

Special Section on Drug Delivery Technologies—Minireview

Ocular Drug Delivery: Present Innovations and Future Challenges

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ABSTRACT

Ocular drug delivery has always been a challenge for ophthalmologists and drug-delivery scientists due to the presence of various anatomic and physiologic barriers. Inimitable static and dynamic ocular barriers not only exclude the entry of xenobiotics but also discourage the active absorption of therapeutic agents. Designing an ideal delivery scheme should include enhanced drug bioavailability and controlled release of drug at the site of action, which can overcome various ocular barriers. Conventional ophthalmic medications include the use of topical eye drops and intravitreal injections of anti-vascular endothelial growth factor agent for treatment of anterior and posterior segment disorders, respectively. Current inventions for anterior ocular segment disorders such as punctum plugs, ocular implants, drug-eluting contact lenses, and ocular

iontophoresis represent state-of-the-art inventions for sustained and controlled drug release. Parallel efforts for ocular drug delivery technologies for back of the eye disorders have resulted in the approval of various intravitreal implants. Novel drug-delivery technologies, including nanoparticles, nanomicelles, dendrimers, micro-needles, liposomes, and nanowafters, are increasingly studied for anterior and posterior disorders. To achieve patient compliance for back of the eye disorders, novel approaches for noninvasive delivery of potent therapeutic agents are on the rise. In this review article, we discuss past successes, present inventions, and future challenges in ocular drug-delivery technologies. This expert opinion also discusses the future challenges for ocular drug-delivery systems and the clinical translatable potential of nanotechnology from benchtop to bedside.

Introduction

In the past two decades, the arena of ocular drug-delivery technologies has dynamically advanced and resulted in newer therapeutic interventions for chronic ocular disorders. The primary objectives of any ocular drug-delivery system are to maintain therapeutic drug concentrations at the target site, reduce dosage frequency, and overcome various dynamic and static ocular barriers. Most importantly, the drug-delivery system should cause no adverse ocular reactions and aim to achieve enhanced drug bioavailability. Ocular pathologic disorders are generally described as anterior segment and posterior segment disorders. Clinicians treat anterior segment disorders such as dry eye disease, cataract, and allergic conjunctivitis by topical eye drops. The major disadvantage of topically applied ophthalmic formulations is relatively low ocular bioavailability. This can be attributed to high tear-fluid turnover rates and high nasolacrimal

drainage. Novel ocular drug-delivery systems include nanomicelles, nanoparticles, drug-eluting contact lenses, ocular inserts, and ocular devices that allow enhanced peroneal residence and enhance the bioavailability of the therapeutic agents (Achouri et al., 2013; Fanguero et al., 2016).

Ocular pathologic conditions involving the posterior segment generally result in vision loss due to damage to the retina. Hyperglycemia for a prolonged period of time can cause damage to the retinal endothelial cells, causing back of the eye disorders such as diabetic retinopathy (DR), diabetic macular edema (DME), and retinal vein occlusion (RVO). High oxidative stress, endoplasmic reticulum stress, and aging can damage the retinal pigmented epithelial cells (RPE) and Bruch's membrane in the macular region, leading to the death of the photoreceptors. Such pathologic conditions can cause retinal degenerative disorders such as age-related macular degeneration (AMD) (Yasukawa et al., 2004; Janoria et al., 2007). Retinal and choroidal neovascularization (CNV), evident in back of the eye disorders, is primarily due to overexpression of vascular endothelial growth factor (VEGF) receptor. Before the invention of anti-VEGF agents, the gold standard treatment of these disorders was the

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ABBREVIATIONS: AMD, age-related macular degeneration; BRB, blood-retinal barrier; CAC, composite alginate-collagen; CL, contact lens; CNV, choroidal neovascularization; CPP, cell-penetrating peptide; CRVO, central retinal vein occlusion; Dex-NW, dexamethasone-loaded nanowafers; DME, diabetic macular edema; DR, diabetic retinopathy; ECT, encapsulated cell technology; FDA, Food and Drug Administration; GDNF, XXX; IOP, intraocular pressure; LE, loteprednol etabonate; MMP-9, matrix metalloproteinases-9; MN, microneedle; NP, nanoparticle; o/w, oil in water; PAMAM, polyamidoamine; PCL, polycaprolactone; PEG, polyethylene glycol; PLGA, poly lactide-co-glycolide; PPDS, punctum plug delivery system; RGD, Arginylglycylaspartic acid; RPE, retinal pigmented epithelial cells; RVO, retinal vein occlusion; TA, triamcinolone acetate; VEGF, vascular endothelial growth factor.

application of laser photocoagulation to lower overall oxygen demand of the retina. This therapy allowed suppression of CNV and retinal neovascularization. Since then, clinicians have introduced a plethora of anti-VEGF agents in the market, including pegaptanib, bevacizumab (off-label), ranibizumab, and aflibercept, for the treatment of back of the eye disorders with neovascularization. Clinicians administer these agents as intravitreal injections, which has drawbacks such as retinal hemorrhage and retinal detachment. Moreover, intravitreal injections lack patient compliance. Novel ocular drug-delivery technologies such as nanoformulations, implants, and other ocular devices allow enhanced drug residence time at the target tissue along with improvements in pharmacological response (Peyman et al., 2009).

In this article, we present a comprehensive and detailed review of past successes, current inventions, and future challenges in anterior and posterior ocular drug-delivery systems. Developments in novel drug-delivery technologies can ultimately improve pharmacological action of drugs at the target tissue by elevating the concentrations and ocular bioavailability of the required therapeutic agent.

Barriers to Ocular Drug Delivery and Routes of Drug Administration

Human ocular anatomy possesses static and dynamic ocular barriers to prevent toxic chemical substances, including therapeutic molecules, to reach various tissues of the eye. Ocular barriers of anterior and posterior segments retard the passive absorption of various therapeutic agents and thus reduce the ocular bioavailability of various drugs. Both static (corneal epithelium, corneal stroma, corneal endothelium, blood-aqueous barrier) and dynamic barriers (tear dilution, conjunctival barrier, and retinal-blood barrier) hinder drug absorption, affecting drug bioavailability of topical formulation (<5%) (Chrai et al., 1973, 1974). The globular shape of the human eye and precorneal factors such as blinking and continuous tear turnover reduce absorption of topically applied formulations (Mishima et al., 1966; Lee and Robinson, 1986; Schoenwald, 1990) (Fig. 1). The lipophilic corneal epithelium allows absorption of hydrophobic drugs but acts as a barrier for paracellular diffusion of hydrophilic drugs due to tight junctions (Huang et al., 1983; Hornof et al., 2005). Corneal epithelia efficiently prevents absorption of more than

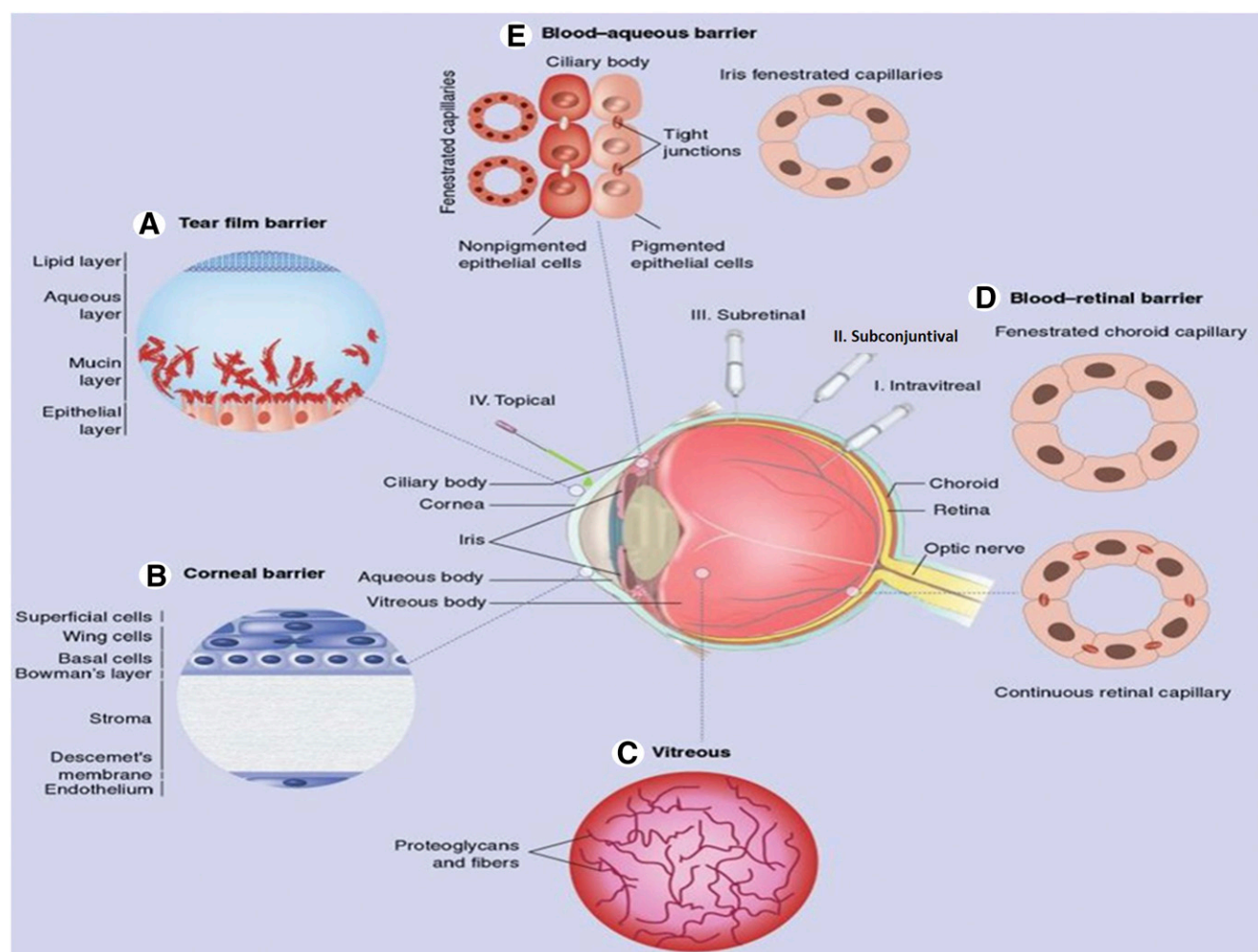


Fig. 1. Ocular anatomic barriers and routes of drug administration. Ocular barriers to topical administration (iv) of therapeutic agents to the anterior surface of the eye and to the posterior segment are illustrated. These include (A) tear film barrier; (B) corneal barrier; (C) vitreous barrier; (D) blood-retinal barrier and (E) blood-aqueous barrier. Various methods for drug delivery to the eye include; (I) intravitreal injection, (II) subconjunctival injection, (III) subretinal injection and (IV) topical administration. Topical administration of eye drops is one of the non-invasive route of administration and has minimum side effects. Intravitreal injections on the other hand are invasive, can cause retinal damage but can easily bypass all ocular barriers. While subconjunctival and subretinal injections can bypass some of the ocular barriers and are less invasive. (Alqawlaq et al., 2012).

10-Å molecules, with a higher drug-distribution coefficient limiting the barrier for hydrophobic drugs. Therefore, drug absorption requires overcoming corneal epithelia efficiently. Decrease in transcorneal diffusion of drug through the aqueous humor and expression of efflux transporters on the plasma membrane of corneal cells are major restrictions for drug delivery to the targeted ocular tissues. The use of prodrugs, permeation enhancers, and recent use of nanomicelles can enhance permeability of the drug through the corneal barriers (Cholkar et al., 2012; Huang et al., 2018).

While in the posterior segment of the eye, the scleral, choroidal, and retinal epithelial and the blood-retinal barrier account for limiting ocular drug bioavailability. The sclera provides higher trans-scleral permeability than the cornea for hydrophilic compounds diffusing through the collagen network. Permeation through the sclera is largely dependent on molecular weight, molecular radius, and charge. Macromolecules exhibit lower penetration through scleral pores than small molecules. This is the reason why macromolecules, including anti-VEGF agents, exhibit low diffusion through the sclera and are administered by intravitreal injections (Huang et al., 2018). The choroid is a vascular-natured dynamic barrier, which impedes drug delivery by the trans-scleral pathway (Tsai et al., 2018). The retina is a significant limiting factor for diffusion of molecules with a larger radius and a molecular mass greater than 76 kDa (Jackson et al., 2003). The inner limiting membrane of the retina severely confines the passage of macromolecules over 150-kDa molecular mass (Mordenti et al., 1999; Jackson et al., 2003; Tao et al., 2007). Moreover, the inner limiting membrane progressively restricts molecules with a larger radius. Retinal pigmented epithelia and choriocapillaries collaboratively produce Bruch's membrane. The thickness of Bruch's membrane increases with age, inhibiting drug transport into tissues and draining hydrophobic drugs through systemic circulation (Cholkar et al., 2012). The blood-retinal barrier (BRB) comprises two subdivisions, an outer BRB and an inner BRB. Both the outer BRB and inner BRB are permeation barriers between the blood and the retina

having tight junction proteins between the cells (Kamei et al., 1999; Achouri et al., 2013). The BRB also exhibits efflux transporters, which reduce bioavailability of several therapeutic agents (Mitra, 2009; Vadlapatla et al., 2014). The blood-aqueous barrier consists of an epithelial and an endothelial barrier. The permeability of drugs through the blood-aqueous barrier is determined by osmotic pressure and physical-chemical characteristics of drug molecules (Dubald et al., 2018). Ocular drug delivery presents a unique challenge due to its incredibly specialized tissue barriers that act as obstacles to therapies (Gaudana et al., 2010). Table 1 summarizes present routes of ocular therapy administration, and Fig. 1 details the anatomic makeup, indicating how each therapy travels to its active site.

Past Successes in Ocular Drug-Delivery Technologies

Drug Delivery to the Anterior Segment of the Eye

Topical delivery of ophthalmic formulations is the most preferred route for the delivery of therapeutic agents to the anterior segment of the eye. Ocular formulations (solutions, suspensions, emulsions, gels, and ointments) are most commonly used to treat common anterior segment disorders such as dry eye diseases, allergic conjunctivitis, and glaucoma (Kaur and Kanwar, 2002). Topical ocular administration gains merit over systemic ocular administration. This is because topical administration is (i) relatively non-invasive, (ii) minimizes systemic side effects of the drug, (iii) avoids first pass metabolism, (iv) reduces drug dosage due to localized drug delivery (v) and increases patient compliance due to ease of topical administration. Factors limiting absorption of topically applied ophthalmic formulations are high tear turnover rate (1 μ l/ml), loss of drug due to rapid blinking, reflex tear production, and limited absorption due to the tear-film barrier (Lee and Robinson, 1986; Schoenwald, 1990; Cholkar et al., 2013). To enhance the drug bioavailability, ophthalmic formulation requires a higher precorneal residence

TABLE 1
Comparison of various routes of ocular drug administration: benefits and obstacles (Gaudana et al., 2010)

Route	Benefits	Obstacles	Diseases/Disorders Treated
Topical	Patient compliance is high; self-administration and noninvasive nature	Corneal barrier difficult to penetrate; dilution and efflux via tears is high	Conjunctivitis, keratitis, uveitis, episcleritis, scleritis, blepharitis
Intravitreal	Direct delivery to retinal and vitreal structures; drug has high bioavailability	Patient compliance low; risk of retinal detachment, hemorrhage, development of endophthalmitis or cataracts	AMD, BRVO, CRVO, DME, CMV retinitis
Sub-Tenton	Relatively noninvasive, decreased risk of comorbidity compared with intravitreal delivery, maintains high vitreal drug levels	Retinal pigment epithelium is a barrier; subconjunctival hemorrhage, chemosis	DME, AMD, RVO, uveitis
Posterior juxtascleral	Advantageous for drug depository; avoids intraocular damage, and macula can sustain drug level for 6 mo	Retinal pigment epithelium barrier, and surgical procedure required;	AMD, risk of endophthalmitis
Systemic/oral	Promotes patient compliance, noninvasive mode of delivery	Retinal and blood-aqueous barriers; low bioavailability leading to systemic toxicity	Scleritis, episcleritis, CMV retinitis, posterior uveitis
Intracameral	Reduces systemic and corneal side effects vs. topical steroid use; high anterior chamber drug concentration	Toxic endothelial cell destruction syndrome and toxic anterior segment syndrome pose major risks to patients	Anesthesia, prevention of endophthalmitis, inflammation, pupil dilation
Subconjunctival	Anterior and posterior delivery method, ideal for depot formation	Choroidal and conjunctival circulation of therapies increases toxicity	Glaucoma, CMV retinitis, AMD
Retrobulbar	Minimal IOP involvement, ideal for high local anesthetic administration	Respiratory arrest, retrobulbar hemorrhage, globe perforation	Anesthesia

BRVO, branched retinal vein occlusion; CMV retinitis, cytomegalovirus retinitis; CRVO, central retinal vein occlusion; IOP, intraocular pressure.

time and an enhanced drug penetration. Therefore, a drug-delivery system offering longer retention and a sustained release of the drug molecule to pass through these barriers is essential (Khar et al., 2010; Reimondez-Troitiño et al., 2015). Novel drug-delivery technologies utilizing cyclodextrins, prodrugs, and colloidal systems such as nanoparticles, liposomes, and nanomicelles have been studied extensively (Tiruchera and Mitra, 2003; Gunda et al., 2006; Vaka et al., 2008). Conventional eye drops in the form of solutions, suspensions, and emulsions have been used over a long period of time to treat anterior segment disorders. The following section describes topical ophthalmic formulations in detail.

Ophthalmic Solutions. Topical eye drop solutions are patient-compliant, noninvasive, immediate-acting drug formulations. Eye drop solutions are instilled in the cul-de-sac, which is followed by a rapid first-order absorption into the corneal and conjunctival tissues. An increase in drug permeation and drug bioavailability can be attained by modifying the drug properties or properties of the drug-delivery system.

Modification of drug properties by utilizing prodrug strategy. Drug molecules require appropriate lipophilic and hydrophilic properties to overcome the ocular tear barrier and to reach the corneal membrane. The prodrug approach modifies the physiochemical properties of the drug for better absorption of the drug by passive or active diffusion (Mandal et al., 2016a,b). Once the prodrug reaches the corneal tissue, cellular enzymes cleave it into the active drug. Dipivefrine (Propine, Allergan) is an ester prodrug of epinephrine, that demonstrates a 17-fold higher corneal permeation, resulting in 10 times higher epinephrine bioavailability in the corneal tissues than the unmodified drug. Cyclosporine-A is a lipophilic drug, which poses a challenge for formulation development and corneal permeation. UNIL088 [(1R,2R,E)-1-((2S,5S,11S,14S,17S,20S,23R,26S,29S,32S)-5-ethyl-11,17,26,29-tetraisobutyl-14,32-diisopropyl-1,7,10,16,20,23,25,28,31-nonamethyl-3,6,9,12,15,18,21,24,27,30,33-undeca-oxo-1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontan-2-yl)-2-methylhex-4-en-1-yl N-(N-((1-acetoxyethoxy)carbonyl)-O-phosphono-L-seryl)-N-methylglycinate] is a hydrophilic prodrug of cyclosporine-A, demonstrating 25,000 times higher solubility than the parent drug at pH 7 (Lallemand et al., 2005). Another prodrug of cyclosporine-A (OPPH008) was characterized, and its efficacy in the treatment of dry eye disease was determined. OPPH008 achieved higher tissue concentrations as compared with a cyclosporine-A ophthalmic emulsion (Restasis, Allergan) in rabbit ocular tissues (Rodriguez-Aller et al., 2012). Prodrug strategy is also useful for reducing the dose of drugs with a narrow therapeutic index. Latanoprost is an ester prodrug of prostaglandin used to treat glaucoma. It has a higher bioavailability than the parent compound at lower doses (Kompella et al., 2010; Alm, 2014).

Modification of formulation properties.

I. Cyclodextrins for solubilizing hydrophobic drugs. Cyclodextrins are cyclic oligosaccharides arranged in a truncated cone-like structure. Cyclodextrins allow hydrophobic drugs to form complexes, enhancing drug solubility and bioavailability. Such complexation also improves corneal residence time and reduces local tissue inflammation (Achouri et al., 2013). Cyclodextrin complexation permits aqueous formulation of various drugs, including dexamethasone, chloramphenicol, and corticosteroids, for ocular disorders (Loftssona and Jarvinen, 1999; Loftsson and Stefansson, 2002; Sigurdsson et al., 2007). A study by Saari et al. (2006) concluded that 0.7% dexamethasone-cyclodextrin eye drops demonstrated significantly higher safety and efficacy as

an anti-inflammatory medication for postcataract inflammation than 0.1% dexamethasone sodium phosphate eye drops.

II. Viscosity and permeation enhancers. Ophthalmic formulations traditionally use viscosity enhancers to improve precorneal residence time of the drug. Various viscosity enhancers, such as hydroxyl propyl methylcellulose, polyalcohol, sodium carboxyl methylcellulose, and hydroxyl methylcellulose, improve drug retention time and absorption. Permeability of ophthalmic drugs is elevated by the addition of permeation enhancers (Achouri et al., 2013). Such agents temporarily adjust the corneal and conjunctival surface to facilitate rapid drug penetration. Ophthalmic preservatives such as benzalkonium chloride, surfactants such as polyethylene glycol, ethers, EDTA, chelating agents, and bile salts are a few examples of permeation enhancers that raise drug bioavailability (Burgalassi et al., 2001; van der Bijl et al., 2001, 2002; Hornof and Bernkop-Schnurch, 2002). Despite the various advantages offered by penetration enhancers, these agents can cause tissue irritation and damage the corneal and conjunctival tissues (Achouri et al., 2013).

Suspensions. Ocular suspensions are a dispersion of finely divided insoluble drug particles suspended in an aqueous medium containing dispersing and solubilizing agents. The precorneal cavity retains drug particles in suspension, enhancing the contact time of the drug. The particle size of the drug determines the time required for the absorption of the drug molecules into corneal tissue, thus ultimately affecting the drug bioavailability. Tobradex ST, Alcon, Inc. is a suspension of (0.3%) tobramycin and (0.05%) dexamethasone indicated for bacterial ocular infections (Scoper et al., 2008). Tobradex ST was developed from Tobradex to overcome the high viscosity of the initial formulation. Tobradex ST demonstrated higher tissue concentrations of the drugs tobramycin and dexamethasone in rabbits along with improvements in formulation quality and pharmacokinetic parameters. Clinical studies also showed similar results with higher concentrations of dexamethasone in the aqueous humor after Tobradex ST administration as compared with Tobradex. Yet another US Food and Drug Administration (FDA)-approved ophthalmic suspension is Besivance. (Bausch & Lomb) Besivance is a suspension of 0.6% besifloxacin and is prescribed to treat bacterial conjunctivitis. A multicenter, randomized, double-masked, vehicle-controlled clinical trial in adults and children demonstrated that administration of 0.6% besifloxacin ophthalmic suspension twice daily resulted in reduction of signs and symptoms of bacterial conjunctivitis (Silverstein et al., 2011). In another phase III study, 2% rebamipide suspension (OPC-12759) was effective for treatment of dry eye disease as compared with the control group (NCT00885079). Also, the formulation was well tolerated and demonstrated high efficacy for the treatment of dry eye disease (Diestelhorst et al., 1998; Kinoshita et al., 2012).

Emulsions. An emulsion is a biphasic system composed of two immiscible phases. Ophthalmic emulsions can offer advantages in improvement of drug solubility and bioavailability of previously water-insoluble drugs. Pharmaceutical emulsions can be widely categorized as water in oil and oil in water (o/w). Ophthalmic formulations widely use the o/w system, which consists of a hydrophobic drug mixed in oil and dispersed in an aqueous medium. An o/w emulsion is preferred over a water in oil emulsion for the reasons of better ocular tolerability and lower ocular irritation due to the external aqueous phase. Some examples of marketed ophthalmic eye drops are Restasis (Allergan), AzaSite (Akorn), Refresh Endura (Allergan), and Durezol (Alcon). Restasis is

a 0.05% emulsion of cyclosporine-A indicated for the treatment of dry eye disease. AzaSite is a 1% azithromycin ophthalmic emulsion used to treat bacterial conjunctivitis and various other ocular infections, while Refresh Endura is a nonmedicated emulsion for dry eye disease (Opitz and Harthan, 2012). Durezol is an emulsion of difluprednate, an anti-inflammatory corticosteroid used to treat anterior ocular uveitis. Studies have demonstrated that Durezol can be applied to treat DME and for the management of postoperative ocular pain and inflammation (Korenfeld et al., 2009; Kang-Mieler et al., 2014). Emulsions can sustain drug release, improve corneal drug absorption, and prolong the formulation residence time in the precorneal cavity. This helps in enhancing the bioavailability of lipophilic drugs for the treatment of anterior segment disorders (Liang et al., 2008).

Drug Delivery to Back of the Eye

Intravitreal Injections of Anti-VEGF Agents. The first indication of VEGF in ophthalmology can be traced back to 1940, when a group of scientists proposed that a diffusible factor was responsible for normal vasculature development. Imbalance in the particular factor resulted in neovascularization evident in proliferative DR. By the late 1990s, VEGF was identified as a potential mediator of choroidal neovascularization and intraocular neovascularization for patients suffering from AMD (Amin et al., 1994; Lopez et al., 1996). Proof-of-concept studies established that VEGF blockage resulted in inhibition of neovascularization in various animal models (Aiello et al., 1995; Zhu et al., 1999; Campochiaro and Hackett, 2003) and indicated VEGF blockage can be a potential new approach to overcome retinal disorders involving neovascularization (Adamis et al., 1996).

Forty years after cloning of VEGF, a humanized monoclonal antibody, bevacizumab (148 kDa), was developed as a VEGF-specific antibody. Bevacizumab was approved for treatment of various cancers, but soon its effectiveness in choroidal neovascularization was recognized. Currently, Avastin, Genentech (bevacizumab) is a realistic off-label treatment of wet AMD and DR. Pegaptanib sodium (Macugen, Bausch & Lomb) was the first antiangiogenic VEGF aptamer approved by the US FDA for the treatment of wet or nonvascular AMD in 2004. An intravitreal injection of pegaptanib sodium (pegylated anti-VEGF aptamer) alleviated the conditions of wet AMD and reduced vision loss (Gragoudas et al., 2004; Ng et al., 2006). Subsequently, an F(ab) fragment of bevacizumab, ranibizumab (49 kDa), was developed by Genentech (Presta et al., 1997). Ranibizumab demonstrated a higher binding affinity than pegaptanib to VEGF and better penetration into the retinal layers as compared with bevacizumab (Mordenti et al., 1999). Due to prior success of earlier clinical trials (phase I and phase II) of ranibizumab intravitreal injection, a phase III trial (MARINA) was conducted with 716 patients as a treatment of wet AMD. More than 94% of the patients in the treatment group showed signs of improved vision as compared with the control group ($P < 0.001$) (Rosenfeld et al., 2006). Now, Lucentis (ranibizumab intravitreal injection) has been approved for treatment of patients with neovascular (wet) AMD once every month (LUCENTIS, 2006). The most recent approved monoclonal antibody for the treatment of wet AMD is aflibercept (97 kDa), a recombinant fusion protein. Eylea (Regeneron Pharmaceuticals) (aflibercept, an intravitreal

injection) acts by blocking the action of VEGF and inhibiting neovascularization. Aflibercept has revealed approximately 200 times higher binding affinity to VEGF as compared with ranibizumab. While ranibizumab only binds to the VEGF-A isoform (Sarwar et al., 2016; Zhang et al., 2017), aflibercept binds to various isoforms of VEGFs (VEGF-A and VEGF-B) and placental growth factor. Binding of aflibercept to various growth factors suppresses all of the actions of VEGF and blocks many pathways, such as cell migration, cell proliferation, and cellular differentiation, leading to neovascularization. Both Eylea and Lucentis are biotech drugs extensively used in the form of intravitreal injections and now serve as the gold standard for the treatment of wet AMD and DME (Chang et al., 2012; Rodrigues et al., 2018).

Recent Inventions for Ocular Drug-Delivery Technologies

Anterior Segment Ocular Drug-Delivery Technologies

Punctum Plugs. Punctum plugs are biocompatible devices inserted in the tear ducts to block tear drainage. These are also known as occludes or lacrimal plugs, which have a size of 2–5 mm. Punctum plugs are noninvasive and can provide controlled drug release to the anterior segment of the eye. Construction of such ocular inserts is possible from nonbiodegradable and biodegradable materials. Nonbiodegradable punctum plug delivery systems (PPDS) are made from silicone, polycaprolactum, and hydroxyethyl methacrylate, which is intended to provide controlled drug release up to 180 days. After this period, the insert is removed. Recently, a PPDS (SmartPlug, Medennium Inc.) was developed from a thermosensitive hydrophobic acrylic polymer for the treatment of dry eye disease. The thermosensitive PPDS undergoes modification from rigid solid to a soft gel-like structure after insertion into the eye (<http://www.eyecconsultant.info/pdfs/smartplug.pdf>). Ocular Therapeutix (Bedford, MA) has developed OTX-TP (travoprost punctum plug insert) to deliver travoprost to the ocular tissues for 90 days. Currently, a phase III clinical trial is set for evaluating the safety and efficacy of OTX-TP for reduction of intraocular pressure (IOP) and ocular hypertension (NCT02914509). Recently, Ocular Therapeutix also completed a phase III clinical study for the safety and efficacy of OTX-DP (dexamethasone punctum plug insert) for the treatment of chronic allergic conjunctivitis and for treatment of inflammation after cataract surgery as compared with a placebo punctum plug (NCT02988882, NCT02736175). High efficacy and safety of OTX-DP led to the US FDA approval of Dextenza (dexamethasone insert; Ocular Therapeutix) for the treatment of pain following ophthalmic surgery (Dextenza, 2018). The company has also developed OTX-TP2 (a prostaglandin trap), which can be used for the treatment of glaucoma and postoperative ocular care (Kang-Mieler et al., 2014). Several clinical trials have been conducted to investigate the effectiveness of PPDS for the treatment of open-angle glaucoma, glaucoma, and ocular hypertension (NCT00650702, NCT01845038).

Subconjunctival/Episcleral Implants. Ocular implants can be inserted into the anterior segment of the eye for controlled drug delivery for a prolonged period. Such implants can be surgically inserted into the subconjunctival region, aqueous humor, and episcleral region. These implants provide

the advantage of sustained localized drug delivery and higher patient compliance as compared with topical eye drops. An insertion is made on the conjunctiva for the insertion of the implants. While some inserts are implanted in the junction between the conjunctiva and the sclera (Nicoli et al., 2009), others are inserted into the aqueous humor (Molokhia et al., 2013). Surodex (Allergan Inc.) is an example of an anterior segment insert, which is inserted into the anterior ocular segment post cataract surgery to alleviate postsurgery inflammation. Surodex is a rod-shaped biodegradable insert consisting of the drug dexamethasone using polymers such as poly lactide-co-glycolide (PLGA) and hydroxypropyl methyl cellulose, allowing sustained drug release for 7–10 days (Tan et al., 1999, 2001). A study demonstrated that a 7-day drug release with Surodex achieved higher concentrations as compared with maximum peak drug concentrations after topical treatment with dexamethasone eye drops (Tan et al., 1999). Lux Biosciences developed a silicone-based episcleral implant (LX201) for delivery of cyclosporine-A to the anterior ocular tissues for a period of 1 year. In a phase III clinical study, Lux Biosciences also evaluated the effectiveness of LX201 to prevent corneal graft rejection (NCT00447642).

Cul-de-sac Implants. The *cul-de-sac* of the eye is a pocket-like depression where the bulbar and palpebral conjunctiva meet in the upper or lower eyelid. Ocular devices such as Lacrisert (Bausch & Lomb) and Ocusert (Akorn) are examples of cul-de-sac implants designed for drug delivery to the anterior segment of the eye. These devices are safer and less invasive than the conjunctival and episcleral implants. Lacrisert (Bausch & Lomb) is a hydroxypropyl cellulose implant inserted into the inferior cul-de-sac. The implant is suitable for patients with moderate to severe dry eye disease (McDonald et al., 2009). Lacrisert decreased corneal sensitivity, recurrent corneal erosions, and exposure to keratitis. It is also effective for the treatment of conjunctival hyperemia (Lacrisert, 1988). Lacrisert releases cellulose, allowing maintenance of tear film integrity. The implant acts as a lubricant and helps to protect the ocular surface. However, Lacrisert can cause discomfort. It causes foreign body sensation, ocular irritation, hypersensitivity, hyperemia, and blurry vision. Ocusert is a drug-eluting implant delivering pilocarpine over a period of 7 days and directed for the treatment of glaucoma. However, pilocarpine in the insert caused unwanted side effects, such as eyebrow ache and miosis. This resulted in removal of Ocusert from the market (Pollack et al., 1976). Yet another cul-de-sac implant is DSP-Visulex (Aciont Inc., Salt Lake City, UT), which has completed a phase II clinical trial for the treatment of anterior uveitis (NCT02309385). DSP-Visulex contains dexamethasone and is inserted into the bulbar conjunctiva (Papangkorn et al., 2018).

Drug-Eluting Contact Lenses. Drug-eluting contact lenses (CLs) are light-transparent corneal dressings acting as drug reservoirs and sustaining drug discharge near the postlens tear fluid for the treatment of anterior ocular disorders. Drug-loaded soft contact lenses are an innovative drug-delivery system to not only prolong and sustain drug release but also enhance drug penetration across the corneal epithelium as compared with conventional eye drops. Contact lenses can increase bioavailability of the drug by increasing the contact time of the drug (Mandal et al., 2017a). Various soft contact lenses have been developed for antifungal agents, which can prolong drug delivery up to 21 days (Phan et al., 2014). A clinical trial was conducted for evaluation of the

safety and efficacy of drug-eluting contact lenses for the management of glaucoma. The contact lenses are loaded with timolol maleate and dorzolamide HCl along with vitamin E as an additive for achieving sustained drug release (NCT02852057). Various technologies have been used to load drugs on contact lenses instead of just soaking the lens with the drug. Recently, Gulsen and Chauhan (2004) advanced a novel drug-eluting contact lens, which embedded lidocaine-laden nanoparticles. The investigators studied the drug release from the formulation and observed a sustained lidocaine release in vitro over 7 to 8 days (Gulsen and Chauhan, 2004). Similarly, Ciolino et al. (2009) fabricated a drug-eluting contact lens using a polymer-embedded matrix for ciprofloxacin and econazole. The in vitro data demonstrated a zero-order drug-release profile, which can sustain drug release up to 1 month (Ali et al., 2007; Ciolino et al., 2009). Figure 2 depicts the advantage of soft drug-loaded contact lenses over conventional eye drops.

Contact lenses offer the highest drug bioavailability as compared with other noninvasive ophthalmic medications due

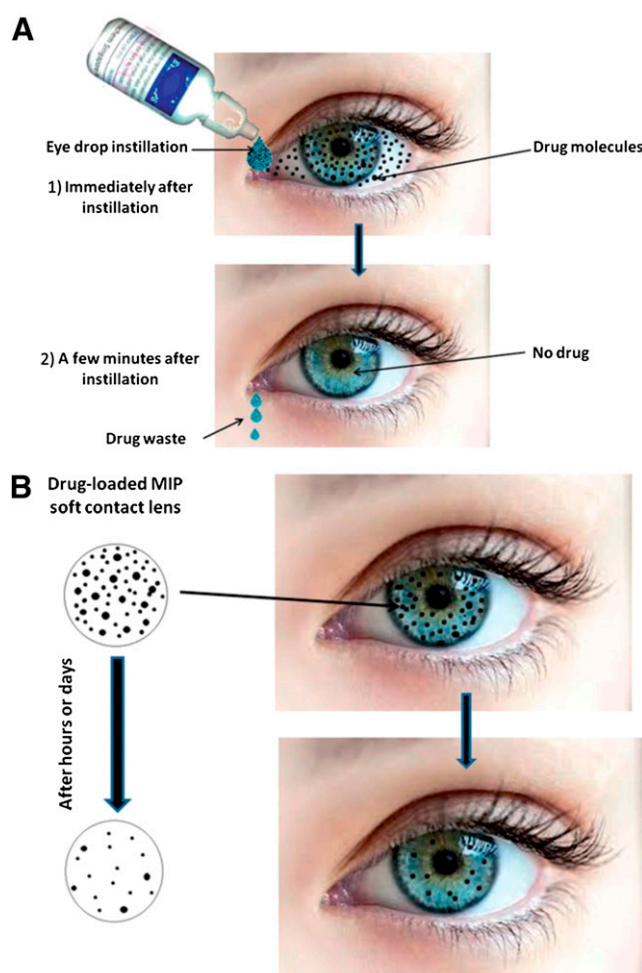


Fig. 2. Ocular drug-delivery system using drug-loaded soft contact lenses. (A) Ophthalmic drugs delivered through conventional eye drops. Majority of the drug administered gets drained a few minutes after instillation. (B) Drug delivery through molecularly imprinted soft contact lenses. This approach can increase the residence time of the drug molecules on the ocular surface increasing drug bioavailability as compared to conventional eye drop formulations. (Tashakori-Sabzevar F et al. 2015). MIP: molecularly imprinted polymer.

to close proximity of the contact lens with the cornea. They also provide a significant dosing advantage as compared with frequent topical eye drops. Many drug-eluting contact lenses have been developed, but none of them are yet US FDA-approved. The major challenge faced by this therapy is successful demonstration of significantly higher safety and efficacy over conventional eye drops. A prolonged use of contact lenses can be associated with corneal toxicity (Dumbleton, 2002). Many factors, including oxygen diffusion, microbial resistance, and effective and continuous drug release, are yet to be addressed for successful commercialization of contact lenses (Malthiery et al., 1989; Dixon et al., 2015).

Bioinspired hydrogels for drug-eluting CLs are the current state-of-the-art technology for ocular delivery. Most bioinspired contact lenses appear to reverse the engineering process to generate binding sites inside CLs for drug molecules which mimic the natural receptors. Such molecularly imprinted hydrogels with specific binding affinity used for making drug-eluting contact lenses allow enhanced drug loading and, consequently, prolong drug-release kinetics. Each synthetic molecule is designed selectively to fit a natural receptor in the human body to trigger the pharmacological effects. The bioinspired strategy contains the hydrogel polymers which form the spatial arrangement of the active site, where the drug can bind and be loaded on the CLs. Molecular imprinted CLs mimic this environment in synthetic receptors for higher drug loading in the CLs (Alvarez-Lorenzo et al., 2019).

Ocular Iontophoresis. Ocular iontophoresis is a method for active drug delivery utilizing mild electric charges for effective delivery through the ocular barriers. Iontophoresis enhances ocular drug delivery by utilizing electroporation (electric field-induced ocular tissue structure alteration and pore formation), electrophoresis (direct application of electric field), and electro-osmosis (convective solvent flow through an applied electric potential). Iontophoresis is a noninvasive method having advantages over invasive techniques requiring surgical interventions. This technique of drug permeation can be used for anterior and posterior ocular disorders by utilizing trans-corneal and trans-scleral routes, respectively. Trans-corneal iontophoresis can be used for treatment of anterior segment disorders such as corneal ulcers, dry eye disease, ocular inflammation, keratitis, and ocular uveitis. Trans-corneal iontophoresis is unsuitable for posterior segment delivery due to the presence of barriers such as the lens diaphragm and iris-ciliary. However, the trans-scleral pathway allows drug transport at the back of the eye due to avoidance of anterior segment barriers (Molokhia et al., 2013). The success of iontophoresis-mediated drug delivery depends on several factors, such as charge density of the intended molecule, electric current applied, duration of treatment application, and position of electrode placement (Molokhia et al., 2007; Gratieri et al., 2017).

EyeGate Pharmaceuticals Inc. has developed trans-scleral iontophoresis for delivering drugs in the intended target tissues. The company conducted several clinical trials on the safety and efficacy of a dexamethasone phosphate (EGF-437) formulation for distribution through the EyeGate II Delivery System for the treatment of dry eye disease, anterior uveitis, cataract, postoperative pain, anterior chamber inflammation, and anterior scleritis (NCT01129856, NCT02517619, NCT03180255, NCT01059955). EGF-437 delivered through

the EyeGate II Delivery System resulted in reduction of dose frequency as compared with standard dexamethasone eye drops. The US FDA has granted an orphan drug designation for the delivery of EGF-437 through the EyeGate II Delivery System as a treatment option for corneal graft rejection. Iontophoresis is a valuable treatment option for patients who are nonresponsive to eye drop therapy (Kompella et al., 2010). The treatment also resulted in fewer incidences of increased IOP and controlled drug delivery with lower iontophoresis dose (mA-min) (<http://www.eyegatepharma.com/technology/iontophoresis-delivery-system/>). Visulex-P (Aciont Inc.) and OcuPhor (Iomed Inc., Salt Lake City, UT) are ocular iontophoresis systems currently under investigation for trans-scleral iontophoresis.

Iontophoresis has certain advantages over other ocular drug-delivery modalities, including injections and topical drops. It can achieve higher bioavailability and reduced clearance as compared with topical eye drops. Treatment with the iontophoresis method usually has better patient compliance as compared with ocular injections. Nonetheless, certain patients screened for ocular iontophoresis experienced some discomfort and burning sensation (Parkinson et al., 2003). Posterior segment ocular disorders such as AMD, DR, DME, and central retinal vein occlusion (CRVO) require sustained drug delivery at higher doses. Aciont Inc. has evaluated the potential of ocular iontophoresis for the treatment of AMD by a Visulex-I-noninvasive ocular drug device for the delivery of Avastin (bevacizumab) and Lucentis (ranibizumab) through the trans-scleral route (<https://www.sbir.gov/sbirsearch/detail/1070943>) (Pescina et al., 2010). Table 2 summarizes currently available ocular drug-delivery devices in clinical trials for the management of anterior segment disorders.

Posterior Segment Ocular Drug-Delivery Technologies

Novel drug-delivery systems, such as implants, are currently used by the clinicians to sustain and prolong drug release to cure back of the eye disorders such as DR, AMD, DME, retinal vein occlusion (CRVO), and posterior uveitis. Intravitreal implants are injected or surgically implanted in the vitreous humor of the eye. Intravitreal implants can prolong the drug action up to many months and reduce the need for frequent intravitreal injection of therapeutic agents. Such frequent administration can cause retinal detachment and retinal hemorrhage, and can be painful for the patients. Such disadvantages of intravitreal injections can be minimized with the use of intravitreal implants. The following section illustrates various intravitreal ocular implants currently available in the clinic and those under clinical investigation.

Durasert Drug-Delivery Technology System. The Durasert technology system (pSivida Corp., Watertown, MA) delivers drugs at various predetermined time points depending on the implant design. The drug release ranges from days to years. Durasert consists of a drug core with surrounding polymer layers. The drug release is a function of the polymer layer permeability. Vitrasert (Bausch & Lomb) is the first intravitreal drug-delivery system loaded with an antiviral drug (ganciclovir) for the treatment of cytomegalovirus retinitis. It utilizes the Durasert technology system and releases the active drug through a small opening in the insert for a period of 6–8 months (Chang and Dunn, 2005). The Retisert

TABLE 2
Currently available ocular drug-delivery systems in clinical trials for the treatment of anterior segment disorders (Kang-Mieler et al., 2014)

Drug	Brand Name	Mode of Administration	Excipient Controlling Release Characteristic of Drug	Target Indication	Developmental Stage	Clinical Trial #
Azithromycin	AzaSite (Akorn, Inc.)	Eye drops	Polycarbophil (DuraSite)	Bacterial conjunctivitis	Launched	NCT00105469
Azithromycin/dexamethasone (ISV-502)	AzaSite Plus (Akorn Inc.)	Eye drops	Polycarbophil (DuraSite)	Blepharoconjunctivitis	Launched	NCT00578955
Betaxolol	Betoptic S (Novartis pharmaceuticals)	Eye drops		Glaucoma	Launched	NCT000061542
Bimatoprost	Lumigan (Allergan)	Eye drops		Glaucoma	Launched	NCT01589510
Bromfenac	Prolensa (Bausch & Lomb)	Eye drops		Postoperative inflammation	Launched	NCT01847638
Cyclosporine-A	Restasis (Allergan Inc.)	Eye drops	Cationic emulsion	Dry eye due to keratitis sicca	Launched	NCT02554981
Difluprednate	Durezol (Novartis Pharmaceuticals)	Eye drops	Emulsion	Anterior uveitis	Launched	NCT01201798
Timolol maleate	Timoptic (Bausch & Lomb)	Eye drops		Glaucoma/intraocular hypertension	Launched	
Tobramycin/dexamethasone	TobraDex ST (Novartis Pharmaceuticals)	Eye drops	Xanthan gum	Blepharitis	Launched	NCT01102244
Timolol maleate	Timoptic-XE (Merck & Co., Inc)	Eye drops	Gellan gum	Glaucoma	Launched	NCT01446497
Ophthalmic emulsion	Cationorm (Santen Pharmaceuticals)	Eye drops	Cationic emulsion	Mild dry eye	Launched	NCT03460548
Travoprost	iStent Inject (Glaukos Healthcare)	Punctum plug		Open-angle glaucoma	Phase IV	NCT03624699
Cyclosporine (LX201)	EyeGate II (Eye Gate Pharma)	Episcleral implant	Silicone	Keratoconjunctivitis	Phase III	NCT00447642
Dexamethasone phosphate (EGP-437)		Iontophoresis		Anterior uveitis	Phase III	NCT01129856
Dexamethasone (OTX-DP)		Punctum plug	Hydrogel	Postoperative inflammation	Phase II	NCT00650702
Latanoprost	Durasert (pSivida Corp.)	Subconjunctival insert	PLGA	Glaucoma	Phase I/II	NCT00224289
Loteprednol etabonate mucus-penetrating particles	Inveltys (Kala Pharmaceuticals, Inc)	Nanoparticle	Mucus-penetrating particles	Kerato conjunctivitis sicca	Phase III	NCT03616899
Urea		Nanoparticle	Amphiphilic block copolymer PluronicF-127	Cataract	Phase II	NCT03001466
Omega-3 fatty acids	Remogen Omega (TRB Chemedica)	Microparticle	Microemulsion of polyunsaturated fatty acids and hydrating polymers	Dry eye disease	Phase I/II	NCT02908282

intravitreal implant (Bausch & Lomb, Inc.) is a steroid-eluting device implanted surgically in the vitreous humor. Retisert releases fluocinolone acetonide up to 3 years into the vitreous humor (Jaffe et al., 2006; Kempen et al., 2011). Retisert has received a fast-track US FDA approval for treatment of posterior uveitis as an orphan drug treatment. Posterior uveitis, also called choroiditis, is the inflammation of the choroid capillaries. This can lead to damage to the optic nerve and permanent loss of vision. Retisert contains a fluocinolone acetonide tablet encapsulated within a silicone elastomer cup containing an orifice made with a polyvinyl alcohol membrane (Haghjou et al., 2011).

Iluvien (fluocinolone acetonide intravitreal implant, Alimera Sciences, Inc.) is the most recent US FDA-approved intravitreal injectable insert indicated for the treatment of DME. Multicenter, randomized clinical trials demonstrated that both a low dose and high dose of Iluvien resulted in a significant visual improvement with lower side effects. The onset of treatment was very rapid. Patients suffering from DME for more than 3 years had received almost twice the treatment effectiveness as compared with the control group (Campochiaro et al., 2012; Cunha-Vaz et al., 2014). Iluvien is being evaluated in phase II clinical trials for its efficacy of dry AMD (NCT00695318), wet AMD (NCT00605423), and macular edema secondary to RVO as compared with Lucentis (ranibizumab) treatment (NCT00770770).

NOVADUR Drug-Delivery Technology. The NOVADUR (Allergan Inc.) system consists of therapeutic agents in a polymer matrix of PLGA. PLGA is a biodegradable and biocompatible polymer which breaks down to lactic and glycolic acid when it comes in contact with the vitreous humor fluid (Haghjou et al., 2011). Ozurdex (Allergan) is a controlled-release intravitreal dexamethasone implant approved by the US FDA for the treatment of DME, RVO, and posterior uveitis (Haller et al., 2011; Boyer et al., 2014; Sangwan et al., 2015). Ozurdex contains 0.7 mg of dexamethasone in a PLGA matrix which releases the drug up to 90 days. Mayer et al. (2012) recently investigated the effects of intravitreal bevacizumab followed by Ozurdex and Ozurdex monotherapy for the treatment of CRVO and macular edema. The research group concluded that there was no difference between the aforementioned treatment strategies for treatment of CRVO. However, for branched retinal vein occlusion, Ozurdex monotherapy resulted in a better functional outcome (Mayer et al., 2012). Currently, a phase III clinical trial is being conducted for the possible effectiveness of intravitreal implant of Ozurdex monotherapy for the treatment of DME (NCT00168389). PLGA containing brimonidine tartrate (Allergan) is another intravitreal implant in clinical trials for dry AMD (NCT00658619) and retinitis pigmentosa (NCT00661479). Brimonidine is an α_2 adrenergic agonist which releases neurotrophic factors such as ciliary neurotrophic factor and brain-derived neurotrophic factor (Kim et al., 2007). Brimonidine protects retinal cells like photoreceptor cells, RPE and ganglion cells from apoptotic cell death. (Zhang et al., 2009).

I-vation Triamcinolone Acetonide Drug-Delivery Technology. I-vation TA (SurModics Inc.) is also an intravitreal drug-delivery implant for triamcinolone acetonide (TA). I-vation is a titanium helical coil implant coated with TA in a nonbiodegradable polymer. Preclinical experiments suggested that I-vation TA can sustain TA release in vivo up to 2 years. A phase I safety and preliminary efficacy study was

conducted in 31 patients with DME after implantation of I-vation TA. The TA intravitreal implant was well tolerated by the patients as indicated by a minimal rise in IOP. The I-vation TA treatment also aided the reduction of macular thickness from baseline, indicating alleviation of DME (Dugel et al., 2009).

Encapsulated Cell Technology. Renexus (NT-501) is an encapsulated cell technology (ECT) for ocular implant of human RPE transfected with plasmid encoding ciliary neurotrophic factor. Renexus (NT-501) is under a phase III investigation for dry AMD, glaucoma, and retinitis pigmentosa (NCT03316300). The implant consists of a hollow tube capsule consisting of a polymeric matrix which can be loaded with genetically modified cells (Sieving et al., 2006; Emerich and Thanos, 2008). Various biocompatible polymers such as collagen and hyaluronic acid hydrogel are used for forming the ECT matrix. The implant capsule is semipermeable, allowing diffusion of proteins across the membrane but inhibiting the entry of immune cells. The genetically modified cells in the matrix draw nutrients from the surrounding tissue after implantation. The encapsulated cell technology is implanted in the pars plana and affixed to the sclera.

ECT can be advantageous as compared to other corticosteroid implants as they can secrete biologically active molecules for a prolonged period of time, requiring less frequent implant replacement. Kontturi et al. (2015) demonstrated genetically modified RPE capable of secreting soluble VEGF receptor to suppress VEGF activity in choroidal neovascularization and retinal neovascularization. This proof-of-concept study indicated that the human RPE cell line remained viable with a constant secretion of soluble VEGF-1 receptor up to 50 days (Kontturi et al., 2015). Although the researchers found a modest VEGF inhibition in vivo model, this delivery technology displays promise for utilization of ECT to treat disorders such as wet AMD, DR, and DME. ECT can be considered as a versatile platform that can be used for secreting targeted therapeutic biotech drugs such as antibodies, antibody fragments, growth factors, cytokines, and prostaglandins for back of the eye disorders (Tao, 2006). Wong et al. formulated an injectable composite alginate-collagen (CAC) matrix ECT gel having human retinal pigment epithelial cells and glial cell-derived neurotrophic factor (GDNF) secreted by HEK293 cells. The GDNF-secreting HEK293 cells were transfected with lipofectamine repressor (Tet R) DNA and pro-caspase 8 transcription DNA. Tet R can be used as a biosafety switch for the ECT drug-delivery system, whereas pro-caspase 8 can trigger the in-built apoptotic pathway in the retinal cells. The researchers witnessed a continuous supply of bioactive glial cell-derived GDNF in vitro and effective proliferation control in rat ocular tissues. Intravitreal injections of CAC ECT in rats with retinal damage resulted in decreased apoptosis of photoreceptor and retinal function loss. Similarly, dual intravitreal injections of the ECT resulted in further reduction of photoreceptor death and gain of retinal structure and function without compromising gel viability (Fig. 3). The CAC ECT demonstrated high encapsulation efficiency of the transfected cells, high cell viability, and high mechanical stability of the implant without the use of immunosuppressant (Wong et al., 2019). Thus, ECT can be considered as a safe, effective, and well controlled platform for the treatment of back of the eye disorders with retinal dysfunction (Baranov et al., 2017).

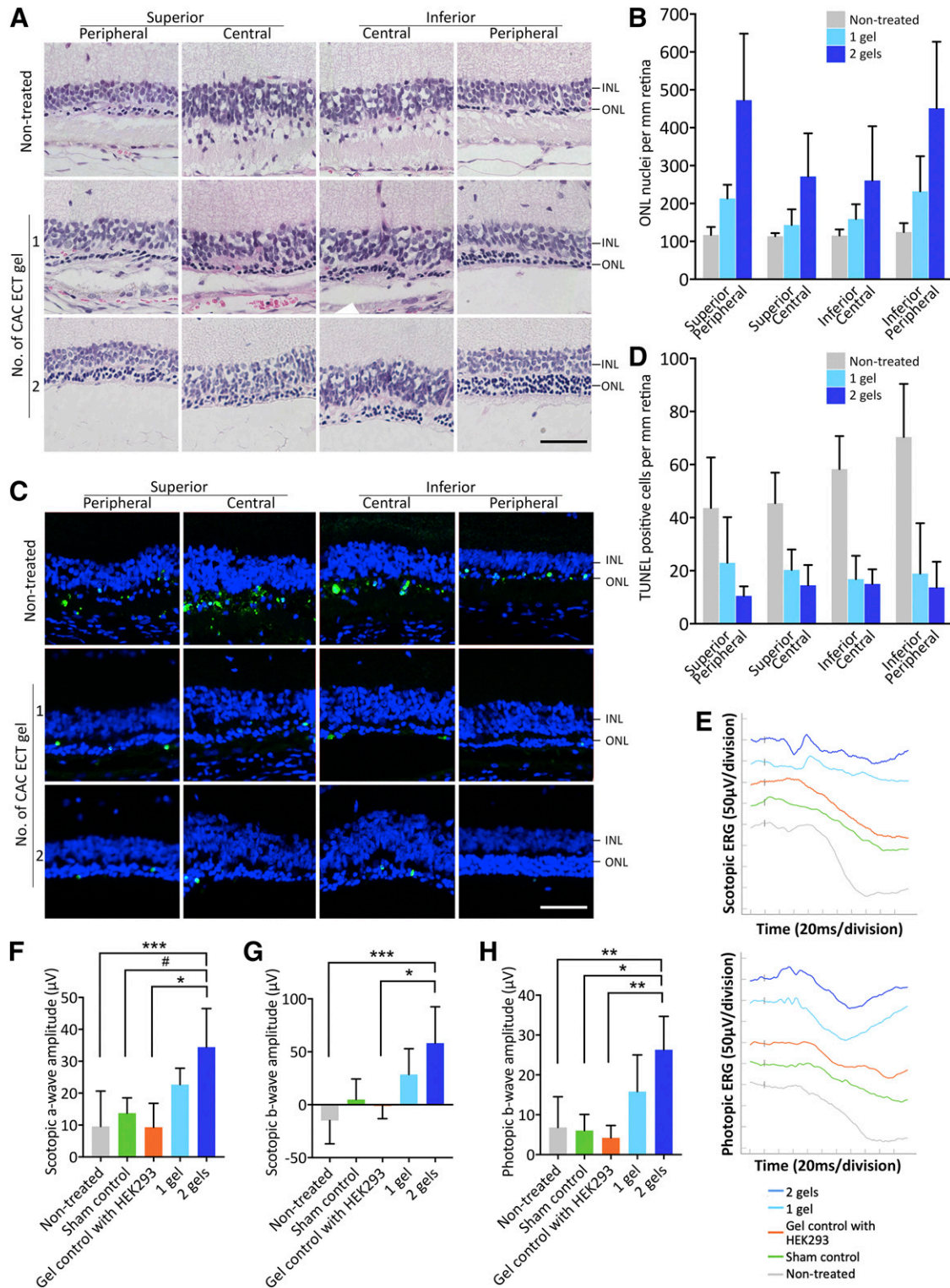


Fig. 3. ECT for back of the eye disorders. CAC ECT gel treatment on rats with inherited retinal degeneration. One or two units of GDNF-delivering CAC ECT gel was intravitreally injected into the eyes of dystrophic RCS/lav rats. (A) Representative H&E sections of nontreated, single, and double gel-treated rats showed different degrees of photoreceptor nuclei retention and organization in the outer nuclear layer (ONL). (B) ONL nuclei density was calculated by normalizing ONL count with retinal length. (C) Representative images showing the distribution of apoptotic cells (green) in the retina of nontreated, single, and double gel-treated animals detected by terminal deoxynucleotidyl transferase-mediated digoxigenin-deoxyuridine nick-end labeling (TUNEL) assay with 4',6-diamidino-2-phenylindole (DAPI) nuclear counterstaining. (D) Density of apoptotic cells in the ONL. (E) Representative scotopic and photopic electroretinogram wave forms showing the retinal function of dystrophic rats receiving 1 or 2 U of GDNF-secreting gel. (F) Scotopic a-wave. (G) Scotopic b-wave. (H) Photopic b-wave. # $P < 0.05$; * $P \leq 0.02$; ** $P \leq 0.005$; *** $P < 0.0005$ by one-way ANOVA with Bonferroni post hoc test (Wong et al., 2019). ERG, electroretinogram; INL, inner nuclear layer.

TABLE 3
 Currently available ocular drug-delivery systems in clinical trials for the treatment of posterior segment disorders (Kang-Mieler et al., 2014)

Drug	Brand Name	Mode of Administration	Excipient Controlling Release Characteristic of Drug	Target Indication	Developmental Stage	Clinical Trial #
Dexamethasone	Ozurdex (Allergan)	Intravitreal implant	PLGA (Novadur)	Macular edema	Launched	NCT01427751
Ganciclovir	Vitraser (Auritec Pharmaceuticals Inc.)	Intravitreal implant	PVA/EVA	Posterior uveitis	Launched	NCT00000135
Fluocinolone acetonide	Retisert (Bausch & Lomb)	Intravitreal implant	PVA	CMV retinitis	Launched	NCT00570830
Verteporfin	Visudyne (Bausch & Lomb)	i.v. injection	Liposome	Posterior uveitis	Launched	NCT00242580
Dexamethasone	Dexycu (EyePoint Pharmaceuticals, Inc.)	Intravitreal implant	Acetyl triethyl citrate	Wet AMD	Launched	NCT02547623
Difluprednate	Durezol (Novartis Pharmaceuticals)	Eye drops	Emulsion	Postoperative inflammation	Off-label	NCT00429923
Betamethasone	Renexus (Neurotech Pharmaceuticals)	Intravitreal implant	Chroninject	DME	Phase II/III	NCT01546402
CNTF (NT-501)	Renexus (Neurotech Pharmaceuticals)	Intravitreal implant	Semipermeable hollow fiber membrane/NTC-200	Atrophic AMD	Phase II/III	NCT03316300
Dexamethasone	Iluvien (Alimera Sciences)	Eye drops	Cyclodextrin microparticles	DME	Phase II	NCT01523314
Fluocinolone acetonide		Intravitreal implant	Polyamide/PVA	Posterior uveitis	Phase IV	NCT01304706
Triamcinolone acetonide with ranibizumab				Macular edema	Phase II/III	
Brimonidine		Intravitreal injection	Verisome	Wet AMD	Phase II	NCT02806752
Triamcinolone acetonide (IBI-20089)		Intravitreal implant	PLGA	Dry AMD	Phase II	NCT02087085
Triamcinolone acetonide (RETAAC)		Intravitreal implant	Benzyl benzoate	RP	Phase I/II	NCT01175395
Dexamethasone produg (NOVA-63035)		Intravitreal implant	PLGA	Wet AMD	Phase II	
Ranibizumab VEGFR-Fc (NT-503)	Cortiject (Novagali Pharma S.A)	Intravitreal implant	Emulsion	DME	Phase I/II	NCT00407849
Human embryonic stem cell-derived retinal pigment epithelium (MA09-hRPE) cells		Drug port	Refillable port	DME	Phase I	NCT00665106
AR-1105 (dexamethasone implant)		Intravitreal implant	Semipermeable hollow fiber membrane/NTC-200	Wet AMD	Phase I	NCT03677934
		Cells transplantation via subretinal injection	Cell suspension	Wet AMD	Phase I	NCT02228304
		Intravitreal implant	Biodegradable implant	Advanced dry AMD	Phase I/II	NCT01344993
				Macular edema due to RVO	Phase II	NCT03739593

CMV retinitis, cytomegalovirus retinitis; CNTF, ciliary neurotrophic factor; EVA, Ethylene-vinyl acetate copolymer; PVA, Poly(vinyl alcohol); RP, Retinitis pigmentosa.

Suprachoroidal Drug Delivery Utilizing Hollow Micro-needles and Microsurgical Cannulas. Delivery of therapeutics at the suprachoroidal space has demonstrated promising potential for delivering therapeutic agents at the target tissue (retina and choroid) at a higher concentration. This can be confirmed from anatomic studies demonstrating the diffusion of therapeutic agents after drug delivery at the suprachoroid space (Patel et al., 2012; Kadam et al., 2013; Chiang et al., 2016). Patel et al. (2012) demonstrated suprachoroid drug delivery through the posterior pars plana of a rabbit model using a hollow microneedle. The suprachoroid drug delivery was a minimally invasive procedure demonstrating safe delivery into the retina and choroid with no adverse effects. Gilger et al. (2013) reported the successful suppression of acute inflammation with corticosteroid delivered through the suprachoroid route in a porcine model of noninfectious posterior uveitis. Drug delivery through the suprachoroid route utilizing microsurgical cannulas in primate and procaine models has shown increased drug bioavailability. The researchers investigated delivery of triamcinolone acetonide and bevacizumab to evaluate the tolerability, safety, efficacy, and pharmacokinetics of suprachoroidal drug-delivery technology. Higher bioavailability of triamcinolone acetonide at the target tissue without deleterious side effects such as cataract and hypertension suggests its positive impact (Olsen et al., 2006). In contrast, bevacizumab demonstrated low bioavailability at target tissue with faster diminishing therapeutic response as compared with intravitreal injections (Olsen et al., 2011). Currently, various phase III clinical trials utilizing triamcinolone acetonide suprachoroidal injection along with various anti-VEGF agents are being investigated for the treatment of DME and posterior uveitis (NCT03203447, NCT02980874, NCT01789320). Table 3 summarizes currently available ocular drug-delivery systems in clinical trials for the treatment of posterior segment disorders.

Novel Ocular Drug-Delivery Technologies

Colloidal Nanocarriers for Anterior Segment Disorders

The chronic nature of many ocular disorders requires frequent and prolonged drug treatments. Along with this, ocular barriers reduce the bioavailability of the topically applied therapeutic agents to less than 5%. Recent developments in nanotechnology can provide opportunities to overcome drawbacks and limitations of conventional drug-delivery systems, such as low drug bioavailability and low drug permeation through ocular barriers. Nanocarriers can prolong drug action by sustained and controlled release of the drug, protect the drug from ocular enzymes, and aid in overcoming ocular barriers. This can greatly reduce the frequency of dosing and improve tissue concentrations of the drug for better pharmacological action. Colloidal nanocarriers including nanoparticles, nanomicelles, nanowafers, and microneedles are capable of encapsulating small molecules and biotech drugs for ocular delivery. The size of the nanocarriers ranges from 1 to 1000 nm. Nanoparticles greater than 10 μm can cause foreign body sensation and ocular irritation (Ali and Lehmussaari, 2006; Liu et al., 2012). Nanocarriers can also improve the ability of drug penetration into the deeper ocular tissues, decrease drug toxicity, and reduce precorneal drug loss taking place due to rapid tear turnover. Nanocarriers

engineered from biodegradable and biocompatible polymers overcome ocular barriers and result in higher drug absorption in the anterior and posterior segments of the eye (Reimondez-Troitiño et al., 2015). Nanomedicine for ocular drug delivery can be highly patient compliant and have a higher tolerability than conventional eye drops for anterior segment ocular disorders (Vandervoort and Ludwig, 2007; Bachu et al., 2018; Mandal et al., 2019a).

Nanomicelles. Nanomicelles are colloidal drug-delivery systems that self-assemble in a solution and can entrap therapeutic agents at their core. Their size ranges from 10 to 200 nm, and they are made up of amphiphilic surfactants or block copolymers. Nanomicelles are formed instantaneously in a solution when the concentration of the polymers is above a specific concentration called the critical micellar concentration. Nanomicelles have the capacity to encapsulate hydrophobic drugs in the hydrophobic core of the micelles due to hydrophobic interactions. The hydrophilic corona interacts with the external aqueous fluid, increasing the solubility of a relatively lipophilic drug. This colloidal dosage form has the ability to form clear aqueous solutions which can be used as topical eye drops. Nanomicelles can be broadly classified as surfactant nanomicelles and polymeric nanomicelles. Cequa

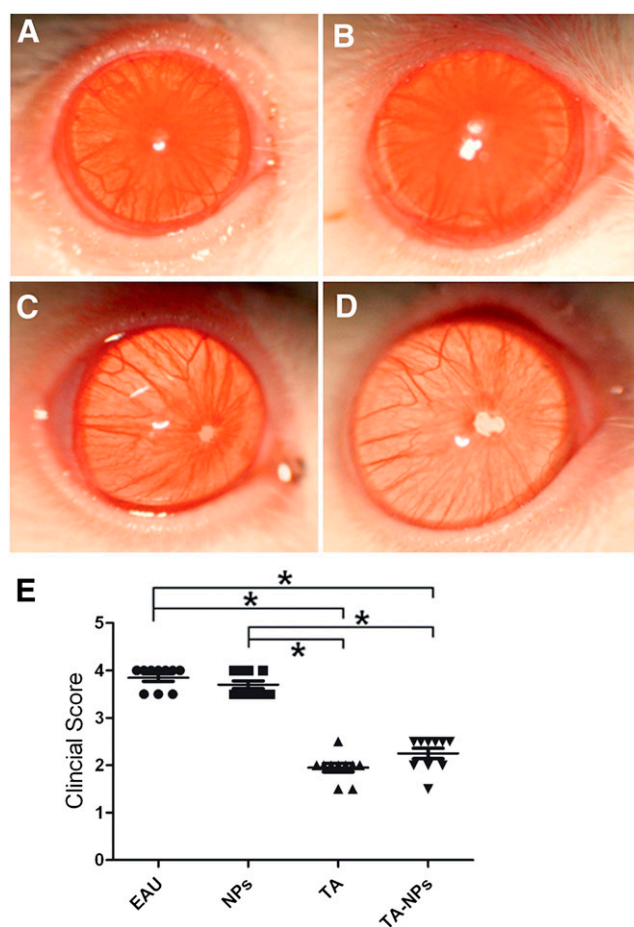


Fig. 4. TA-encapsulated methoxy PEG (mPEG)-PLGA nanoparticles for treating experimental autoimmune uveitis (EAU). (A–D) photographs taken by a hand-held retinal camera on day 12 after treatments: the EAU group (A), the mPEG-PLGA nanoparticle-treated group (B), the TA injection-treated group (C), the TA-loaded mPEG-PLGA nanoparticle-treated group (D), and clinical scores in the different groups (E).

(Sun Pharmaceuticals Inc.) is a nanomicellar formulation of 0.09% cyclosporine-A recently approved by the US FDA for dry eye disease. Cequa demonstrated improved rapid onset of action as early as 4 weeks and improvement in tear production as compared with cyclosporine-A emulsion in phase II and phase III clinical trials (Mandal et al., 2019a). The *in vivo* studies of the nanomicellar formulation of cyclosporine-A conducted in rabbits demonstrated enhanced bioavailability in the anterior ocular tissues as compared with cyclosporine-A emulsion with no ocular adverse effects. Here, the nanomicellar system was prepared from a polymeric mixture of two low-molecular-weight surfactants, hydrogenated castor oil-40 and octoxynol-40, which resulted in formation of a clear solution of cyclosporine-A. Mitra et al. demonstrated efficient encapsulation and enhanced ocular pharmacokinetics of

hydrophobic drugs such as voriconazole, cyclosporine-A, rapamycin, triamcinolone acetonide, cidofovir prodrug, and curcumin for the treatment of various anterior and posterior ocular disorders neurotropic. Various surfactant polymers such as vitamin E tocopheryl polyethylene glycol succinate (Vit E TPGS); hydrogenated castor oil-40,60,100; and octoxynol-40 were used for entrapping hydrophobic drugs in the nanomicellar core (Cholkar et al. 2015, Mandal et al., 2017b, 2019b, Trinh et al., 2017). Mandal et al. demonstrated the entrapment of hydrophobic drug and hydrophilic peptides within the core of nanomicelles for ocular drug delivery. A lipid prodrug of cyclic cidofovir (B-C12-cCDF) was encapsulated within surfactant-based nanomicelles for antiviral drug delivery for cytomegalovirus retinitis, and multilayered nanomicelles were developed for the delivery of ocriotide peptide to the

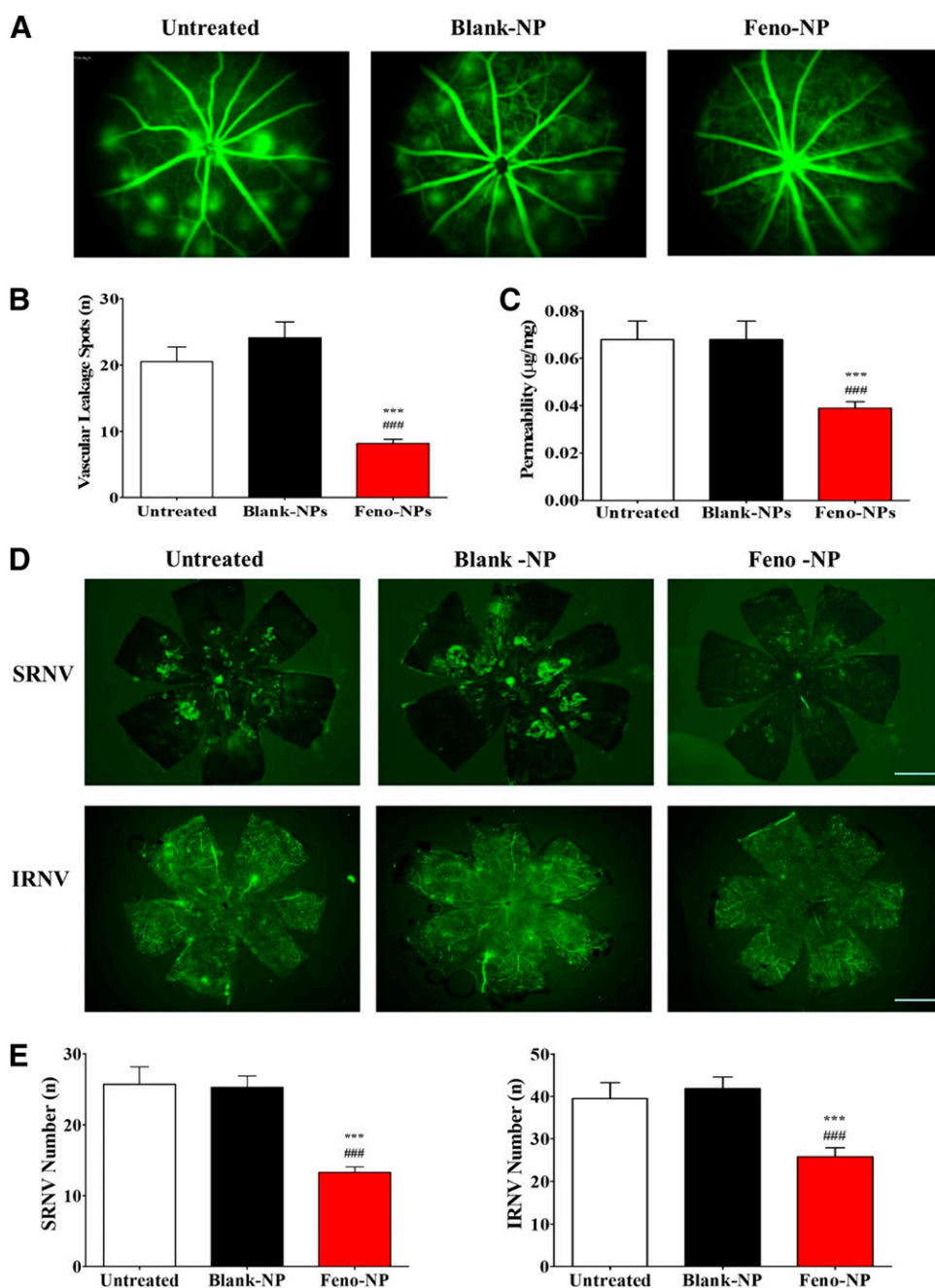


Fig. 5. In vivo efficacy of PLGA fenofibrate NPs (Feno-NP) on vascular leakage and vascular permeability measured with Fundus Fluorescein Angiography (FFA). Formation of subretinal neovascularization (SRNV) and intraretinal neovascularization (IRNV) evaluated by neovascular tufts in flat-mounted choroid and retina in *Vldlr*^{-/-} mice 1 month after Feno-NP treatment. (A) Representative images of FFA. (B) Numbers of leakage spots in FFA. (C) Quantification of retinal vascular permeability. (D) Representative images of SRNV and IRNV in FFA. Scale bar, 1000 μm. (E) Quantification of SRNV and IRNV in flat-mounted choroid and retina. Mean ± S.E.M. (*n* = 8–16; one-way ANOVA followed by Bonferroni post hoc test). ****P* < 0.001 vs. untreated *Vldlr*^{-/-} mice; ####*P* < 0.001 vs. blank-NP-treated *Vldlr*^{-/-} mice (Qiu et al., 2019).

anterior segment of the eye (Mandal et al., 2017b). The researchers also demonstrated that a mixed micellar structure designed from a fixed ratio of low-molecular surfactants had a lower critical micellar concentration. This indicates that the nanomicellar structure is stable over dilution in the systemic fluids and will not result in premature drug release. These highly lipophilic agents form a clear solution when encapsulated in the nanomicelles. Also, nanomicelle aid is sustained, and release of the drug to the ocular tissue is controlled (Cholkar et al., 2015; Mandal et al., 2017b, 2019b; Trinh et al., 2017).

Nanomicelles constructed from block copolymers such as PLGA, polyethylene glycol (PEG), polycaprolactone (PCL), and polylactide are called polymeric nanomicelles. The polymers can be conjugated to form diblock (A-B type), triblock (A-B-A), or pentablock (A-B-C-B-A) copolymers. Block polymers have distinct hydrophilic and hydrophobic parts which impart the polymer amphiphilicity. Nanomicelles can solubilize hydrophobic drugs and improve their delivery to the ocular tissues. Methoxy poly(ethylene glycol) poly(lactides) diblock copolymer was used for constructing polymeric nanomicelles of Cyclosporine-A for efficient drug supply to the anterior ocular segment. The in-vivo results demonstrated excellent ocular biocompatibility and high ocular bioavailability of the nanomicellar formulation. The results suggested that methoxy poly(ethylene glycol) poly(lactides) nanomicelles encapsulating cyclosporine-A can be used for treatment of dry eye disease, prevention of corneal graft rejection, and treatment of autoimmune uveitis (Di Tommaso et al., 2011). Polymeric micelles often offer certain advantages over surfactant micelles, such as sustained drug release and lower incidence of drug toxicity, whereas surfactant nanomicelles offer advantage of smaller nanomicellar size and rapid onset of action. Both surfactant and polymeric nanomicelles can be surface conjugated with various targeting moieties for higher drug transport through the ocular tissue (Yellepeddi and Palakurthi, 2016). Nanomicellar delivery of nucleic acids like siRNA, microRNA, plasmidDNA, and oligonucleotides is an emerging field of research. Liaw and Robinson used a nonionic copolymeric system, poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) (PEO-PPO-PEO) for gene delivery (Liaw, Chang, and Hsiao, 2001). The polymeric nanomicelles encapsulated plasmid DNA with lacZ gene demonstrating greater delivery of the therapeutic cargo to the cells (Tong et al., 2007). Nanomicelles also reduce drug toxicity, reduce drug degradation, improve drug permeation through the ocular tissues, and thus improve ocular bioavailability of lipophilic potent drugs (Mandal et al., 2019a).

Nanoparticles. The size of drug-loaded nanoparticles can range from 50 to 500 nm to effectively overcome ocular barriers and to deliver the drug to the ocular tissue either by passive or active transport. A solution of nanoparticles (NPs) can be deposited in the cul-de-sac to attain sustained drug delivery over a prolonged period of time. The surface charge of the NPs highly influences their efficient ocular absorption. The cornea and the conjunctival tissues have a negatively charged surface. It is observed that cationic NPs have a higher retention time on ocular surfaces as compared with anionic NPs. This can enhance the drug permeation into the ocular surfaces (Akhter et al., 2016). Colloidal NPs can also increase the solubility of highly hydrophobic drugs and increase the trans-corneal permeability of such agents. Various

biodegradable and nonbiodegradable NPs for treating anterior and posterior segment ocular disorders have been developed. The commonly used polymers for nanoparticle (NP) ocular applications are PLGA, PEG, PCL, chitosan, albumin, and gelation (Table 1). PLGA polymer is widely used for encapsulating various small-molecular and biotech drugs intended to treat anterior and posterior ocular disorders. PLGA undergoes biotransformation in vivo to form lactic and glycolic acid having minimal systemic toxicity. Hence, PLGA is widely used for ocular drug delivery. PLGA nanoparticles encapsulating anti-inflammatory corticosteroid fluocinolone acetonide were prepared by Guo et al. (2019) for the treatment of posterior uveitis and autoimmune uveitis (Fig. 4). Cañadas et al. (2016) estimated the delivery of pranoprofen, a nonsteroidal anti-inflammatory drug entrapped in PLGA NPs. The in vitro study on a human retinoblastoma cell line demonstrated lower toxicity of pranoprofen PLGA NPs on the cells as compared with the free drug. Pranoprofen PLGA NPs were further demonstrated to be effective in corneal penetration on an ex vivo bovine model as compared with the drug alone. In vivo ocular anti-inflammatory activity and ocular pharmacokinetics of the formulation were studied in rabbit eyes. The corneal penetration of pranoprofen NPs was 4 times higher and had a quick onset of anti-inflammatory action. Pranoprofen NPs also showed prolonged retention on the corneal surface of the rabbit eyes, which resulted in significant reduction of corneal inflammation (Cañadas et al., 2016). Connexin43 mimetic peptide has demonstrated efficacy in improving retinal ganglion cell survival after retinal ischemia. Rupenthal et al. and Bishat et al. evaluated connexin43 mimetic peptide PLGA NPs for retinal ischemia in zebrafish and live embryos. The study resulted in no toxicity to the ocular tissues (Chen et al., 2015; Bisht and Rupenthal, 2018). Qiu et al. (2019) developed fenofibrate PLGA nanoparticles for the management of DR and AMD. Fenofibrate is an agonist of peroxisome proliferator-activated receptor α and has efficacy against DR. The in vivo studies in diabetic rats reduced retinal vascular leakage, ameliorated retinal dysfunctions, and downregulated the overexpressed VEGF-A and ICAM-1 at 8 weeks after one intravitreal injection of fenofibrate PLGA NPs (Qiu et al., 2019). PLGA can also be used to encapsulate many well known anti-VEGFs, such as bevacizumab, ranibizumab, and aflibercept (Elsaid et al., 2016; Sousa et al., 2017; Kelly et al., 2018). However the major problem associated with the intravitreal delivery of NPs is the floating of the particles in the vitreous humor and vision obstruction (Bachu et al., 2018) (Fig. 5).

Nonsteroidal anti-inflammatory drugs such as ibuprofen, indomethacin, and flurbiprofen encapsulated in NPs can be used for the treatment of anterior segment ocular inflammation. Ibuprofen encapsulated in Eudragit RS100 (Evonik Health Care) NPs demonstrated improved drug concentrations in the aqueous humor of rabbit eyes in comparison with ibuprofen ocular solution (Pignatello et al., 2002). Eudragit RS100 was used to prepare flurbiprofen NPs for lowering anterior segment inflammation after surgical trauma. In vivo studies performed in rabbits demonstrated higher aqueous humor concentrations of flurbiprofen as compared with the control group (Pignatello et al., 2002a,b; Gupta et al., 2007; Cao et al., 2010). Biodegradable polymers such as PCL, PEG, PLGA, and poloxamer 188 were used for formulation of flurbiprofen-encapsulated nanoparticles. Topical administration of flurbiprofen nanoparticles demonstrated enhanced

TABLE 4

Ocular drug-delivery systems investigated for anterior segment disorders (inflammation) (Cholkar et al., 2013)

Delivery System	Drug	Polymeric Component	Remarks	References
Nanoparticles	Ibuprofen	Eudragit RS100	Significant improvement of drug bioavailability in rabbit model compared with control aqueous drops	Pignatello et al., 2002
	Flurbiprofen	Eudragit RS100	Improved ocular bioavailability due to strong interaction between positive charged nanoparticle to the anionic corneal surface	Pignatello et al., 2002
	Flurbiprofen	PLGA, PCL	Colloidal systems enhance ocular bioavailability; PLGA nanoparticles showed ~2-fold higher drug transport than that of PCL nanoparticles	Valls et al., 2008
	Indomethacin	PCL, Miglyol 840, poloxamer 188	Colloidal formulation shows 3-fold higher ex vivo penetration than commercial eye drops	Calvo et al., 1996
	Cyclosporine-A	Chitosan and cholesterol-conjugated chitosan	Both nanoparticles deliver higher amount of drugs in cornea and conjunctiva as compared with cyclosporine-A suspension	De Campos et al., 2001
Nanomicelles	Dexamethasone	Pluronic/chitosan system	Nanomicelles entrapping dexamethasone significantly improved bioavailability to anterior ocular tissues by 2.4-fold relative to unformulated dexamethasone	Pepic et al., 2010
	Voclosporin, dexamethasone, rapamycin	Vitamin E TPGS and octoxynol-40 nanomicelles	In vivo studies showed mixed nanomicellar system have higher bioavailability with topical dosing of dexamethasone and rapamycin	Pepic et al., 2010
	Cyclosporine-A	Methoxy poly(ethylene glycol)-hexylsubstituted poly(lactide)	Transparent, highly stable, biocompatible formulation	Di Tommaso et al., 2011
	Plasmid DNA with lacZ gene	PEO-PPO-PEO	Significant elevation of β -gal activity, transgene expression marker, elevated mRNA levels of bcl-x(L) by 2.2-fold, and reduced corneal apoptosis in mouse and rabbit cornea.	Tong et al., 2007
Liposomes	C6-ceramide	Methoxy PEG(2000) and PEG(750)-C6-ceramide	Significantly efficacious in reducing corneal inflammation	Sun et al., 2008
	Dexamethasone	Human serum albumin; bis(sulfosuccinimidyl) suberate; tris(hydroxymethyl) aminomethane; 3,3-dithiobis-(sulfosuccinimidylpropionate)	Significantly higher drug accumulation in the eye (~13.5 ng/mg tissue) than unformulated drug (2.4 ng/mg tissue)	Arakawa et al., 2007

PEO-PPO-PEO, poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide); TPGS, tocopheryl polyethylene glycol succinate.

anti-inflammatory efficiency and minimal toxicity, such as ocular irritation, in the rabbit eyes (Calvo et al., 1996; Valls et al., 2008). Chitosan is also a widely used anionic biocompatible and biodegradable polymer used to prepare NPs and can improve their precorneal residence time. Cyclosporine-A is a strong immunosuppressive agent which is used to treat dry eye disease. Chitosan can be used to prepare NPs entrapping cyclosporine-A, which has shown 2-fold improved precorneal residence and higher conjunctival permeability in rabbit eyes. Chitosan polymer can also be used for the delivery of lipophilic drugs, hydrophilic drugs, and polynucleotides to the anterior ocular surface (De Campos et al., 2001; de la Fuente et al., 2010). Mitra et al. developed pentablock copolymers from polymers such as PEG, polylactide, PGA, PCL, and PLGA for making nanoparticles encapsulating hydrophilic drugs such as dexamethasone and macromolecules such as IgG, IgG(Fab), and various peptides for controlled drug delivery to the anterior as well as posterior sections of the eye (Patel et al., 2016; Agrahari et al., 2017). Glaucoma is the leading cause of blindness throughout the world. Li et al. (2019) created a mouse model of glaucoma demonstrating elevated intraocular pressure after the administration of dexamethasone nanoparticles composed of pentablock copolymers. This can streamline the clinical evaluation of drug candidate for glaucoma (Li et al., 2019). Current research is utilizing ligand-targeted functionalized nanoparticles for enhanced delivery of therapeutic agents as compared with nonfunctionalized nanoparticles. Targeting ligands can specifically target receptors and nutrient transporters on the

conjunctiva and corneal surface. The CD44 hyaluronic acid receptor is located on the corneal and conjunctival cells. It was proven that hyaluronic acid surface-functionalized chitosan NPs encapsulating an oligomer demonstrated higher uptake in the ocular tissues as compared with NPs not surface functionalized with hyaluronic acid. Such NPs undergo active transportation mediated by the CD44 hyaluronic acid receptor utilizing the caveolin-dependent endocytosis pathway (Contreras-Ruiz et al., 2011). Surface-functionalized nanoparticles with targeting agents such as peptides, antibodies, vitamins (such as biotin and folic acids), and aptamers have resulted in higher uptake as compared to the nonfunctionalized nanoparticles. Kompella et al. (2006) demonstrated that transferrin-conjugated NPs had 74% higher transport across the cornea and conjunctiva in ex vivo bovine eyes as compared with nontargeted NPs. Epigallocatechin-3-gallate is a natural polyphenol compound having antioxidant, anti-inflammatory, and antiangiogenesis activity and can have efficacy against CNV. Gelatin NPs were surface functionalized with hyaluronic acid and conjugated to an RGD peptide. Encapsulated epigallocatechin-3-gallate-RGD peptide was evaluated for treatment of corneal neovascularization (CNV). Lee et al. In vivo studies in a CNV mouse model showed fewer and thinner blood vessels for mice treated with topical epigallocatechin-3-gallate-RGD peptide NPs as compared with the blank NPs (Lee et al., 2014). This result suggests a potential role of targeted nanoparticles for the treatment of CNV. Active targeting of NPs can provide efficient and rapid transport of cargo across the corneal and conjunctival epithelium.

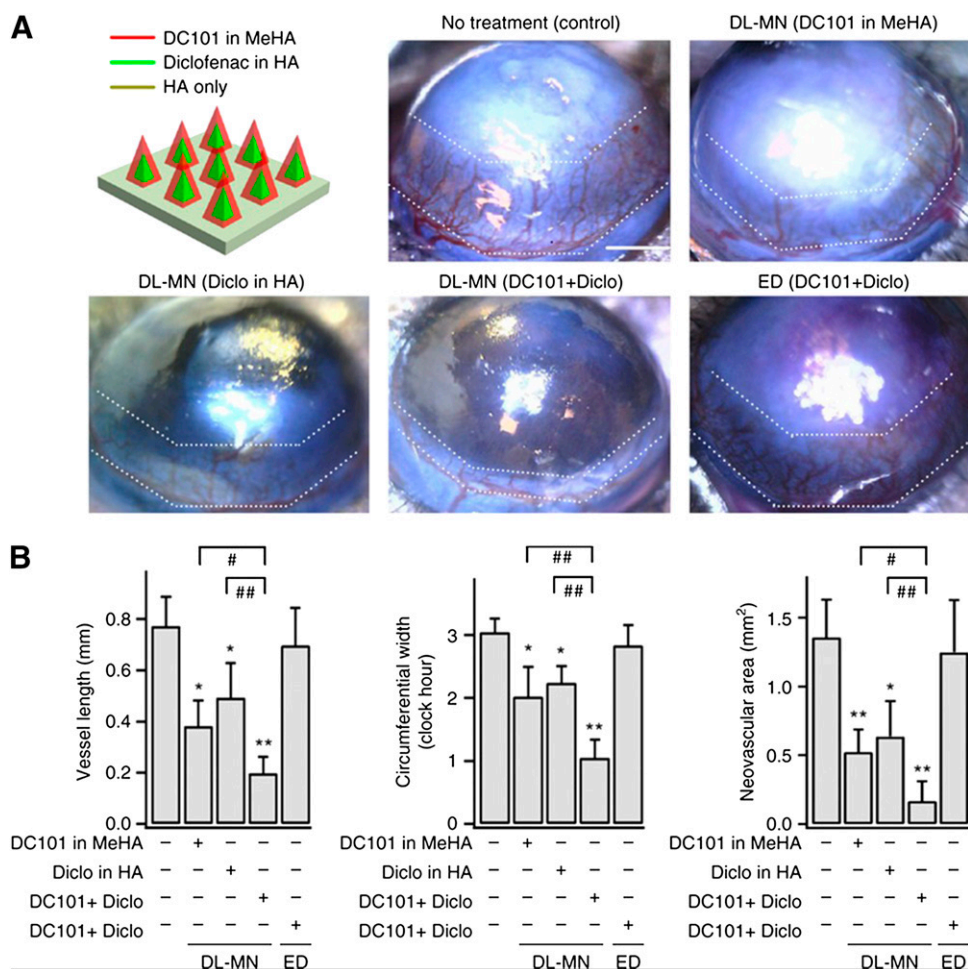


Fig. 6. Microneedles for enhanced drug delivery to the cornea. Drug-loaded, DC101, and diclofenac microneedle (DL-MN) patch for synergistic effect. Mouse eyes were treated 2 days after being inflicted with alkali burn and examined on day 7. (A) Illustration of drug loadings in DL-MNs and representative images of differently treated eyes. (B) Quantifications of corneal neovascularization. The white dotted lines indicate the extent of neovascular outgrowth from the limbus. Statistical comparison between groups was performed using one-way ANOVA. * $P < 0.05$; ** $P < 0.01$ vs. control; # $P < 0.05$; ## $P < 0.01$ between indicated pairs (Than et al., 2018). Diclo, Diclofenac; ED, eye drop; HA, hyaluronic acid; MeHA, methacrylated hyaluronic acid.

Nanoparticles can also serve as an effective vehicle for gene delivery. Gold NPs conjugated to a 2-kD polyethylenimine were evaluated for gene delivery to rabbit cornea. The researchers observed a high uptake of the gold NPs through the rabbit stroma and a gradual clearance over time (Sharma et al., 2011).

Liposomes. Liposomes are used as ocular drug-delivery vehicles which can encapsulate hydrophilic and hydrophobic drugs. Polymers from a liposome form a lipid bilayer vesicle which separates the inner aqueous core from the exterior aqueous environment. Although liposomes have poor stability and a short half-life, they have been explored for ocular drug delivery for anterior segment disorders (Law et al., 2000). Sun et al. (2008) entrapped short-chain-conjugated ceramide and C6-ceramide in liposomes and applied to the treatment of corneal inflammation in mice. Ceramides are known for their role as an antiproliferative and proapoptotic agents in sphingolipid metabolism. The C6-ceramide liposomal formulation demonstrated significant efficacy in corneal inflammation reduction in a murine model (Sun et al., 2008). This implies an affirmative role of ceramide-loaded liposomes for treating anterior segment ocular inflammation (Sun et al., 2008) (Table 4). Hathout et al. (2019) showed that timolol maleate gelatinized liposome treatment resulted in lowering the IOP when evaluated in vivo on the eyes of glaucomatous rabbits. Song et al. developed a tocopheryl polyethylene glycol succinate (TPGS) modified nanoliposome ocular drug-delivery system for brinzolamide for the treatment of glaucoma. White

New Zealand rabbits treated with brinzolamide liposomes maintained an effective reduction in IOP after drop instillation. Such results indicate a high potential for clinical translation for liposomal drug delivery of hydrophilic agents for the treatment of glaucoma. Ren et al. investigated azithromycin liposomes for the treatment of dry eye disease. In vivo pharmacodynamic studies in rats showed a reduction in the symptoms of dry eye disease, and the azithromycin liposomal treatment had higher safety and efficacy as compared with hyaluronic acid sodium eye drops (Ren et al., 2018). Topical voriconazole liposomes were developed by de Sá et al. (2015) for fungal keratitis treatment. Liposome-mediated ocular drug delivery was also explored for posterior segment drug delivery. Bevacizumab (Avastin) was encapsulated by annexin A5-conjugated liposomes for drug delivery to the back of the eye by Davis et al. (2014). The study reported that topical application of the liposomes could successfully deliver bevacizumab to the retinal tissue with a final concentration of 127 ng/g in rat retinal tissue and 18 ng/g in rabbit retinal tissue (Davis et al., 2014).

Dendrimers. Dendrimers are polymeric nanocarriers having a branched star-shaped structure. The size and shape of the dendrimer can be controlled and customized during the synthesis to form a dendrimer with specific functional groups and a specific architecture. These nanoconstructs have unique physiochemical properties such as high drug encapsulation and conjugation ability, high water solubility, monodispersity,

and a plethora of functional groups on the surface for chemical modification. Hydrophilic and lipophilic drugs can either be conjugated to the surface of the dendrimer or be encapsulated by caging in the internal structure of the dendrimer (Kalomiraki et al., 2015; Lancina and Yang, 2017). A polyamidoamine (PAMAM) polymer having carboxylic and hydroxyl functional groups is the most commonly used dendrimer for ocular drug delivery. High branching of the PAMAM polymer can lead to primary, secondary, and tertiary generations of the dendrimer nanocarrier. Soiberman et al. (2017) designed a gel formulation of the G4-PAMAM dendrimer with cross-linked hyaluronic acid, entrapping dexamethasone intended for the treatment of corneal inflammation. Subconjunctival injection of the dendrimer formulation led to reduction in central corneal thickness and improved corneal clarity in an alkali burn rat model, which was highly clinically relevant (Soiberman et al., 2017). Another group of investigators evaluated the potential of dexamethasone-PAMAM dendrimers for the delivery to the back of the eye for the treatment of diseases such as DR and AMD. In vivo studies in rats showed that the drug-loaded dendrimers enhanced the ocular permeability of dexamethasone after subconjunctival injection as compared with the free drug (Yavuz et al., 2016). Matrix metalloproteinases-9 (MMP-9) can trigger corneal damage and result in dry eye disease. Cerofolini et al. (2017) synthesized an MMP-9 inhibitor and solubilized with PAMAM dendrimers. The synthesized inhibitor had high binding affinity to MMP-9 and can be used for the treatment of corneal inflammation and dry eye disease (Cerofolini et al., 2017). Vandamme and Brobeck (2005) entrapped tropicamide and pilocarpine nitrate in PAMAM dendrimers to study the effect of drug-release kinetics after altering the size, molecular weight, carboxylate and hydroxyl surface groups, and total number of amines present in the PAMAM dendrimer. In vivo results in New Zealand albino rabbits revealed higher drug residence

time of dendrimers functionalized with carboxylic and hydroxyl functional groups (Vandamme and Brobeck, 2005).

Microneedles. Microneedle drug-delivery technology was originally used for overcoming the stratum corneum and was used for transdermal drug delivery (Lee et al., 2008). The effectiveness of microneedles for transdermal drug-delivery systems inspired researchers to investigate their potential to treat anterior and posterior segment ocular disorders. This minimally invasive technique can also be applied for ocular drug delivery of hydrophilic and hydrophobic drugs. Solid stainless-steel microneedles (MNs) coated with drugs such as sunitinib malate and pilocarpine resulted in higher drug bioavailability in the anterior ocular segment compared with topical drop applications in vivo (Jiang et al., 2007; Song et al., 2015). Microneedles can also be used to deliver therapeutic agents for the treatment of back of the eye disorders. Microneedle nanoparticles and microparticle suspension can be delivered to the suprachoroidal space (Patel et al., 2011). Than et al. (2018) have shown a polymeric eye patch consisting of an array of detachable and biodegradable MNs for controlled and localized ocular drug delivery. These MNs could penetrate into the corneal layers and deliver antiangiogenic monoclonal antibody (DC101) for the treatment of CNV. The MNs were double layered with DC101 to provide biphasic drug-release kinetics to enhance the therapeutic efficacy of the MNs. The DC101 MN eye patch produced approximately 90% reduction in CNV in a CNV disease mouse model as compared with a topical eye drop. The researchers also suggested that the MN patch is minimally invasive and can be self-applied by patients on their corneas (Than et al., 2018). Microneedles can greatly aid in increasing the bioavailability of a certain drug in a particular tissue by localizing the drug-delivery system. Microneedles can be a paradigm shift for the way ocular formulations are administered, but their current limitations demand further research in the field for desired clinical translation (Thakur Singh et al., 2017) (Fig. 6).

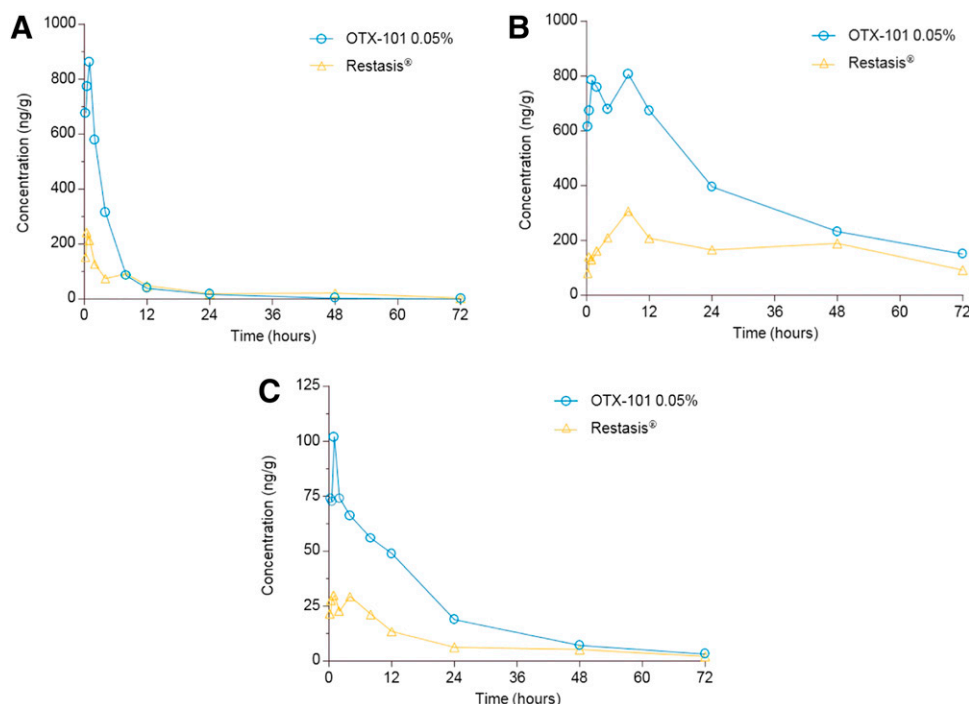


Fig. 7. Comparison of cyclosporine-A nanomicellar formulation (OTX-101, Cequa) and cyclosporine-A emulsion (Restasis) evaluated in New Zealand white rabbits after a single topical administration. Concentration was determined in ocular tissues such as superior bulbar conjunctiva (A), cornea (B), and sclera (C).

Nanowafer. Nanowafer is small, transparent, rectangular membranes or circular discs containing drug loaded into nanoreservoirs which can be smeared on the ocular surface using a fingertip. Controlled drug release from the nanowafer can increase the residence and contact time of the drug with the corneal and conjunctival surfaces. This can aid in higher drug absorption into anterior ocular tissues. The nanowafer not only enhances the drug bioavailability but also acts as a protective polymer membrane to heal injured and abraded corneal surfaces commonly found in CNV and dry eye disease. This novel nanocarrier is designed from biodegradable and biocompatible polymers which can be eliminated over a period of time. Coursey et al. (2015) and Bian et al. (2016) developed a dexamethasone-loaded nanowafer (Dex-NW) for the treatment of dry eye disease. The nanowafer was fabricated using carboxymethyl cellulose polymer and consisted of an array of nano drug reservoirs filled with dexamethasone. The in vivo efficacy of Dex-NW was tested in a dry eye disease mouse model. Dex-NW was administered as once-a-day treatment on alternating days for a 5-day period of time. After the treatment duration, it was observed that Dex-NW was able to restore the corneal barrier function along with a healthy ocular surface which was similar to twice-a-day treatment of topically applied dexamethasone eye drops. Yet another interesting finding the scientists reported was that Dex-NW was effective in lowering the overexpression of inflammatory cytokines such as tumor necrosis factor- α , interferon- γ , interleukin-1 β , and interleukin-6. Also, the expression of inflammatory chemokines such as CXCL-10, CCL-5, and MMP-3 and MMP-9 was lowered (Coursey et al., 2015; Bian et al., 2016). Axitinib-loaded nanowafer were developed by Yuan et al. for the treatment of CNV (Yuan et al., 2015). A murine ocular burn model was used to evaluate the in vivo efficacy of axitinib-loaded nanowafer. The laser-scanning confocal imaging and reverse-transcription polymerase chain reaction results revealed that the once-a-day axitinib-loaded nanowafer was twice as effective as compared with axitinib daily topical eye drops (Yuan et al., 2015). These findings have shown the potential of nanowafer for further evaluation in clinical trials.

Ocular Nanocarriers Currently Approved and under Clinical Investigation. Nanocarriers, such as nanoparticles and nanomicelles, have been widely explored for their potential to cure anterior and posterior ocular disorders. Despite the plethora of research on nanocarriers, Cequa (0.09% cyclosporine-A ophthalmic nanomicellar solution) is the only nanotechnology-derived ophthalmic approved by the US FDA for dry eye disease (Cequa, 2018). Cequa is a preservative-free, clear, and sterile nanomicellar formulation of a highly hydrophobic drug, cyclosporine-A. The phase III clinical trials of Cequa were conducted in a total of 745 patients with dry eye disease. The study showed a statistically ($P < 0.0001\%$) significant increase in the primary endpoints of the study, Schirmer's test (measurement of tear production), and secondary endpoints. Instillation site pain (22%) and hyperemia (6%) were the adverse effects noted with the clinical trial, which are a common scenario for the drugs evaluated in this category (Sheppard et al., 2014; Tauber et al., 2015). The phase III results clearly established the safety and efficacy of Cequa (0.09% cyclosporine-A ophthalmic nanomicellar formulation) in mitigating the signs and symptoms of dry eye disease (Mandal et al., 2019a).

There are a handful of ophthalmic nanocarrier drugs currently being investigated in clinical trials to establish their safety and efficacy for the treatment of ocular disorders. A randomized, single-blind study is evaluating the efficacy of hydrating polymers and polyunsaturated fatty acid micro-emulsion for the treatment of dry eye disease (NCT02908282). In a yet another randomized, single-blind phase II clinical trial, urea-loaded nanoparticles are being evaluated as a possible treatment of cataract management (NCT03001466). A clinical study was conducted by Sun Yat-sen University to compare the efficacy of two tear substitutes, Tears Naturale Forte (Alcon Laboratories Inc.) and Liposic (Bausch & Lomb), for dry eye diseases (NCT02992392). Aston University evaluated the efficacy of liposomal spray for dry eye disease in an interventional randomized study (NCT02420834). Kala Pharmaceuticals (Waltham, MA) has developed nanoparticle-based mucus-penetrating particles of loteprednol etabonate (LE). LE is a corticosteroid, and encapsulating in mucus-penetrating particles can improve drug delivery across the ocular endothelial cells. Currently, Kala Pharmaceuticals is investigating the potential of Inveltys (KPI-121 1.0% LE) for relieving inflammation following ocular surgery (NCT02793817) and KPI-121 0.25% LE for alleviating the symptoms of dry eye disease in a phase III clinical trial (NCT03616899). The effect of KPI-121 1.0% and 0.25% LE is also being investigated for the treatment of diabetic macular edema and retinal vein occlusion (NCT02245516).

Fewer nanoformulations in clinical trials can be attributed to the limitations in the industrial development and scale-up of nanoparticles. Another major challenge involved in the clinical translation of nanoparticles is the toxicity profile of various polymers used in nanoparticles (Suresh and Sah, 2014). The majority of nanoparticles for ocular drug delivery are evaluated for their efficacy in vivo in mice, rats, and rabbits. Although rabbit ocular anatomy is similar and comparable to human ocular anatomy, rabbit ocular anatomy does not completely mimic human ocular anatomy. Rabbits have higher mucus production, higher surface sensitivity, and lower rate of blinking, which can result in better drug retention and drug penetration in comparison to human eyes (Weng et al., 2017). It is also a challenge to achieve homogeneity of particle size and particle-size distribution for a nanoparticle formulation on an industrial scale. Optimization of various formulation parameters for nanoparticle preparation is still a challenging task for many pharmaceutical scientists. Dendrimers have been shown to cause blurring of vision (Wadhwa et al., 2009). On the other hand, liposomes have limited long-term stability and lower drug-loading potential. Higher concentrations of surfactants in the nanoformulation can be associated with potential ocular toxicity (Bachu et al., 2018). The recent US FDA approval of Cequa has led to an inception of the era of nanotechnology in ophthalmology. Despite limiting factors for the successful clinical translation of nanomedicine for ophthalmology, one can predict nanotechnology products being approved for ocular ailments in the near future (Fig. 7).

Noninvasive Drug-Delivery Systems for the Posterior Disorders

All marketed ophthalmic products used for the management of retinal disorders are invasive in nature. The intravitreal

TABLE 5

Topically administered therapeutic agents for back of the eye disorders in various preclinical models (Rodrigues et al., 2018)

Compound	Formulation	Preclinical Data	Reference
TG100801	Solution	Murine CNV model and edema in rat	Doukas et al., 2008
Pazopanib	Solution	Rat CNV model	Yafai et al., 2011, Singh et al., 2014
Acrizaniib	Suspension	Murine CNV	Adams et al., 2018
Memantine	Solution	Drug levels in rabbit retina	Hughes et al., 2005
Dorzolamide	Solution	Drug levels and carbonic anhydrase activity in corneal endothelial cells, ciliary body, lens epithelial cells, and retina in rabbit	Inoue et al., 2004
Dexamethasone	Iontophoresis	Drug levels in retina and vitreous of rabbit	Ambati and Adamis, 2002
Bevacizumab	Solution	Drug levels in iris/ciliary body, vitreous, retina/choroid, and plasma in rabbit	Ambati et al., 2000a
Anti-intercellular adhesion molecule-1 antibody	Solution by osmotic pump	Drug levels and VEGF-induced leukostasis in the choroid and retina in rabbit	Ambati et al., 2000b
28-kD single-chain antibody fragment	Sodium caprate	Drug levels in vitreous in rabbit	Williams et al., 2005
Bevacizumab	Annexin A5-based liposomes	Drug levels in retina of rat and rabbit	Davis et al., 2014
Transforming growth factor β 1	Annexin A5-based liposomes	Drug levels in vitreous in rabbit	Platania et al., 2017
Acidic fibroblast growth factor	CPP (TAT)	Ischemia reperfusion model in rat	Wang et al., 2010
Calpain inhibitory peptide	CPP (TAT)	Drug levels in rabbit retina	Ozaki et al., 2015
Green fluorescent protein	CPP (POD)	Drug levels in mouse cornea	Johnson et al., 2010
Bevacizumab	CPP (R6)	Drug levels in vitreous and retina in rat and murine CNV model	de Cogan et al., 2017

CPP (R6), cell-penetrating peptide poly-arginine-6; POD, peptide of ocular delivery; TAT, transactivator of transcription.

route is widely used for administration of biopharmaceuticals to the back of the eye. This route is associated with various complications, such as intraocular inflammation, retinal detachment, glaucoma or intraocular pressure elevation, endophthalmitis, ocular hemorrhage, and cataract (Mandal et al., 2018). The following section illustrates current-state scientific research pertaining to topical delivery of potent therapeutic interventions and drugs for back of the eye diseases.

Small Molecules. Eye drops instilled topically are non-invasive and the most patient-compliant route of administration. Although the route is widely explored for anterior segment disorders, it remains a major challenge for delivering drugs at therapeutic concentrations at the back of the eye. Various static barriers, such as blood-retinal barrier and tear-film barrier, and dynamic barriers, such as clearance mechanisms by vitreous and aqueous humor, hinder the drug passage from the front to the back of the eye. TG100801 is a topical therapy which has demonstrated reduction in CNV in a murine model and edema reduction in rats with RVO (Doukas et al., 2008). TG100801 is a small-molecule multikinase inhibitor prodrug which is cleaved to its active form by hydrolysis in the cornea. Due to the promising results of TG100801 in the preclinical setting, it was further advanced to clinical trials. Although TG100801 was well tolerated by patients, it did not demonstrate any efficacy for alleviating the condition of AMD (NCT00509548). Pazopanib is another small-molecule multikinase inhibitor which was administered topically in a laser-induced CNV rat model (Yafai et al., 2011). Similar to TG100801, pazopanib failed to demonstrate efficacy in patients with subfoveal CNV, secondary to AMD (Singh et al., 2014). Along similar lines, acrizanib was investigated for reduction of nonvascular AMD in preclinical mouse models. Acrizaniib is a VEGF receptor-2 inhibitor and demonstrated a 99% inhibitory effect for CNV, which was 3 times the daily topical application of 1% suspension in mice (Adams et al., 2018). Despite positive preclinical evaluation of acrizanib in a mouse model, topically administered acrizanib is clinically ineffective for the treatment of AMD (NCT02355028).

Although some multikinase inhibitors have failed in clinical settings, topical delivery of therapeutic agents to the back of the eye is an active area of research. A multikinase inhibitor, PAN-90806, is currently being investigated in clinical trials (phase I/II) to assess its feasibility in AMD treatment (NCT03479372). Topical application of a memantine drug (Namzaric, Actavis Plc.) was able to achieve a sufficient concentration in the retina to provide retinal neuroprotection (Hughes et al., 2005). Another small-molecular drug, dorzolamide, was administered topically to inhibit carbonic anhydrase II in a rabbit model (Inoue et al., 2004). Dexamethasone administered topically by iontophoresis showed promising results in a rabbit model. Topically administered dexamethasone by iontophoresis was further evaluated in clinical trials for macular edema. However, the clinical trial was terminated due to insufficient enrollment (NCT02485249).

Biotech Drugs. Biotech drugs such as antibodies or antibody fragments are high-molecular-weight charged compounds which cannot be easily absorbed by the lipid bilayer. Although topical delivery of small-molecular drugs to the back of the eye has shown some efficacy in clinical trials, the biologics face various ocular barriers to reach the posterior segment (Ambati et al., 2000a; Miao et al., 2013). Topically administered bevacizumab, an anti-VEGF IgG antibody, failed to reach the therapeutic concentration in the rabbit retina after topical dosing of 1.25 mg/0.05 ml six times daily for a week (Ambati et al., 2000a). However, topical administration of antibody against intercellular adhesion molecule 1 was able to achieve therapeutic concentrations at the retina, which resulted in successful inhibition of VEGF-induced leukostasis in the choroid (Ambati et al., 2000b). To further improve topical delivery of biologics to the back of the eye, colloidal nanoformulations such as liposomes and nanomicelles with various permeability enhancers were used. Williams et al. (2005) demonstrated that permeability enhancer sodium caprate can enhance the delivery of antibody fragment in a rabbit model. Platania et al. (2017) used annexin A5-associated liposomes for topical delivery of bevacizumab to the back of the eye. Various cell-penetrating peptides (CPPs) are increasingly

being investigated for ocular delivery of proteins and peptides (Fonseca et al., 2009). CPPs are a group of short cationic peptides which can enhance the membrane permeation and translocation of desired therapeutic cargo. Therapeutic agents administered with CPP enhance corneal and scleral permeability (Fonseca et al., 2009). Wang et al. (2010) applied human immunodeficiency virus transactivator of transcription for CPP to topically deliver acidic fibroblast growth factor in a rat model. Similarly, Ozaki et al. (2015) proved that delivery of topically administered calpain inhibitory peptide conjugated to transactivator of transcription factor to the retina of the rat eye. Johnson et al. (2010) conjugated to green fluorescence protein with a peptide of ocular delivery, which highlights the pathway of drug disposition and absorption from the corneal epithelium to the retinal pigment epithelium. The most recent and promising study was conducted by de Cogan et al. (2017). The researchers achieved therapeutic levels of bevacizumab in the posterior ocular tissues, such as the retina and choroid, by topical coadministration of the antibody and CPP poly-arginine-6 (de Cogan et al., 2017). Nanoformulations may be applied as intravitreal injections as well as topical eye drops for back of the eye delivery (Table 5).

Discussions: Challenges and Future Perspectives for Ocular Drug-Delivery Technologies

The shortcomings of the current ocular drug-delivery system, such as lower drug bioavailability for topically administered drugs and the invasive nature of posterior implants, create challenges, allowing novel technologies to rise with superior and effective treatment of ocular disorders. Ocular disorders such as cataract, dry eye disease, wet and dry AMD, glaucoma, DR, and DME are predicted to escalate in the next two decades. For a majority of the anterior segment disorders, eye drops are regarded as the safest and most convenient dosage form. Eye drops face the challenge of having low drug bioavailability at the target tissue. Controlled drug delivery with the help of nanoformulations such as nanomicelles, nanoparticles, liposomes, dendrimers, nanowafers, and micro-needles can achieve high bioavailability of drugs at the anterior tissues, such as the conjunctiva and cornea. Currently, all treatments for back of the eye disorders are invasive in nature. Frequent intravitreal injections can lead to retinal detachment, hemorrhage, and discomfort to the patients. Design of a noninvasive sustained drug-delivery system for the posterior segment is challenging for ocular drug-delivery scientists. Thus, there is an urgent need for the development of novel noninvasive drug-delivery systems that can overcome ocular barriers, sustain drug release, and maintain effective drug levels at the back of the eye.

Conclusion

Novel ocular drug-delivery systems such as nanoparticles and nanomicelles face a major challenge for technology transfer and large-scale manufacturing. Nanotechnology has a high clinical translatable potential for treating various ophthalmic disorders. Nanotechnologies can have the capacity to replace traditional ophthalmic medications in the near future.

Parallel efforts not only in novel product development but also in product scale-up are required.

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