In a nutshell, the balance between the production and drainage of aqueous humor gets disturbed (*i.e.*, excessive production of aqueous humor or inadequate drainage), resulting in the elevation of IOP. Such elevated IOP compresses the axons of the RGCs at the optic nerve head and reduces blood flow to the optic nerve head, leading to ischemia. The resultant ischemia can cause apoptosis of RGCs while causing elevated production of neurotoxic substances, such as glutamate, which in turn worsens the condition. Glaucoma initially affects peripheral vision and can progress to tunnel vision and blindness. Therapeutic interventions for glaucoma therapy include the administration of IOP-lowering agents, laser therapy, or surgical methods, which are described below.[19]

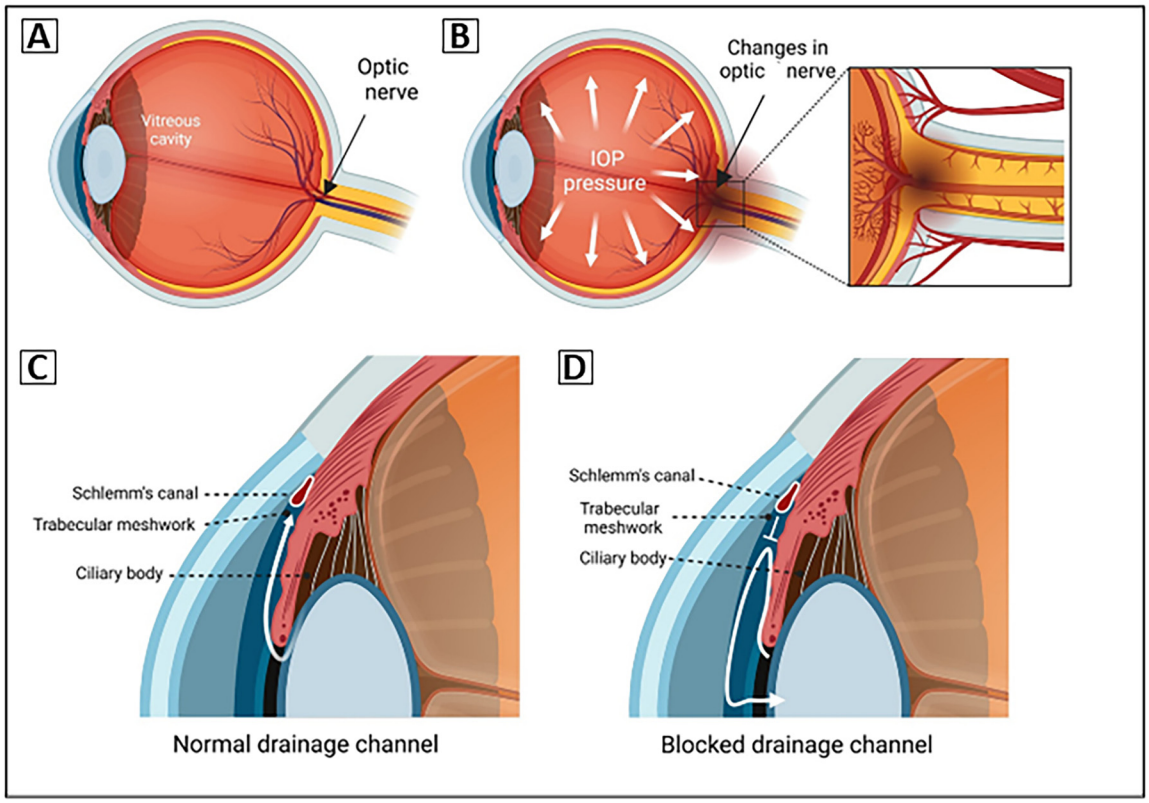

Fig. 2 Anatomical changes during glaucoma progression. A. Normal eye; B. elevated IOP leading to optic nerve damage in glaucoma; C. normal drainage channel of aqueous humor; D. blocked drainage channel of aqueous humor.

3.2 Therapeutic interventions for glaucoma

Medicated eye drops are the preferred treatment. LASER therapies and surgical methods are explored if the condition is not treatable using eye drops. This section briefly elaborates on different therapeutic interventions for glaucoma.

3.2.1 Medicated eye drops. Topical administration of medicaments (such as prostaglandins, rho kinase inhibitors, *etc.*) can lower IOP by promoting fluid drainage from the eye, whereas other medications (beta blockers, alpha-adrenergic agonists, *etc.*) decrease the amount of fluid produced in the eye.[20,21] An exhaustive list of glaucoma medications is presented in Table 1.

3.2.2 Laser therapy

3.2.2.1 Trabeculoplasty. This technique is primarily used for OAG to improve aqueous humor drainage through the TM. Selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT) are commonly used techniques.[30]

Table 1 Drugs used for glaucoma therapy and their mechanism of action

Sl. no.	Category/classification of the drug	Therapeutic agent	Mechanism of action	Ref.
1.	Alpha-adrenergic agonists	Apraclonidine, brimonidine	These drugs cause vasoconstriction in the ciliary body and decrease aqueous humor production.	22 and 23
2.	Beta-blockers	Betaxolol, levobunolol, timolol	These drugs reduce aqueous humor production.	24
3.	Carbonic anhydrase (CA) inhibitors	Acetazolamide, dorzolamide, brinzolamide	CA inhibitors diminish aqueous humor production, thereby lowering IOP.	25
4.	Cholinergic agonists (para sympathomimetics)	Carbachol, pilocarpine	These drugs induce the contraction of the ciliary muscle (smooth muscle), thereby causing pupil constriction. Consequently, TM and SC get widened, thereby causing increased outflow of aqueous humor.	26 and 27
5.	Prostaglandin analogues	Latanoprost, travoprost and bimatoprost.	These drugs promote uveoscleral outflow by acting on prostaglandin receptors.	13 and 28
6	Rho kinase inhibitors	Netarsudil	These newer drugs enhance aqueous humor outflow across the TM.	29

3.2.2.2 Laser peripheral iridotomy. This procedure creates a small hole in the iris to improve aqueous humor flow in ACG, thereby preventing a sudden increase in IOP.[30]

3.2.3 Surgical interventions

3.2.3.1 Trabeculectomy. This is a standard surgical procedure wherein a small part of the TM is eliminated to generate a fresh drainage pathway that helps to lower IOP.[31]

3.2.3.2 Glaucoma drainage devices. These devices (aqueous shunts or tubes) help in the diversion of aqueous humor to an external reservoir to reduce IOP.[31]

3.2.3.3 Minimally invasive glaucoma surgery (MIGS). This procedure involves inserting tiny implants called stents into the TM to reduce IOP.[32] Various types of stents used for MIGS include:

iStent (Glaukos) (generation 1): 1 mm stent made of heparin-coated titanium with a central lumen of 120 μm.[33]

iStent inject (Glaukos) (generation 2): 360 μm stent made of heparin-coated titanium with a central lumen of 80 μm.[34]

CyPass micro-stent: 6.35 mm stent with 76 μm fenestration along its length with a 300 μm lumen.[35]

Suprachoroidal shunt: this structure consists of two rectangular fused leaflets with a proximal (round) end and a distal end. This architecture allows the device to be anchored in the suprachoroid space.[35]

Hydrus micro-stent (Ivantis): 8 mm stent composed of nititol.[36]

Xen gel stent: a flexible hydrophilic tube with a 45 μm lumen. This device is composed of porcine gelatin (cross-linked with glutaraldehyde).[37]

4. Need for the development of novel drug delivery interventions and possible ways to improve drug delivery in glaucoma therapy

Among the available therapeutic interventions, drug-based therapies using IOP-lowering agents are the preferred choice for glaucoma due to their ease of administration and lower cost of therapy. The drugs can be delivered *via* different routes, such as topical, systemic, intra-vitreal, or periocular injections. Among these routes, topical administration is the most preferred choice due to its non-invasiveness and amenability for self-administration. However, a significant drawback of the topical route is its low bioavailability (*i.e.*, less than 5% of the instilled dose is available at the site of interest) due to the presence of ocular barriers.[2] The following section mentions various barriers to ocular drug delivery.

4.1 Ocular barriers for drug delivery

Ocular barriers can be broadly classified into anterior and posterior barriers. The anterior ocular barriers such as tear film, corneal epithelium, conjunctiva, sclera, retinal pigmented epithelium, choroidal vasculature, and the blood–aqueous humor barrier disallow or readily clear the administered drugs, thereby resulting in lower bioavailability. In the context of glaucoma treatment, the anterior ocular barriers present significant challenges for effective drug delivery. Furthermore, posterior barriers also play an essential role during advanced stages of glaucoma, when therapeutic interventions are targeted towards posterior eye tissues such as the optic nerve head or retina. These barriers include vitreous humor, inner limiting membrane (ILM), and blood–retinal barrier (BRB).[38] Understanding these barriers helps formulation scientists develop novel drug delivery strategies that can improve drug delivery to the target site. These ocular barriers are briefly described in the following section.

4.1.1. Tear film. Tear film covers the surface of the eye and is the first and foremost barrier encountered after topical administration of medicaments. Tear film consists of three layers: a mucin layer, an aqueous layer, and a lipid layer. This barrier dilutes and washes away the topically administered drugs, thereby reducing the contact time with the cornea. Reflex tearing, induced by eye drop instillation, further decreases drug concentration by increasing tear flow, leading to the loss of a substantial portion of the administered drug (>90% of the administered dose).[39]

4.1.2. Corneal epithelium. The corneal epithelium is the most critical barrier for the penetration of drugs. This is a multi-layered structure with tight junctions between the cells, which cause hindrance to the passage of hydrophilic and large-sized molecules. Since the corneal epithelium is lipophilic, this may favor the absorption of small-sized lipophilic molecules. These characteristics of corneal epithelium limit the entry of hydrophilic drugs, which are often more effective for glaucoma treatment.[40]

4.1.3. Conjunctiva and sclera. Conjunctival and scleral tissues cover the anterior part of the eye and act as substantial barriers to drug permeation. Since the conjunctiva has a large surface area and rich blood supply, systemic absorption of drugs takes place, which can lead to lower bioavailability of topically administered drugs in the anterior eye tissues. However, the sclera may not be a substantial barrier for hydrophilic drugs compared with the cornea. However, the sclera can limit the penetration of larger molecules.[41]

4.1.4. Blood–aqueous barrier (BAB). This barrier regulates the entry of constituents from the blood into the aqueous humor. This barrier is composed of tight junctions of the endothelial cells of the iris blood vessels and the non-pigmented epithelium of the ciliary body. The BAB restricts the passage of large, hydrophilic molecules and proteins, thereby preventing the absorption of drugs from the systemic circulation into the aqueous humor.[42] However, the absorption of topically administered drugs may not be affected by this barrier.

4.1.5. Vitreous humor. The vitreous fills the space between the retina and lens. This acts as a physical barrier for the diffusion of the majority of drugs, especially for larger molecules. On the other hand, the slow turnover of the vitreous facilitates the residence of intravitreally administered drugs in the vitreous humor, thereby prolonging therapeutic action.

However, a fraction of the therapeutic agents reaches the retina or optic nerve head due to its slow turnover rate.[43]

4.1.6. Inner limiting membrane (ILM). The ILM constitutes the innermost layer of the retina, acting as a selective barrier that limits the penetration of substances from the vitreous into the retina. The ILM acts as a barrier for more prominent, hydrophilic drugs. In recent times, DDS have been specifically designed to penetrate or bypass the ILM, and as a consequence, bioavailability in the posterior segment can be improved.[44]

4.1.7. Blood–retinal barrier (BRB). The BRB is analogous to the blood–brain barrier, consisting of tight junctions of endothelial cells (inner BRB) and the retinal pigment epithelium (outer BRB). The BRB restricts the entry of drugs from the bloodstream into the retina and optic nerve head, which makes systemic drug delivery less effective. The literature reveals that smaller lipophilic molecules can cross the BRB, while larger or hydrophilic drugs are primarily excluded.[38]

Drugs instilled as eye drops exit ocular tissues *via* tear ducts, conjunctival, or choroidal circulation. Drug diffusion into the cornea and bulbar conjunctiva and subsequent accumulation in these tissues may contribute to optimal bioavailability. However, physiological mechanisms such as blinking reflexes, lacrimal turnover, drug binding to conjunctival mucins, melanin, efflux transporters, or tear proteins may cause clearance and/or limited bioavailability of free drug.[45] In addition to this, diseased eyes with pathophysiological alterations may experience even more obstacles. For example, during anterior uveitis, the presence of precipitates of keratin or white blood cells and corneal surface proteins hinders the transport and/or delivery of topically administered drugs.[46] Moreover, diseased eyes show elevated albumin levels in the tear fluid compared with healthy eyes.[47] Such an elevated concentration of albumin facilitates drug–protein interactions, thereby causing hindrance to drug absorption (unbound drug can be easily transported into the ocular tissue) and consequential bioavailability. In addition, reports have demonstrated that there is a substantial difference in the clearance of drugs among aphakic eyes, unmodified candida-infected eyes, phakic eyes, and aphakic vitrectomy eyes. These data imply that clearance differences need to be studied when designing therapeutic delivery systems during diseased states.[48]

4.2 Methods to overcome ocular barriers

Anterior ocular tissues such as the cornea, conjunctiva, or sclera act as strong physical barriers and cause hindrance to the permeation of drugs. The major pathways for drug absorption and/or permeation across these ocular tissues can be classified into two types, *i.e.* (i) paracellular and (ii) transcellular. The paracellular pathway involves the transport of administered nanoparticles between the epithelial cells (of corneal or conjunctival tissues), whereas, the transcellular pathway includes transport of nanoparticles through the epithelial cells.[49] The literature reveals that corneal tissue is composed of cellular (epithelium and endothelium) and acellular components (Descemet membrane, Bowman's layer, and stroma). Furthermore, corneal epithelial cells are tightly bound together by cell adhesion proteins – occludins such as ZO-1 and ZO-2.[50] These tight junctional proteins can cause hindrance to the paracellular transport of nanoparticles. The conjunctival tissue is composed of basal lamina, goblet cells, and epithelial cells that possess tight intercellular junctional proteins, which strongly disallow free diffusion of high molecular weight molecules and nanoparticles *via* the paracellular route. Therefore, the major pathway of nanoparticle transport in these tissues (cornea and conjunctiva) may be the transcellular pathway. The literature reveals that nanoparticles, when they come into contact with ocular tissues, readily undergo internalization. Subsequently, the internalized particles get transported into the intracellular organelles through any of the following processes: (a) fusion with early endosomes; (b) recycling back to the plasma membrane; (c) transport to lysosomes; (d) localization in subcellular compartments; or (e) transport across the cell (transcytosis).[51] It is speculated that nanoparticles (due to their smaller size and high aspect ratio) may undergo transcytosis thereby crossing the cellular barriers, and subsequently get infiltrated through the acellular barriers. However, no studies thus far have demonstrated the mechanism of nanoparticle transport across the ocular barriers. In addition to these transport processes, the ocular retention time (intracellular, intercellular, or acellular) of nanoparticles also plays a pivotal role in ophthalmic drug delivery.

The development of innovative ocular DDS that can sustain the release of entrapped medicaments while improving the permeability and residence time of administered drugs at the ocular tissues is the need of the hour. The literature reveals that various strategies have been explored thus far to improve drug delivery to ocular tissues. These strategies include (i) the use of nanocarriers such as liposomes, nanoparticles, or dendrimers to enhance drug penetration and prolong drug retention in the eye;[52] (ii) the development of prodrugs that facilitate corneal permeability and are subsequently converted into the active drug at the tissue of interest;[53] (iii) inclusion of permeation enhancers in ophthalmic formulations that can reversibly open tight junctional proteins present between corneal/conjunctival epithelium;[54] or (iv) development of *in situ* gel systems that increase the residence time of drugs on the ocular surface.[55] These approaches aim to bypass or mitigate the barrier properties of ocular tissues, thereby improving drug bioavailability and therapeutic effect in glaucoma treatment.

The emergence of advanced drug delivery strategies wherein pathological or physiological stimulus is used for non-invasive or minimally invasive site-specific delivery of therapeutic agents in quantities that enable therapeutic effect for extended durations has helped to achieve effective treatment for glaucoma. Furthermore, the use of nanoparticulate systems such as polymeric nanoparticles, micelles, dendrimers, microemulsions, liposomes, nanosuspensions, nanoimplants/needles, or hydrogels has offered substantial benefits, including increased solubility and stability, targeted

release of therapeutic agents, extended residence time, and enhanced permeability, together contributing to improved therapeutic efficacy. The developed DDS can be injected into the eye (through intravitreal, subretinal, subchoroidal, intrastromal, suprachoroidal, intrascleral, subconjunctival, or intracameral routes), implanted at specific tissues, or administered topically as an eye drop.[56]

The following section discusses various routes for drug administration and the pathway of drug diffusion after administration.

5. Routes of drug administration and pathway/diffusion of anti-glaucoma drugs

Various invasive as well as non-invasive routes of drug administration enable the ocular bioavailability of administered drugs. These routes can be broadly classified into topical, systemic, periocular, and intraocular routes.

5.1. Topical administration

The majority of commercially available ophthalmic formulations are administered topically. Conventional dosage forms such as gels, solutions, suspensions, and ointments are routinely employed formulations for topical drug delivery. These formulations are intended to deliver therapeutic agents to the cornea, conjunctiva, sclera, and other anterior segment tissues, including the iris and ciliary body.[57] Drug absorption takes place *via* conjunctival or corneal pathways, and <5% of the administered dose is delivered to the anterior eye tissues.[58] However, it is challenging to achieve therapeutic drug concentrations at the posterior ocular tissues following topical application.[59]

5.2. Systemic administration

Due to the presence of relatively higher vasculature in the choroid, systemic administration may be employed for the delivery of therapeutic agents to treat diseases affecting choroidal tissue. Drug molecules can quickly equilibrate between the extravascular space of the choroid and the blood circulation due to the presence of highly permeable fenestrated choriocapillaries. Although systemic administration is explored in ophthalmology to treat retinal diseases, the presence of the BRB causes hindrance to drug permeability. It reduces retinal bioavailability,[60] thereby demanding larger dosages (that often cause systemic toxicity) to elicit clinically evident therapeutic effects.[61] Therefore, researchers have explored nanoparticulate DDS to improve ocular residence and/or accumulation of therapeutic agents while administering the minimum possible and safe dose.

5.3. Periocular and intraocular injections

Intraocular injections involve intracameral and intravitreal routes of administration, whereas periocular injections include subretinal, retrobulbar, peribulbar, subtenon, and subconjunctival routes of administration. In clinical practice, providing therapeutic concentrations of drugs to the posterior part of the eye remains a challenging task due to the complex anatomy and physiology of ocular tissues. To address bioavailability issues after topical and systemic administrations, intraocular and periocular routes of administration are being explored to achieve therapeutic drug concentration at the posterior segment.[62] However, a significant drawback with such a highly invasive route of administration includes low patient compliance and increased risk of ocular complications such as vitreous hemorrhage, cataracts, ocular hypertension, endophthalmitis, and retinal detachment. Therefore, the topical route of administration has received increasing attention due to its decreased risk of ocular complications, non-invasiveness, reduced systemic toxicity, and improved patient compliance. However, a high rate of tear turnover and reduced permeability through ocular layers cause very low bioavailability after topical administration. Approximately <5% of lipophilic drugs and <0.5% of hydrophilic drugs reach intraocular tissues.[63] In order to overcome the challenge of low bioavailability, researchers have explored particulate delivery systems and other stimuli-responsive systems that can potentially improve ocular residence time and bioavailability upon topical route of administration.[52]

6. Non-invasive or minimally invasive anti-glaucoma therapy: current scenario and challenges

The goal of glaucoma therapy is to reduce IOP to physiological levels and to protect the visual nerves. However, the complex anatomical and physiological barriers of the eye cause hindrances for effective drug delivery in glaucoma therapy. The prominent causes of therapeutic failure are noted below.

6.1. Distribution and clearance of drug

The eye is a complex organ consisting of layered structures such as cornea, conjunctiva, and sclera. Topically administered drugs come in direct contact with tear fluid and get cleared through the nasolacrimal duct. Furthermore, nasolacrimal drainage, reflex tear formation, high tear turnover rate (1 μl ml^{-1}), and blinking of the eyes, in turn lead to loss of the administered dose. The interior structures, such as the iris, lens, and ciliary body of the eye, obstruct intraocular drug distribution. Furthermore, systemic or lymphatic absorption in turn leads to clearance of drugs from the ocular tissues.[64] As a consequence, the bioavailable dose is insufficient to elicit a therapeutic effect. This demands the development of advanced DDS that offer enhanced permeation and extended residence of topically administered drugs in the eye. The literature reveals that molecules with a negative charge enter the corneal epithelium slowly when compared with positively charged molecules due to the presence of negatively charged pores at

physiological pH. Additionally, some drugs get metabolized rapidly at the ocular pH, which in turn reduces their bioavailability at the target site.[3] Furthermore, proteins present in aqueous humor also affect drug bioavailability due to their binding and consequential effect on the drug permeability. Reports have demonstrated that protein concentration in aqueous humor samples from glaucoma patients is higher [32 mg dL^{-1} (range: 8–137 mg dL^{-1})] as compared with healthy individuals [16 mg dL^{-1} (range: 2–85 mg dL^{-1})].[65]

6.2. Patient non-compliance

The preferred choice for glaucoma therapy includes the use of IOP-lowering medications. The patient's compliance with prescribed medications determines the therapeutic outcome.[66] Non-compliance is observed due to the necessity of frequent drug administrations, and may eventually cause therapeutic failure. Therefore, a sustained-release DDS that enables more extended drug residence in ocular tissues is needed to overcome this challenge.[67]

6.2.1 Polymeric nanoparticles as novel DDS for glaucoma treatment. The use of nanotechnology in medicine is among its most interesting applications. Nanomedicine enables early diagnosis, detection, prevention, and treatment of various diseases, including ocular complications. This next generation of medicines shows several advantages, such as improvement of solubility, extended shelf life, minimal tissue irritation, targeted delivery, non-invasive and sustained drug delivery, improved bioavailability, and dose accuracy.[14,68,69] The various nanomedicines explored thus far include polymeric nanoparticles, nanoemulsions, nanocrystals, liposomes, dendrimers, solid lipid nanoparticles, nanorobots, *etc*. The therapeutic agent can be entrapped in the nanocarriers so as to facilitate its administration with increased ease and to achieve higher bioavailability at the targeted site.[70] The smaller size and/or functional groups present on the nanomedicines facilitate better interaction with the cells and subsequent internalization and drug release at the desired site. Furthermore, the medication can be shielded from enzymatic or chemical breakdown. Therefore, nanomedicines are emerging as modern carrier systems to attain improved and prolonged therapeutic effects for glaucoma treatment.[71] The various nanocarriers explored thus far for glaucoma therapy have been summarized in Table 2. In addition to pristine polymeric nanoparticles, researchers have also explored surface-functionalized nanocarriers for effective glaucoma therapy. The following discussion briefly mentions a few case studies that showed improved bioavailability and consequential therapeutic effects of different nanocarriers.

In a study, Swetledge *et al.* investigated the ocular biodistribution of Cy5-loaded poly(lactide-*co*-glycolide) (PLGA) nanoparticles. PLGA nanoparticles were prepared using an emulsion and solvent evaporation technique using polyvinyl alcohol (PVA) as a protective colloid. Cy5-labeled PLGA nanoparticles were applied topically to mice eyes, and ocular biodistribution of nanoparticles was measured after 15, 30, and 60 minutes of eye drop application. A substantial increase in fluorescence intensity was observed in the whole eye at 30 minutes, particularly in the cornea, episcleral tissue, and sclera (Fig. 3A & B). However, the fluorescence intensity was decreased after 60 minutes, indicating rapid clearance of the nanoparticles from these tissues. Minimal nanoparticle penetration into the inner eye was observed, with no significant increase in fluorescence intensity in the retina, possibly due to the presence of the blood–retina barrier (BRB) (Fig. 3B). These data indicated limited penetration of nanoparticles into the deeper eye structures. The corneal epithelium, being a substantial barrier to hydrophilic particles, can limit the permeation of nanoparticles into the deeper ocular tissues. Furthermore, the rapid clearance of nanoparticles from episcleral tissue and choroid (which contain dense vasculature), in turn, reduces bioavailability.[98]

Therefore, there is a need for the development of advanced formulations (surface modification) to improve the bioavailability of pristine nanoparticles further. In another study, Mahaling *et al.* demonstrated that physico-chemical properties such as size, surface charge, *etc*., also affect ocular permeation, retention, and consequential bioavailability of administered medicaments.[99]

Furthermore, researchers explored biodegradable *in situ* gelling polymeric carrier systems, such as chitosan*graft*-PNIPAAm (Chi-PN), to achieve sustained drug release and improved bioavailability. This study introduced Chi-PN as a novel carrier system for the delivery of pilocarpine. The designed system was characterized for phase transition temperature, *in vitro* degradation, drug encapsulation, and release kinetics. Furthermore, the authors demonstrated that the developed delivery system is biocompatible and offers long-lasting anti-glaucoma effects when tested in a rabbit model.[100] In yet another study, Lee *et al.* developed poly(ε-caprolactone) (PCL) nanoparticles as carriers for sustained drug delivery, specifically for glaucoma treatment using the drug pilocarpine. In this study, the authors synthesized two types of PCL nanoparticles: nanospheres (NSs), which are solid structures that embed the drug in their mass, and nanocapsules (NCs), which have a hollow core for encapsulating the drug. The authors demonstrated that the developed NCs showed higher drug loading efficiency than NSs (~3 fold). Furthermore, NCs exhibited a slower and sustained release profile, with the drug being released throughout for more than 40 days, whereas NSs showed a rapid burst of drug release, depleting most of the drug within a week. *In vivo* studies in rabbit models showed that a single intravitreal injection of pilocarpine-loaded NCs effectively reduced IOP for >42 days, while NSs were only effective for about 7 days. Furthermore, NCs also alleviated other adverse consequences of elevated IOP, such as corneal edema and retinal injuries, demonstrating their long-term therapeutic potential. Both NSs and NCs were biocompatible and safe, as evidenced by low toxicity towards corneal endothelial cells. This study concluded that PCL NCs showed great promise as a long-term treatment option for glaucoma and can potentially improve patient compliance. These findings open the possibility for the use of biodegradable PCL nanocap-

Table 2 Different types of nanoparticulate and gel-based DDS for glaucoma therapy

Sl. no.	Drug delivery system	Therapeutic agent used	Experimental models	Summary of the study results	Ref.
1	PLGA nanoparticles	Dexamethasone and melatonin	A rabbit glaucoma model	PLGA nanoparticles showed prolonged drug release (no burst release), improved retinal penetration, and consequential reduction in IOP. Cytocompatibility studies demonstrated negligible toxicity towards R28 cells.	72
2	Microneedle ocular patch composed of soluble PVA and PVPM	Pilocarpine	*Ex vivo* studies using porcine eye and excised human cornea.	Better penetration of pilocarpine was observed using the developed patch. As a consequence, higher bioavailability of the drug was observed in the aqueous humor of the porcine eye within 30 min.	73
3	Gellan gum and its methacrylate derivatives as *in situ* mucoadhesive gels	Pilocarpine	Chinchilla rabbits	Pilocarpine-loaded gellan gum and methacrylate derivative-based formulation improved therapeutic efficacy.	74
4	*In situ* gelling solution	Brinzolamide	New Zealand rabbits (white)	In comparison with the commercial suspension (Azopt® – 4.9 h), the developed formulations were safe and effective and showed an improvement in IOP for an extended time (7.4 to 17.7 h).	75
5	Multi-drug (three neuroprotective agents)-loaded PLGA microspheres	Coenzyme Q10, melatonin and dexamethasone.	Chronic ocular hypertension model (rodents)	*In vitro* studies in R28 cells showed improved neuroprotective effects with microspheres. *In vivo* studies demonstrated that the formulation offered improved neuroprotection in RGCs as compared with control.	76
6	Thermo-responsive *in situ* gelling systems with cellulose nanocrystals	Pilocarpine	*In vitro* studies	The developed formulation showed prolonged drug release and lower toxicity.	77
7	Chitosan/hydroxyethyl cellulose inserts for prolonged drug release	Dorzolamide	Male Wistar rats	Ocular inserts substantially decreased IOP for two weeks.	78
8	PLGA nanoparticles	Memantine	Morrison's (in dark Agouti rats) ocular hypertension model	*Ex vivo* and *in vitro* studies showed that nanoparticles offered sustained drug release and improved drug permeation when compared with other formulations. *In vivo* efficacy studies in a rodent model demonstrated a substantial reduction of RGC loss.	79
9	Liposomes	Latanoprost/ thymoquinone	White albino rabbits	Drug-loaded liposomes substantially reduced IOP for 84 h.	80
10	Gelatin–chitosan hydrogel	Timolol maleate	Male albino rabbits	The developed hydrogel system showed prolonged timolol release and offered long-lasting effects.	81
11	Nanoliposomes	Dorzolamide	A randomized control trial	The study (in POAG patients) was based on the measurement of the effectiveness of dorzolamide-loaded nanoliposome-based eye drops in reducing IOP. Results showed a substantial decrease in IOP in the intervention group (as in the control group, where a dorzolamide-marketed formulation was used).	82
12	Ion-sensitive *in situ* gelling system (gellan gum-based)	Brinzolamide	New Zealand rabbits	The formulation was found to be safe and bio-adhesive, as evidenced by the formation of a firm gel when coming in contact with simulated tear fluid. Furthermore, the developed gel system enabled the controlled release of brinzolamide.	83
13	Nano emulsion-based ion-sensitive *in situ* gels	Acetazolamide	*In vitro*	Sustained drug release was observed when compared with the plain nanoemulsion. The gel that was developed showed a long-lasting reduction in IOP compared with oral tablets and commercial drops.	84
14	PLGA nanoparticles	Brinzolamide	Male New Zealand albino rabbits	Sub-conjunctival injection of nanoparticles in normotensive albino rabbits reduced the IOP for 10 days.	85

Table 2 *(Contd.)*

Sl. no.	Drug delivery system	Therapeutic agent used	Experimental models	Summary of the study results	Ref.
15	Chitosan-*g* poly(*N*-isopropyl acrylamide) *in situ* gel system	Pilocarpine	A rabbit model	The formulation was non-toxic and sustained drug release for 42 days.	86
16	Chitosan coated liposomes	Timolol maleate	New Zealand white rabbits	The developed liposomes not only showed better mucoadhesive properties but also prolonged drug retention in the corneal tissue. As a consequence, showed a better anti-glaucoma effect when compared with commercially available timolol drops.	87
17	Microsphere formulation	Timolol maleate	Male New Zealand white rabbits	Subconjunctival administration of timolol microspheres resulted in sustained delivery of the drug and consequential reduction in IOP for 90 days.	88
18	Carbosilane dendrimers (water-soluble and mucoadhesive)	Acetazolamide	New Zealand white rabbits	The eye drop formulation caused a rapid (<1 hour) and extended (up to 7 h) decrease in IOP.	89
19	Thermosensitive *in situ* hydrogel	Betaxolol hydrochloride	A rabbit model	The developed formulation sustained the release of betaxolol. *In vivo* efficacy studies confirmed improved bioavailability and reduction of IOP.	90
20	Intracameral administration with gelatin-*g* poly(*N*-isopropylacrylamide) *in situ* gelling system	Pilocarpine	A rabbit model of experimental glaucoma	The developed formulation offered sustained release of pilocarpine and consequential reduction in IOP.	91
21	Liposome-loaded ion-sensitive *in situ* gels	Timolol maleate	New Zealand rabbits	The developed formulation effectively reduced IOP for 240 min.	92
22	Poly(propylene imine) dendrimer nanoarchitecture	Acetazolamide	Male New Zealand albino rabbits	The developed formulation effectively reduced IOP for four hours when compared with the Acetazolamide solution (2 h).	93
23	Liposome/microemulsion	Latanoprost	An open-label, pilot study in humans suffering from ocular hypertension or POAG	Sub-conjunctival injection of latanoprost liposomes was well tolerated. A substantial reduction of IOP within one hour (lasting up to 3 months) was reported.	94
24	pH-Triggered polymeric nanoparticulate *in situ* gel	Acetazolamide	A rabbit model	*Ex vivo* studies demonstrated higher Acetazolamide permeation when compared with conventional eye drop and suspension-based formulations. A modified Draize test confirmed non-irritant properties, and no corneal toxicity was observed. The developed *in situ* gel also caused a substantial reduction of IOP in rabbits as compared with conventional eye drops.	95
25	Drug-resin thermosensitive *in situ* gelling system	Brinzolamide	A rabbit model	The developed formulation was stable and non-irritant and offered a controlled release of brinzolamide over eight hours.	96
26	Nanoparticle-loaded silicone-hydrogel contact lenses	Timolol	Beagle dogs	Incorporation of nanoparticles into silicone hydrogels decreased oxygen and ion permeability and increased modulus. The gel system with 5% nanoparticles delivered timolol for 30 days.	97

sules in treating other chronic eye diseases that demand long-term treatment.[101]

The bioavailability issues of topically administered formulations can also be improved using suitable active targeting approaches as well. In a study, Dillinger *et al.* developed actively targeted siRNA-loaded hyaluronic acid (HA)-coated nanoparticles for targeting CD44 receptors present in the SC and TM (anterior part of the eye).[102] In this study, the authors prepared poly(ethylene imine) (PEI)-stabilized poly(lactide-*co*-glycolide) (PLGA) nanoparticles and sandwiched the siRNA [for connective tissue growth factor (CTGF)] between two PEI layers. CTGF acts as a mediator for various pathological events in the TM and SC, ultimately leading to increased resistance to aqueous humor outflow in glaucoma. Hence, therapeutic strategies that aim to reduce CTGF expression could tackle causative pathologies, thereby providing a permanent solution for controlling IOP. Therefore, the authors fabricated siRNA-loaded nanoparticles against CTGF and then coated with HA

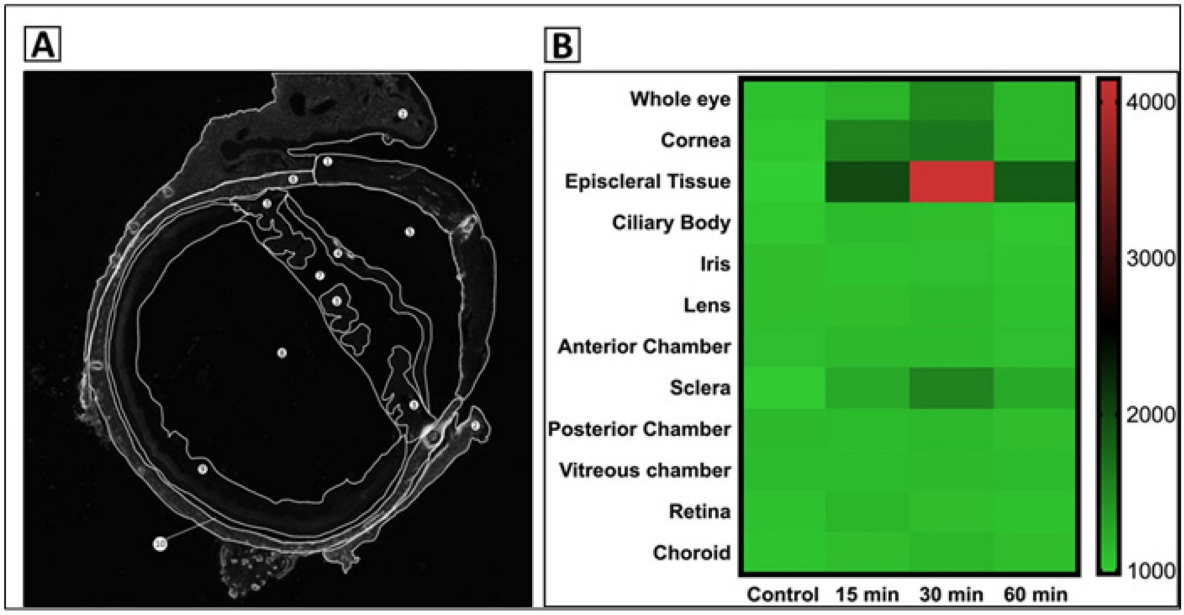

Fig. 3 A. Schematic representation of the eye showing different regions of interest: (1) cornea, (2) episcleral tissue, (3) ciliary body, (4) iris, (5) anterior chamber, (6) sclera, (7) posterior chamber, (8) vitreous, (9) retina, (10) choroid; B. heat map depicting average fluorescence intensity of each region of interest. Reproduced with permission from ref. 98. Copyright Springer Nature Limited.

using a layer-by-layer (LbL) approach. The fabricated nanoparticles were intended for the intracameral delivery of small interfering RNA (siRNA) against CTGF (Fig. 4A). The developed drug delivery system was expected to pass through the extracellular matrix of ocular tissues and bind to the CD44 receptors present in TM and SC cells of glaucomatous patients, thereby offering precision delivery of entrapped siRNA molecules. The authors fabricated PLGA nanoparticles using the nanoprecipitation method and stabilized them using polycationic polymer PEI. Subsequently, the authors experimented with different molecular weights (7.5, 13, 289, and 752 kDa) of HA. They observed that coating of PLGA nanoparticles with 13 kDa HA showed reduced agglomeration and improved stability of nanoparticles as compared with other molecular weight HAs. These nanoparticles showed spherical morphology with ~240 nm size and −18 mV zeta potential. Furthermore, the authors studied the pathway of nanoparticle diffusion across the porcine eye using a perfusion model. For this study, the authors fabricated rhodamine B-labeled PEI and HA-coated PLGA nanoparticles and perfused them into the anterior chamber of porcine eyes. Subsequently, the anterior chamber was dissected (the portion of the tissue depicted in Fig. 4B) and imaged using a fluorescence microscope. The results revealed that PEI nanoparticles were distributed irregularly, as evidenced by their fluorescence intensity in a few areas of the outflow ring, whereas HA-coated nanoparticles were homogeneously distributed all the way through the whole outflow ring of porcine eyes (Fig. 4B), which was in turn evidenced by higher fluorescence intensity (~3-fold) in HA-coated nanoparticle-administered eyes as compared with PEI nanoparticle-administered eyes (Fig. 4B). Furthermore, the authors were interested in demonstrating the spatial distribution of PEI and HA nanoparticles in the outflow system.

For this, the authors stained the sagittal tissue sections using CD44 antibodies and demonstrated a homogeneous distribution of CD44 (green fluorescence) in the entire TM and SC (Fig. 4C). Subsequently, counterstaining of CD44 revealed that spatial distribution (red fluorescence) of PEI nanoparticles was limited to the corneoscleral TM (depicted by asterisks) and did not reach the juxtacanalicular tissue (JCT) or the aqueous plexus (AP) [depicted by arrows]. Meanwhile, HA nanoparticles were distributed in the entire TM and AP (Fig. 4C), indicating an improved accumulation of HA-coated nanoparticles at the site of interest. Furthermore, the authors investigated the efficacy of the developed drug delivery system in primary human TM cells. Western blot analysis revealed that HA-targeted siRNA-loaded nanoparticles substantially reduced the CTGF protein expression to about 50%. In contrast, non-targeted PEI-based nanoparticles did not elicit any effect (Fig. 4D), indicating improved targeting ability of HA-coated nanoparticles. These results revealed that the actively targeted nanoparticle-based delivery system effectively silenced the CTGF gene in TM cells and, as a consequence, could prevent glaucoma progression.[102]

Nanocarriers can also be employed to alleviate surgical complications after trabeculectomy. The major complication following this glaucoma surgery is fibrosis or scarring, which often leads to bleb failure and increased intraocular pressure (IOP). Current therapeutic interventions for fibrosis are mainly focused on the administration of anti-metabolite drugs. However, these therapies are associated with non-specific cytotoxicity that can cause serious vision-threatening compli-

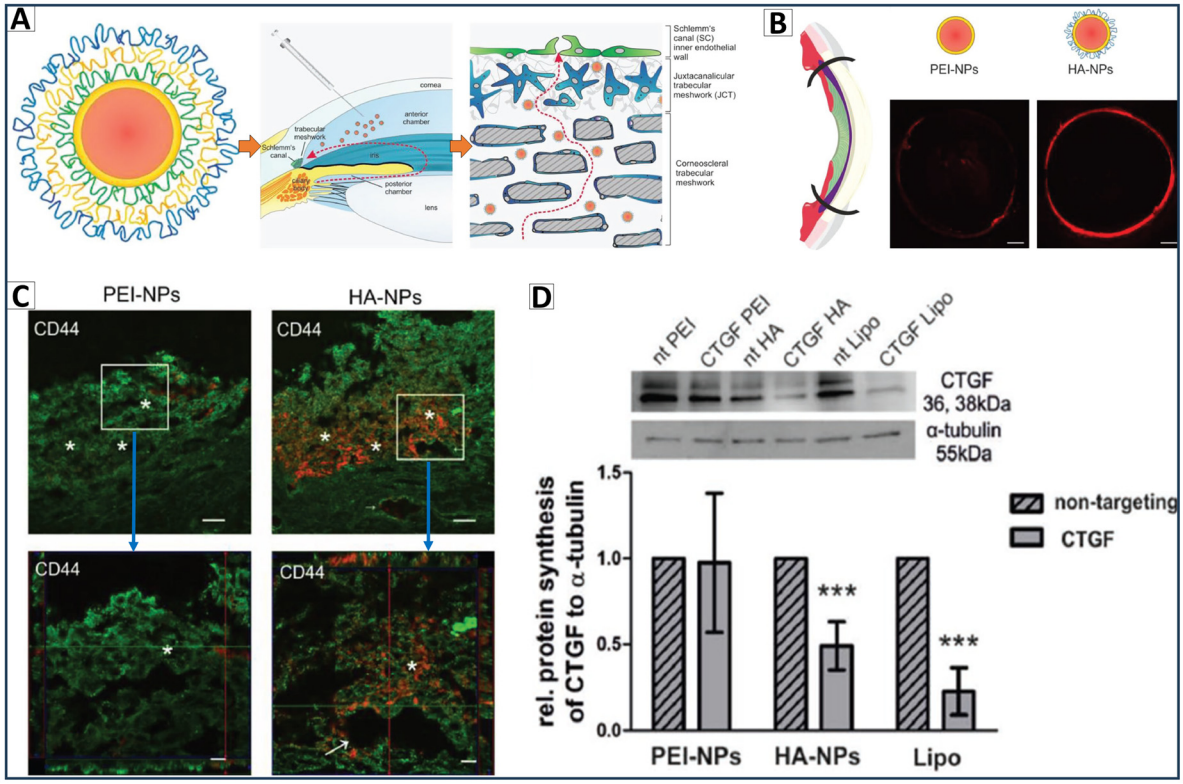

Fig. 4 Actively targeted siRNA nanoparticles (NPs) for glaucoma; A. schematic representation of LbL-assembled nanoparticles [PLGA nanoparticles (red core) are stabilized by PEI (25 kDa) (orange shell), followed by siRNA (green) layer of and PEI (orange). Lastly, HA (blue) coating] and pathway of trabecular outflow showing JCT TM, corneoscleral, and internal endothelial wall of SC; B. *ex vivo* studies data showing anterior eye segment after perfusion with rhodamine-labeled PEI- and HA-NPs; C. CLSM images showing spatial distribution of PEI and HA nanoparticles in the outflow system; D. western blotting data showing reduced CTGF protein expression in TM cells after treatment with the developed delivery system. Reproduced with permission from ref. 102. Copyright Wiley & Sons, Inc.

cations. The literature reveals that elevated secreted protein, acidic, and rich in cysteine (SPARC) protein expression causes tissue scarring and fibrosis.[103] Therefore, therapeutic strategies that decrease SPARC expression can potentially improve the pathological condition. In a study, Tan *et al*. fabricated layer-by-layer (LbL) nanoparticles by encapsulating SPARC siRNA in the bilayers of poly(L-arginine) (ARG) and dextran (DXS) polyelectrolytes. The study results demonstrated that LbL nanoparticles were cytocompatible and caused a substantial SPARC-gene knockdown in treated FibroGRO cells as compared with untreated control cells.[104] Inferences may be drawn from such studies to develop improved therapeutic interventions for the alleviation of glaucoma-associated complications. Since pathological complications in glaucoma manifest at both anterior (canal of Schlemm) and posterior (retina) eye tissues, nanoparticulate systems can also be explored to improve the bioavailability of neuroprotective agents at the retina. In a study, Beatriz Silva *et al.* developed a nanoparticulate system composed of chitosan and hyaluronic acid (CS/HA) for delivering erythropoietin beta (EPOβ) to the retina so as to achieve improved neuroprotection after topical administration. In this study, the authors studied the physicochemical stability, mucoadhesive properties, and biological safety of the developed system. The developed nanoparticulate system released ~60% of EPOβ instantaneously (within 15 minutes), followed by a slow and sustained release of up to 90% over a six-hour time interval. *Ex vivo* studies demonstrated better permeation, as evidenced by higher EPOβ absorption through conjunctival, scleral, and corneal tissues when compared with a commercial EPOβ solution (NeoRecormon). The CS/HA-EPOβ nanoparticles delivered ~60% higher EPOβ through the conjunctiva, 85.3% higher through the sclera, and 2.5 times higher through the cornea. Cytotoxicity assays demonstrated that the formulation was non-toxic to human ARPE-19 and HaCaT cells. Furthermore, *in vivo* studies in Wistar Hannover rats demonstrated the presence of EPOβ in the RGCs of treated eyes as early as 12 hours after administration, and the fluorescence persisted in the retina for up to 21 days. Based on these data, the authors proposed that EPOβ reached the retina *via* a conjunctival–scleral pathway. The CS/HA nanoparticles provided sustained delivery of EPOβ, as evidenced by the presence of the drug in the corneal stroma and endothelium up to 14 days after administration. This prolonged drug retention suggested that the mucoadhesive properties of the nanoparticles enhanced their precorneal residence time and facilitated trans-corneal and conjunctival absorption over an

extended period. Immunofluorescence results showed no EPOβ in control eyes, confirming the specificity of the nanoparticulate system. Safety assessment studies indicated that nanoparticles were well-tolerated, with no signs of ocular lesions, discomfort, or abnormal behavior observed in rats. Furthermore, IOP remained within normal physiological ranges, and no systemic side effects were observed (as evidenced by hematocrit values that remained within normal limits throughout the study). Histological analyses revealed no changes in ocular morphology or tissue structure, confirming the biological safety of the CS/HA-EPOβ nanoparticles. Taken together, the study suggested that the CS/HA nanoparticulate system delivered EPOβ to the retina *via* non-invasive means. Current glaucoma treatments mainly focus on managing IOP but there is a lack of targeted therapies for preventing vision loss due to retinal degeneration. In this study, the authors highlighted the potential of EPOβ as a neuroprotective agent that could preserve vision by slowing the progression of neuronal cell damage. However, further research is needed to explore the long-term effects and potential clinical applications of this nanoparticulate system for treating other retinal diseases.[105]

In addition to particulate systems alone, novel tailored delivery systems need to be developed for combinatorial drug delivery in glaucoma therapy. Three-dimensional, flexible hydrophilic polymer networks give rise to nanogels (NGs), which are nanosized structures that can swell in aqueous conditions without changing the internal network structure. NGs are desirable materials for controlled drug delivery as their nanoporous structure offers higher drug loading. Furthermore, these NGs can be combined with dendrimers, liposomes, micelles, and other nano-systems. NGs can also be tailored to promote muco-adhesion with consequential improvement in drug residence time for long-term glaucoma therapy.[100] Table 2 summarizes various nanoparticulate and gel-based delivery technologies that have been developed thus far for the delivery of various therapeutic agents for improved glaucoma therapy.

6.3. Challenges with nanoparticulate DDS and formulation development strategies to improve residence time of drug formulations in ocular tissues

As mentioned in previous sections, numerous studies have demonstrated the therapeutic potential of biodegradable nanoparticulate delivery systems for ocular drug delivery. Although these formulations are effective, their clinical translation is still an unmet need due to several reasons, such as issues with sterilization, stability, reduced drug loading, elevated cost, *etc*.[3] Therefore, drug delivery scientists have aimed to address these challenges and improve the potential of novel drug formulations for the treatment of ocular diseases.

The global market for ophthalmic drugs has been valued at $29.2 billion.[106] Although drug delivery to the anterior part of the eye using conventional formulations was clinically accepted, their limited residence time in ocular tissues demands frequent administrations, particularly in the treatment of chronic eye diseases. As mentioned in the previous sections, drugs delivered topically into the tears experience a multitude of barriers and clearance pathways, leading to infinitesimal bioavailability. Although the corneal bioavailability of eye drop-based solutions is less than 5%, these formulations account for about 90% of ophthalmic preparations for the treatment of anterior eye diseases.[107] Since the majority of droppers dispense up to 30 μL of volume, rapid drainage (loss) of administered drops takes place within 30 seconds of instillation. In addition, based on the composition, these eye drops augment reflex tear production in order to maintain homeostasis, which in turn results in reduced bioavailability.[108]

Furthermore, the pH of tears is 7.4. Due to the lack of a strong buffering effect, the pH of eye drop formulations should be kept between 7.0 and 7.7.[109] The viscosity of tear fluid [1.5 millipascal seconds (mPa s)][110] and its rheological properties play a pivotal role in determining the retention/clearance of eye drops. These formulation characteristics of eye drops influence the residence time of eye drops. The literature revealed that extending the retention of drugs on the cornea can improve the bioavailability of eye drops. Therefore, viscosity enhancers are used in eye drop formulations not only to stabilize the medication but also to minimize the rate of elimination from the eye. This would lead to better patient compliance and reduced frequency of eye drop instillations. A range of hydrophilic polymers with different molecular weights (5–10 kDa) can be used as viscosity enhancers. Because of their low diffusivity and lack of penetration into the ocular tissues, these polymers can persist in the tear film and attribute viscosity to the formulation after eye drop administration. In a study, Zhu *et al.* demonstrated improved retention of eye drops when the viscosity was raised to over 10 mPa s.[111] It is anticipated that the optimal viscosity of ophthalmic formulations should be within the range of 15–30 mPa s, taking into account the administrability of drops.[110] The other ingredients in eye drop formulations or artificial tears include preservatives, lubricants, surfactants, and electrolytes.[112] An exhaustive list of different formulation ingredients used in conventional eye drop formulations is given in Table 3.

An ideal eye drop formulation needs to comply with the following criteria: easy to use, absence of preservatives, neutral pH, provision for constant drug delivery, single dosage, sterile, minimal discomfort, and negligible influence on visual acuity. In the majority of formulations, the drug concentration is in the range of 0.1–4%. However, for hydrophobic drugs, it is difficult to achieve such drug concentrations for ophthalmic solutions. Therefore, the majority of topical eye drop formulations intended for the delivery of hydrophobic drugs are available in the form of suspensions.[128] A significant drawback of suspension-based ophthalmic formulations is poor knowledge and understanding of their biopharmaceutical properties. Reports reveal that the particle size of fluorometholone and dexamethasone in the respective eye drop formulations plays a vital role in drug absorption.[128] Furthermore, improved absorption of drugs was observed when formulated as nano-

Table 3 Various ingredients used in eye drop formulations and their function

Sl. no.	Category	Materials	Function	Ref.
1.	Viscosity enhancers	Sodium carboxy methyl cellulose, poly acrylic acids, poly(vinyl alcohol) (PVA), sodium hyaluronate, poloxamer, *etc.*	Increases ocular retention and consequential bioavailability of the drug	113–115
2.	Permeability enhancers	Cyclodextrins, cell-penetrating peptides, bile acids and salts, chelating agents, crown ethers, disodium EDTA, benzalkonium chloride, azones, *etc.*	Increases permeability and consequential bioavailability of the drug	116 and 117
3.	Mucoadhesive agents	Glycan, chitosan, thiolated poly aspartic acid, hydroxypropyl methylcellulose (HPMC), β-cyclodextrin (BCD), lectin helix pomatia agglutinin (HPA), glutathione (GSH), hyaluronic acid (HA), *etc.*	Increases ocular retention time and bioavailability	118–120
4.	Vasoconstrictors	Epinephrine, phenylephrine, brimonidine tartrate, oxymetazoline hydrochloride *etc.*	Decreases systemic uptake while improving retention of the drug in the aqueous humor; decreases clearance by choroid and conjunctiva, thereby helping in drug delivery to the posterior part of the eye	121 and 122
5.	Lacrimal occlusion	Punctal plugs [cylindrical hydroxy ethyl methacrylate (HEMA)] in combination with topical treatments	Provides pain relief; increases bioavailability; decreases systemic uptake; serves as a drug depot. The occlusion may be temporary or permanent, according to the patient's need	123 and 124
6.	Nanocarriers	Chitosan, poly(lactic-*co*-glycolic acid), lipids, colloidal particles, polycaprolactone, *etc.*	Allows for controlled release, protects the drug from enzymatic degradation, increases drug bioavailability	125
7.	Prodrugs	Esters and diester functional groups, carbamate, oxime, oxazolidine, sulphonamide, dipivalyl epinephrine (DPE), *O*-butyryl timolol, *etc.*	It increases bioavailability, and specific sites can be targeted	126 and 127

particulate systems.[129] In addition, viscosity is an essential consideration for ophthalmic suspensions. Studies demonstrated that an increase in viscosity can improve ocular drug (budesonide) absorption from solution and suspension-based eye drop formulations.[130] Alternatively, higher viscosity increases the thickness of the unstirred water layer around particles, which can potentially decrease the dissolution rate and drug absorption. Hence, the thickening of the unstirred water layer is not beneficial in *in vivo* settings. However, the impact of viscosity on drug retention on the ocular surface is also an essential factor. Hence, a balance between these two factors determines the extent of bioavailability and consequential therapeutic effect. In addition to these aspects, rheological properties also play an essential role in drug absorption, particularly for polymers with non-Newtonian flow properties and pseudo-plastic spreading characteristics (*e.g.*, carboxy methyl cellulose, hydroxyl propyl cellulose).[128] It is apparent that higher viscosity enables the retention of solution and/or suspension particles in the tear fluid.

Viscous formulations are prepared in two significant ways: *in situ*-forming gels and conventional preformed gels. *In situ*-forming gels are viscoelastic gels that are formed when they come in contact with various physical stimuli. In contrast, classically preformed gels are viscous liquids that do not change their viscosity after instillation. Bio-adhesive hydrogels made of sodium hyaluronate, polyacrylic derivatives, and cellulose derivatives are commonly used gel preparations. In a study, the use of sodium carboxymethyl cellulose, a viscous carrier, increased the ocular bioavailability of timolol fivefold in rabbits.[131] Researchers also employed polyacrylic derivatives like poly(vinyl alcohol) (PVA) in order to increase the viscosity of ophthalmic formulations. Due to their high water-holding capacity, lower toxicity, and muco-mimetic qualities, polyacrylic acids are found to be suitable for ophthalmic formulations.[132] For ophthalmic applications, preformed gels still have certain limitations. Due to the hydrogel's extensive coverage of the cornea and its adhesive qualities, these hydrogels have the potential to induce both discomfort and blurred vision.[133]

Additionally, these are difficult to apply due to a lack of control over the volume of the eye drop during the instillation. Apart from conventional and nanoparticulate ophthalmic formulations, stimuli-responsive ophthalmic formulations have gained much attention in recent times due to their ability to respond to physiological or pathological internal stimuli or any other external stimuli that enable the release of entrapped therapeutic agents. The following section discusses stimuli-responsive ophthalmic formulations.

7. Stimuli-responsive ophthalmic drug delivery systems

In recent years, there has been a lot of interest in stimuli-responsive DDS because they can offer tunable drug release based on the physiological or pathological condition of the patient and control drug release in a spatiotemporal manner. By imitating biological processes, these systems react to environmental triggers or external stimuli and cause a variety of responses at a particular target site that ultimately result in

drug release. Stimuli-responsive DDS can be divided into exogenous and endogenous categories based on the type of trigger employed. Exogenous systems utilize exogenous stimuli, such as ultrasound, magnetic field, light, and electric field, to trigger drug release. Meanwhile, endogenous systems utilize physiological enzyme concentration, elevated active oxygen species, and temperature changes to trigger drug release.[134] Researchers have developed ophthalmic formulations that respond to physical stimuli such as pH, temperature, or ion concentration so as to achieve higher bioavailability. This section discusses various stimuli-responsive formulations. Furthermore, a summary of such systems is presented in Table 4.

7.1. Endogenous stimuli

The use of endogenous stimuli of chemical and biochemical origin includes temperature-responsive, pH-responsive, ionic microenvironment-responsive, and enzyme-responsive drug delivery systems. Drug release is triggered in these DDS by microenvironmental regulation conditions, over-expression of specific enzymes, and changes in pH or temperature at specific sites.

7.1.1. Temperature-responsive gels. Thermo-gels are polymer systems that respond to temperature changes by switching their form from a free-flowing state to a gel state. In other words, they use temperature changes as the trigger that controls their gelling behavior. These thermo-responsive gels showed promising results in various biomedical applications. Since poloxamer acquires gel-like consistency at elevated temperatures, it is a commonly used ingredient for the fabrication of thermo-responsive gels. Reports reveal that viscous formulations enable longer retention of administered medicaments in ocular tissues and consequential bioavailability. It has been demonstrated that adding poloxamer (25%) or a mixture of poloxamer (15%) and methylcellulose (3%) to timolol maleate aqueous eye drops considerably increased the concentration of the drug in the aqueous humor.[149] Over the past few decades, the development of chitosan-based DDS has garnered significant research interest. Specifically, injectable thermosetting chitosan hydrogels, which combine biodegradability, biocompatibility, and *in situ* gel-forming capability, are promising materials for controlled release.[150]

In a study, Fedorchak *et al.* developed a sustained-release eye drop formulation that combines a gel matrix with drug-loaded microspheres (GSM) to prolong the retention of drugs on the ocular surface. This novel system is composed of drug-loaded polymeric microspheres and thermoresponsive hydrogel carriers (Fig. 5A). The gel–microsphere hybrid system was designed to improve contact with the corneal surface, thus improving the therapeutic effect while reducing the frequency of administration. The developed microspheres are non-porous with an average diameter of 7.46 ± 2.86 μm. These microspheres were incorporated into a pNIPAAm gel matrix, with the gel showing a lower critical solution temperature (LCST) of 33.5 °C (Fig. 5B(left)). The gel exhibited negligible degradation over 28 days (Fig. 5B(right)) and sustained drug

Table 4 Stimuli-sensitive polymeric DDS for glaucoma

Polymers used	Stimulus	Drug used	Administration route	Delivery/therapeutic performance	Ref.
Gelatin/PNIPAAm	Temperature	Pilocarpine	Intracameral	Sustained pilocarpine release and lowered IOP values to normal levels for 56 days	135
Chitosan/PNIPAAm	Temperature	Pilocarpine	Intracameral	Sustained pilocarpine release and lowered IOP values to normal levels for 63 days	136
PLGA/PEG/PNIPAAm	Temperate	Brimonidine	Subconjunctival	Reduced IOP to normal levels for 28 days	137
Gelatin/chitosan/ β-glycerolphosphate	Temperate	Latanoprost	Subconjunctival	Sustained latanoprost release over 28 days and lowered IOP values to normal levels for 31 days after administration of a single dose	138
Gelatin/chitosan/ glycerolphosphate	Temperate	Latanoprost	Conjunctival	Sustained latanoprost release and offered IOP reduction efficiency by seven-folds	139
Elastin/silk fibroin	Temperate	Timolol	Conjunctival	Sustained timolol release and offered IOP reduction efficiency by two-fold	140
Poloxamer	Temperate	Timolol	Conjunctival	Offered IOP reduction efficiency by two-fold	141
PLGA/PEG/PLGA	Temperate	Brimonidine	Corneal/ conjunctival	Sustained brimonidine release for 168 h and offered IOP reduction efficiency by approx. five-fold	142
Poloxamer F127, Carbopol® 934P	Temperate	Brinzolamide	Corneal/ conjunctival	A sol–gel at 33.2 ± 1.1 °C; controlled brinzolamide release over a period of 8 h	96
Poloxamer 407, Poloxamer 188	Temperate	Dorzolamide hydrochloride	Corneal	Faster onset of action and prolonged effect relative to either drug solution or the market product	143
PLGA/PEG/PLGA	Temperate	Cyclosporine A	Subconjunctival	Lowered IOP and maintained at normal levels for over 70 days	144
PEG/PCL/PEG	Temperate	Bevacizumab	Intracameral	Adequate time of IOP reduction by approx. 4.7-fold	145
Carbopol®/HPMC	pH	Dorzolamide	Conjunctival	Increased IOP reduction efficiency by approx. six-fold	146
Carbopol®, chitosan	pH	Timolol maleate	Conjunctival	Showed controlled drug release over 24 h	147
Carbopol®/HPMC	pH	Brimonidine	Conjunctival	IOP reduction efficiency by >2-fold	148
Gellan gum	Ion	Brinzolamide, timolol	Conjunctival	Sustained drug release and lowered IOP for 48 h	92
Gellan gum/xanthan gum, HPMC	Ion	Acetazolamide	Corneal	Offered IOP reduction efficiencies by >2-fold	84

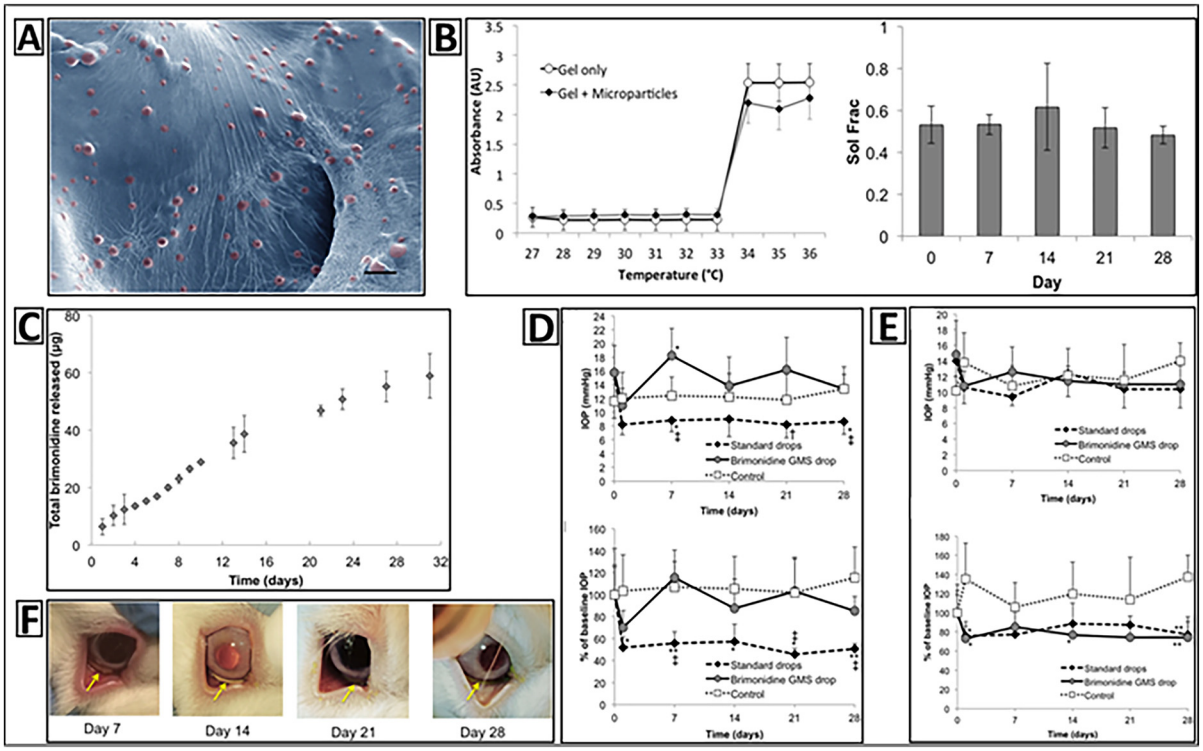

Fig. 5 A. SEM micrograph of homogeneous suspension of microspheres in a gel matrix (pNIPAAm gel) scale bar – 20 μm; B. graph showing LCST of the developed gel; C. brimonidine release kinetics from the developed delivery system; D. IOP in animals treated with BT-loaded gel/microsphere drops and aqueous BT drops actual IOP (above) and percent change in IOP (below). E. Data showing IOP in the treated eye and untreated contralateral eye (OS); F. photographs of animal eyes showing retention of GMS drops throughout the study (arrows indicate the presence of gels). Reproduced with permission from ref. 137, Copyright Springer Nature Limited.

release for one month (Fig. 5C). The therapeutic efficacy of the resultant gel was evaluated in normotensive rabbits after administration of brimonidine-loaded GMS drop (single administration). It was observed that GMS administration offered a therapeutic effect for 28 days (single drop) with a possible decrease in systemic absorption as evidenced by a lack of significant IOP effects on the other, untreated, eye (Fig. 5D and E). Furthermore, the authors also confirmed the retention of GMS drops in the conjunctival cul-de-sac of rabbits (Fig. 5F). This novel formulation could potentially transform current therapeutic interventions for glaucoma by reducing the burden of frequent eye-drop administration while providing consistent IOP control, thereby improving patient compliance. Taken together, this study concludes that the developed delivery system offers a promising avenue for long-term glaucoma management and can be extrapolated to other ocular diseases requiring chronic treatment.[137]

In another study, Lai *et al.* synthesized two types of chitosan-*g*-poly(*N*-isopropyl acrylamide) (Chi-PN) copolymers by varying the ratio of thermo-responsive polymer segments grafted onto chitosan. These polymers were designed to undergo temperature-triggered gelation at body temperature, as shown in Fig. 6A. The authors developed an *in situ* gelling system using these polymers and encapsulating pilocarpine so as to achieve controlled drug release over a prolonged period. The efficiency of drug encapsulation, release profiles, biocompatibility, and antiglaucoma efficacy were examined *in vitro* and *in vivo* (in a rabbit model of glaucoma). The higher grafting ratio of PNIPAAm to chitosan in the copolymers (Chi-PN20) allowed for better encapsulation and controlled release of pilocarpine compared with the lower ratio (Chi-PN10). The Chi-PN20 system released pilocarpine over 42 days, whereas Chi-PN10 showed a drop in drug concentration after 28 days. *In vivo* studies in a rabbit experimental glaucoma model showed that the Chi-PN20 formulation effectively reduced IOP for up to 42 days, while Chi-PN10 was effective for 28 days (Fig. 6B). Furthermore, the sustained release profile of pilocarpine from the Chi-PN carriers also helped to preserve corneal endothelial cells, thereby preventing glaucoma-associated corneal damage (Fig. 6C). In conclusion, the study highlighted the potential of Chi-PN copolymers as a promising DDS for the extended release of pilocarpine in glaucoma treatment. This approach could reduce the need for frequent medication and improve therapeutic outcomes in managing chronic eye disease and glaucoma.[86]

In addition to the aforementioned polymers, Pluronic F127 is also used widely as a thermoresponsive polymer for ophthalmic drug delivery applications. Pluronic F127 is a triblock copolymer consisting of poly(ethylene oxide) (PEO) and poly (propylene oxide) (PPO) segments. This polymer is widely used

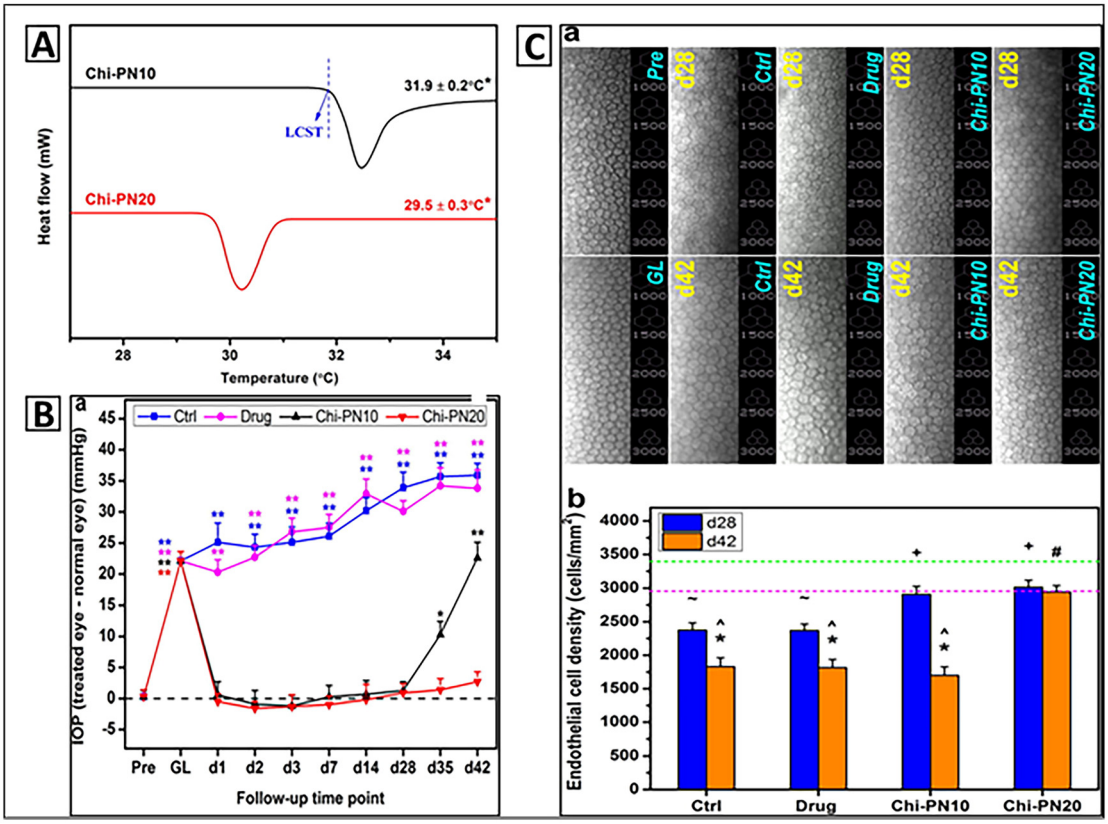

Fig. 6 A. DSC thermograms of Chi-PN copolymers with different PN composition; B. graph showing IOP values after injection (intracameral) of various pilocarpine-containing Chi-PN gel systems and free pilocarpine solutions; C. (a) specular microscopic images of corneal endothelium at pre-operation (Pre) and (b) glaucoma (GL) eyes during 28 and 42 days after intracameral injection of free pilocarpine solutions and prepared co-polymeric gel formuations (pink and green lines denote the cell densities in glaucomatous and preoperative eyes respectively). Reproduced with permission from ref. 86, Copyright Elsevier.

because its sol-to-gel transition occurs at temperatures near that of the human body, making it a suitable material for biomedical applications. F127 exhibits viscoelastic behavior, transitioning from liquid-like to solid-like properties with increasing temperature. In a study, Kim *et al.* attempted the use of Pluronic F127 to improve drug ocular delivery upon topical administration. F127 has a critical gel concentration (CGC) of around 15–16% (w/w) under physiological conditions. In this study, the authors developed a novel formulation using F127 at concentrations below the CGC to avoid premature gelation. This lower concentration, combined with hypotonicity, allows the eye drops to spread and concentrate on the ocular surface through osmotically induced water absorption.

As a result, a thin, clear, uniform gel will be formed that can reside on the corneal surface for a longer duration than conventional isotonic formulations, thereby improving drug delivery without causing irritation or visual impairment. The study compared the efficacy of a hypotonic formulation (12% F127, hypo) with two conventional formulations, *i.e.*, isotonic 12% F127 (12% iso) and isotonic 18% F127 (18% iso). Optical coherence tomography (OCT) imaging in rats revealed that the 12% hypo formulation generated a uniform coating on the eye surface and persisted after blinking. In comparison, the 18% iso formulation formed a clumpy gel that was quickly cleared. Using fluorescent labeling, the researchers confirmed that the 12% hypo formulation remained on the eye longer than the isotonic formulations. To confirm the drug delivery efficiency, the authors tested the hypotonic F127 formulations with two common drugs: brimonidine tartrate (BT) (which is used to lower IOP) and cyclosporine A (CsA) (which is used to increase tear production). Both drugs showed optimal therapeutic effect at a polymer concentration of 12%. The prolonged residence time and gel formation of the 12% hypo formulation were further confirmed by multiple-particle tracking (MPT). This revealed that nanoparticles administered in the 12% hypo formulation were trapped within the gel, demonstrating gel formation *in vivo*.

In contrast, the 12% iso formulation did not cause gelation in *in vitro* conditions, and the nanoparticles moved freely, showing no significant gel formation. The researchers evaluated the pharmacodynamic effects of the formulations in normotensive rabbits, comparing the 12% hypo formulation with commercial eye drops like Alphagan P. The 12% hypo formulation showed higher drug concentration in aqueous humor and cornea as compared with commercial products and demonstrated a prolonged reduction in IOP. The study

also tested brinzolamide (BRZ), a hydrophobic drug used to lower IOP, and found that the 12% hypo formulation delivered higher concentrations of the drug to the conjunctiva and cornea compared with Azopt, a commercial formulation. Similarly, for CsA, the 12% hypo formulation increased drug concentrations in the cornea compared with Restasis. The authors also explored the ability of the 12% hypo formulation to deliver drugs to the posterior part of the eye, particularly for conditions like choroidal neovascularization (CNV). Two drugs, sunitinib malate (SM) and acriflavine hydrochloride (ACF) were tested for their anti-angiogenic effects. Both drugs significantly suppressed laser-induced CNV in rats when delivered through the 12% hypo formulation. This suggests that the formulation could potentially deliver drugs to the posterior eye, which is challenging with traditional eye drops. By addressing the limitations of current eye drop formulations such as rapid clearance and poor drug availability, this new approach has the potential to improve treatment outcomes for chronic eye conditions like glaucoma while also reducing dosing frequency and systemic side effects.[151]

7.1.2. pH-Responsive gels. pH-Responsive gels are hydrophilic polymeric gel systems that respond to pH variations and release entrapped therapeutic agents. Through pH-dependent swelling or collapse behavior, these hydrogels offer regulated drug release kinetics.[152] As a consequence, maximal therapeutic efficiency can be achieved while minimizing side effects and toxicity and controlling their spatiotemporal biodistribution in ocular tissues.

The commonly used pH-sensitive hydrogel that increases the viscosity is cross-linked polyacrylic acid. This polymer exhibits a transition from sol to gel when the pH rises above its pK_a.[107] As a result, a sol–gel transition takes place immediately. In a study, Srividya *et al.* developed an Ofloxacin eye drop using 0.3% Carbopol®, a high molecular weight cross-linked polyacrylic acid, as a gelling agent. When the pH was raised from 6.0 to 7.4, the eye drop showed a rapid *in situ* gelation, causing the medication to be released over eight hours.[153] However, Carbopol® may cause ocular discomfort due to its acidic nature. Hence, HPMC can be used as an alternative to improve the viscous properties of eye drops. In a study, Kouchak *et al.* employed different compositions of carbopol® and HPMC using a 3^2-complete factorial design and prepared *in situ* gel. The authors found that 0.1% was the ideal concentration for both polymers (HPMC and carbopol®) to develop a pH-and/or thermo-responsive *in situ* gelling system for the delivery of dorzolamide. At this concentration, the HPMC/carbopol® solution formed a thick gel on the ocular surface (pH 7.4; 34 °C temperature) and flowed freely in ambient conditions (pH of 5 to 5.8; 25 ± 2 °C temperature). *In vivo* efficacy studies in male rabbits demonstrated that the developed delivery system offered better therapeutic efficacy in glaucoma treatment.[146] Based on these studies, it can be inferred that stimuli-responsive polymeric carrier systems are intriguing possibilities for prolonging the therapeutic activity of medicaments. Such formulations do not demand frequent drug administration, which can potentially enhance patient comfort and compliance. The aforementioned study deals with pH-responsive (at physiological pH) gelation properties and consequential ocular residence time of topically administered ophthalmic formulation. On the other hand, pathological microenvironment (*e.g.* inflammation)-responsive drug delivery carriers need to be explored because such carriers may serve as superior systems for the treatment of a variety of inflammatory diseases that affect the eye. Since inflammation causes a shift in pH towards acidic (pH 6–6.5), pH-responsive drug delivery approaches offer tremendous potential for site-specific delivery of therapeutic agents in ophthalmology. In a study, Guo *et al*. developed an acidic pH-responsive copolymer, PACD, [an A–B–C type non-viral vector copolymer constituted of a pH-responsive block (C), a siRNA binding block (B) and a hydrophilic PEG block (A)] intended for cytosolic delivery of siRNA to treat retinal neovascularization. Such pH-responsive polymers may be explored for the delivery of therapeutic agents during inflammatory conditions in glaucoma.

7.1.3. Ionic strength responsive gels. Polymers that respond to ions exhibit quick transition with respect to their physical and/or chemical properties when a small change in environmental conditions (such as slight variations in concentration of specific substances/ions) occurs.[154] When combined with simulated tear fluid, the solution quickly transforms into a flowing gel, which allows for the controlled release of entrapped therapeutic agents. Furthermore, a study demonstrated that the use of gellan gum loaded with brinzolamide is safe for topical administration. *In vivo* efficacy studies demonstrated that the developed formulation (ion-responsive) effectively reduced IOP when compared with the drug solution. When applied topically to the eye's conjunctival sac, the developed formulation transformed into a gel, extending its residence period (up to 16–24 hours). When compared with treatment with three to four instillations of the commercial medication Azopt®, single-dose instillations of the developed formulation showed comparative results. The studied formulations decreased the IOP from 25–28 mmHg to 12–14 mmHg and were well tolerated.[155]

In addition, the test formulations showed a more extended residence (7.4 to 17.7 h) compared with the marketed Azopt® solution (4.9 h). Furthermore, a notable increase in the area under the change in IOP was observed. Additionally, it has been shown that while maintaining the ion-responsive characteristics of gellan gum, combining it with other polymers like HPMC and xanthan gum substantially improved the mucoadhesive force of gellan gum-based formulations. When compared with commercially available eye drops, formulations based on a combination of gellan gum/HPMC and gellan gum/xanthan gum showed long-lasting effects on IOP reduction and higher therapeutic efficacy. Furthermore, the gellan gum/xanthan gum showed improved therapeutic properties over the gellan/HPMC. Therefore, it can be concluded that such ion-responsive polymeric formulations show promising results for topical administration of Acetazolamide.[84]

7.1.4 Enzyme-responsive systems. Enzyme-responsive drug delivery systems (ERDDS) are innovative carriers that leverage

the specific activity of enzymes to release drugs at targeted sites. These systems respond to the enzymatic changes that occur under both physiological and pathological conditions. In the ocular environment, a variety of enzymes, including matrix metalloproteinases, hyaluronidase, lysozyme, and esterase, are present and can trigger drug release in ERDDS. The specificity towards enzymes ensures that the drug is released when the enzymes are present, thereby enhancing the treatment precision while reducing undesired toxicity at off-target sites. The ERDDS are composed of enzyme-responsive polymers that release drugs through physical or chemical changes in response to enzymatic activity. These polymers are composed of enzyme substrates that undergo physical or chemical transformations that cause the destabilization of drug carriers, ultimately leading to the release of the drug.[156]

One application of enzyme-triggered systems is lysozyme-triggered drug release. A study by Kim *et al.* developed a contact lens embedded with nano-diamonds (NDs) and lysozyme-responsive chitosan to release timolol maleate for treating glaucoma. Lysozyme in tears hydrolyses chitosan (breaks down its 1,4-β-glycosidic bonds). The NDs, coated with polyethyleneimine, form nanogels with chitosan, which are then embedded into poly-HEMA contact lenses. In the presence of lysozyme, the system releases timolol maleate in a controlled manner (the drug release rate in these contact lenses was slower and more sustained compared with traditional lenses). In conclusion, ERDDS are promising for controlled and targeted drug delivery, particularly in ocular treatments.[157]

7.2. Exogenous stimuli

Exogenous stimuli-responsive DDS have the potential advantage of overcoming inter-patient variability and alterations in drug release rate when compared with endogenous stimuli-responsive DDS, as externally induced stimuli can be uniform and reproducible. There have been reports of using a variety of external stimuli, including light, magnetic field, electrical field, and ultrasound, to regulate medication releases.[158] The issue of early drug release can be resolved by using external stimuli-responsive drug delivery devices. As a result, research has shifted towards exogenous stimuli-responsive DDS, and it has also been noted that combining two or more stimuli-responsive systems can improve targeting efficacy. The following section discusses various exogenous stimuli-responsive drug delivery approaches.

7.2.1 Light responsive. Light-responsive DDS for ophthalmology exploit the transparency of the eye and advances in laser technology so as to offer non-invasive control over drug release. Three types of light can be used: near-infrared (NIR, 700–1000 nm), visible (Vis, 400–700 nm), and ultraviolet (UV, 200–400 nm). While UV light has high energy, its phototoxicity and poor tissue penetration limit its *in vivo* use. NIR light penetrates deeper but has low energy, making it unsuitable for direct drug release.[159] The literature reveals that four mechanisms can control light-triggered drug release: (i) photolysis – which uses UV light to release drugs by cleaving photoresponsive groups; (ii) photoisomerization – that alters hydrophilic/hydrophobic balance to release drugs; (iii) photocrosslinking/decrosslinking – which involves light-controlled polymer structural changes; and (iv) photothermal mechanisms, often utilizing gold nanoparticles – that convert light to heat, thereby destabilizing carriers for drug release.[160] Gold nanoparticles and hydrogels have been used to release biological macromolecules with enhanced precision. Light-responsive DDS reduces the need for invasive procedures, prolongs drug retention, and minimizes toxicity. However, challenges include UV and chromophore toxicity and potential cellular damage from photocrosslinking agents.[161]

7.2.2. Ultrasound. Ultrasound has become a key tool in drug delivery, particularly for ocular drug delivery applications, due to its non-invasive nature, precise targeting, and lack of ionizing radiation. It can facilitate drug release by either breaking down drug carriers or disrupting chemical bonds, with cavitation being a primary mechanism. Two types of cavitation exist: non-inertial (stable) cavitation and inertial (transient) cavitation, both of which enhance drug delivery by releasing drugs from carriers or creating reversible pores on the cell membrane.[162] Ultrasound has been shown to increase corneal and scleral permeability, enhance gene transfection, and improve drug delivery across ocular barriers without damaging sensitive structures.[163] Studies using nanobubbles and microbubbles have demonstrated the potential of ultrasound to direct drug carriers effectively to the posterior eye. These findings suggest ultrasound is a promising approach for targeted drug delivery in ophthalmology.

7.2.3. Electrically triggered. Intrinsically conducting polymers (ICPs) are organic materials with alternating single and double bonds that provide them with unique electrical, optical, and magnetic properties. These polymers, including poly-pyrrole (PPy), polyaniline, and poly(3,4-ethylenedioxythiophene), are commonly used in DDS due to their biocompatibility, stability, and electrochemical performance. ICPs allow for precise, electrically stimulated drug release *via* mechanisms like redox reactions, carrier destruction, or heat generation. In ocular applications, ICP-based systems can enhance the controlled release of drugs like dexamethasone for conditions such as diabetic macular edema (DME) and age-related macular degeneration (AMD).[164] However, challenges include the lack of biodegradability, which may require invasive surgeries for removal. Future developments may focus on combining ICPs with biodegradable materials or other flexible polymers to enhance performance and reduce invasiveness.

7.2.4. Magnetically triggered. Magnetic fields play an essential role in biomedical applications, including drug delivery. Iron oxide nanoparticles (IONPs) are commonly used systems for magnetically triggered drug delivery due to their low toxicity and biocompatibility. Here, drug release takes place *via* two main mechanisms: (i) magnetic field-guided drug release and (ii) heat (generated by magnetic fields)-triggered drug release (from thermal-responsive carriers). Systems like MEMS devices use magnetic fields to release drugs. Magnetic fields can also speed up drug delivery using magnetic micro-propellers. These systems deliver drugs at the

optic disc faster than the passive diffusion. Although these technologies show promise for targeted drug delivery, their physiological compatibility, safety and potential long-term effects on the ocular tissues must be considered prior to clinical use.[165] Future advancements could involve combining magnetic materials with nanocarriers like liposomes and micelles for remote, magnetically guided drug delivery in the eye.

8. Biocompatibility and safety assessment

Biocompatibility implies an appropriate host response *i.e.*, the ability of a material to perform its intended function (cellular or tissue response), without eliciting any undesirable local or systemic effects, whereas safety is concerned with the potential harm that a material can cause, either immediately or during long-term use.[166] Both biocompatibility and safety are primary factors for any medical device or medicinal product (including nanoparticulate delivery systems). The biocompatibility of nanoparticles can be assessed by studying their cytotoxicity, hemocompatibility, irritation, sensitization, genotoxicity, *etc*.[167] Since nanoparticles possess a small size and high aspect ratio, these carriers are readily internalized by the cells thereby leading to tissue accumulation. The nano–bio interactions such as cellular internalization, intracellular localization/distribution, and ability to generate free radicals/reactive oxygen species can cause damage to organelles (mitochondria, Golgi apparatus) or even cells.[168] Such damage caused by nanocarriers can be assessed *in vitro* using various cell culture techniques such as trypan blue staining, propidium iodide assay (to detect live and dead cells), lactate dehydrogenase assay (for cell membrane integrity), neutral red assay (for lysosomal membrane integrity), MTT or alamarBlue assay (for mitochondrial metabolism), ATP assay (for cell functional integrity), transepithelial electrical resistance assay (for cell barrier integrity), and comet assay (for DNA damage).[169] Since the majority of ocular diseases (including glaucoma) are chronic in nature, the genotoxicity and mutagenicity potential of nanocarriers should also be assessed prior to clinical use. Furthermore, inflammatory responses to nanoparticles need to be monitored by quantifying various inflammatory mediators such as cytokines (IL-6, IL-8) and the tumor necrosis factor (TNF)-α and complement activation.[169] In a nutshell, a detailed evaluation of cellular toxicity and the mechanistic pathways needs to be performed so as to understand the safety profile of nanoparticles intended for ophthalmic drug delivery applications. Upon satisfactory *in vitro* compatibility, the nanocarriers need to be tested *in vivo* to assess their interaction with ocular tissues, tendency to cause irritation [Draize test and hen's egg test-chorioallantoic membrane (HET-CAM)], ability to elicit immune cell infiltration and inflammatory responses, propensity for thrombogenicity, acute and chronic toxicity, *etc*. In order to minimize the usage of animals, the Organization for Economic Co-Operation and Development (OECD) has developed several *in vitro* and *ex vivo* test methods, which include bovine corneal opacity and permeability (BCOP) test method, reconstructed human cornea-like epithelium (RhCE) test system, fluorescein leakage (FL) test method, isolated chicken eye (ICE) test method, vitrigel-eye irritancy (EIT) test method, short-time exposure (STE) test method, and Ocular Irritection® macromolecular test method.[170] Various studies have reported the safety profile of polymeric nanoparticles for ophthalmic applications. A study by Ogura and Kimura investigated biodegradation and intracellular (in RPE cells) accumulation of microspheres composed of PLGA 50 : 50 and PLGA 75 : 25 in rabbit eyes after subretinal administration. The results demonstrated that the microspheres were internalized by RPE and hydrophobicity enhanced the internalization of microspheres. Furthermore, the microspheres were present for approximately 4 weeks without causing any adverse cellular or tissue responses.[171] This study indicates the biocompatibility and safety of PLGA-based particulate drug delivery systems for ophthalmic applications. In yet another study, Zhang *et al*. evaluated the safety and efficacy of tacrolimus-loaded liposomes after intravitreal injection. The authors observed a reduction in inflammation without any change in retinal function in liposome-treated animals when compared with free tacrolimus-administered animals. Furthermore, an improvement in drug residence time along with a reduction in drug-related toxicity towards inner retinal cells was observed with liposomal formulation. These results suggest that the safety profile of the drug can be improved using liposomes.[172] Moreover, another independent study demonstrated that an intravitreally administered PEGylated liposomal formulation improved residence time and minimized drug accumulation at off-target sites, ultimately causing an improvement in the safety profile.[173] Such studies suggest that nanoparticulate systems composed of biodegradable polymers and liposomes are safe for ophthalmic applications. Furthermore, hydrophilization of such particulate systems using PEG in turn improves the safety profile of the delivery system.

In addition to nanoparticulate systems, stimuli-responsive hydrogel systems have also been evaluated to assess their safety profile. In a study, Turturro *et al*. studied the influence of cross-linked PNIPAAm-based hydrogel injection on retinal function. The results revealed a substantial decrease in arterial and venous diameters, retinal thickness, and an increase in venous blood velocity for 1 week following injection, indicating the acute toxicity of the PNIPAAm polymer. However, these parameters returned to normal values afterwards, indicating the transient effect of the PNIPAAm without causing any long-term effects.[174] In yet another study, Dalvin *et al*. investigated the safety profile of Carbopol® 980 and HPMC in rabbits after subconjunctival administration. The results indicated that exposure of ocular tissues to carbopol® 980-based ocular lubricants led to a chronic histiocytic inflammatory response, whereas HPMC-based lubricants are safe and well tolerated.[175] These results indicate the toxicity of carbopol® for ophthalmic applications. Although a few materials have been investigated for their toxicity potential, a detailed comparative toxicity evaluation of various polymeric (both nano and gel-based

systems) and liposomal drug delivery systems towards ocular cells has not been undertaken. Based on the available literature and patent databases, it can be inferred that liposomes and polymeric nanoparticles composed of PLGA, PEG, PVA, albumin, gelatin, dextran, or pluronics are relatively safer nanocarriers, whereas nanoparticles composed of inorganic materials, PNIAAm, poly(orthoesters), poly L-lysine are relatively toxic to ocular tissues.[176] The suitability of a few other polymeric systems such as PCL[177–179] and chitosan[180] is under investigation. The cytocompatibility and safety of various polymeric materials intended for ophthalmic drug delivery applications are detailed in Table 5.

In addition to cellular uptake and cytocompatibility, the circulation time in turn influences the safety profile of nanoparticles. Since nanoparticles are composed of foreign materials, the biological system aims to eliminate these carriers when administered intravenously or absorbed into the systemic circulation. Such an elimination process is mediated by immune cells or the reticuloendothelial system (RES). Physico-chemical characteristics of nanoparticles such as size, shape, surface composition, the presence of protein corona, targeting ligands, *etc*. influence the rate and extent of nanoparticle clearance.[199] It has been demonstrated that particles composed of hydrophobic materials get engulfed by the immune cells and quickly cleared from the systemic circulation when compared with particles that are hydrophilic in nature. This can lead to the accumulation of nanoparticles in major organ systems and consequential tissue toxicity, thereby posing safety concerns. Therefore, hydrophilization of nanoparticles using polymers such as polyethylene glycol (PEGylation) is a commonly employed approach in drug delivery science for minimizing long-term toxicity and off-target tissue accumulation.[199] This process minimizes RES uptake of nanoparticles and, as a consequence, enhances the bioavailability and/or therapeutic efficacy of nanomedicines. Such hydrophilization is beneficial for minimizing the clearance of nanocarriers intended for systemic administration during the treatment of ophthalmic complications. In addition to this, periocular or intraocular clearance of nanoparticles also a crucial aspect for drug delivery systems intended for topical instillation. Various physicochemical factors (such as size and surface characteristics) and physiological factors affect the clearance of nanoparticles after topical or intraocular administration. Similar to topically administered drug solutions, nanoparticulate delivery systems also get cleared by various physiological factors (blinking reflexes) and dynamic ocular barriers such as tear turnover, nasolacrimal drainage, aqueous humor drainage, lymphatic circulation, iris-ciliary and conjunctival blood flow, resulting in reduced bioavailability.[50] In a study, Amrite *et al.* studied the clearance of negatively charged polystyrene nanoparticles of varying sizes, such as 20 nm, 200 nm, and 2000 nm in Sprague Dawley rats upon subconjunctival administration. The results revealed that 20 nm particles were rapidly cleared from the periocular area with 8 and 15% of administered dose remaining after 7 and 1 days, respectively, whereas larger sized particles (200 nm or more) were retained at the site of administration for two months, indicating that particle size plays an important role in clearance of particulate systems.[200] In yet another study, Sonntag *et al*. investigated the influence of particle size and surface properties of gold nanoparticles [pristine and hyaluronic acid (HA) coated] on tissue accumulation. In this study, the authors intracamerally administered 5 nm, 60 nm, 80 nm, and 120 nm-sized particles in a perfused porcine eye model (*ex vivo*) and observed that 120 nm-sized particles exhibited highest volume-based accumulation in TM while showing negligible distribution in other anterior eye tissues including cornea and lens. Furthermore, HA coating prevented the aggregation of nanoparticles inside the TM. These results demonstrated that 120 nm-sized nanoparticles with HA coating resist clearance by dynamic ocular barriers as compared with lower-sized particles.[201] Based on the aforementioned studies, it can be concluded that nanoparticles of 120–200 nm may improve ocular retention.[200,201] In yet another study, Chhonker *et al*. evaluated comparative bioavailability of amphotericin B using a marketed formulation (Fungizone) and a lecithin/chitosan-based mucoadhesive nanoparticulate formulation in New Zealand albino rabbits. The results demonstrated that the nanoparticulate formulation improved bioavailability (~2.04-fold) and precorneal retention (~3.36-fold) when compared with Fungizone.[202] These studies indicate that nanoparticles with specific physico-chemical properties can be designed to resist clearance by dynamic ocular barriers.

9. Challenges for scale-up, regulatory approvals, and clinical translation

The development of advanced DDS and stimuli-responsive systems for glaucoma treatment poses several key challenges during scaling up, regulatory approval, and clinical translation. Moving from lab-scale to industrial-scale production of these delivery systems is complex due to the involvement of multiple processing steps. Precise control over the unit operations such as mixing, extrusion, homogenization, evaporation, centrifugation, lyophilization, or sterilization needs to be achieved so as to maintain uniformity among the batches consistently and to achieve quality target product profile (QTPP). Additionally, scaling up often increases production costs, requiring innovative approaches for maintaining cost-efficiency without compromising quality. Stringent quality control processes are essential to ensure consistency, safety, and efficacy throughout the production cycle.[203] Another major obstacle to advanced DDS is regulatory approval. Regulatory agencies often lack specific guidelines for the materials used for the fabrication of advanced drug delivery systems. In addition, regulatory agencies often demand extensive documentation to establish their safety and efficacy. The complexity of these systems can lead to long approval timelines, as developers must present comprehensive data on stability, biocompatibility, and con-

Table 5 Cytocompatibility, immunogenicity, biodegradation and safety of various polymeric materials intended for ophthalmic drug delivery applications

S. no.	Material	Type/ category	Intended application	Cytocompatibility and/or toxicity	Immunogenicity	Biodegradability	Safety	Ref.
1	PLGA	Synthetic	Sustained drug delivery	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS (generally recognized as safe)	181
2	PLA	Synthetic	Sustained drug delivery	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	[50]
3	PCL	Synthetic	Sustained drug delivery	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Need to assess the safety thoroughly for ophthalmic applications	177
4	PEG	Synthetic	To improve hydrophilicity and circulation time	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	182
5	PVA	Synthetic	To improve hydrophilicity and colloidal stability	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	183
6	Poly(amidoamine) (PAMAM)	Synthetic	Sustained drug delivery; dendrimer preparation	Relatively cytotoxic	Non-immunogenic	Non-biodegradable	Need to assess the safety thoroughly for ophthalmic applications	184
7	PEI	Synthetic	To improve cellular uptake and intracellular transport	Cytotoxic	Non-immunogenic	Non-biodegradable	Marginal safety profile	185
8	Poly(acrylate)s and poly (methacrylate)s	Synthetic	To improve wettability	Cytocompatible and non-toxic	Non-immunogenic	Non-biodegradable	Safe; GRAS	186
9	HA	Natural	Targeted drug delivery	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe	187
10	Chitosan	Natural	Stimuli-responsive delivery (lysozyme triggered), sustained drug delivery and to improve mucoadhesion	Cytocompatible and non-toxic	Low immunogenicity	Biodegradable	Safe at lower concentrations	180
11	Gelatin	Natural	To improve hydrophilicity, mucoadhesion and to extend circulation time	Cytocompatible and non-toxic	Low immunogenicity	Biodegradable	Safe; GRAS	188
12	Gellan	Natural	Gelating agent and viscosity enhancer	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe	189
13	Collagen	Natural	To improve hydrophilicity and mucoadhesion	Cytocompatible and non-toxic	Low immunogenic	Biodegradable	Safe; GRAS	190
14	Sodium CMC	Natural	Viscosity enhancer	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	191
15	Sodium alginate	Natural	Viscosity enhancer and mucoadhesive agent	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	192
16	PNIPAAm	Synthetic	Thermoresponsive material	Cytocompatible	Can elicit acute inflammatory responses	Non-biodegradable	Marginal safety profile	174
17	Poloxamers	Synthetic	Thermoresponsive material	Cytocompatible	Non-immunogenic	Biodegradable	Safe; GRAS	193
18	Carbopol®	Synthetic	pH-Responsive material that in turn improves mucoadhesion	Cytocompatible	Can elicit acute inflammatory responses	Not readily biodegradable	Marginal safety profile	175
19	HPMC	Synthetic	Thermoresponsive material	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	175
20	Gellan gum	Natural	Ionic strength responsive	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	194
21	Xanthan gum	Natural	Mucoadhesive and ionic strength responsive	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	195
22	Poly(3,4-ethylene dioxythiophene)	Synthetic	Electroresponsive	Cytocompatible	Non-immunogenic	Non-biodegradable	Marginal safety profile	196
23	Poly-pyrrole (PPy)	Synthetic	Electroresponsive	Cytotoxic	Non-immunogenic	Non-biodegradable	Marginal safety profile	197
24	Polyaniline	Synthetic	Electroresponsive	Cytotoxic	Non-immunogenic	Non-biodegradable	Marginal safety profile	197
25	Liposomes [phosphatidylcholine (PC)]	Natural	Slow drug release and improves safety profile of drug	Cytocompatible and non-toxic	Non-immunogenic	Biodegradable	Safe; GRAS	198

trolled-release capabilities under varied physiological/pathological conditions. Meeting these requirements can be resource-intensive and time-consuming. Furthermore, advanced delivery systems must demonstrate reliable biocompatibility and safety in preclinical studies to gain acceptance for clinical trials. Proving efficacy in targeted delivery to eye tissues is essential for conditions like glaucoma, where precise drug release is critical. The systems must also fulfill the requirement of patient compliance and ease of use, especially for the treatment of chronic eye diseases like glaucoma.[204] Additionally, achieving market acceptance requires educating healthcare providers and patients about the benefits of these advanced systems, which may differ from traditional eye treatment methods. Overall, the successful translation of these innovative DDS for glaucoma treatment will require interdisciplinary collaboration and targeted efforts to overcome production, regulatory, and clinical challenges.

10. Conclusions and future prospects

The complex anatomy and physiology of ocular tissues limit the bioavailability of topically administered therapeutic agents that demand frequent drug administration for the treatment of glaucoma. This drawback can be partially surmounted using advanced DDS that enable ocular residence of administered therapeutic agents for longer durations while controlling the extent of drug accumulation and release in ocular tissues. The emergence of nanomedicine brought a paradigm shift in ophthalmology wherein nanoparticulate systems such as nanoemulsions, liposomes, polymeric nanoparticles, *etc*., showed improved therapeutic effects in glaucoma. These advanced DDS composed of polymeric materials leverage their natural biocompatibility, biodegradability, and versatility to achieve controlled/sustained/targeted drug release. Furthermore, the development of stimuli-responsive systems and active targeting systems improved precision drug delivery in ophthalmology by (i) enhancing drug bioavailability, (ii) controlling drug distribution spatially and temporally, (iii) improving drug accumulation at the tissue of interest, and (iv) reducing frequency of administration.

As a consequence, these advanced DDS improved patient compliance while minimizing the untoward effect of drugs on sensitive ocular tissues. However, challenges remain for their scale-up, production at the industrial scale, and clinical translation. Efforts should be made to achieve large-scale production while fulfilling regulatory guidelines so as to achieve clinical translation of advanced delivery systems for the treatment of glaucoma.

Author contributions

Dadi A. Srinivasarao: conceptualization, funding acquisition, project administration, resources, supervision, manuscript writing – original draft; manuscript writing – review and editing. Sourabh Kundu: conceptualization, data curation, manuscript writing – original draft. Gitika Kumari: data curation; manuscript writing – review and editing.

Conflicts of interest

The authors declare that there is no conflict of interest.

Consent for publication

All authors approved for publication.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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