Ocular Drug Delivery: Present Innovations and Future Challenges.

Vrinda Gote, BS, Sadia Sikder BS, Jeff Sicotte BS, Dhananjay Pal* Ph.D., MH&A

Division of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Missouri-Kansas City, 2464 Charlotte Street, Kansas City, MO 64108, USA

* Corresponding Author
Dhananjay Pal Ph.D., MH&A
Research Associate Professor
University of Missouri-Kansas City,
2464 Charlotte Street, Kansas City, MO 64108
Ph. 816-235-2431; Fa: 816-235-5779
pald@umkc.edu

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Abbreviations

DR diabetic retinopathy; DME diabetic macular edema; RVO retinal vein occlusion; wet AMD wet age-related macular degeneration; CNV choroidal neovascularization; VEGF vascular endothelial growth factor; RPE retinal pigmented epithelial cells; BRB blood retinal barrier; oBRB outer blood retinal barrier; iBRB inner blood retinal barrier; BRVO branched retinal vein occlusion; CRVO central retinal vein occlusion; RVO retinal vein occlusion, IOP intraocular pressure; CMV retinitis Cytomegalovirus retinitis; PPDS punctum pug delivery system; PLGA poly(lactic-co-glycolic acid), PCL Polycaprolactone, PEG Polyethylene glycol.
Abstract

Ocular drug delivery has always been a challenge for ophthalmologists and drug delivery scientists due to presence of various anatomical and physiological 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 site of action which can overcome various ocular barriers. Conventional ophthalmic medications includes; the use of topical eye drops and intravitreal injections of anti-VEGF agent for treatment of anterior and posterior segment disorders, respectively. Current inventions for anterior ocular segment disorders like 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, microneedles, liposomes and nanowafers, 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 a rise. In this review article we discuss the 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.
Keywords

Anterior and posterior ocular drug delivery, intravitreal implants, nanomicelles, nanoparticles, encapsulated cell therapy, drug eluting contact lenses, ocular Iontophoresis, punctum plugs, dexamethasone, triamcinolone acetonide,

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1. 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 is to maintain therapeutic drug concentrations at the target site, reduce dosage frequency and to 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 pathological disorders are generally described as anterior segment and posterior segment disorders. Clinicians treat anterior segment disorders like 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 accounted to high tear-fluid turnover rates and high nasolacrimal drainage. Novel ocular drug delivery approaches including nanomicelles, nanoparticles, drug eluting contact lenses, ocular inserts and ocular devices that allow enhanced peroneal residence and enhance bioavailability of the therapeutic agents (Achouri, Alhanout et al. 2013, Fangueiro, Veiga et al. 2016).

Ocular pathological 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 like diabetic retinopathy (DR), diabetic macular edema (DME) and retinal vein occlusion (RVO). High oxidative stress, endoplasmic reticulum (ER) stress and ageing can damage the retinal pigmented epithelial cells (RPE) and Bruch’s membrane in the macular region leading to the death of the photoreceptors. Such pathological conditions can cause retinal degenerative disorders like age-related macular degeneration (AMD) (Yasukawa, Ogura et al. 2004, Janoria, Gunda et al. 2007). Retinal and choroidal neovascularization (CNV) evident in back of the eye disorders is primarily due to
overexpression of vascular endothelial growth (VEGF) receptor. Before the invention of anti-VEGF agents, the gold standard treatment of these disorders was the 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 treatment of back of the eye disorders with neovascularization. Clinicians administer these agents as intravitreal injections, which has drawbacks like retinal hemorrhage and retinal detachment. Moreover, intravitreal injections lack patient compliance. Novel ocular drug delivery technologies like nanoformulations, implants and other ocular devices allow enhanced drug residence time at the target tissue along with improvements of pharmacological response (Peyman, Lad 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.

2. 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 and retinal-blood barriers) hinder drug absorption affecting drug bioavailability of topical formulation (<5%) (Chrai, Patton et al. 1973, Chrai, Makoid et al. 1974). The globular shape of human eye, and precorneal factors such as blinking and continuous tear turn over reduce absorption of topically applied formulations. (Mishima, Gasset et al. 1966, Lee and Robinson 1986, Schoenwald 1990). (Figure 1). Lipophilic corneal epithelia allows absorption of hydrophobic drugs but acts as a barrier for paracellular diffusion of hydrophilic drugs due to tight junctions (Huang, Schoenwald et al. 1983, Hornof, Toropainen et al. 2005). Corneal epithelia efficiently prevent absorption of more than 10 Å molecules with higher drug distribution coefficient limiting barrier for hydrophobic drugs. Therefore, drug absorption requires overcoming corneal epithelia efficiently. Decrease in transcorneal diffusion of drug through 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, Patel et al. 2012, Huang, Chen et al. 2018).

While in the posterior segment of the eye, the scleral, choroidal and retinal epithelial and the blood retinal barrier accounts 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 have low diffusion through the sclera and are administered by intravitreal injections (Huang, Chen et al. 2018). The choroid is a vascular natured dynamic barrier, which impedes drug delivery by trans-scleral pathway. (Tsai, Wang et al. 2018). The retina is a significant limiting factor for diffusion of molecules with larger
radius and molecular weight greater than 76 kDa (Jackson, Antcliff et al. 2003). The inner limiting membrane (ILM) of retina severely confines passaging of macromolecules over 150 kDa molecular weight (Mordenti, Cuthbertson et al. 1999, Jackson, Antcliff et al. 2003, Tao, Li et al. 2007). Moreover, the ILM progressively restricts molecules with larger radius. Retinal pigmented epithelium 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, Patel et al. 2012). The blood retinal barrier (BRB) comprises two subdivisions, an outer blood retinal barrier (oBRB) and an inner blood retinal barrier (iBRB). Both the oBRB and iBRB are permeation barriers between the blood and the retina having tight junction proteins between the cells (Kamei, Misono et al. 1999, Achouri, Alhanout et al. 2013). BRB also exhibits efflux transporters, which reduces bioavailability of several therapeutic agents (Mitra 2009, Vadlapatla, Vadlapudi et al. 2014). 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, Bourgeois et al. 2018). Ocular drug delivery presents a unique challenge due to its incredibly specialized tissue barriers that act as obstacles to therapies (Gaudana, Ananthula et al. 2010). Table 1 summarizes present routes of ocular therapy administration, and Figure 1 details the anatomical makeup indicating how each therapy travels to its active site.

3. Past Successes in Ocular Drug Delivery Technologies

3.1 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 like dry eye diseases, allergic conjunctivitis and glaucoma (Kaur and Kanwar 2002). Topical administration gains merit over systemic administration in being relatively noninvasive, minimizing systemic side effects of the drug, avoidance of drug first-pass metabolism, dose reduction due to localized drug delivery and patient compliance due to ease of administration. Factors limiting absorption of topically applied ophthalmic formulations are high tear turnover rate (1 µL/mL), loss of drug due to rapid blinking, reflex tear production and limited absorption due to tear film barrier (Cholkar, Patel et al. 2013) (Lee and Robinson 1986, Schoenwald 1990). To enhance the drug bioavailability, ophthalmic formulation requires a higher precorneal residence 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 (Reimondez-Troitino, Csaba et al. 2015) (Khar, Jain et al. 2010). Novel drug delivery technologies utilizing cyclodextrins, prodrugs and colloidal systems like nanoparticles, liposomes and nanomicelles are studied extensively (Tirucherai and Mitra 2003, Gunda, Hariharan et al. 2006, Vaka, Sammeta et al. 2008). Conventional eye drops in the form of solutions, suspensions and emulsions have been utilized over a long period of time to treat anterior segment disorders. The following section describes topical ophthalmic formulations in detail.

3.1.1 Ophthalmic Solutions

Topical eye drop solutions are patient compliant, non-invasive, immediate acting drug formulations. Eye drop solutions are installed 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. Prodrugs approach modifies the physiochemical properties of the drug for better absorption of the drug by passive or active diffusion (Mandal, Pal et al. 2016, Mandal, Patel et al. 2016). Once the prodrug reaches the corneal tissue, cellular enzymes cleave it into the active drug. Dipivefrine (Propine®) is an ester prodrug of epinephrine, which 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 is a hydrophilic prodrug of Cyclosporine-A demonstrating 25,000 times higher solubility than the parent drug at pH 7 (Lallemand, Perottet et al. 2005). Another prodrug of Cyclosporine-A (OPPH008) was characterized and determined for its efficacy in the treatment of dry eye disease. OPPH008 achieved higher tissue concentrations as compared to a CsA ophthalmic emulsion (Restasis®) in rabbit ocular tissues (Rodriguez-Aller, Kaufmann 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, Kadam et al. 2010, Alm 2014).

Modification of Formulation Properties

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, Alhanout et al. 2013). Cyclodextrin-complexation permits aqueous formulation of various drugs including dexamethasone, chloramphenicol and corticosteroids for ocular disorders (Loftsson and Jarvinen 1999, Loftsson and Stefansson 2002, Sigurdsson, Konraethsdottir et al. 2007). A study by Saari et al. concluded that 0.7% dexamethasone-cyclodextrin eye drops demonstrated significantly higher safety and efficacy as an anti-inflammatory medication for post-cataract inflammation than 0.1% dexamethasone sodium phosphate eye drops (Saari, Nelimarkka et al. 2006).

**Viscosity and Permeation Enhancers**

Ophthalmic formulations traditionally utilize viscosity enhancers to improve precorneal residence time of the drug. Various viscosity enhancers like 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, Alhanout et al. 2013). Such agents temporarily adjust the corneal and conjunctival surface to facilitate rapid drug penetration. Ophthalmic preservatives like benzalkonium chloride, surfactants like polyethylene glycol, ethers, EDTA, chelating agents, and bile salts are few examples of permeation enhancers that raise drug bioavailability (Burgalassi, Chetoni et al. 2001, van der Bijl, van Eyk et al. 2001, Hornof and Bernkop-Schnurch 2002, van der Bijl, van Eyk et al. 2002). Despite the various advantages offered by penetration enhancers, these agents can cause tissue irritation and damage the corneal and conjunctival tissues (Achouri, Alhanout et al. 2013).

**3.1.2 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. TobraDexST® is a suspension of (0.3%) tobramycin and (0.05%) dexamethasone indicated for bacterial ocular infections (Scoper, Kabat et al. 2008). TobraDexST® was developed from TobraDex® to overcome the high viscosity of the initial formulation. TobraDexST® demonstrated higher tissue concentrations of 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 TobraDexST® administration as compared to TobraDex®. A yet another US FDA approved ophthalmic suspension is Besivance®. 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 in signs and symptoms of bacterial conjunctivitis (Silverstein, Allaire et al. 2011). In another Phase III study, 2% rebamipide suspension (OPC-12759) was effective for treatment of dry eye disease as compared to the control group (NCT00885079). Also the formulation was well tolerated and demonstrated high efficacy for the treatment of dry eye disease (Diestelhorst, Kwon et al. 1998, Kinoshita, Awamura et al. 2012).

3.1.3 Emulsions

An emulsion is a biphasic system composed of two immiscible phases. Ophthalmic emulsions can offer advantages improvement in drug solubility and bioavailability of previously water insoluble drugs. Pharmaceutical emulsions can be widely categorized as water in oil (w/o) and oil in water (o/w). Ophthalmic formulations widely utilize 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 w/o 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®, AzaSite®, Refresh Endura® and Durezol®. Restasis® is a 0.05% emulsion of Cyclosporine-A indicated for 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 non-medicated 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, Silverstein et al. 2009, Kang-Mieler, Osswald et al. 2014). Emulsions can sustain drug release, improve corneal drug absorption and prolong the formulation residence time in precorneal cavity. This helps in enhancing the bioavailability of lipophilic drugs for treatment of anterior segment disorders (Liang, Brignole-Baudouin et al. 2008).

3.2 Drug Delivery to Back of the Eye

3.2.1 Intravitreal Injections of Anti-VEGF Agents

The first indication of vascular endothelial growth factor (VEGF) in ophthalmology 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 diabetic retinopathy (DR). By the late 1990’s VEGF was identified as a potential mediator of choroidal neovascularization and intraocular neovascularization for patients suffering with age-related macular degeneration (AMD) (Amin, Puklin et al. 1994, Lopez, Sippy et al. 1996). Proof of concept studies established that VEGF blockage resulted in inhibition of
neovascularization in various animal models (Aiello, Pierce et al. 1995, Zhu, Lu et al. 1999, Campochiaro and Hackett 2003) and indicated VEGF blockage can be a potential new approach to overcome retinal disorders involving neovascularization (Adamis, Shima et al. 1996).

Forty years after cloning of VEGF, a humanized monoclonal antibody, bevacizumab (148kDa) 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® (bevacizumab) is a realistic off label treatment for wet AMD and DR. Pegatanib sodium (Macugen) was the first anti-angiogenic VEGF aptamer approved by US FDA for the treatment of wet or nonvascular AMD in 2004. An intravitreal injection of Pegatanib sodium (pegylated anti-VEGF aptamer) alleviated the conditions of wet AMD and reduced vision loss (Gragoudas, Adamis et al. 2004, Ng, Shima et al. 2006). Subsequently a F(ab) fragment of bevacizumab, the ranibizumab (49 kDa) was developed by Genentech (Presta, Chen et al. 1997). Ranibizumab demonstrated a higher binding affinity than Pegatanib to VEGF and better penetration into the retinal layers as compared to bevacizumab (Mordenti, Cuthbertson 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 for wet AMD. More than 94% of the patients in the treatment group showed signs of improved vision as compared to control group (p<0.001) (Rosenfeld, Brown et al. 2006). Now Lucentis® (ranibizumab intravitreal injection) is approved for treatment of patients with neovascular (wet) AMD once every month.(Genentech 2006). The most recent approved monoclonal antibody for the treatment of wet AMD is aflibercept (97kDa), a recombinant fusion protein. Eylea® (aflibercept, an intravitreal injection) acts by blocking the action of VEGF and inhibit neovascularization. Aflibercept has revealed approximately 200 times higher binding affinity to VEGF as compared to ranibizumab.
While ranibizumab only binds to VEGF-A isoform (Sarwar, Clearfield et al. 2016, Zhang, Chioreso et al. 2017), aflibercept binds to various isoforms of VEGFs (VEGF-A and VEGF-B) and PGF (placental growth factor). Binding of aflibercept to various growth factors suppresses all 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 the gold standard for the treatment of wet AMD and DME (Chang, Garg et al. 2012, Rodrigues, Lutz et al. 2018).

4. Recent Inventions for Ocular Drug Delivery Technologies

4.1 Anterior Segment Ocular Drug Delivery Technologies

4.1.1 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 non-biodegradable and biodegradable materials. Non-biodegradable punctum pug delivery system (PPDS) are made from silicone, polycaprolactum and hydroxyethyl methacrylate, which intends to provide controlled drug release up to 180 days. After this period, the insert is removed. Recently, a PPDS (SmartPlug®) 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 (Weber W). Ocular Theraputix™ (Bedford, MA, USA) 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 safety and efficacy of OTX-TP for
reduction in intraocular pressure (IOP) and ocular hypertension (NCT02914509). Recently Ocular Theraputix has also completed a Phase III clinical study for 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 to a placebo punctum plug (NCT02988882, NCT02736175). High efficacy and safety of OTX-DP lead to the US FDA approval of Dextenxa® (dexamethasone insert, Ocular Theraputix™) for treatment of pain following ophthalmic surgery (Ocular Therapeutics™ 2018). The company has also developed OTX-TP2 (a prostaglandin trap), which can be utilized for the treatment of glaucoma and postoperative ocular care (Kang-Mieler, Osswald 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).

4.1.2 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 in the sub-conjunctival region, aqueous humor and the episcleral region. These implants provide the advantage of sustained localized drug delivery and higher patient compliance as compared to 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, Ferrari et al. 2009), others are inserted into the aqueous humor (Molokhia, Thomas et al. 2013). Surodex® is an example of an anterior segment insert, which is inserted into the anterior ocular segment post cataract surgery to alleviate post-surgery inflammation. Surodex® is a rod shaped biodegradable insert consisting of drug dexamethasone using polymers like PLGA (poly lactide-co-glycolide) and hydroxypropyl methyl cellulose allowing sustained drug release for 7-10 days (Tan, Chee et al. 1999, Tan, Chee
et al. 2001). A study demonstrated that a 7 day drug release with Surodex® achieved higher concentrations as compared to maximum peak drug concentrations after topical treatment with dexamethasone eye drops (Tan, Chee 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 one year. In a Phase III clinical study, Lux Biosciences also evaluated the effectiveness of LX201 to prevent corneal graft rejection NCT00447642.

4.1.3 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 like Lacrisert® and Ocusert® 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 the episcleral implants, since these are the exterior inserts into portion. 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, D’Aversa et al. 2009). Lacrisert® decreased corneal sensitivity, recurrent corneal erosions and exposure to keratitis. It is also effective for the treatment of conjunctival hyperemia (MERCK & CO. 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 seven days and directed for the treatment of glaucoma. However, pilocarpine in the insert caused unwanted side effects like eyebrow ache and miosis. This resulted in removal of Ocusert® from the market (Pollack, Quigley et al. 1976). Yet another cul-de-sac implant is DSP-Visulex (Aciont, Inc.) which has completed Phase II clinical trial for
the treatment of anterior uveitis (NCT02309385). DSP-Visulex contains dexamethasone and is inserted into the bulbar conjunctiva (Papangkorn, Truett et al. 2018).

4.1.4 Drug Eluting Contact Lenses

Drug Eluting Contact lenses (CLs) are light-transparent corneal dressings acting as drug reservoir and sustain drug discharge near the post-lens tear fluid for the treatment of anterior ocular disorders. Drug loaded soft contact lenses is an innovative drug delivery system to not only prolong and sustain drug release but also enhance drug penetration across the corneal epithelium as compared to conventional eye drops. Contact lenses can increase bioavailability of the drug by increasing the contact time of the drug (Mandal, Bisht et al. 2017). Various soft contact lenses have been developed for antifungal agents which can prolong drug delivery up to 21 days (Phan, Subbaraman et al. 2014). A clinical trial was conducted for evaluation of 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 utilized to load drugs on contact lenses, instead of just soaking the lens with the drug. Recently Gulsen and Chauhan have 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 7-8 days (Gulsen and Chauhan 2004). Similarly, Ciolino et al. have fabricated a drug eluting contact lens using polymer embedded matrix for ciprofloxacin and econazole. The in-vitro data demonstrates a zero-order drug release profile, which can sustain drug release up to one month (Ali, Horikawa et al. 2007, Ciolino, Hoare et al. 2009). Figure 2 depicts advantage of soft drug loaded contact lenses over conventional eye drops.
Contact lenses offer highest drug bioavailability as compared to other non-invasive ophthalmic medications due to close proximity of the contact lens with the cornea. They also provide a significant dosing advantage as compared to 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 yet to be addressed for successful commercialization for contact lenses (Malthiery, Marriq et al. 1989, Dixon, Shafor 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 a reverse engineering process to generate binding sites inside CL for drug molecules which mimic the natural receptors. Such molecularly imprinted hydrogel with specific binding affinity utilized for making drug-eluting contact lenses, allow enhanced drug loading and consequently prolong drug-release kinetics. Each synthetic molecules is designed selectively to fit a natural receptor in the human body in order 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 mimics this environment in synthetic receptors for higher drug loading in the CLs (Alvarez-Lorenzo, Anguiano-Igea et al. 2019).

4.1.5 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 advantage over invasive techniques requiring surgical interventions. This technique of drug permeation can be utilized for anterior and posterior ocular disorders by utilizing trans-corneal and trans-scleral routes respectively. Trans-corneal iontophoresis can be employed for treatment of anterior segment disorders like corneal ulcers, dry eye disease, ocular inflammation, keratitis and ocular uveitis. Trans-corneal iontophoresis is unsuitable for the posterior segment delivery due to the presence of barriers like 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, Thomas 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, Jeong et al. 2007, Gratieri, Santer 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 for the safety and efficacy of a dexamethasone phosphate (EGF-437) formulation for distribution through EyeGate® II Delivery System for the treatments of dry eye disease, anterior uveitis, cataract, post-operative pain, anterior chamber inflammation and anterior scleritis (NCT01129856, NCT02517619, NCT03180255, NCT01059955). EGF-437 delivered through EyeGate® II Delivery System resulted in reduction of dose frequency as compared to standard dexamethasone eye drops. US FDA has granted an orphan drug designation for the delivery of EGF-437 through EyeGate® II Delivery System as a treatment option for corneal graft rejection. Iontophorosis is a valuable
treatment option for patients non responsive to eye drop therapy (Kompella, Kadam et al. 2010). The treatment also resulted in fewer incidences of increased IOP and controlled drug delivery with lower iontophoresis dose (mA-min) (Eye Gate Pharma 271 Waverley Oaks Road). Visulex-P® (Aciont Inc., Salt Lake City, UT, USA) and OcuPhor® (Iomed Inc., Salt Lake City, UT, USA) 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 to topical eye drops. The treatments with iontophoresis method usually has better patient compliance as compared to ocular injections. Nonetheless, certain patients screened for ocular iontophoresis experienced some discomfort and burning sensation (Parkinson, Ferguson et al. 2003). Posterior segment ocular disorders like AMD, DR, DME and CRVO require sustained drug delivery at higher doses. Aciont Inc., USA has evaluated the potential of ocular iontophoresis for the treatment AMD by Visulex-I-noninvasive ocular drug device for the delivery of Avastin® (bevacizumab) and Lucentis® (ranibizumab) through the trans-scleral route (Higuchi 2010) (Pescina, Ferrari et al. 2010). Table 2 summarizes currently available ocular drug delivery devises in clinical trials for the management of anterior segment disorders.

4.2 Posterior Segment Ocular Drug Delivery Technologies

Novel drug delivery systems like implants are currently used by the clinicians to sustain and prolong drug release to cure back of the eye disorders like 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, retinal hemorrhage and 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.

### 4.2.1 Durasert™ Drug Delivery Technology System

Durasert™ technology system (pSivida Corp., MA, USA) 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® is the first intravitreal drug delivery system loaded with an antiviral drug (gancyclovir) for the treatment of cytomegalovirus (CMV) retinitis. It utilizes 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). Retisert® intravitreal implant (Bausch & Laumb, Inc, USA) is a steroid-eluting device implanted surgically in the vitreous humor. Retisert® releases fluocinolone acetonide up to three years into the vitreous humor (Jaffe, Martin et al. 2006, Multicenter Uveitis Steroid Treatment Trial Research, 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 as choroiditis is the inflammation of the choroid capillaries. This can lead to damage to the optic nerve and permanent loss of vision. Retisert® contains fluocinolone acetonide tablet encapsulated within a silicone elastomer cup containing an orifice made with polyvinyl alcohol membrane (Haghjou, Soheilian et al. 2011).

Iluvien® (fluocinolone acetonide intravitreal implant) is the most recent US FDA approved intravitreal injectable insert indicated for the treatment of DME. Multicenter, randomized clinical trials demonstrated that both 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 to the control group (Campochiaro, Brown et al. 2012, Cunha-Vaz, Ashton 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 to Leucentis® (ranibizumab) treatment (NCT00770770).

4.2.2 Novadur™ Drug Delivery Technology

Novadur™ 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, Soheilian et al. 2011). Ozurdex® (Allergan, CA, USA) is a controlled release intravitreal dexamethasone-implant approved by US FDA for the treatment of DME, RVO and posterior uveitis (Haller, Bandello et al. 2011, Boyer, Yoon et al. 2014, Sangwan, Pearson et al. 2015). Ozurdex® contains 0.7 mg of dexamethasone in a PLGA matrix which releases the drug up to 90 days. Mayer W.J. et al. recently investigated effects of intravitreal bevacizumab followed by Ozurdex® and Ozurdex® mono-therapy for the treatment of central retinal vein occlusion (CRVO) and macular edema. The research group concluded that there was no difference between the above mentioned treatment strategies for treatment of CRVO. But for branched retinal vein occlusion, Ozurdex® mono-therapy resulted in better functional outcome (Mayer, Remy et al. 2012). Currently a Phase III clinical trial is conducted for the possible effectiveness of intravitreal implant of Ozurdex® mono-therapy for the treatment of DME (NCT00168389). PLGA containing brimonidine tartrate (Allergan) is another intravitreal implant is in clinical trials for dry AMD (NCT00658619) and retinitis pigmentosa (NCT00661479). Brimonidine is an α2 adrenergic agonist, which releases neurotrophic factors like ciliary neurotrophic factor (CNTF) and brain derived neurotrophic factor (BDNF) (Kim,
Chang et al. 2007). Brimonidine protects apoptotic retinal cell death like photoreceptors, RPE and ganglion cells (Zhang, Mo et al. 2009).

4.2.3 I-vation™ TA Drug Delivery Technology

I-vation™ TA (SurModics Inc.) is also an intravitreal drug delivery implant for triamcinolone acetonide (TA). I-vation™ technology. I-vation™ is a titanium helical coil implant coated with TA in a non-biodegradable polymer. Preclinical experiments suggested that I-vation™ TA can sustain TA release in-vivo up to two 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 to reduce macular thickness from the baseline indicating alleviation of DME (Erickson 2009).

4.2.4 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 (CNTF). 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, Caruso et al. 2006, Emerich and Thanos 2008). Various biocompatible polymers like collagen and hyaluronic acid hydrogel are utilized for forming the matrix of ECT. 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 that they can produce biologically active molecules indefinite period of time requiring less frequent implant replacement. Kontturi LS et al 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 indicates human RPE cell line remained viable with a constant secretion of soluble VEGF-1 receptor up to 50 days (Kontturi, Collin et al. 2015). Although the researchers found a modest VEGF inhibition in-vivo model, this delivery technology displays a promise for utilization of ECT to treat disorders like wet AMD, DR and DME. ECT can be considered as a versatile platform that can be employed for secreting targeted therapeutic biotech drugs like antibodies, antibody fragments, growth factors, cytokines, and prostaglandins for back of the eye disorders. (Tao 2006). Chu AMW et al. formulated an injectable composite alginate-collagen (CAC) matrix ECT gel having human retinal pigment epithelial cells and glial-cell derived GDNF secreted by HEK293 cells. The GDNF secreting HEK293 cells were transfected with lipofectamine repressor (Tet R) DNA and pro-caspase 8 (pro-Casp8) transcription DNA. Tet R can be used as a biosafety switch for the ECT drug delivery system. While pro-Casp8 can trigger the in-built apoptotic pathway in the retinal cells. The researchers witnessed 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 in photoreceptor death and gain of retinal structure and function without compromising gel viability (Figure 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, Tsang et al. 2019). ECT thus can be considered as a safe,
effective and well-controlled platform for the treatment of back of the eye disorders with retinal dysfunction (Baranov, Lin et al. 2017).

4.2.5 Suprachoroidal Drug Delivery utilizing hollow microneedles 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 anatomical studies demonstrating the diffusion of therapeutic agents after drug delivery at the suprachoroid space (Patel, Berezovsky et al. 2012, Kadam, Williams et al. 2013, Chiang, Venugopal et al. 2016). Patel et al. demonstrated suprachoroid drug delivery through the posterior pars plana of a rabbit model using a hollow microneedle. The suprachoroid drug delivery was minimally invasive procedure demonstrating safe delivery of into the retina and choroid with no adverse effects. Gilger et al. reported the successful suppression of acute inflammation with corticosteroid delivered through suprachoroid route in a porcine model of noninfectious posterior uveitis (Gilger, Abarca et al. 2013). Drug delivery through suprachoroid route utilizing microsurgical cannulas in primate and procaine models has showed increased drug bioavailability (143). 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 like cataract and hypertension suggests its positive impact (Olsen, Feng et al. 2006). In contrast, bevacizumab demonstrated low bioavailability at target tissue with faster diminishing therapeutic response as compared to intravitreal injections (Olsen, Feng et al. 2011). Currently, various Phase III clinical trials utilizing triamcinolone acetonide suprachoroidal injection along with various anti-VEGF agents are investigated for enhanced safety.
and efficacy alleviating the conditions 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.

5. Novel Ocular Drug Delivery Technologies

5.1 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 like low drug bioavailability and low drug permeation through ocular barriers. Nanocarriers can prolong drug action by sustained and controlled release of the drug and 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, microneedles are capable of encapsulating small molecules and biotech drugs for ocular delivery. The size of the nanocarriers ranges from 1-1000 nm. Nanoparticles greater than 10µm can cause foreign body sensation and ocular irritation. (Ali and Lehmussaari 2006, Liu, Jones 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 segment of the eye. (Reimondez-Troitino, Csaba et al. 2015). Nanomedicine
for ocular drug delivery can prove to be highly patient compliant and have a higher tolerability than conventional eye drops for anterior segment ocular disorders. (Vandervoort and Ludwig 2007, Bachu, Chowdhury et al. 2018, Mandal, Gote et al. 2019).

5.1.2 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 10-200 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 as the critical micellar concentration (CMC). Nanomicelles have the capacity to encapsulate hydrophobic drugs in the hydrophobic core of the micelles due to hydrophobic interactions. While 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 utilized as topical eye drops. Nanomicelles can be broadly classified as surfactant nanomicelles and polymeric nanomicelles. Cequa® (Sun Pharmaceuticals Inc) is a nanomicellar formulation of 0.09% cyclosporine-A recently approved by US FDA for dry eye disease. Cequa® demonstrated improved rapid onset of action, as early as four weeks and improvement in tear production as compared to Cyclosporine-A emulsion in Phase II and Phase III clinical trails (Mandal, Gote et al. 2019). The in-vivo studies of the nanomicellar formulation of Cyclosporine-A conducted in rabbits demonstrated enhanced bioavailability in the anterior ocular tissues as compared 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. has demonstrated efficient encapsulation and enhanced ocular pharmacokinetics of
hydrophobic drugs like voclosporin, cyclosporine-A, rapamycin, triamcinolone acetonide, cidofovir prodrug and curcumin for the treatment of various anterior and posterior ocular disorders. Various surfactant polymers like vitamin E TPGS, hydrogenated castor oil-40,60,100, octoxynol-40 were used for entrapping hydrophobic drugs in the nanomicellar core by Mitra et al. 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 a surfactant based nanomicelles for antiviral drug deliver for CMV retinitis and a multi-layered nanomicelles were developed for the delivery of octeriotide peptide to the anterior segment of the eye (Mandal, Cholkar et al. 2017, Mandal, Patel et al. 2019). The researchers also demonstrated that a mixed miceller structure designed from a fixed ratio of low molecular surfactants had a lower CMC. This indicates that the nanomicellar structure is stable over dilution in the systemic fluids and will not result is premature drug release. These highly lipophilic agents forms a clear solution when encapsulated in the nanomicelles. Also nanomicelles aid is sustained and controlled release of the drug to the ocular tissue. (Cholkar, Trinh et al. 2015, Mandal, Cholkar et al. 2017, Trinh, Cholkar et al. 2017, Mandal, Patel et al. 2019).

Nanomicelles constructed from block copolymers like PLGA, PEG, PCL, PLA are called as 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 imparts the polymer amphiphilicity. Nanomicelles can solubilize hydrophobic drugs and improve their delivery to the ocular tissues. methoxy poly (ethylene glycol) poly (lactides) (mPEG-hexPLA) 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 MPEG-hexPLA nanomicelles encapsulating Cyclosporine-A can be used for treatment of dry eye disease, prevention of corneal graft rejection and to treat autoimmune uveitis (Di Tommaso, Torriglia et al. 2011). Polymeric micelles often offer certain advantages over surfactant micelles. These are sustained drug release and lower incidence of drug toxicity. While 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 and gene delivery is an emerging field of research. Liaw and Robinson utilized a nonionic co-polymeric system for gene delivery. The polymeric nanomicelles encapsulated plasmid DNA with lacZ gene demonstrated greater delivery of the therapeutic cargo to the cells (Tong, Chang 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, Gote et al. 2019).

5.1.1 Nanoparticles

The size of drug loaded nanoparticles can range from 50-500 nm so as 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 conjunctiva tissues have a negatively charged surface. It is observed that cationic NPs have higher retention time on ocular surfaces as compared to anionic NPs. This can enhance the drug permeation into the ocular surfaces. (Akhter, Anwar et al. 2016). Colloidal NPs can also increase the solubility of highly hydrophobic drugs and increase the transcorneal permeability of such agents. Various biodegradable and non-biodegradable NPs for
treating anterior and posterior segment ocular disorders are developed. The commonly used polymers for NPs for ocular applications are, poly lactide co glycolide (PLGA), poly ethylene glycol (PEG), poly caprolactum (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 was prepared by Bi H et al. for the treatment of posterior uveitis and autoimmune uveitis (Guo, Li et al. 2019) (Figure 4). Canadas et al. estimated the delivery of pranoprofen, a non-steroidal anti-inflammatory drug (NSAID) entrapped in PLGA NPs. The in-vitro study on human retinoblastoma cell line demonstrated lower toxicity of pranoprofen PLGA NPs on the cells as compared to the free drug. Pranoprofen PLGA NPs were further demonstrated effective corneal penetration on a ex-vivo bovine model as compared to the drug alone. In-vivo ocular anti-inflammatory activity and ocular pharmacokinetic studies of the formulation were studied in rabbit eyes. The corneal penetration of pranoprofen NPs was four 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 (Canadas, Alvarado et al. 2016). Connexin43 (Cx43) mimetic peptide has demonstrated efficacy in improving retinal ganglion cell survival after retinal ischemia. Rupenthal ID et al. and Bishat et al have evaluated Connexin43 (Cx43) mimetic peptide PLGA NPs for retinal ischaemia in zebrafish and live embryos. The study resulted in no toxicity to the ocular tissues (Chen, Green et al. 2015, Bisht and Rupenthal 2018). Qiu F et al. developed fenofibrate PLGA nanoparticles (Feno-NP) for the management of DR and AMD. Fenofibrate is a agonist of peroxisome proliferator-activated
receptor α (PPARα) 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 Feno-NPs (Qiu, Meng et al. 2019). PLGA can also be utilized to encapsulate many well-known anti-VEGF like bevacizumab, ranibizumab and aflibercept. (Elsaid, Jackson et al. 2016, Sousa, Cruz et al. 2017, Kelly, Hirani 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, Chowdhury et al. 2018). (Figure 5)

NSAID’s like ibuprofen, indomethacin and flurbiprofen encapsulated in NPs can be used for the treatment of anterior segment ocular inflammation. Ibuprofen encapsulated in Eudragit RS100 NPs demonstrated improved drug concentrations to the aqueous humor of rabbit eyes in comparison to ibuprofen ocular solution (Pignatello, Bucolo 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 to the control group (Pignatello, Bucolo et al. 2002, Pignatello, Bucolo et al. 2002, Gupta, Jain et al. 2007, Cao, Zhang et al. 2010). Biodegradable polymers like PCL, PEG, PLGA and Poloxamer 188 were used for formulation of flurbiprofen-encapsulated nanoparticles. Topical administration of flurbiprofen nanoparticles demonstrated enhanced anti-inflammatory efficiency and minimal toxicity like ocular irritation in the rabbit eyes (Calvo, Vila-Jato et al. 1996, Valls, Vega 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 entraping Cyclosporine-A which has shown two-fold improved precorneal residence and
higher conjunctival permeability in rabbit eyes. Chitosan polymer can also be used for the delivery of lipophilic, hydrophilic drugs and polynucleotides to the anterior ocular surface. (de la Fuente, Ravina et al. 2010). (De Campos, Sanchez et al. 2001). Mitra et al. has developed pentablock copolymers from polymers like PEG, PLA, PGA, PCL, PLGA for making nanoparticles encapsulating hydrophilic drugs like dexamethasone and macromolecules like IgG, IgG(Fab) and various peptides for controlled drug delivery to the anterior as well as posterior sections of the eye (Patel, Vaishya et al. 2016, Agrahari, Li et al. 2017). Glaucoma is the leading cause of blindness throughout the world. Navarro et al. 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, Lee et al. 2019). Current research is utilizing ligand targeted functionalized nanoparticles for enhanced delivery of therapeutic agents as compared to non-functionalized nanoparticles. Targeting ligands can specifically target receptors and nutrient transporters on the conjunctiva and corneal surface. 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 to NPs not surface functionalized with Hyaluronic Acid. Such NPs undergo active transportation mediated by the CD44 HA receptor utilizing the caveolin-dependent endocytosis pathway (Contreras-Ruiz, de la Fuente et al. 2011). Surface functionalized nanoparticles with targeting agents like peptides, antibodies, vitamins like biotin and folic acids and aptamers have resulted in higher uptake as compared to the non functionalized nanoparticles. Kompella et al demonstrated that transferrin conjugated NPs had 74% higher transport across the cornea and conjunctiva in ex vivo bovine eyes as compared to non-targeted NPs (Kompella, Sundaram et al. 2006). Epigallocatechin-3-gallate (EGCG) is a
natural polyphenol compound having anti-oxidant, anti-inflammatory and anti-angiogenesis activity and can have efficacy against choroidal neovascularization (CNV). Gelatin NPs surface functionalized with hyaluronic acid (HA) and conjugated to a RGD peptide. Encapsulating EGCG (GEH-RGD) was evaluated for treatment of corneal neovascularization by Tseng CL et al. In-vivo studies in CNV mouse model showed fewer and thinner blood vessels for mice treated with topical GEH-RGD NPs as compared to the blank NPs (Lee, Jun et al. 2014). This result suggests potential role of targeted nanoparticles for treatment of CNV. Active targeting of NPs can provide efficient and rapid transport of cargo across the corneal and conjunctival epithelium. Nanoparticles can also serve as an effective vehicle for gene delivery. Gold NPs conjugated to a 2kD polyethylenimine was evaluated for gene delivery to rabbit cornea. The researchers observed high uptake of the gold NPs through the rabbit stroma and a gradual clearance over time (Sharma, Tandon et al. 2011).

5.1.3 Liposomes

Liposomes are utilized as ocular drug delivery vehicles which can encapsulate hydrophilic and hydrophobic drugs. Polymers form 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 are explored for ocular drug delivery for the anterior segment disorders (Law, Huang et al. 2000). Sun et al. entrapped short-chain-conjugated ceramide and C6-ceramide in liposomes and applied to treat corneal inflammations in mice. Ceramides are known for their role as an anti-proliferative and pro-apoptotic agent in sphingolipid metabolism. The C6-ceramide liposomal formulation demonstrated significant efficacy in corneal inflammation reduction in murine model. (Sun, Fox et al. 2008). This implies an affirmative role of ceramide loaded liposomes for treating anterior segment ocular inflammations. (Sun, Fox et al. 2008). (Table 4). Metwally AA et al. showed that timolol maleate gelatinized liposome treatment resulted in
lowering the intra ocular pressure (IOP) when evaluated in-vivo on glaucomatous rabbit's eyes (Hathout, Gad et al. 2019). Song X et al. developed a 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. Tang X et al. investigated azithromycin liposomes for the treatment of dry eye disease. In-vivo pharmacodynamics studies in rats showed reduction in the symptoms of dry eye disease and the azithromycin liposomal treatment had higher safety and efficacy as compared to hyaluronic acid sodium eye drops (Ren, Lin et al. 2018). Topical voriconazole (VOR) liposomes were developed by DeSá et al. for fungal keratitis treatment (de Sa, Taveira et al. 2015). Liposome mediated ocular drug delivery is 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.. 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 18ng/g in rabbit retinal tissue (Davis, Normando et al. 2014).

5.1.4 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 have a dendrimer with specific functional groups and 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 be either conjugated to the surface of the
dendrimer or be encapsulated by caging in the internal structure of the dendrimer (Kalomiraki, Thermos et al. 2016), (Lancina and Yang 2017). Polyamidoamine (PAMAM) polymer having carboxylic and hydroxyl functional group is the most commonly used dendrimer for ocular drug delivery. High branching of PAMAM polymer can lead to primary, secondary and tertiary generations of the dendrimer nanocarrier. Kannan RM et al. designed a gel formulation of G4-PAMAM dendrimer with hyaluronic acid cross-linked entrapping dexamethasone intended for the treatment of corneal inflammation. Subconjuntival injection of the dendrimer formulation lead to reduction in central corneal thickness and improved corneal clarity in an alkali burn rat model which was highly clinically relevant (Soiberman, Kambhampati 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 like DR and AMD. In-vivo studies in rats showed that the drug loaded dendrimers enhanced the ocular permeability of dexamethasone after subconjuntival injection as compared to the free drug (Yavuz, Bozdag Pehlivan et al. 2016). matrix metalloproteinases-9 (MMP-9) can trigger corneal damage and result in dry eye disease. Nativi C et al synthesized a 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 or corneal inflammation and dry eye disease (Cerofolini, Baldoneschi et al. 2017). Vandamme et al. 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 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).

5.1.5 Microneedles
Microneedles drug delivery technology was originally used for overcoming stratum corneum and was utilized for transdermal drug delivery (Lee, Park 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 MN coated with drugs like sunitinib malate and pilocarpine resulted in higher drug bioavailability in the anterior ocular segment compared to topical drop applications in-vivo (Jiang, Gill et al. 2007, Song, Lee et al. 2015). Microneedles can also be used to deliver therapeutic agents for the treatment of back of the eye disorders. Microneedles nanoparticles and microparticle suspension can be delivered to the suprachoroidal space (Patel, Lin et al. 2011). Duong PK et al. have shown a polymeric eye patch consisting of an array of detachable and biodegradable microneedles (MNs) for controlled and localized ocular drug delivery. These MNs could penetrate into the corneal layers and deliver anti-angiogenic monoclonal antibody (DC101) for the treatment of corneal neovascularization (CNV). The MNs were double layered with DC101 to provide biphasic drug release kinetics to enhance the therapeutic efficacy of the MNs. DC101 MNs eye patch produced approximately 90% reduction in CNV in a CNV disease mouse model as compared to a topical eye drop. The researchers also suggest that the MNs patch is minimally invasive and can be self-applied by the patients on their corneas (Than, Liu 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 its current limitations demands further research in the he field for desired clinical translation (Thakur Singh, Tekko et al. 2017) (Figure 6)

5.1.6 Nanowafers
Nanowafers are small transparent rectangular membranes or circular discs containing drug loaded into nanoreservoirs which can be smeared to the ocular surface using a fingertip. Controlled drug release from the nanowafer can increases 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 surface commonly found in CNV and dry eye disease. This novel nanocarrier is designed from biodegradable and biocompatible polymers which can be eliminated over the period of time. Pflugfelder SC et al. developed 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 five-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. A yet another interesting finding the scientists reported was that Dex-NW was effective in lowering the overexpression of inflammatory cytokines like TNF-α, IFN-γ, IL-1β and IL-6. Also the expression of inflammatory chemokines like CXCL-10 and CCL-5 and MMP-3 and MMP-9 was lowered (Coursey, Henriksson et al. 2015, Bian, Shin et al. 2016). Axitinib-loaded nanowafers were developed by Xiaoyong et al. for the treatment of CNV. A murine ocular burn model was used to evaluate the in-vivo efficacy of Axitinib-loaded nanowafers. The laser scanning confocal imaging and RT-PCR results revealed that once a day Axitinib-loaded nanowafer was twice as effective as compared to axitinib daily topical eye drops.
These findings have shown the potential of nanowafers for further evaluation in clinical trials.

### 5.1.7 Ocular nanocarriers currently approved and under clinical investigational

Nanocarriers like nanoparticles and nanomicelles, have been widely explored for their potential to cure anterior and posterior ocular disorders. In spite of 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 (2018). Cequa® is 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 statistically (p<0.0001%) significant increase in the primary endpoint 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 trail which are a common scenario for the drugs evaluated in this category (Sheppard, Torkildsen et al. 2014) (Tauber, Karpecki 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, Gote et al. 2019).

There are a handful of ophthalmic nanocarrier drugs currently being investigated in the clinical trials to establish their safety and efficacy for the treatment of ocular disorders. A randomized, single-blind study evaluating the efficacy of hydrating polymers and polyunsaturated fatty acids microemulsion for the treatment of dry eye disease (NCT02908282). In a yet another randomized, single-blinded Phase II clinical trial, urea loaded nanoparticles are evaluated as a possible treatment for cataract management (NCT03001466). A clinical study was conducted by Sun Yat-sen University to compare the efficacy of two tear substitutes Tears Naturale Forte and Liposic 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 (Massachusetts, U.S.A.) has developed nanoparticle based Mucus Penetrating Particles (MPPs) of loteprednol etabonate (LE). LE is a corticosteroid and encapsulating in MPPs can improve drug delivery across the ocular endothelial cells. Currently they are 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 investigated for the treatment of Diabetic Macular Edema and Retinal Vein Occlusion NCT02245516.

A fewer nanoformulations in the 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). A 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, rabbits ocular anatomy does not completely mimic human ocular anatomy. Rabbits have higher mucus production, higher surface sensitivity, lower rate of blinking which can result in better drug retention and drug penetration in comparison to human eyes (Weng, Liu 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 shown to cause blurring of vision (Wadhwa, Paliwal 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, Chowdhury et al. 2018). The recent US FDA approval of Cequa® has lead to an inception of the era of nanotechnology in ophthalmology. In spite of limiting factors for the successful clinical translation of nano medicine for ophthalmology, one can predict to see nanotechnology products being approved for ocular ailments in the near future. (Figure 7)

7.2 Noninvasive drug delivery systems for the posterior disorders

All marketed ophthalmic products utilized for the management of retinal disorders are of invasive in nature. The intravitreal route is widely used for administration of biopharmaceutics to the back of the eye. This route is associated with various complications like intraocular inflammation, retinal detachment, glaucoma or intraocular pressure elevation, endophthalmitis, ocular hemorrhage and cataract (Mandal, Pal 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.

7.2.1 Small molecules

Eye drops installed 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 like blood-retinal barrier and tear film barrier and dynamic barriers like 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 murine model and edema reduction in rat with RVO (Doukas, Mahesh 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 settings it was further advanced to the
clinical trials. Although TG100801 was well tolerated by patients, did not demonstrate any efficacy for alleviating the condition of AMD (NCT00509548). Prazopanib is another small molecule multikinase inhibitor which was administered topically to laser-induced CNV rat model (Yafai, Yang et al. 2011). Similar to TG100801, prazopanib failed to demonstrate efficacy in patients with subfoveal CNV, secondary to AMD (Singh, Wurzelmann et al. 2014). On the similar lines acrizanib was investigated for reduction in nonvascular AMD in preclinical mouse models. Acrizanib is a VEGF receptor-2 (VEGFR-2) inhibitor and demonstrated 99% inhibitory effect for CNV, three times daily topical application of 1% suspension in mice (Adams, Anderson et al. 2018). Despite positive preclinical evaluation of acrizanib in mouse model, topically administered acrizanib is clinically ineffective for the treatment of AMD (NCT02355028). Although some multikinase inhibitors have failed in the 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 memantine drug (Namzaric®) was able to achieve sufficient concentration in the retina to provide retinal neuroprotection (Hughes, Olejnik et al. 2005). Another small molecular drug dorzolamide administered topically to inhibit carbonic anhydrase II in a rabbit model (Inoue, Oka 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. But the clinical trial was terminated due to insufficient enrollment (NCT02485249).

7.2.2 Biotech drugs

Biotech drugs like 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, Canakis et al. 2000, Miao, Wu 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, Canakis et al. 2000). 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, Gragoudas et al. 2000). To further improve topical delivery of biologics to the back of the eye, colloidal nanoformulations like liposomes and nanomicelles with various permeability enhancers were employed. William et al. demonstrated that permeability enhancer sodium caprate can enhance the delivery of antibody fragment in rabbit model (Williams, Brereton et al. 2005). Davis et al. utilized annexin A5–associated liposomes for topical delivery of bevacizumab to the back of the eye (Platania, Fisichella et al. 2017). Various cell-penetrating peptides (CPPs) are increasingly investigated for ocular delivery of proteins and peptides (Fonseca, Pereira 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, Pereira et al. 2009). Wang et al. applied HIV transactivator of transcription (TAT) for CPP to topically deliver acidic fibroblast growth factor in a rat model (Wang, Lin et al. 2010). Similarly, Ozaki et al. proved delivery of topically administered calpain inhibitory peptide conjugated to TAT to the retina of the rat eye (Ozaki, Nakazawa et al. 2015). Johnson LN et al. conjugated to green fluorescence protein (GFP) with a peptide of ocular delivery (POD), which highlights the pathway of drug disposition and absorption from the corneal epithelium to the retinal pigment epithelium (Johnson, Cashman et al. 2010). The
most recent and promising study was conducted by Cogan et al. The researchers achieved therapeutic levels of bevacizumab in the posterior ocular tissues like retina and choroid by topical co-administration of the antibody and CPP poly-arginine-6 (de Cogan, Hill et al. 2017). Nanoformulations may be applied as intravitreal injections, as well as topical eye drops for back of the eye delivery. (Table 5)

6. Discussions: Challenges and Future Perspectives for Ocular Drug Delivery Technologies

The shortcomings of the current ocular drug delivery system like lower drug bioavailability for topical administered drugs and invasive nature of posterior implants creates challenges allowing novel technologies to rise with superior and effective treatment for ocular disorders. Ocular disorders like cataract, dry eye disease, wet and dry AMD, glaucoma, DR and DME are predicted to escalate with the next two decades. For a majority of the anterior segment disorders, eye drops are regarded as the safest and the most convenient dosage form. Eye drops face a challenge of having low drug bioavailability at the target tissue. Controlled drug delivery with the help of nanoformulations like nanomicelles, nanoparticles, liposomes, dendrimers, nanowafers and microneedles can achieve high bioavailability of drugs at the anterior tissues like 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 noninvasive sustained drug delivery system for the posterior segment is challenging to ocular drug delivery scientists. Thus an urgent need for the development novel noninvasive drug delivery systems that can overcome ocular barriers, sustain drug release and maintain effective drug levels at the back of the eye.
7. Conclusion

Novel ocular drug delivery systems like 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. They can have the capacity to replace traditional ophthalmic medications in the near future. Parallel efforts not only in novel product development but also for product scale-up are required is the need of the hour.

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Authorship Contributions

Contributed in sections; Introduction and Barriers to ocular drug delivery and routes of drug administration: Sicotte,

Contributed in section; Past successes in ocular drug delivery technologies: Sikder

Contributed in sections, Present inventions for ocular drug delivery technologies, Novel Ocular Drug Delivery Technologies, Discussions: Challenges and Future Perspectives for Ocular Drug Delivery Technologies and Conclusion; Gote

Contributed in final editing and proofreading of the manuscript by Pal, Gote and Sicotte
References:

(2018). CEQUA™ (cyclosporine ophthalmic solution) 0.09% Label for topical ophthalmic use. N. 210913.


Genentech, I. (2006 ). HIGHLIGHTS OF PRESCRIBING INFORMATION. These highlights do not include all the information needed to use LUCENTIS safely and effectively. LUCENTIS™ (ranibizumab injection).


Footnotes

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Legends for Figures

Figure 1: Ocular anatomical barriers and routes of drug administration (Alqawlaq, Huzil et al. 2012).

Figure 2: Ocular drug delivery system using drug loaded soft contact lenses.

Figure 3: Encapsulated Cell Therapy (ECT) for back of the eye disorders. Composite alginate-collagen 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 non-treated, 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 non-treated, single and double gel treated animals detected by TUNEL assay with 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 one or two units of GDNF-secreting gel. (F) scotopic-wave, (G)scotopicb-wave and (H) photopicb-wave .#p < 0.05,*p≤0.02,**p≤0.005and***p < 0.0005 by one-way ANOVA with Bonferroni post-hoc test (Wong, Tsang et al. 2019).

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

Figure 5: In-vivo efficacy of PLGA Fenofibrate NPs (Feno-NP) on vascular leakage and vascular permeability measured with FFA. formation of SRNV and IRNV evaluated by neovascular tufts in flat-mounted choroid and retina in Vldlr−/− mice one 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 ± SEM (n = 8–16. One-way ANOVA followed by Bonferroni post hoc test. *** P < 0.001 versus untreated Vldlr−/− mice. ### P < 0.001 versus Blank-NP treated Vldlr−/− mice (Qiu, Meng et al. 2019).

**Figure 6:** Microneedles for enhanced drug delivery to the cornea. Drug loaded, DC101 and diclofenac microneedles (DL-MNs) patch for synergistic effect. Mouse eyes were treated 2 days after being inflicted with alkali-burn, and examined at 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, Liu et al. 2018).

**Figure 7:** Comparision 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 like (a) superior bulbar conjunctiva, (b) cornea and (c) sclera.
### Table 1: Comparison of various routes of ocular drug administration: benefits and obstacles.

(Gaudana, Ananthula et al. 2010)

<table>
<thead>
<tr>
<th>Route</th>
<th>Benefits</th>
<th>Obstacles</th>
<th>Diseases/Disorders Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td>Patient compliance is high; self-administration and noninvasive nature</td>
<td>Corneal barrier difficult to penetrate; dilution and efflux via tears is high</td>
<td>Conjunctivitis, keratitis, uveitis, episcleritis, scleritis, blepharitis</td>
</tr>
<tr>
<td>Intravitreal</td>
<td>Direct delivery to retinal and vitreal structures; drug has high bioavailability.</td>
<td>Patient compliance low; Risk of retinal detachment, hemorrhage, development of endophthalmitis or cataracts.</td>
<td>AMD, BRVO, CRVO, DME, CMV retinitis</td>
</tr>
<tr>
<td>Subtenon</td>
<td>Relatively noninvasive, decreased risk of comorbidity compared to intravitreal delivery.</td>
<td>Retinal pigment epithelium is a barrier; subconjunctival hemorrhage, chemosis</td>
<td>DME, AMD, RVO, uveitis</td>
</tr>
<tr>
<td>Delivery Method</td>
<td>Advantages</td>
<td>Side Effects/Complications</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Posterior juxtascleral</td>
<td>Advantageous for drug depository; avoids intraocular damage and macula can sustain drug level for 6 months</td>
<td>AMD; risk of endophthalmitis; surgical procedure required;</td>
<td></td>
</tr>
<tr>
<td>Systemic/ Oral</td>
<td>Promotes patient compliance, noninvasive mode of delivery</td>
<td>Scleritis, episcleritis, CMV retinitis, posterior uveitis;</td>
<td></td>
</tr>
<tr>
<td>Intra-cameral</td>
<td>Reduces systemic and corneal side effects versus topical steroid use; high anterior chamber drug concentration</td>
<td>Toxic endothelial cell destruction syndrome and toxic anterior segment syndrome pose major risks to patients; Anesthesia, prevention of endophthalmitis, inflammation, pupil dilation</td>
<td></td>
</tr>
<tr>
<td>Subconjunctival</td>
<td>Anterior and posterior delivery method- ideal for depot formation</td>
<td>Glaucoma, CMV retinitis, AMD</td>
<td></td>
</tr>
<tr>
<td>Retrobulbar</td>
<td>Minimal IOP involvement, ideal for high local anesthetic administration</td>
<td>Respiratory arrest, retrobulbar hemorrhage, globe perforation</td>
<td>Anesthesia</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Mode of administration</th>
<th>Excipient controlling release characteristic of drug</th>
<th>Target Indication</th>
<th>Developmental Stage</th>
<th>Clinical Trial #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>AzaSite®</td>
<td>Eye drops</td>
<td>Polycarbophil (DuraSite®)</td>
<td>Bacterial conjunctivitis</td>
<td>Launched</td>
<td>NCT00105469</td>
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<tr>
<td>Azithromycin/Dexamethasone (ISV-502)</td>
<td>AzaSite Plus™</td>
<td>Eye drops</td>
<td>Polycarbophil (DuraSite®)</td>
<td>Blepharocconjunctivitis</td>
<td>Launched</td>
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<tr>
<td>Betaxolol</td>
<td>Betoptic S</td>
<td>Eye drops</td>
<td></td>
<td>Glaucoma</td>
<td>Launched</td>
<td>NCT00061542</td>
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<tr>
<td>Bimatoprost</td>
<td>Lumigan</td>
<td>Eye drops</td>
<td></td>
<td>Glaucoma</td>
<td>Launched</td>
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<tr>
<td>Bromfenac</td>
<td>Prolensa™</td>
<td>Eye drops</td>
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<td>Postoperative</td>
<td>Launched</td>
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<tr>
<td>Drug Name</td>
<td>Brand Name</td>
<td>Formulation</td>
<td>Indication</td>
<td>Status</td>
<td>NCT Number</td>
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</tr>
<tr>
<td>Cyclosporine-A</td>
<td>Restasis</td>
<td>Eye drops</td>
<td>Cationic emulsion</td>
<td>Dry eye due to keratitis sicca</td>
<td>Launched</td>
<td>NCT02554981</td>
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<tr>
<td>Difluprednate</td>
<td>Durezol</td>
<td>Eye drops</td>
<td>Emulsion</td>
<td>Anterior uveitis</td>
<td>Launched</td>
<td>NCT01201798</td>
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<td>Timolol maleate</td>
<td>Timoptic</td>
<td>Eye drops</td>
<td>Glaucoma/Intraocular hypertension</td>
<td>Launched</td>
<td>NCT0110244</td>
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<td>Tobramycin/Dexamethasone</td>
<td>TobraDex® ST</td>
<td>Eye drops</td>
<td>Xanthan gum</td>
<td>Blepharitis</td>
<td>Launched</td>
<td>NCT01102244</td>
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<tr>
<td>Timolol maleate</td>
<td>Timoptic-XE®</td>
<td>Eye drops</td>
<td>Gellan gum</td>
<td>Glaucoma</td>
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<td>NCT01446497</td>
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<tr>
<td>Ophthalmic emulsion</td>
<td>Cationorm®</td>
<td>Eye drops</td>
<td>Cationic emulsion</td>
<td>Mild dry eye</td>
<td>NCT03460548</td>
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<tr>
<td>Travoprost t</td>
<td>iStent Injectable</td>
<td>Punctum plug</td>
<td>Open angle glaucoma</td>
<td>Phase IV</td>
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<td></td>
<td>Episceral Implant</td>
<td>Silicone Aeratoconjunctivitis</td>
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<tr>
<td>Cyclosporine (LX201)</td>
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<td>Aeratoconjunctivitis</td>
<td>Phase III</td>
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<td>Dexamethasone phosphate (EGP-437)</td>
<td>EyeGate® II</td>
<td>Iontophoresis</td>
<td>Anterior uveitis</td>
<td>Phase III</td>
<td>NCT01129 856</td>
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<tr>
<td>Dexamethasone (OTX-DP)</td>
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<td>Hydrogel</td>
<td>Postoperative inflammation</td>
<td>Phase II</td>
<td>NCT00650 702</td>
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<td>Latanoprost</td>
<td>Durasept™</td>
<td>Subconjunctival insert</td>
<td>PLGA</td>
<td>Glaucoma</td>
<td>Phase I/II</td>
<td>NCT00224 289</td>
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<tr>
<td>Loteprednol etabonate mucus penetrating particles</td>
<td>Inveltys™</td>
<td>Nanoparticle</td>
<td>Mucus penetrating particles (MPPs)</td>
<td>Keratoconjunctivitis Sicca</td>
<td>Phase III</td>
<td>NCT03616 899</td>
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<td>Urea</td>
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<td>Amphiphilic block</td>
<td>Cataract</td>
<td>Phase II</td>
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<tr>
<td>Omega-3 Fatty Acids</td>
<td>REMOGEN® OMEGA</td>
<td>Microparticle</td>
<td>Microemulsion of polyunsaturated fatty acids and hydrating polymers</td>
<td>Dry Eye Disease</td>
<td>Phase I/II</td>
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</table>
**Table 3:** Currently available ocular drug delivery systems in clinical trials for the treatment of posterior segment disorders (Kang-Mieler, Osswald et al. 2014).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>Mode of administration</th>
<th>Excipient controlling release characteristic of drug</th>
<th>Target Indication</th>
<th>Developmental Stage</th>
<th>Clinical Trial #</th>
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<td>Dry AMD RP</td>
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<tr>
<th>Drug Name</th>
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<td>Ranibizumab</td>
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<td>VEGFR-Fc (NT-503)</td>
<td>Intravitreal implant</td>
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<td>Wet AMD</td>
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<td>human embryonic stem cell derived</td>
<td>Cells transplantation via</td>
<td>Cell suspension</td>
<td>Advanced dry AMD</td>
<td>Phase I/II</td>
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<td>retinal pigment epithelium (MA09-hRPE) cells</td>
<td>subretinal injection</td>
<td>AR-1105 (dexamethasone implant)</td>
<td>Intravitreal implant</td>
<td>PRINT®-manufactured implant</td>
<td>Macular Edema due to RVO</td>
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AMD: Age Related Macular Degeneration, DME: Diabetic Macular Edema, RVO: Retinal Vein Occlusion
Table 4: Ocular drug delivery systems investigated for anterior segment disorders (inflammation)  
(Cholkar, Patel et al. 2013).

<table>
<thead>
<tr>
<th>Delivery system</th>
<th>Drug</th>
<th>Polymeric component</th>
<th>Remarks</th>
<th>Reference</th>
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<tr>
<td>Nanoparticles</td>
<td>Ibuprofen</td>
<td>Eudragit RS100</td>
<td>Significant improvement of drug bioavailability in rabbit model compared to control aqueous drops</td>
<td>(Pignatello, Bucolo et al. 2002)</td>
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<tr>
<td></td>
<td>Flurbiprofen</td>
<td>Eudragit RS100</td>
<td>Improved ocular bioavailability due to strong interaction between+ve charged nanoparticle to the anionic corneal surface</td>
<td>(Pignatello, Bucolo et al. 2002)</td>
</tr>
<tr>
<td></td>
<td>Flurbiprofen</td>
<td>PLGA, PCL</td>
<td>Colloidal systems enhance ocular bioavailability; PLGA nanoparticles showed ~2-fold higher drug transport than that of PCL nanoparticles</td>
<td>(Valls, Vega et al. 2008)</td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>PCL, Migliol 840, Poloxamer 188</td>
<td>Colloidal formulation showes 3-fold higher ex-vivo penetration than commercial eye drops</td>
<td>(Calvo, Vila-Jato et al. 1996)</td>
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<tr>
<td>Nanomicelles</td>
<td>Dexamethasone</td>
<td>Pluronic/chitosan system</td>
<td>Nanomicelles entrapping dexamethasone have significantly improved bioavailability to anterior ocular tissues by 2.4-fold relative to unformulated dexamethasone</td>
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<tr>
<td>Voclosporine, Dexamethasone, Rapamycin</td>
<td>Vitamin E TPGS and octoxynol-40 nanomicelles</td>
<td>In-vivo studies showed mixed nanomicellar system have higher bioavailability with topical dosing of dexamethasone and rapamycin</td>
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<tr>
<td>Cyclosporine-A</td>
<td>Methoxy poly(ethylene glycol)-hexylsubstituted poly(lactide)</td>
<td>Transparent, highly stable, biocompatible formulation</td>
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<tr>
<td>Cyclosporine-A</td>
<td>Chitosan and cholesterol-conjugated chitosan</td>
<td>Both nanoparticles deliver higher amount of drugs in cornea and conjunctiva as compared to CS-A suspension</td>
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<tr>
<td>Dexamethasone</td>
<td>Pluronic/chitosan system</td>
<td>Nanomicelles entrapping dexamethasone have significantly improved bioavailability to anterior ocular tissues by 2.4-fold relative to unformulated dexamethasone</td>
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<tr>
<td>(Pepic, Hafner et al. 2010)</td>
<td>(Pepic, Hafner et al. 2010)</td>
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<tr>
<td>Plasmid DNA with lacZ gene</td>
<td>PEO-PPO-PEO</td>
<td>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.</td>
<td>(Tong, Chang et al. 2007)</td>
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<tr>
<td>Liposomes C6-ceramide methoxy PEG(2000) and PEG(750)-C6-ceramide</td>
<td></td>
<td>Significantly efficacious in reducing corneal inflammation</td>
<td>(Sun, Fox et al. 2008)</td>
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<tr>
<td>Dexamethasone human serum albumin; bis(sulfo succinimidyl) suberate; Tris(hydroxy methyl) aminomethane; 3,3-dithiobis(sulfo succinimide)</td>
<td></td>
<td>Significantly higher drug accumulation in the eye (~13.5 ng /mg tissue) than unformulated drug (2.4 ng/ mg tissue)</td>
<td>(Arakawa, Hashida et al. 2007)</td>
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</table>
midylpropionate

PLGA: poly(lactic-co-glycolic acid), PCL: Polycaprolactone, PEG: Polyethylene glycol.
Table 5: Topically administered therapeutic agents for back of the eye disorders in various preclinical models. (Rodrigues, Lutz et al. 2018)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formulation</th>
<th>Preclinical data</th>
<th>Reference</th>
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<tr>
<td>TG100801</td>
<td>Solution</td>
<td>Murine CNV model and edema in rat</td>
<td>(Doukas, Mahesh et al. 2008)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Solution</td>
<td>Rat CNV model</td>
<td>(Yafai, Yang et al. 2011, Singh, Wurzelmann et al. 2014)</td>
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<tr>
<td>Acrizanib</td>
<td>Suspension</td>
<td>Murine CNV</td>
<td>(Adams, Anderson et al. 2018)</td>
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<td>Memantine</td>
<td>Solution</td>
<td>Drug levels in rabbit retina</td>
<td>(Hughes, Olejnik et al. 2005)</td>
</tr>
<tr>
<td>Dorzoxide</td>
<td>Solution</td>
<td>Drug levels and carbonic anhydrase activity in corneal endothelial cells, ciliary body, lens epithelial cells, and retina in rabbit</td>
<td>(Inoue, Oka et al. 2004)</td>
</tr>
<tr>
<td>Substance</td>
<td>Delivery Method</td>
<td>Drug Levels</td>
<td>Reference</td>
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<tr>
<td>Dexamethasone</td>
<td>Iontophoresis</td>
<td>Drug levels in retina and vitreous of rabbit</td>
<td>(Ambati and Adamis 2002)</td>
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<tr>
<td>Bevacizumab</td>
<td>Solution</td>
<td>Drug levels in iris/ciliary body, vitreous, retina/choroid, and plasma in rabbit</td>
<td>(Ambati, Canakis et al. 2000)</td>
</tr>
<tr>
<td>Anti–intercellular adhesion molecule-1 antibody</td>
<td>Solution by osmotic pump</td>
<td>Drug levels and VEGF-induced leukostasis in the choroid and retina in rabbit</td>
<td>(Ambati, Gragoudas et al. 2000)</td>
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<td>28-kD single-chain antibody fragment</td>
<td>Sodium caprate</td>
<td>Drug levels in vitreous in rabbit</td>
<td>(Williams, Brereton et al. 2005)</td>
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<td>Annexin A5–based liposomes</td>
<td>Drug levels in retina of rat and rabbit</td>
<td>(Davis, Normando et al. 2014)</td>
</tr>
<tr>
<td>Transforming growth factor beta 1</td>
<td>Annexin A5–based liposomes</td>
<td>Drug levels in vitreous in rabbit</td>
<td>(Platania, Fisichella et al. 2017)</td>
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<td>Acidic fibroblast growth factor</td>
<td>CPP (TAT)</td>
<td>Ischemia reperfusion model in rat</td>
<td>(Wang, Lin et al. 2010)</td>
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<td>Calpain inhibitory peptide</td>
<td>CPP (TAT)</td>
<td>Drug levels in rabbit retina</td>
<td>(Ozaki, Nakazawa et al. 2015)</td>
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<tr>
<td>Green fluorescent protein</td>
<td>CPP (POD)</td>
<td>Drug levels in mouse cornea</td>
<td>(Johnson, Cashman et al. 2010)</td>
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<tr>
<td>Bevacizumab</td>
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<td>Drug levels in vitreous and retina in rat and murine CNV model</td>
<td>(de Cogan, Hill et al. 2017)</td>
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</tbody>
</table>

Figures

Figure 1
Figure 2
Figure 4
Figure 5
Figure 6
Figure 7