# Ocular Drug Delivery

Burcin Yavuz and Uday B. Kompella

## Contents

**Abstract**

Although the eye is an accessible organ for direct drug application, ocular drug delivery remains a major challenge due to multiple barriers within the eye. Key barriers include static barriers imposed by the cornea, conjunctiva, and retinal pigment epithelium and dynamic barriers including tear turnover and blood and lymphatic clearance mechanisms. Systemic administration by oral and

B. Yavuz
University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 East Montview Blvd., C238-V20, Aurora, CO 80045, USA

Department of Biomedical Engineering, Tufts University, Medford, MA 02155, USA

U.B. Kompella (✉)
University of Colorado, Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 East Montview Blvd., C238-V20, Aurora, CO 80045, USA
e-mail: Uday.Kompella@ucdenver.edu

parenteral routes is limited by static blood–tissue barriers that include epithelial and endothelial layers, in addition to rapid vascular clearance mechanisms. Together, the static and dynamic barriers limit the rate and extent of drug delivery to the eye. Thus, there is an ongoing need to identify novel delivery systems and approaches to enhance and sustain ocular drug delivery. This chapter summarizes current and recent experimental approaches for drug delivery to the anterior and posterior segments of the eye.

# 1 Introduction

Ocular drug delivery systems or dosage forms range from the most common eye drops and other conventional formulations that are dosed daily to more complex implant systems that can be dosed once every few years. Conventional dosage forms like solutions, suspensions, emulsions, and ointments are only able to treat a limited number of ocular diseases. Ocular inserts and/or implants; preformed gels; in situ gels; microparticles; liposomes; nanotechnology-derived drug delivery systems such as nanoparticles, nanoemulsions, and nanomicelles; and the physical approaches to enhance drug delivery like iontophoresis and microneedles are some of the widely investigated ophthalmic drug delivery systems and approaches to meet unmet medical needs while overcoming ocular drug delivery challenges.

Each ocular tissue layer might act like a barrier based on drug physicochemical properties, drug carrier properties, and clearance mechanisms of a given route of administration. Thus, a delivery system or approach should be optimized for a given target tissue. For drug delivery purposes, the eye can be divided into two major segments, the anterior segment from the front of the eye to the lens and the posterior segment including eye tissues beyond the lens. These two different ocular regions are unique and face different challenges in drug delivery and should be dealt separately. Current studies are promising in terms of overcoming the challenges in treating various anterior and posterior segment diseases.

This chapter will briefly discuss the general considerations for ocular drug delivery and focus on drug delivery to both the anterior and posterior segments of the eye. The challenges, different application routes, and recent efforts to overcome these challenges will be elaborated for both segments separately.

# 2 General Considerations for Ocular Drug Delivery

A multitude of ocular diseases affect millions of individuals all over the world, and most of them have a significant negative impact on vision, leading to a decrease in patients' quality of life. The major ocular diseases include age-related macular

degeneration (AMD), diabetic retinopathy (DR), cataract, uveitis, and glaucoma, which can lead to blindness unless treated (Pascolini and Mariotti 2012).

The human eye is a 7.5 g globular structure with a diameter of approximately 24 mm, comprised of various tissues each presenting different features and playing a necessary role in vision (Hosoya et al. 2011). Since the eye is an extension of the central nervous systems, it is well protected from toxic materials through multiple barriers that inherently restrict drug delivery. Drug delivery barriers are specific depending on the target tissue and administration route (Gaudana et al. 2009, 2010).

One of the main problems with ocular drug delivery via conventional dosage forms is eye irritation that results in patient discomfort as well as reduced ocular bioavailability due to reflex tear flow. Most of the ophthalmological drugs are weak bases, and to enhance their solubility, they are usually formulated in an acidic pH, which may result in poor ocular diffusion due to the ionized state of the drug molecule. Another drug-related concern for ocular drug delivery is frequent dosing to maintain therapeutic amounts in the target tissue due to short drug residence time in the precorneal area. Drug administered in a drop is rapidly drained into the nose via the nasolacrimal ducts, resulting in unwanted systemic absorption and side effects.

Several factors need to be considered when designing an ocular drug delivery system that overcomes current limitations. These include improved dose accuracy, enhanced ocular bioavailability by overcoming static and dynamic barriers, and sustained and targeted drug delivery in order to enhance treatment efficacy and patient convenience (Macha and Mitra 2003).

## 2.1    Drug Administration Routes

Ocular barriers are generally specific for application route. The main administration routes for ocular drug delivery include topical, periocular, intraocular, and systemic.

Topical administration is the most common route for treating diseases of the anterior segment of the eye, due to ease of application, drug localization and adequate efficacy, and low cost. However, only about 30–50 μl of ophthalmic solution is delivered using a dropper, due to limited holding capacity of the precorneal area. The eye drop mixes with tears and drains rapidly from the eye surface via nasolacrimal drainage till it reaches approximately 7 μl, the normal resident tear volume in the eye. As a result of this and continuous tear replacement, drug on the eye surface is rapidly lost, and the remaining drug encounters permeability barriers, resulting in less than 5% dose delivery to the anterior segment of the eye for most therapeutic agents. Drug entering the intraocular tissues is rapidly cleared through turnover of aqueous humor and blood circulation. Therefore, frequent drug application is required to maintain adequate drug concentrations in the eye. In addition to low corneal permeability, short precorneal residence time is a critical rate-limiting factor for drugs to cross corneal barrier after topical instillation (Shell 1985; Lee and Robinson 1986; Hughes et al. 2005). Because of poor drug

delivery, topical administration is usually reserved for ocular surface and anterior segment diseases but not posterior segment diseases, although there are studies indicating that topical application can deliver drugs to the posterior segment of the eye (Furrer et al. 2009).

Oral and parenteral applications are the most common methods for systemic delivery, with the oral route being more convenient. Even though systemic administration might be useful in treating posterior segment eye diseases, high doses and frequent dosing may be required since there are various limitations including extensive drug dilution in the blood, low cardiac output to the eye, and blood–ocular barriers that restrict drug permeability. Furthermore, drugs administered by the systemic route are subjected to metabolism by the liver and clearance by the kidney, resulting in only a small quantity of the drug typically reaching the vitreous humor (Furrer et al. 2009; Duvvuri et al. 2003; Barar et al. 2008). High drug doses and frequent administrations usually result in systemic side effects.

Subconjunctival and sub-Tenon routes are commonly employed periocular routes for off-label drug dosing via injections. Other periocular modes of administration include posterior juxtascleral, peribulbar, and retrobulbar. The sclera has a large surface area (16.3 cm$^2$) (Olsen et al. 1998), and the subconjunctival space can expand and serve as a depot location for both anterior and posterior segment drug delivery (Ranta et al. 2010; Mac Gabhann et al. 2007).

When compared to noninvasive modes of administration including topical and oral routes, intraocular administration via injection or implantation is more difficult and uncomfortable for the patients; however, it is the only option to treat the diseases of the posterior segment of the eye in most cases. Intravitreal injection, one type of intraocular injection, gained widespread acceptance in the recent years with the commercial success of a few approved drug products. Other intraocular routes of administration include subretinal and suprachoroidal routes. Thus, intravitreal, periocular, subretinal, and suprachoroidal routes are the key routes that have been studied to overcome the drug delivery challenges where topical and systemic applications were not adequate (Gaudana et al. 2009; Raghava et al. 2004). Key advantages and disadvantages of the intraocular as well as conventional drug administration routes are summarized in Table 1.

## 2.2 Pharmacokinetic Considerations

Ocular pharmacokinetics including absorption, distribution, metabolism, and excretion are more complicated and harder to describe than systemic pharmacokinetics. This is due in part to the unique structure of the eye, various application routes, and formulation types that are used for ocular drug delivery. Since it is difficult to collect ocular pharmacokinetic data and data modeling may be difficult, the literature is very limited about ocular pharmacokinetics and mostly covers the measurement of drug levels in aqueous humor following ocular administration (Macha and Mitra 2003; Schoenwald 1990; Mishima 1981; Davies 2000). It is difficult to develop quantitative predictions for interspecies dose adjustments since

**Table 1** Advantages and disadvantages of key routes for ocular drug delivery (modified from Gaudana et al. 2010)

| Route | Advantages | Disadvantages |
|---|---|---|
| Topical | – Noninvasive<br>– Self-administration possible<br>– Patient convenience<br>– Sustained delivery for a day is possible; inserts allow more prolonged release | – Low ocular bioavailability<br>– Nasolacrimal drainage<br>– Epithelial barriers<br>– Not yet approved/effective for posterior segment |
| Systemic | – Noninvasive<br>– Self-administration possible<br>– Patient convenience | – Low ocular bioavailability<br>– Blood–aqueous barrier<br>– Blood–retinal barriers<br>– Systemic toxicity and side effects |
| Periocular/<br>suprachoroidal | – Delivery possible for both anterior and posterior segments<br>– Possible depot site | – Invasive<br>– Patient inconvenience<br>– Clearance by circulation<br>– Retinal pigment epithelial (RPE) barrier for retinal delivery<br>– Potential hemorrhage |
| Subretinal | – Useful for retinal gene delivery<br>– Bypasses RPE barrier<br>– Sustained retinal gene delivery | – Invasive<br>– Patient inconvenience<br>– Retinal detachment and risk of retinal damage |
| Intravitreal | – Effective retinal delivery<br>– Sustained delivery up to about 3 years<br>– Bypasses multiple ocular barriers | – 100% vitreal bioavailability<br>– Invasive<br>– Patient inconvenience |

most of these studies were performed in rabbit eyes with different anatomical and physiological features (such as blinking rate, tear volume, and corneal dimensions) relative to human eyes and because there is little or no data available in human eyes. However, predictive models are being developed to estimate vitreal half-life of a new chemical entity (Durairaj et al. 2009a).

Drug physicochemical properties such as molecular weight, solubility, lipophilicity, and degree of ionization play an important role in drug absorption into the eye. The cornea is the most important barrier with a multilayered structure for drug absorption into the anterior segment; however, the conjunctiva is generally more permeable than the cornea. Elimination processes from the eye vary for different drugs. Tear drainage, aqueous humor turnover, and entry into systemic circulation from the eye tissues are some of the major elimination routes. These aspects and ocular pharmacokinetics are discussed in detail in another chapter.

## 2.3    Transporters in the Eye

Several transporters including influx and efflux transporters are present in the cornea, conjunctiva, retina and blood–ocular barriers, which may influence drug bioavailability (Gaudana et al. 2009; Macha and Mitra 2003). Modifications targeting these transporters might be an alternative approach to improve ocular bioavailability of drugs.

Efflux transporters tend to reduce cellular bioavailability by transporting drugs out of the cell. Key efflux transporters associated with ocular tissues are P-glycoprotein (P-gp) and multidrug resistance protein (MRP), which belong to the ATP-binding cassette (ABC) superfamily (Eytan and Kuchel 1999; Dey et al. 2003; Mannermaa et al. 2006). P-gp effluxes lipophilic drugs and prevents drug accumulation in the cells. P-gp is present in the cornea, conjunctiva, ciliary nonpigmented epithelium, iris, and retina (Saha et al. 1998; Wu et al. 1996). MRP works in a similar way as P-gp to efflux organic anions and their conjugates (Aukunuru et al. 2001; Steuer et al. 2005).

On the other hand, influx transporters that belong to the solute carrier (SLC) superfamily transport essential nutrients and xenobiotics across biologic membranes (Hosoya et al. 2005; Hosoya and Tachikawa 2012). Influx transporters include amino acid, peptide, vitamin, glucose, lactate, and nucleoside carriers. Designing prodrugs targeting these influx transporters has been an important approach for ocular drug delivery, and two key influx transporters are the amino acid and peptide transporters. Some amino acid transporters identified in ocular tissues include ASCT1, ASCT2, B(0,+), LAT1, and LAT 2 (Hosoya et al. 1997, 2005; Hosoya and Tachikawa 2012; Hosoya and Lee 1997; Jain-Vakkalagadda et al. 2003, 2004). Peptide transporters in the eye have also been investigated, and it was reported that PEPT1 and PEPT2 were detected in the corneal epithelium (Zhang et al. 2008; Xiang et al. 2009). In addition to these transporters, organic cation/anion, monocarboxylate, nucleoside, and vitamin transporters have been identified in various ocular tissues (Talluri et al. 2006; Janoria et al. 2006).

Both anterior and posterior segment tissues of the eye express various transporters, which are promising for the design of prodrugs for transporter-targeted drug delivery.

## 3    Drug Delivery to the Anterior Segment of the Eye

### 3.1    Recent Anterior Segment Drug Delivery Approaches

Various approaches have been studied in order to improve drug delivery across ocular tissues and enhance therapeutic efficacy of drugs intended for the treatment of anterior segment diseases such as dry eye syndrome, conjunctivitis, glaucoma, postoperative inflammation, and uveitis. Conventional dosage forms including solutions, suspensions, emulsions, and ointments are routinely used for treating anterior segment diseases. Viscous gels, mucoadhesive agents, prodrugs, and

nanosystems are some of the novel approaches employed to increase or sustain drug delivery and efficacy, to reduce systemic side effects, and to improve patient comfort and compliance. Some key novel dosage forms are further discussed below.

### 3.1.1 Mucoadhesive Formulations

Increasing the retention time in the precorneal area is one of the main approaches to enhance ocular bioavailability. Mucoadhesion, which refers to attachment to mucus either by hydrogen bonding or electrostatic binding with mucin layer, may influence drug absorption (Sigurdsson et al. 2013). The most common mucoadhesives employed in ocular formulations are water-soluble polymers that cannot cross ocular barriers such as the polyacrylic derivatives including carbomers and thiomers, xanthan gum, carrageenan, chitosan, and hyaluronic acid. Bioadhesive microspheres are also prepared to adhere to ocular mucin layer and prolong corneal contact time of any associated therapeutic agents (Gu et al. 1988; Ruponen and Urtti 2015; Kaur and Smitha 2002). Horvat et al. (2015) tested new hyaluronic acid (HA) derivatives for their mucoadhesive properties in ocular formulations (Horvat et al. 2015). Cross-linked sodium-, linear sodium-, and zinc-hyaluronate formulations of a nanosize were all characterized as potential ocular drug delivery systems. Another approach is to combine nanotechnology with mucoadhesive systems. As a recent example to this approach, Chaiyasan and co-workers have developed and characterized mucoadhesive chitosan–dextran sulfate nanoparticles for sustained ocular drug delivery. Based on the mucoadhesion and in vitro release studies, the system was reported as promising (Chaiyasan et al. 2013).

### 3.1.2 Gels: In Situ Gels

The main focus of the research is on in situ gels, which are solutions that start gelation upon contact with the ocular tissues via pH- or temperature-dependent activation. These systems have the advantage to be easily instilled as a regular eye drop and can provide prolonged retention time and sustained drug release with unique gelation properties. Gels and in situ gel-forming systems have been investigated to increase the retention time. Pilocarpine formulated in a gel has proved to be more effective than the solution form (Ticho et al. 1979). Sachinkumar et al. (2015) prepared a pH-triggered in situ gel formulation of norfloxacin using hydroxypropyl methylcellulose (HPMC) for the treatment of ocular infections. The system was tested in vitro and still requires in vivo studies to confirm in situ gelation properties (Sachinkumar et al. 2015).

Hydrogels have a variety of applications in ophthalmology including in situ gelling formulations, soft contact lenses, foldable intraocular lenses, and ocular adhesives for wound repair. High water content of hydrogels may be advantageous in preserving peptide/protein stability. Chemically cross-linked temperature-sensitive hydrogels that have high water content and retain transparency have been used as in situ forming gels (Kirchhof et al. 2015).

A dendrimeric hydrogel system has been developed using polyamidoamine (PAMAM) dendrimer G3.0 for delivery of antiglaucoma drugs brimonidine and

timolol maleate. Dendrimeric hydrogel was found to be mucoadhesive to mucin particles on the cornea. PAMAM dendrimers were linked with polyethylene glycol (PEG) acrylate to achieve in situ gelation upon UV light activation (Holden et al. 2012).

Yu et al. have developed a crossed-linked PEG in situ hydrogel for sustained bevacizumab delivery (Yu et al. 2014). The same group has also prepared cross-linked polysaccharide hydrogels using glycol chitosan and oxidized alginate for sustained bevacizumab release (Xu et al. 2013). Following in vitro and cell culture studies, both systems have been suggested to be promising for the treatment of intraocular neovascularization. Examples of in situ forming gels in the market include timolol maleate-loaded gellan gum-based product (Timoptic XE®) and another timolol maleate-containing formulation based on methyl cellulose, sodium citrate, and polyethylene glycol (Rysmon® TG) (Agrawal et al. 2012).

### 3.1.3 Prodrugs

Prodrugs are intended to be pharmacologically inactive or less-active derivatives of drug molecules, and ophthalmic prodrugs are typically designed to achieve improved drug delivery and/or therapeutic index. Following tissue entry, the prodrug is expected to be metabolized and produce the active form of the drug. Prodrugs are chemically synthesized to usually contain ester, amide, or other enzymatically cleavable chemical bonds. The enzymes in the ocular tissues play an important role in the conversion of prodrug to drug. Esterases and amidases are the most common enzymes in ocular tissues with high enzyme activity detected in the iris–ciliary body, cornea, and aqueous humor (Lee 1983; Stratford and Lee 1985). Latanoprost is a successful ocular prodrug with high ocular penetration that hydrolyzes via an esterase enzyme to produce the active form of the drug (Sjoquist and Stjernschantz 2002).

Several prodrug strategies including transporter-targeted and lipophilic ester prodrugs have been assessed to improve corneal and conjunctival permeability of drugs targeting the anterior segment. Some prodrug strategies for anterior segment drug delivery are summarized in Table 2.

### 3.1.4 Colloidal Drug Delivery Systems

Various types of colloidal dosage forms have been designed to increase precorneal residence time and anterior segment drug delivery. Some of these particles can interact with ocular mucosa and enhance permeability across the cornea and conjunctiva. Polymeric nanoparticles, nanomicelles, nanosuspensions, nanoemulsions, nanocrystals, liposomes, niosomes, cubosomes, and dendrimers are among the most studied drug delivery systems for anterior segment diseases such as dry eye, inflammation, glaucoma, uveitis, and retinopathies. Colloidal drug delivery systems offer the advantage of being able to deliver a variety of drugs (including macromolecules), providing stability for labile drugs and improving ocular bioavailability (Reimondez-Troitino et al. 2015a).

A number of studies focused on these systems in the last decade. These colloidal drug delivery systems have been classified and summarized in Table 3. Despite

**Table 2** Summary of prodrug studies for anterior segment drug delivery

| Drugs | Prodrugs | Outcome |
| --- | --- | --- |
| Timolol (Chang et al. 1987) | Lipophilic esters | Increase in corneal permeation<br>Decrease in systemic drug exposure |
| PGF2α (Chien et al. 1997) | Lipophilic esters | Increase in corneal permeation |
| Acyclovir (Hughes and Mitra 1993; Katragadda et al. 2006; Vadlapudi et al. 2012a, b, 2014) | Aliphatic acyl esters<br>Amino acid prodrugs<br>Peptide prodrugs<br>Lipid prodrugs | Increase in corneal permeation<br>Enhancement of stability<br>Increase in efficacy<br>Increase in cell accumulation |
| Ganciclovir (Tirucherai et al. 2002; Majumdar et al. 2005) | Lipophilic esters | Increase in solubility<br>Increase in corneal permeation<br>Increase in activity |
| Dexamethasone (Civiale et al. 2004) | Esters | Increase in corneal permeation |
| Cyclosporine A (Lallemand et al. 2005, 2007; Rodriguez-Aller et al. 2012) | Phosphate ester | Therapeutic concentrations in precorneal area immediately after application<br>Increase in water solubility |
| Flurbiprofen (Shen et al. 2011) | Flurbiprofen axetil | Less irritation<br>Increase in efficacy |
| Cannabinoid receptor (CB$_{1/2}$) agonist (Mainolfi et al. 2013) | Esters | Improved solubility<br>Increased corneal permeation<br>Enhanced ocular bioavailability |
| Resolvin E1 (de Paiva et al. 2012) | Methyl ester | Reduced corneal disruption |

many promising results, reaching posterior segment via topically administered systems is still a challenge. There is still more to be investigated, especially regarding delivery of complex biomacromolecules to the eye.

### 3.1.5 Ocular Inserts and Implants for Anterior Segment Diseases

Ocular inserts and implants are designed to enhance the bioavailability and achieve sustained drug delivery. These systems can be placed under the eyelid, in the conjunctival cul-de-sac, anterior chamber, subconjunctival space, or episcleral region to deliver drugs to the anterior segment of the eye. They can be either in the biodegradable or nonbiodegradable form. Ocusert® was the first marketed ocular insert, which provides an extended therapeutic effect for a week with a low amount of pilocarpine. It consists of two ethylene–vinyl acetate copolymer membranes that control drug release to achieve zero-order kinetics (Ghate and Edelhauser 2006).

Anterior chamber implants can be placed in the aqueous humor. Subconjunctival/episcleral implants require a small incision in the conjunctiva. Surodex™ is a biodegradable anterior chamber insert made of poly(lactic-co-glycolic acid) (PLGA) and provides sustained-release dexamethasone for about

**Table 3** Colloidal systems for anterior segment drug delivery

| Delivery system | Drug | Formulation type/component | Animal models | Results | References |
|---|---|---|---|---|---|
| Nanoparticles | Ibuprofen | Eudragit RS100® | Rabbits with ocular trauma | Increase in AH concentration<br>Good in vivo tolerance | Pignatello et al. (2002) |
| | Flurbiprofen | PLGA, PCL | | Increase in ocular bioavailability | Valls et al. (2008) |
| | | PLGA, poloxamer 188 | Rabbits with inflammation | Increase in activity | Vega et al. (2006) |
| | | Chitosan | Rabbits | Increase in corneal AUC<br>Increase in retention time | Luo et al. (2011) |
| | Indomethacin | Chitosan | Rabbits with corneal ulcer | Increase in AH and corneal concentrations<br>Corneal healing<br>Good in vivo tolerance | Badawi et al. (2008) |
| | | PCL | Rabbits | Increase in corneal, AH, and CB concentrations | Calvo et al. (1996) |
| | Cyclosporine A | Chitosan, cholesterol-conjugated chitosan | Rabbits | Increase in retention time<br>Increase in corneal and conjunctival concentrations | De Campos et al. (2001), Hu et al. (2006) |
| | | Hyaluronic acid, PCL | Rabbits | Increase in corneal, AH, and CB concentrations | Yenice et al. (2008) |
| | | Cysteine–PEG monostearate | Rabbits | Increase in concentration and duration of exposure for the cornea, AH, CB, and conjunctiva<br>Good in vivo tolerance | Shen et al. (2010) |
| | | Propylene glycol | Rabbits | Eye tissue concentrations similar to Restasis®<br>Good in vivo tolerance | Khan et al. (2012) |

| Drug | Material | Model | Effect | Reference |
|---|---|---|---|---|
| | Carbopol®–PLGA, Eudragit®–PLGA | Rabbits | Increase in tear AUC | Aksungur et al. (2011) |
| Rapamycin | Chitosan, PLA | Rabbits with inflammation | Decrease in inflammation | Yuan et al. (2008) |
| Prednisolone, gatifloxacin | Eudragit RS100® Hyaluronic acid | Rabbits | Increase in ocular bioavailability | Ibrahim et al. (2010) |
| Levofloxacin | PLGA | Rabbits | Increase in corneal retention time Good in vivo tolerance | Gupta et al. (2011) |
| Amikacin | PACA, dextran | Rabbits | Increase in corneal and AH concentrations | Losa et al. (1991) |
| MUC5AC Plasmid DNA | Cationized gelatin | Rabbits; mice with dry eye | Conjunctival transfection of MUC5AC Increase in tear production | Konat Zorzi et al. (2011), Contreras-Ruiz et al. (2013) |
| Pilocarpine | PLGA | Rabbits | Increase in miotic response and duration | Nair et al. (2012) |
| Metipranolol | PCL | Rabbits | Decrease in systemic absorption | Losa et al. (1993) |
| Dorzolamide HCl | Chitosan | Rabbits | Decrease in systemic absorption Increase in precorneal residence | Katiyar et al. (2014) |
| Timolol maleate Dorzolamide HCl | Hyaluronic acid, chitosan | Rabbits with elevated intraocular pressure | Increase in activity Decrease in systemic absorption Good in vivo tolerance | Wadhwa et al. (2010) |

(continued)

**Table 3** (continued)

| Delivery system | Drug | Formulation type/component | Animal models | Results | References |
|---|---|---|---|---|---|
| | Brimonidine tartrate | Eudragit® | Rabbits with elevated intraocular pressure | Increase in activity and duration of residence/activity | Bhagav et al. (2011) |
| Nanomicelles | Dexamethasone | NIPAAM | Rabbits with inflammation | Increase in activity and duration of activity | Rafie et al. (2010) |
| | | Polyhydroxyethylaspartamide | Rabbits | Increase in AH AUC | Civiale et al. (2009) |
| | | Chitosan | Rabbits | Increase in anterior eye tissue AUC | Pepic et al. (2010) |
| | | Pluronic/chitosan | Rabbits | Increase in bioavailability | Pepic et al. (2010) |
| | Ketorolac | NIPAAM | Rabbits with inflammation | Increase in efficacy | Gupta et al. (2000) |
| | Pilocarpine | Pluronic F127 | Rabbits | Increase in AUC and duration of activity | Pepic et al. (2004) |
| | Voclosporin Dexamethasone Rapamycin | Vitamin E Octoxynol-40 | Rabbits | Increase in bioavailability | Mitra et al. (2010) |
| | Cyclosporine A | Polyoxyl stearate 40 | Rabbits | Increase in anterior tissue AUC | Kuwano et al. (2002) |
| | | MPEG–hexPLA | Rabbits | Good in vivo tolerance | Di Tommaso et al. (2011) |
| | Plasmid DNA with lacZ gene | PEO–PPO–PEO | Mice and rabbits | Increase in β-gal activity Decrease in corneal apoptosis | Tong et al. (2007) |
| Nanoemulsions | Indomethacin | Negatively and positively charged | Rabbits | Increase in AH, scleral, and retinal concentrations Good in vivo tolerance | Klang et al. (2000) |

| | Diclofenac | N-Octenylsuccinate starch | Porcine cornea (ex vivo) | Increase in corneal permeability | Baydoun and Muller-Goymann (2003) |
|---|---|---|---|---|---|
| | Flurbiprofen axetil | Castor oil, Tween 80 | Rabbits with uveitis | Increase in efficacy | Shen et al. (2011) |
| | Prodrug pilocarpine Dorzolamide HCl | Soybean oil, lecithin | Rabbits | Increase in activity and duration of activity | Sznitowska et al. (1999) |
| | Tetrahydrocannabinol | – | Rabbits (normal and with elevated intraocular pressure) | Increase in activity Good in vivo tolerance | Muchtar et al. (1992) |
| Nanosuspensions | Cyclosporine A | Kelcogel® | Rabbits | Increase in ocular bioavailability | Gan et al. (2009) |
| | Indomethacin | Sesame oil | Human subjects | Increase in AH concentration | Sanders et al. (1983) |
| | Rofecoxib | Polystyrene, Poloxamer 407 Hydroxypropyl methyl cellulose | Rabbits | Increase in anterior chamber concentration | Santipharp and Laman (2008) |
| | Diclofenac Cyclosporine A | Sophisen | Human subjects | Increase in precorneal residence time Increase in tear production | Quintana-Hau et al. (2005) |
| | Prednisolone Hydrocortisone Dexamethasone | Pluronic F68 | Rabbits | Increase in AH concentration | Kassem et al. (2007) |
| Liposomes | Acyclovir | – | Rabbits | Increase in corneal penetration | Law et al. (2000) |
| | Ganciclovir | – | Rabbits | Increase in corneal penetration | Shen and Tu (2007) |
| | Dexamethasone | Human serum albumin | Mice with uveoretinitis | Increase in ocular concentration | Arakawa et al. (2007) |
| | Fluconazole | – | Rabbits with keratomycosis | Increase in activity | Habib et al. (2010) |

**Table 3** (continued)

| Delivery system | Drug | Formulation type/component | Animal models | Results | References |
|---|---|---|---|---|---|
| | Ciprofloxacin hydrochloride | Chitosan coated | Rabbits with conjunctivitis | Increase in activity | Mehama et al. (2010) |
| | | | Rabbits | Increase in ocular residence time<br>Good in vivo tolerance | Abdelbary (2011) |
| | Diclofenac | Chitosan coated | Rabbits | Increase in AUC and prolonged retention<br>Good in vivo tolerance | Li et al. (2009) |
| | Cyclosporine A | Supercritical fluid mediated | Rabbits with dry eye | Increase in tear AUC<br>Increase in tear production | Kam et al. (2014) |
| | Tropicamide | – | Rabbits | Increase in residence time<br>Increase in mydriatic activity | Nagarsenker et al. (1999) |
| | Pilocarpine HCl<br>Timolol<br>Brimonidine tartrate | – | Rabbits with elevated intraocular pressure | Sustained decrease in intraocular pressure | Monem et al. (2000) |
| | Ibuprofen | Silk fibroin-coated liposomes | Rabbit cornea (ex vivo) | Sustained drug release<br>Increase in corneal transport<br>No detectable toxicity | Dong et al. (2015) |
| Cubosomes | Dexamethasone | Poloxamer 407<br>Carbopol 974<br>Carboxy methyl cellulose sodium | Rabbits | Increase in corneal permeability<br>Increase in AH AUC | Gan et al. (2010) |
| Niosomes | Brimonidine tartrate | – | Rabbits | Sustained decrease in intraocular pressure | Maiti et al. (2011) |

| | | | | | |
|---|---|---|---|---|---|
| Dendrimers | Brimonidine tartrate Timolol Acetazolamide | – | Rabbits with elevated intraocular pressure | Sustained decrease in intraocular pressure | Prabhu et al. (2010) |
| | Gatifloxacin | Polyguanidilyated dendrimers | Rabbits | Increase in corneal and conjunctival AUC | Durairaj et al. (2010) |
| | Carteolol | Phosphorous dendrimers | Rabbits | Increase in AH concentration Good in vivo tolerance | Spataro et al. (2010) |
| | Pilocarpine nitrate Tropicamide Brimonidine Timolol maleate | PAMAM dendrimers | Rabbits | Increase in bioavailability Sustained decrease in intraocular pressure | Vandamme and Brobeck (2005) |

*PCL* poly(e-caprolactone), *PEG* polyethylene glycol, *PLGA* poly(lactic-co-glycolic acid), *PLA* poly(lactic acid), *PEO* poly(ethylene oxide), *PACA* poly(alkyl cyanoacrylate), *PPO* poly(propylene oxide), *NIPAAM* (N-isopropylacrylamide), *MPEG–hexPLA* methoxy poly(ethylene glycol)–hexylsubstituted poly (lactide), *PAMAM* polyamidoamine, *AH* aqueous humor, *CB* ciliary body
Based in part on Reimondez-Troitiño et al. (2015b), Thrimawithana et al. (2011), Gaudana et al. (2009), and the references listed in the table

10 days. It was developed for the treatment of postoperative inflammation following cataract surgeries (Kuno and Fujii 2011).

LX201 (Lux Biosciences) is a cyclosporine A-loaded silicone matrix episcleral implant designed to sustain drug release for a year in order to prevent corneal transplant rejection. A study aimed at a phase III trial (identification number NCT00447187) was terminated in 2012. Another cyclosporine A implant study for LX201 employed subconjunctival implantation that would not affect neovascularization following keratoplasty (Bock et al. 2014). It was also reported that cyclosporine A-loaded PLGA nanoparticles and poly[e-caprolactone] (PCL) subconjunctival implants were prepared for dry eye syndrome treatment, and they were able to extend the drug release up to 2 months and provided faster healing in dry eye-induced mice (Pehlivan et al. 2015). Pfizer Inc. collaborated on a PLGA subconjunctival insert for sustained-release latanoprost for glaucoma treatment; however, the phase I/IIa (NCT01180062) study was terminated due to inadequate supply of inserts.

Ang (2014) has developed prednisolone acetate-loaded PCL microfilms to be implanted subconjunctivally for uveitis treatment and has reported that the formulation was effective in a rabbit uveitis model (Ang 2014). Wong (1989) published a patent (US 7846468) for immunosuppressive biodegradable ocular implants using PLGA and HPMC against transplant rejection. It was reported that these systems were able to prevent allograft rejection in a rat model when implanted into the anterior chamber (Wong 1989).

Freeze-dried mini tablets as ocular inserts are another recent approach that presents several advantages such as easy/noninvasive application, increased corneal residence time, and reduced drug loss due to lacrimation. Cellulose derivatives, acrylates, and chitosan are the most commonly employed polymers for ocular mini tablet formulations (Moosa et al. 2014).

### 3.1.6 Punctal Plugs

Punctal plugs are small biocompatible implants used for dry eye treatment by insertion of the plug into tear ducts or puncta to block tear drainage. Punctal plugs may offer advantages such as being noninvasive and the ability to maintain sustained drug release. Silicone, hydroxyethyl methacrylate, and polycaprolactone were some of the materials used to prepare punctal plugs, but they require removal after drug release (Kompella et al. 2010). Drug release from punctal plugs is usually diffusion controlled, and the drug can be loaded in punctal plugs in various forms including solutions, suspensions, colloids, etc. One of the common designs for punctal plug drug delivery is loading drug to an impermeable core and releasing it from the cross section that is in contact with the eye surface and tears. An alternative approach is coating the plug with drug solution; however, drug loading might be low due to the small surface area (Yellepeddi et al. 2015).

Phase II studies were conducted for latanoprost and bimatoprost punctal plug formulations (QLT Inc. and Vistakon Pharmaceuticals) for glaucoma and ocular hypertension (Kuno and Fujii 2011). The system used for latanoprost is also being studied for the anti-allergy drug olopatadine. Another phase I study assessed

sustained-release moxifloxacin punctal plugs to prevent conjunctivitis after cataract surgery. This system achieved 7-day drug release as a potential alternative to topical antibiotic drops (Chee 2012). Gupta et al. (2011) reported a hydroxyl ethyl methacrylate punctal plug system loaded with cyclosporine A microparticles for dry eye treatment. The plug was covered with impermeable silicone shell and was able to release drug for over 3 months near zero-order kinetics (Gupta and Chauhan 2011).

Overall, drug-loaded punctal plugs are promising for sustained drug delivery to the eye surface. On the other hand, their use is associated with some complications such as conjunctivitis, corneal abrasion, distal lachrymal system blockage, excessive tear production (epiphora), and plug extrusion. These complications may be influenced by the design, size, and insertion method of the plug (Taban et al. 2006; Bourkiza and Lee 2012). It is believed that the experience gained from previous studies will lead to new plugs with less complications for anterior segment drug delivery.

### 3.1.7 Contact Lenses

Contact lenses provide an alternative approach for sustained drug delivery on the ocular surface and beyond. Polymethyl methacrylate was the first widely used polymer for the production of contact lenses, which were not able to allow adequate oxygen permeation for the cornea and had to be removed at night. This was a limitation for the use of contact lenses as a long-term drug delivery system. Highly oxygen-permeable silicone hydrogel contact lenses have overcome this issue, and contact lenses are now more promising as drug delivery systems (Sedlacek 1965; Chauhan 2015; Lu et al. 2013).

Pilocarpine-soaked contact lenses were the first example of these systems, and it was reported to provide reduction in intraocular pressure for a few hours with the equivalent efficacy of an eye drop (Hillman 1974). Cromolyn sodium, dexamethasone sodium phosphate, ketorolac tromethamine, ketotifen fumarate, and natamycin contact lenses were subsequently tested in vitro (Karlgard et al. 2003; Phan et al. 2014). Loading colloid nanoparticles and molecular imprinting have also been investigated as improved drug loading techniques to achieve prolonged release, since the commercial contact lenses are able to release for only 1–2 h (Jung and Chauhan 2012). It was shown that latanoprost- (Mohammadi et al. 2014) and norfloxacin-imprinted (Carmen et al. 2006) 2-hydroxyethylmethacrylate (HEMA) contact lenses were able to provide extended release as well as ciprofloxacin-imprinted silicone hydrogels (Hui et al. 2012).

Vitamin E-loaded contact lenses can provide extended drug release by forming additional diffusion barriers (Peng et al. 2012). Vitamin E loading is also effective for combination therapy. In a recent study, timolol and dorzolamide contact lenses with vitamin E coating were prepared to achieve simultaneous extended release of the two drugs, and the results indicated that the system was able to reduce intraocular pressure at a lower drug dose (Hsu et al. 2015). The main limitations with contact lens delivery systems are their higher cost relative to eye drops and ultimate acceptance by patients and clinicians.

### 3.1.8 Intraocular Lenses (IOL)

Drug-loaded intraocular lenses were developed as an alternative to the currently used postoperative drug products. Biodegradable polymer rings with triamcinolone acetonide were developed, attached to the disk of IOL, and implanted in New Zealand white rabbits, and the results indicated inflammation reduction in inflammatory signals in aqueous humor up to 7 weeks (Eperon et al. 2008). In another study, multilayer-coated intraocular lenses were designed for sustained drug delivery (Shukla et al. 2011).

A nonbiodegradable capsule drug ring has been investigated to serve as a refillable drug depot for multiple drugs. The system is to be placed around the intraocular lens after cataract surgery and can accomplish either anterior or posterior segment drug delivery depending on where the semipermeable membrane's location is in the capsule drug ring. This system has been studied using bevacizumab and showed nearly zero-order release kinetics (Molokhia et al. 2010).

### 3.1.9 Transcorneal Iontophoresis

Iontophoresis is a noninvasive technique that employs electric current in contact with eye tissues to deliver drug molecules across a biological membrane. An iontophoresis device consists of two electrodes: one donor that holds the drug solution and one receiver to close the electrical circuit and enhance drug delivery either by electrophoresis, electroosmosis, or electroporation. Transcorneal iontophoresis can deliver dugs to the anterior chamber, whereas transscleral iontophoresis may deliver drugs to the posterior segment. The efficiency of iontophoresis usually depends on the charge of the drug, electrode placement, and duration of pulse (Molokhia et al. 2008, 2013).

Eyegate® developed a transcorneal iontophoretic system made of soft silicone rubber and tungsten electrodes. The drug solution is placed in the tungsten electrode annularly well and flows through the silicone tubes. Dry eye, scleritis, and anterior uveitis drug indications have been assessed with this system in clinical trials (Halhal et al. 2004). Antibiotics (gentamicin, ciprofloxacin, and tobramycin) delivered via iontophoresis decreased the bacterial colony level when compared to corresponding eye drop applications (Cohen et al. 2012; Hobden et al. 1990). Dexamethasone when delivered using transcorneal iontophoresis exhibited greater corneal penetration than positively charged antibiotics. Using iontophoresis, riboflavin can be delivered across the intact corneal epithelium (epi-on technique) to induce collagen cross-linking in order to treat keratoconus (Bikbova and Bikbov 2014). This technique significantly reduces the application time for riboflavin, and it might be an alternative keratoconus treatment without removing the corneal epithelium. Delivery of macromolecules such as Galbumin, bevacizumab, and FITC dextrans can also be elevated, based on in vitro transcorneal iontophoresis (Molokhia et al. 2009; Chopra et al. 2010; Nicoli et al. 2009).

# 4 Drug Delivery to the Posterior Segment of the Eye

## 4.1 Barriers, Challenges, and Routes of Administration for Posterior Segment Drug Delivery

Posterior segment of the eye includes the sclera, choroid, retinal pigment epithelium, retina, optic nerve, and vitreous humor. Posterior segment diseases such as age-related macular degeneration (AMD), macular edema, diabetic retinopathy (DR), and posterior uveitis are eye diseases that lead to blindness. These diseases are becoming more common with the aging of the general population. Thus, there is a growing need to develop new therapies and delivery approaches to treat diseases of the posterior segment or back of the eye. Posterior segment drug delivery is more difficult than anterior segment delivery, due to the highly protected structure of the back of the eye with static (sclera, RPE, and blood capillary endothelial cell walls) and dynamic barriers (blood and lymph circulation). The delivery route depends on the drug molecule, dosage form, and the target tissue (Gaudana et al. 2009; Ghate and Edelhauser 2006).

Drug delivery to the retina and vitreous humor is limited and generally ineffective with an eye drop, due to the anatomical and physiological barriers. For retinal drug delivery following systemic administration, drugs must cross the blood–ocular barriers, which separate the eye from the rest of the body. Blood–ocular barriers consist of two key components: blood–aqueous barrier and blood–retinal barrier. Both these barriers are comprised of epithelial and endothelial tight junctions that limit drug transport (Macha and Mitra 2003), with the blood–retinal barrier being the limitation for back-of-the-eye drug delivery following systemic administration. Systemic administration requires large doses for therapeutic effects, due to drug dilution in blood prior to reaching the retina, low cardiac output to the eye, and the presence of strong blood–retinal barriers. Thus, the extent of dose delivery by conventional routes to the back of the eye is very limited.

Periocular dosing interfaces the drug with the sclera on one side and the conjunctiva on the other side (Raghava et al. 2004). While the episclera is vascularized, the sclera is the poorly vascularized white part of the globe that contains collagen fibers and mucopolysaccharides. Drug permeability across the sclera decreases with increasing molecular weight and lipophilicity; additionally, drug surface charge affects permeability since positive charges can interact with the negatively charged scleral matrix (Kim et al. 2007; Cruysberg et al. 2002; Dunlevy and Rada 2004). A perioculary dosed drug and particles can be cleared by vascular or lymphatic circulations (Amrite et al. 2008; Amrite and Kompella 2005; Cheruvu et al. 2008).

Suprachoroidal dosing interfaces the drug with the choroid on one side and the sclera on the other side. The choroid is a vascular tissue underlying Bruch's membrane that provides nutrients to the RPE and the retina. While the thickness

of Bruch's membrane increases with age, choroid thickness decreases with age (Spraul et al. 1999). The changes in thickness may affect drug permeability across these barriers. Furthermore, lipophilic drugs may bind to the pigment of choroid and may not reach inner ocular tissues such as the retina (Cheruvu et al. 2008; Cheruvu and Kompella 2006). Nano- and microparticles can potentially reside in the suprachoroidal space to allow prolonged drug delivery (Patel et al. 2012).

Subretinal route interfaces the drug with the retina on one side and the RPE on the other side, ideally suited to treat retinal degenerative diseases using gene therapies (Ghazi et al. 2016; Hauswirth et al. 2008). However, the safety of this route of administration needs further investigation.

Intravitreal injection allows placement of 100% of the dose in the back of the eye. Thus, intravitreal injections are the mainstay at the moment for treating back-of-the-eye diseases. However, the inner limiting membrane, which separates the retina and the vitreous humor, can be a barrier for drug diffusion, particularly macromolecules. As a result, retinal delivery of macromolecules with 76 kDa and larger molecular weight is limited (Jackson et al. 2003). Also, expression of efflux pumps such as P-gp and MRP in eye tissues may restrict retinal delivery of small molecules. Intravitreally dosed drugs are eliminated along the anterior pathway via the aqueous humor or restricted from reaching retinal cells by the inner limiting membrane, as mentioned above (Pederson 2006). Furthermore, drug elimination by the posterior segment tissues is another factor limiting retinal drug exposure. Due to the barriers present in the eye, the vitreal half-life of a molecule can be prolonged by increasing its molecular size (Durairaj et al. 2009a). Additionally, injection of a drug suspension and increasing the dose number of a suspension are suitable approaches to increase the persistence of drug molecules injected in the vitreous humor (Durairaj et al. 2009a, b). Drug and dosage form physicochemical properties, interaction with solute/efflux transporters, site of administration, and pathophysiology all influence drug delivery to the posterior segment.

## 4.2 Penetration Pathways for Posterior Segment Drug Delivery

Penetration pathways to the posterior segment of the eye, for an eye drop application, are summarized in Table 4. Non-corneal route is generally deemed the most efficient for back of the eye drug delivery among the pathways listed, although the bioavailability from a drop is not significant to be typically effective in the back of the eye. By injecting the drug at various depths (e.g., periocular, suprachoroidal, subretinal, and intravitreal with increasing depths of injection into the vitreous humor), as opposed to drops on a surface, some or all of the barriers for posterior segment delivery can be overcome. The preferred administration route is dependent on drug and dosage form, physicochemical properties, and disposition (Ahmed and Patton 1985).

The current first choice for posterior segment delivery is intravitreal administration, which bypasses the corneal, conjunctival, scleral, choroidal, RPE, blood–tissue, and lens barriers to reach the vitreous humor. However, the risks involved

**Table 4** Key pathways of drug delivery to tissues of the posterior segment of the eye from an eye drop

| | |
|---|---|
| Non-corneal pathway | Tears → conjunctiva → sclera → choroid → RPE → neural retina → vitreous humor |
| Systemic recirculation from one eye to the other eye | Tears → conjunctival/choroidal/retinal vessels → systemic circulation → contralateral ocular circulation → intraocular tissues → vitreous humor of the contralateral eye |
| Corneal pathway | Tears → cornea → aqueous humor → posterior chamber/lens → vitreous humor → neural retina |
| Uveal pathway | Tears → cornea → aqueous humor → sclera/choroid → RPE → neural retina → vitreous humor |

Injecting the drug in a deeper layer can bypass the preceding barriers

with repeated injections and low patient compliance are leading to the development of slow-release systems as well as assessment of other routes including subretinal, suprachoroidal, and periocular applications including subconjunctival, sub-Tenon, peribulbar, and retrobulbar (Raghava et al. 2004; Eljarrat-Binstock et al. 2010).

## 4.3 Recent Posterior Segment Drug Delivery Approaches

Even though the anterior segment medications contribute the most to the number of currently marked ophthalmic drug products, the drug product market for the posterior segment is rapidly growing with the development of innovative new molecular therapies and delivery systems. The validated VEGF target alone for wet AMD resulted in three approved intravitreally injectable anti-VEGF products to date: Macugen®, Lucentis®, and Eylea®, with Avastin®, a fourth product being compounded and used off-label. As new therapeutic agents enter the back-of-the-eye market, there is continued effort in developing new drug delivery approaches in order to allow noninvasive dosing, to reduce dosing frequency with invasive approaches, and to improve drug efficacy and safety. Penetration enhancers, prodrugs, and iontophoresis are some of the strategies employed to increase drug flux and enhance bioavailability, whereas colloidal delivery systems, gels, inserts, implants, and intraocular refillable devices are being investigated to achieve sustained release and reduce application frequency. A few noteworthy slow-release systems approved for sustained delivery of small molecule drugs in the back of the eye include Vitrasert®, Retisert®, Ozurdex®, and Iluvien®, with drug release durations ranging from approximately 6 months to 3 years.

### 4.3.1 Colloidal Dosage Forms for Posterior Segment Drug Delivery
Colloidal dosage forms like nanoparticles, nanogels, liposomes, and dendrimers have been evaluated for drug delivery to the posterior segment as well as the anterior segment of the eye. Since drug loading in these systems is generally low, they might be limited to drugs that are effective at low therapeutic doses.

Polymeric nanoparticles have been studied extensively for ocular drug delivery, and the FDA-approved polymer PLGA is one of the most investigated materials in the eye, in addition to polyvinyl alcohol, chitosan, and albumin (Kompella et al. 2013).

Nanogels are hydrogels that swell in water to form compactly packed nanoparticles, and they can be used for controlled release of hydrophilic or lipophilic compounds. Nanogel drug release kinetics may be controlled by pH and temperature. Cationic nanogels have been investigated for gene delivery (Vinogradov et al. 2004).

Dendrimers or highly branched polymers are also among the nanotechnology-based delivery systems studied for posterior segment drug delivery. Dendrimers can be interfaced with drug molecules either covalently or non-covalently. Polyamidoamine (PAMAM) dendrimers are the most studied dendrimers for drug and gene delivery, and they are available in a number of generations or sizes and surface charges. Kang et al. (2009) complexed carboplatin with PAMAM dendrimers for periocular delivery and showed that these complexes can reduce retinoblastoma tumor growth (Kang et al. 2009). In a recent study, PAMAM dendrimers with anionic and cationic charges were investigated for retinal dexa-methasone delivery via topical and subconjunctival applications. It was reported that these systems were able to improve corneal and scleral permeability and provide higher ocular bioavailability; however, drug loading in these systems was limited (Yavuz et al. 2015). PAMAM–triamcinolone acetonide conjugates with 21% drug loading were also prepared, and cell culture studies indicated increased anti-inflammatory activity of triamcinolone acetonide (Kambhampati et al. 2015).

Liposomes are vesicular systems with various sizes in the range of nanometers to micrometers, composed of one or more phospholipid bilayers segregated by aque-ous layers. Liposomes offer many advantages for drug delivery since they can encapsulate both hydrophilic and hydrophobic dugs as well as ionic molecules by using cationic or anionic lipids. It was reported that intravitreally injected liposomal formulations caused minimal toxicity while providing prolonged vitreal residence time (Peyman et al. 1989).

In some studies, macromolecules were delivered to the back of the eye following topical dosing with liposomes. In one study, plasmid DNA-loaded liposomes were found to express genes in retinal ganglion cells following topical application in a rat model (Matsuo et al. 1996). Coating diclofenac-loaded liposomes with hydrophobic PVA enhanced diclofenac delivery to the retina–choroid after topical instillation in rabbits (Fujisawa et al. 2012). Annexin A5-functionalized liposomes enhanced delivery of bevacizumab to the vitreous humor and retina following topical instil-lation to rats and rabbits (Davis et al. 2014). While these studies are promising, more confirmatory studies and mechanistic studies are needed to establish the therapeutic potential of liposomes in achieving macromolecule efficacy in the back of the eye.

Micelles are formed at concentrations above the critical micellar concentration of a substance, and they typically consist of monolayers of amphiphilic molecules that form a core and a corona. Based on the properties of the vehicle or continuous

medium and the properties of the amphiphilic compound, standard, reverse, and unimolecular micelles can be formed. These micelles can be formed at a very small size, typically less than 100 nm. Polyethylene glycol coating of the corona reduces micelle aggregation, and they have the potential for posterior segment drug delivery (Trivedi and Kompella 2010; Trivedi et al. 2012).

### 4.3.2 Prodrugs for Posterior Segment Drug Delivery

Prodrug approach is potentially useful in enhancing drug delivery to the posterior segment as well as the anterior segment. Lipophilic esters with increased permeability are among the most widely assessed prodrugs for ophthalmic drug delivery. In addition to the topical route, prodrugs can be dosed by various routes including intravitreal and periocular routes. Prodrugs can be designed to preferentially traverse solute transporters in the tissue barriers of the eye. Furthermore, incorporation of prodrugs within polymeric carriers may provide controlled drug delivery to the retina and vitreous (Eljarrat-Binstock et al. 2010).

Transporter-targeted gatifloxacin prodrugs have been prepared for topical application, and organic cation transporter, monocarboxylate transporter, and ATB transporters were targeted for enhanced drug delivery to the back of the eye. Ex vivo transport studies were performed against the cornea and sclera–choroid–RPE, as well as in vivo studies in rats. It was reported that prodrug increased solubility and enhanced organic cation transporter-mediated delivery of gatifloxacin (Vooturi et al. 2012). Posterior segment distribution of nepafenac (which is a prodrug for amfenac) has been studied in rabbit and monkey models following topical administration. The study suggested that nepafenac and amfenac were able to distribute in posterior segment tissues via transconjunctival/transscleral delivery (Chastain et al. 2016).

### 4.3.3 Light-Activated Systems

Light-activated systems are drugs and delivery systems that are capable of controlled activation. A classic example in the eye is Visudyne®, which is a clinically approved intravenously administered liposomal light-activated system. Visudyne® localizes a photosensitizer in the eye and activates the same by a nonthermal laser light. Visudyne is predominantly used for classic subfoveal choroidal neovascularization in AMD. Laser light at 689 nm is used for activating Visudyne at 15 min after the start of a 10 min infusion with Visudyne. The laser activates verteporfin, a photosensitizer present as an active ingredient in Visudyne. However, photodynamic therapy itself causes neovascularization; thus, the effect of Visudyne® might be insufficient and repeated treatment might be required (Thrimawithana et al. 2011; Christie and Kompella 2008). Photrex® (rostaporfin) is another liposomal photosensitizing system, which did not meet the primary clinical endpoint in wet AMD trials (Huang 2005).

Dendritic porphyrin-loaded micelles are also of potential value in treating choroidal neovascularization. Following laser application micelles accumulate in the neovascularization area and 80% of them remained there up to 7 days (Ideta et al. 2005). Vectosomes or particles made of VP22 protein were also investigated

in vitro and in vivo for light-induced targeted delivery of antisense oligonucleotides. Once injected intravitreally, white light was exposed transsclerally at 24 h to activate vectosomes and release their contents. The results indicated that vectosomes were able to distribute in the various retinal layers and RPE (Normand et al. 2005). Another approach for light-sensitive drug delivery is gold nanoparticle-loaded liposomes, wherein UV light-induced heating of gold nanorods melts and releases the contents of the liposomes (Paasonen et al. 2007). In a recent study, a light-activated in situ gelling system has been designed for suprachoroidal application of bevacizumab, using polycaprolactone dimethacrylate and HEMA. Following 10 min of cross-linking, the gel was able to release bevacizumab for approximately 1 month in a rodent model (Tyagi et al. 2013).

### 4.3.4 Intraocular Implants for Posterior Segment Drug Delivery

The goal of designing intraocular implants is to provide prolonged and controlled drug delivery up to several months or years using either biodegradable or nonbiodegradable polymers. Sustained-release implants have been studied for chronic diseases that affect the back of the eye such as posterior uveitis, AMD, and diabetic retinopathy. Drug release from these systems occurs either by degradation of the polymer or diffusion through a membrane. Even though some intravitreal implants require surgical implantation, bypassing some drug delivery barriers and reducing dosing frequency and associated side effects are some of their advantages (Jaffe et al. 2006; Guidetti et al. 2008).

Vitrasert® is the first nonbiodegradable, implantable device, designed for ganciclovir delivery and approved by the US FDA in 1996 for the treatment of cytomegalovirus retinitis. Side effects of Vitrasert include endophthalmitis and retinal detachment (Bourges et al. 2006). Retisert®, which is an implant containing fluocinolone acetonide and used for uveitis treatment, was approved by the US FDA in 2005. It is able to release the drug for up to 3 years, but patients who used Retisert® showed a high likelihood of cataract formation and glaucoma (Kempen et al. 2011).

Another FDA-approved intravitreal implant system is Ozurdex®, which is an injectable sustained-release dexamethasone insert approved for posterior uveitis, retinal vein occlusion, and diabetic macular edema. In some cases, it was observed that Ozurdex® implant can migrate into the anterior chamber from its initial location (Khurana et al. 2014; Bratton et al. 2014). Iluvien® is a similarly injectable nonbiodegradable implant system for diabetic macular edema and uveitis treatment, and it was recently approved by the FDA in 2014. It is designed to deliver fluocinolone acetonide for 24–36 months (Pearce et al. 2015).

Neurotech has developed an implant called NT-501 using cell encapsulation technology. Genetically engineered human RPE cells are encapsulated in this implant to secrete ciliary neurotrophic factor. The company is currently conducting clinical trials in patients with early-stage retinitis pigmentosa and Usher syndrome types 2 and 3 (Normand et al. 2005; NeurotechUSA; Lo et al. 2009; Rowe-Rendleman et al. 2014).

### 4.3.5    Refillable Devices

While the above-described slow-release systems need to be readministered after their intended duration of release, an alternative approach to minimize surgical placement of implants is to use refillable systems and reinject drug as required (Lee et al. 2012). Lo et al. (2009) developed a surgically implantable system to be placed under the conjunctiva and release a specified amount of drug following mechanical activation by a patient's finger (Lo et al. 2009). Since it is a refillable system, it only requires implantation once and allows for continual treatment of chronic diseases. The Replenish MicroPump is also an implantable microreservoir that releases drug at a programmed interval with nanoliter doses, while the drug reservoir can be refilled via transconjunctival injection (Saati et al. 2010). The port delivery system is another refillable device that is in phase II trials for (Pearce et al. 2015) sustained release of ranibizumab in wet AMD patients with subfoveal neovascularization.

### 4.3.6    Microneedles

Application of microneedles is a recent approach for suprachoroidal and intrascleral drug delivery. There are solid or hollow microneedles available, which were initially developed for transdermal application. Microneedles can deliver free or encapsulated drugs with minimal invasion and may avoid the safety concerns associated with repeated intravitreal applications (Rowe-Rendleman et al. 2014). Based on animal studies, it was reported that insertion site disappears 1 h after microneedle injection (Patel et al. 2012).

Jiang et al. (2009) used human cadaver eyes to test hollow borosilicate microneedle and investigated distribution of sulforhodamine in the posterior segment of the eye (Jiang et al. 2009). The results indicated that distribution was dependent on conditions such as pressure and no significant effect was observed on delivery. Nevertheless, it should be noted that the microneedles were inserted in the sclera and not in the suprachoroidal space.

In another study, Gilger et al. (2013) compared intravitreal drug delivery with suprachoroidal microneedles using triamcinolone acetonide as a model drug using domestic weanling pigs. The delivery system was reported to be safe and effective (Gilger et al. 2013).

Currently, there is one ongoing clinical trial for suprachoroidal drug delivery using microneedles. It is a phase II trial for triamcinolone acetonide suspension in patients with macular edema associated with noninfectious uveitis (NCT02303184).

### 4.3.7    Transscleral Iontophoresis

Transcorneal iontophoresis has been investigated for anterior segment drug delivery over the years. On the other hand, transscleral iontophoresis is recently gaining attention since it overcomes the lens–iris barrier and delivers drug directly to the back of the eye. In this method an iontophoretic device is placed over the pars plana area on the conjunctiva. A wide variety of drugs have been studied for transscleral iontophoresis including antibiotics, steroids, proteins, genes, drug-containing hydrogels, and nanoparticle delivery systems (Eljarrat-Binstock et al. 2010).

Several studies have shown that transscleral iontophoresis is able to deliver high concentration of drugs to the choroid and retina. Transscleral OcuPhor™ hydrogel has been tested for saline iontophoresis in healthy volunteers. Different intensities have been investigated for 20 and 40 min, and it was reported that the system was well tolerated (Parkinson et al. 2003). DSP-Visulex® is another transscleral iontophoresis system, which consists of a scleral-lens-shaped applicator and currently is in clinical trial phase I/II (Acient).

Molokhia et al. (2009) reported that transscleral iontophoresis was not efficient in delivering macromolecules to the vitreous in a rabbit model. It was shown that Galbumin, the macromolecule used in the study, was only present in the sclera and conjunctiva (Molokhia et al. 2009). On the other hand, using isolated human sclera showed that large molecules ranging from 51 bp to 2 kbp plasmids can be delivered using iontophoresis (Davies et al. 2003).

In spite of the advantages of transscleral iontophoresis in enhancing drug delivery, tissue damage risk is still a concern. The damage depends on the site of application, duration, and density of the current applied (Eljarrat-Binstock and Domb 2006). Side effects caused by iontophoresis include decrease in endothelial cells, burning, epithelial edema, and inflammation. At high densities choroidal damage and destruction of retinal layers have also been reported (Thrimawithana et al. 2011).

## 5 Conclusions

Effective drug delivery for the treatment of ocular diseases has always been a challenge especially for the posterior segment, due to the anatomy of the eye, the ocular barriers, and the physiological changes caused by the nature of the diseases. Scientists continue to work on new drug delivery systems to enhance target access, extent of delivery, and duration of drug exposure in order to improve drug efficacy while reducing side effects, in the hope to ultimately improve patient benefit and convenience.

Sustained drug delivery systems, noninvasive approaches for improving back-of-the-eye drug delivery, and contact lenses to prolong ocular surface drug exposure are currently seeing a lot of innovation for improving ocular drug delivery. Despite the promising research, development of eye drops for back-of-the-eye drug effects remains the most formidable challenge. A combination of approaches and a multidisciplinary effort may be needed to overcome this challenge. Translational sciences including understanding of animal models vs. human subjects are critical for improving the predictability of clinical outcomes based on preclinical studies. For translation of ophthalmic drug and gene therapies, it is necessary to create a functional network between scientists, clinicians, regulatory agencies, and industry representatives.

# References

Abdelbary G (2011) Ocular ciprofloxacin hydrochloride mucoadhesive chitosan-coated liposomes. Pharm Dev Technol 16(1):44–56

Acront. Available from: http://www.aciont.com/technologies/visulex

Agrawal AK, Das M, Jain S (2012) In situ gel systems as 'smart' carriers for sustained ocular drug delivery. Expert Opin Drug Deliv 9(4):383–402

Ahmed I, Patton TF (1985) Importance of the noncorneal absorption route in topical ophthalmic drug delivery. Invest Ophthalmol Vis Sci 26(4):584–587

Aksungur P, Demirbilek M, Denkbas EB, Vandervoort J, Ludwig A, Unlu N (2011) Development and characterization of cyclosporine A loaded nanoparticles for ocular drug delivery: cellular toxicity, uptake, and kinetic studies. J Control Release 151(3):286–294

Amrite AC, Kompella UB (2005) Size-dependent disposition of nanoparticles and microparticles following subconjunctival administration. J Pharm Pharmacol 57(12):1555–1563

Amrite AC, Edelhauser HF, Singh SR, Kompella UB (2008) Effect of circulation on the disposition and ocular tissue distribution of 20 nm nanoparticles after periocular administration. Mol Vis 14:150–160

Ang M (2014) Evaluation of a prednisolone acetate-loaded subconjunctival implant for the treatment of recurrent uveitis in a rabbit model. PLoS One 9(8), e97555

Arakawa Y, Hashida N, Ohguro N, Yamazaki N, Onda M, Matsumoto S et al (2007) Eye-concentrated distribution of dexamethasone carried by sugar-chain modified liposome in experimental autoimmune uveoretinitis mice. Biomed Res 28(6):331–334

Aukunuru JV, Sunkara G, Bandi N, Thoreson WB, Kompella UB (2001) Expression of multidrug resistance-associated protein (MRP) in human retinal pigment epithelial cells and its interaction with BAPSG, a novel aldose reductase inhibitor. Pharm Res 18(5):565–572

Badawi AA, El-Laithy HM, El Qidra RK, El Mofty H, El dally M (2008) Chitosan based nanocarriers for indomethacin ocular delivery. Arch Pharm Res 31(8):1040–1049

Barar J, Javadzadeh AR, Omidi Y (2008) Ocular novel drug delivery: impacts of membranes and barriers. Expert Opin Drug Deliv 5(5):567–581

Baydoun L, Muller-Goymann CC (2003) Influence of n-octenylsuccinate starch on in vitro permeation of sodium diclofenac across excised porcine cornea in comparison to Voltaren ophtha. Eur J Pharm Biopharm 56(1):73–79

Bhagav P, Upadhyay H, Chandran S (2011) Brimonidine tartrate-eudragit long-acting nanoparticles: formulation, optimization, in vitro and in vivo evaluation. AAPS PharmSciTech 12(4):1087–1101

Bikbova G, Bikbov M (2014) Transepithelial corneal collagen cross-linking by iontophoresis of riboflavin. Acta Ophthalmol 92(1):e30–e34

Bock F, Matthaei M, Reinhard T, Bohringer D, Christoph J, Ganslandt T et al (2014) High-dose subconjunctival cyclosporine A implants do not affect corneal neovascularization after high-risk keratoplasty. Ophthalmology 121(9):1677–1682

Bourges JL, Bloquel C, Thomas A, Froussart F, Bochot A, Azan F et al (2006) Intraocular implants for extended drug delivery: therapeutic applications. Adv Drug Deliv Rev 58(11):1182–1202

Bourkiza R, Lee V (2012) A review of the complications of lacrimal occlusion with punctal and canalicular plugs. Orbit 31(2):86–93

Bratton ML, He YG, Weakley DR (2014) Dexamethasone intravitreal implant (Ozurdex) for the treatment of pediatric uveitis. J AAPOS 18(2):110–113

Calvo P, Alonso MJ, Vila-Jato JL, Robinson JR (1996) Improved ocular bioavailability of indomethacin by novel ocular drug carriers. J Pharm Pharmacol 48(11):1147–1152

Carmen AL, Fernando Y, Rafael BI, Angel C (2006) Imprinted soft contact lenses as norfloxacin delivery systems. J Control Release 113:236–424

Chaiyasan W, Srinivas SP, Tiyaboonchai W (2013) Mucoadhesive chitosan-dextran sulfate nanoparticles for sustained drug delivery to the ocular surface. J Ocul Pharmacol Ther 29 (2):200–207

Chang SC, Bundgaard H, Buur A, Lee VH (1987) Improved corneal penetration of timolol by prodrugs as a means to reduce systemic drug load. Invest Ophthalmol Vis Sci 28(3):487–491

Chastain JE, Sanders ME, Curtis MA, Chemuturi NV, Gadd ME, Kapin MA et al (2016) Distribution of topical ocular nepafenac and its active metabolite amfenac to the posterior segment of the eye. Exp Eye Res 145:58–67

Chauhan A (2015) Ocular drug delivery role of contact lenses. Allied Ophthal Sci 26(2):131–135

Chee SP (2012) Moxifloxacin punctum plug for sustained drug delivery. J Ocul Pharmacol Ther 28 (4):340–349

Cheruvu NP, Kompella UB (2006) Bovine and porcine transscleral solute transport: influence of lipophilicity and the Choroid-Bruch's layer. Invest Ophthalmol Vis Sci 47(10):4513–4522

Cheruvu NP, Amrite AC, Kompella UB (2008) Effect of eye pigmentation on transscleral drug delivery. Invest Ophthalmol Vis Sci 49(1):333–341

Chien DS, Tang-Liu DD, Woodward DF (1997) Ocular penetration and bioconversion of prostaglandin F2alpha prodrugs in rabbit cornea and conjunctiva. J Pharm Sci 86(10):1180–1186

Chopra P, Hao J, Li SK (2010) Iontophoretic transport of charged macromolecules across human sclera. Int J Pharm 388(1–2):107–113

Christie JG, Kompella UB (2008) Ophthalmic light sensitive nanocarrier systems. Drug Discov Today 13(3–4):124–134

Civiale C, Bucaria F, Piazza S, Peri O, Miano F, Enea V (2004) Ocular permeability screening of dexamethasone esters through combined cellular and tissue systems. J Ocul Pharmacol Ther 20 (1):75–84

Civiale C, Licciardi M, Cavallaro G, Giammona G, Mazzone MG (2009) Polyhydroxyethylaspartamide-based micelles for ocular drug delivery. Int J Pharm 378 (1–2):177–186

Cohen AE, Assang C, Patane MA, From S, Korenfeld M (2012) Avion study investigators. Evaluation of dexamethasone phosphate delivered by ocular iontophoresis for treating noninfectious anterior uveitis. Ophthalmology 119(1):66–73

Contreras-Ruiz L, Zorzi GK, Hileeto D, Lopez-Garcia A, Calonge M, Seijo B et al (2013) A nanomedicine to treat ocular surface inflammation: performance on an experimental dry eye murine model. Gene Ther 20(5):467–477

Cruysberg LP, Nuijts RM, Geroski DH, Koole LH, Hendrikse F, Edelhauser HF (2002) In vitro human scleral permeability of fluorescein, dexamethasone-fluorescein, methotrexate-fluorescein and rhodamine 6G and the use of a coated coil as a new drug delivery system. J Ocul Pharmacol Ther 18(6):559–569

Davies NM (2000) Biopharmaceutical considerations in topical ocular drug delivery. Clin Exp Pharmacol Physiol 27(7):558–562

Davies JB, Ciavatta VT, Boatright JH, Nickerson JM (2003) Delivery of several forms of DNA, DNA-RNA hybrids, and dyes across human sclera by electrical fields. Mol Vis 9 (68–69):569–578

Davis BM, Normando EM, Guo L, Turner LA, Nizari S, O'Shea P et al (2014) Topical delivery of Avastin to the posterior segment of the eye in vivo using annexin A5-associated liposomes. Small 10(8):1575–1584

De Campos AM, Sanchez A, Alonso MJ (2001) Chitosan nanoparticles: a new vehicle for the improvement of the delivery of drugs to the ocular surface. Application to cyclosporin A. Int J Pharm 224(1–2):159–168

de Paiva CS, Schwartz CE, Gjorstrup P, Pflugfelder SC (2012) Resolvin E1 (RX-10001) reduces corneal epithelial barrier disruption and protects against goblet cell loss in a murine model of dry eye. Cornea 31(11):1299–1303

Dey S, Anand BS, Patel J, Mitra AK (2003) Transporters/receptors in the anterior chamber: pathways to explore ocular drug delivery strategies. Expert Opin Biol Ther 3(1):23–44

Di Tommaso C, Torriglia A, Furrer P, Behar-Cohen F, Gurny R, Moller M (2011) Ocular biocompatibility of novel cyclosporin A formulations based on methoxy poly(ethylene glycol)-hexylsubstituted poly(lactide) micelle carriers. Int J Pharm 416(2):515–524

Dong Y, Dong P, Huang D, Mei L, Xia Y, Wang Z et al (2015) Fabrication and characterization of silk fibroin-coated liposomes for ocular drug delivery. Eur J Pharm Biopharm 91:82–90

Dunlevy JR, Rada JA (2004) Interaction of lumican with aggrecan in the aging human sclera. Invest Ophthalmol Vis Sci 45(11):3849–3856

Durairaj C, Shah JC, Senapati S, Kompella UB (2009a) Prediction of vitreal half-life based on drug physicochemical properties: quantitative structure-pharmacokinetic relationships (QSPKR). Pharm Res 26(5):1236–1260

Durairaj C, Kim SJ, Edelhauser HF, Shah JC, Kompella UB (2009b) Influence of dosage form on the intravitreal pharmacokinetics of diclofenac. Invest Ophthalmol Vis Sci 50(10):4887–4897

Durairaj C, Kadam RS, Chandler JW, Hutcherson SL, Kompella UB (2010) Nanosized dendritic polyguanidilyated translocators for enhanced solubility, permeability, and delivery of gatifloxacin. Invest Ophthalmol Vis Sci 51(11):5804–5816

Duvvuri S, Majumdar S, Mitra AK (2003) Drug delivery to the retina: challenges and opportunities. Expert Opin Biol Ther 3(1):45–56

Eljarrat-Binstock E, Domb AJ (2006) Iontophoresis: a non-invasive ocular drug delivery. J Control Release 110(3):479–489

Eljarrat-Binstock E, Pe'er J, Domb AJ (2010) New techniques for drug delivery to the posterior eye segment. Pharm Res 27(4):530–543

Eperon S, Bossy-Nobs L, Petropoulos IK, Gurny R, Guex-Crosier Y (2008) A biodegradable drug delivery system for the treatment of postoperative inflammation. Int J Pharm 352 (1–2):240–247

Eytan GD, Kuchel PW (1999) Mechanism of action of P-glycoprotein in relation to passive membrane permeation. Int Rev Cytol 190:175–250

Fujisawa T, Miyai H, Hironaka K, Tsukamoto T, Tahara K, Tozuka Y et al (2012) Liposomal diclofenac eye drop formulations targeting the retina: formulation stability improvement using surface modification of liposomes. Int J Pharm 436(1–2):564–567

Furrer E, Berdugo M, Stella C, Behar-Cohen F, Gurny R, Feige U et al (2009) Pharmacokinetics and posterior segment biodistribution of ESBA105, an anti-TNF-alpha single-chain antibody, upon topical administration to the rabbit eye. Invest Ophthalmol Vis Sci 50(2):771–778

Gan L, Gan Y, Zhu C, Zhang X, Zhu J (2009) Novel microemulsion in situ electrolyte-triggered gelling system for ophthalmic delivery of lipophilic cyclosporine A: in vitro and in vivo results. Int J Pharm 365(1–2):143–149

Gan L, Han S, Shen J, Zhu J, Zhu C, Zhang X et al (2010) Self-assembled liquid crystalline nanoparticles as a novel ophthalmic delivery system for dexamethasone: improving preocular retention and ocular bioavailability. Int J Pharm 396(1–2):179–187

Gaudana R, Jwala J, Boddu SHS, Mitra AK (2009) Recent perspectives in ocular drug delivery. Pharm Res 26(5):1197–1216

Gaudana R, Ananthula HK, Parenky A, Mitra AK (2010) Ocular drug delivery. AAPS J 12 (3):348–360

Ghate D, Edelhauser HF (2006) Ocular drug delivery. Expert Opin Drug Deliv 3(2):275–287

Ghazi NG, Abboud EB, Nowilaty SR, Alkuraya H, Alhommadi A, Cai H et al (2016) Treatment of retinitis pigmentosa due to MERTK mutations by ocular subretinal injection of adeno-associated virus gene vector: results of a phase I trial. Hum Genet 135(3):327–343

Gilger BC, Abarca EM, Salmon JH, Patel S (2013) Treatment of acute posterior uveitis in a porcine model by injection of triamcinolone acetonide into the suprachoroidal space using microneedles. Invest Ophthalmol Vis Sci 54(4):2483–2492

Gu JM, Robinson JR, Leung SH (1988) Binding of acrylic polymers to mucin/epithelial surfaces: structure-property relationships. Crit Rev Ther Drug Carrier Syst 5(1):21–67

Guidetti B, Azema J, Malet-Martino M, Martino R (2008) Delivery systems for the treatment of proliferative vitreoretinopathy: materials, devices and colloidal carriers. Curr Drug Deliv 5 (1):7–19

Gupta C, Chauhan A (2011) Ophthalmic delivery of cyclosporine A by punctal plugs. J Control Release 150(1):70–76

Gupta AK, Madan S, Majumdar DK, Maitra A (2000) Ketorolac entrapped in polymeric micelles: preparation, characterisation and ocular anti-inflammatory studies. Int J Pharm 209(1–2):1–14

Gupta H, Aqil M, Khar RK, Ali A, Bhatnagar A, Mittal G (2011) Biodegradable levofloxacin nanoparticles for sustained ocular drug delivery. J Drug Target 19(6):409–417

Habib FS, Fouad EA, Abdel-Rhaman MS, Fathalla D (2010) Liposomes as an ocular delivery system of fluconazole: in-vitro studies. Acta Ophthalmol 88(8):901–904

Halhal M, Renard G, Courtois Y, BenEzra D, Behar-Cohen F (2004) Iontophoresis: from the lab to the bed side. Exp Eye Res 78:751–757

Hauswirth WW, Aleman TS, Kaushal S, Cideciyan AV, Schwartz SB, Wang L et al (2008) Treatment of leber congenital amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: short-term results of a phase I trial. Hum Gene Ther 19 (10):979–990

Hillman JS (1974) Management of acute glaucoma with pilocarpine-soaked hydrophilic lens. Br J Ophthalmol 58(7):674–679

Hobden JA, Reidy JJ, O'Callaghan RJ, Insler MS, Hill JM (1990) Ciprofloxacin iontophoresis for aminoglycoside-resistant pseudomonal keratitis. Invest Ophthalmol Vis Sci 31(10):1940–1944

Holden CA, Tyagi P, Thakur A, Kadam R, Jadhav G, Kompella UB et al (2012) Polyamidoamine dendrimer hydrogel for enhanced delivery of antiglaucoma drugs. Nanomed Nanotechnol Biol Med 8(5):776–783

Horvat G, Budai-Szucs M, Berko S, Szabo-Revesz P, Soos J, Facsko A et al (2015) Comparative study of nanosized cross-linked sodium-, linear sodium- and zinc-hyaluronate as potential ocular mucoadhesive drug delivery systems. Int J Pharm 494(1):321–328

Hosoya K, Lee VH (1997) Cidofovir transport in the pigmented rabbit conjunctiva. Curr Eye Res 16(7):693–697

Hosoya K, Tachikawa M (2012) The inner blood-retinal barrier: molecular structure and transport biology. Adv Exp Med Biol 763:85–104

Hosoya K, Horibe Y, Kim KJ, Lee VH (1997) Na(+)-dependent L-arginine transport in the pigmented rabbit conjunctiva. Exp Eye Res 65(4):547–553

Hosoya K, Lee VH, Kim KJ (2005) Roles of the conjunctiva in ocular drug delivery: a review of conjunctival transport mechanisms and their regulation. Eur J Pharm Biopharm 60(2):227–240

Hosoya K, Tomi M, Tachikawa M (2011) Strategies for therapy of retinal diseases using systemic drug delivery: relevance of transporters at the blood-retinal barrier. Expert Opin Drug Deliv 8 (12):1571–1587

Hsu KH, Carbia BE, Plummer C, Chauhan A (2015) Dual drug delivery from vitamin E loaded contact lenses for glaucoma therapy. Eur J Pharm Biopharm 94:312–321

Hu FQ, Li YH, Yuan H, Zeng S (2006) Novel self-aggregates of chitosan oligosaccharide grafted stearic acid: preparation, characterization and protein association. Pharmazie 61(3):194–198

Huang Z (2005) A review of progress in clinical photodynamic therapy. Technol Cancer Res Treat 4(3):283–293

Hughes PM, Mitra AK (1993) Effect of acylation on the ocular disposition of acyclovir. II: corneal permeability and anti-HSV 1 activity of 2′-esters in rabbit epithelial keratitis. J Ocul Pharmacol 9(4):299–309

Hughes PM, Olejnik O, Chang-Lin JE, Wilson CG (2005) Topical and systemic drug delivery to the posterior segments. Adv Drug Deliv Rev 57(14):2010–2032

Hui A, Sheardown H, Jones L (2012) Acetic and acrylic acid molecular imprinted model silicone hydrogel materials for ciprofloxacin-hcl delivery. Materials 5(1):81–107

Ibrahim HK, El-Leithy IS, Makky AA (2010) Mucoadhesive nanoparticles as carrier systems for prolonged ocular delivery of gatifloxacin/prednisolone bitherapy. Mol Pharm 7(2):576–585

Ideta R, Tasaka F, Jang WD, Nishiyama N, Zhang GD, Harada A et al (2005) Nanotechnology-based photodynamic therapy for neovascular disease using a supramolecular nanocarrier loaded with a dendritic photosensitizer. Nano Lett 5(12):2426–2431

Jackson TL, Antcliff R, Hillenkamp J, Marshall J (2003) Human retinal molecular weight exclusion limit and estimate of species variation. Invest Ophthalmol Vis Sci 44(5):2141–2146

Jaffe GJ, Martin D, Callanan D, Pearson PA, Levy B, Comstock T et al (2006) Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis - thirty-four-week results of a multicenter randomized clinical study. Ophthalmology 113(6):1020–1027

Jain-Vakkalagadda B, Dey S, Pal D, Mitra AK (2003) Identification and functional characterization of a Na+-independent large neutral amino acid transporter, LAT1, in human and rabbit cornea. Invest Ophthalmol Vis Sci 44(7):2919–2927

Jain-Vakkalagadda B, Pal D, Gunda S, Nashed Y, Ganapathy V, Mitra AK (2004) Identification of a Na+-dependent cationic and neutral amino acid transporter, B(0,+), in human and rabbit cornea. Mol Pharm 1(5):338–346

Janoria KG, Hariharan S, Paturi D, Pal D, Mitra AK (2006) Biotin uptake by rabbit corneal epithelial cells: role of sodium-dependent multivitamin transporter (SMVT). Curr Eye Res 31 (10):797–809

Jiang J, Moore JS, Edelhauser HF, Prausnitz MR (2009) Intrascleral drug delivery to the eye using hollow microneedles. Pharm Res 26(2):395–403

Jung HJ, Chauhan A (2012) Temperature sensitive contact lenses for triggered ophthalmic drug delivery. Biomaterials 33(7):2289–2300

Kambhampati SP, Mishra MK, Mastorakos P, Oh Y, Lutty GA, Kannan RM (2015) Intracellular delivery of dendrimer triamcinolone acetonide conjugates into microglial and human retinal pigment epithelial cells. Eur J Pharm Biopharm 95(Pt B):239–249

Kang SJ, Durairaj C, Kompella UB, O'Brien JM, Grossniklaus HE (2009) Subconjunctival nanoparticle carboplatin in the treatment of murine retinoblastoma. Arch Ophthalmol 127 (8):1043–1047

Karlgard CC, Wong NS, Jones LW, Moresoli C (2003) In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and p-HEMA hydrogel contact lens materials. Int J Pharm 257(1–2):141–151

Karn PR, Kim HD, Kang H, Sun BK, Jin SE, Hwang SJ (2014) Supercritical fluid-mediated liposomes containing cyclosporin A for the treatment of dry eye syndrome in a rabbit model: comparative study with the conventional cyclosporin A emulsion. Int J Nanomedicine 9:3791–3800

Kassem MA, Abdel Rahman AA, Ghorab MM, Ahmed MB, Khalil RM (2007) Nanosuspension as an ophthalmic delivery system for certain glucocorticoid drugs. Int J Pharm 340(1–2):126–133

Katiyar S, Pandit J, Mondal RS, Mishra AK, Chuttani K, Aqil M et al (2014) In situ gelling dorzolamide loaded chitosan nanoparticles for the treatment of glaucoma. Carbohydr Polym 102:117–124

Katragadda S, Talluri RS, Mitra AK (2006) Modulation of P-glycoprotein-mediated efflux by prodrug derivatization: an approach involving peptide transporter-mediated influx across rabbit cornea. J Ocul Pharmacol Ther 22(2):110–120

Kaur IP, Smitha R (2002) Penetration enhancers and ocular bioadhesives: two new avenues for ophthalmic drug delivery. Drug Dev Ind Pharm 28(4):353–369

Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Louis TA, Sugar EA et al (2011) Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. Ophthalmology 118(10):1916–1926

Khan W, Aldouby YH, Avramoff A, Domb AJ (2012) Cyclosporin nanosphere formulation for ophthalmic administration. Int J Pharm 437(1–2):275–276

Khurana RN, Appa SN, McCannel CA, Elman MJ, Wittenberg SE, Parks DJ et al (2014) Dexamethasone implant anterior chamber migration risk factors, complications, and management strategies. Ophthalmology 121(1):67–71

Kim SH, Lutz RJ, Wang NS, Robinson MR (2007) Transport barriers in transscleral drug delivery for retinal diseases. Ophthalmic Res 39(5):244–254

Kirchhof S, Goepferich AM, Brandl FP (2015) Hydrogels in ophthalmic applications. Eur J Pharm Biopharm 95(Pt B):227–238

Klang S, Abdulrazik M, Benita S (2000) Influence of emulsion droplet surface charge on indomethacin ocular tissue distribution. Pharm Dev Technol 5(4):521–532

Kompella UB, Kadam RS, Lee VH (2010) Recent advances in ophthalmic drug delivery. Ther Deliv 1(3):435–456

Kompella UB, Amrite AC, Pacha Ravi R, Durazo SA (2013) Nanomedicines for back of the eye drug delivery, gene delivery, and imaging. Prog Retin Eye Res 36:172–198

Konat Zorzi G, Contreras-Ruiz L, Parraga JE, Lopez-Garcia A, Romero Bello R, Diebold Y et al (2011) Expression of MUC5AC in ocular surface epithelial cells using cationized gelatin nanoparticles. Mol Pharm 8(5):1783–1788

Kuno N, Fujii S (2011) Recent advances in ocular drug delivery systems. Polymers (Basel) 3 (1):193–221

Kuwano M, Ibuki H, Morikawa N, Ota A, Kawashima Y (2002) Cyclosporine A formulation affects its ocular distribution in rabbits. Pharm Res 19(1):108–111

Lallemand F, Furrer P, Felt-Baeyens O, Gex-Fabry M, Dumont JM, Besseghir K et al (2005) A novel water-soluble cyclosporine A prodrug: ocular tolerance and in vivo kinetics. Int J Pharm 295(1–2):7–14

Lallemand F, Varesio E, Felt-Baeyens O, Bossy L, Hopfgartner G, Gurny R (2007) Biological conversion of a water-soluble prodrug of cyclosporine A. Eur J Pharm Biopharm 67 (2):555–561

Law SL, Huang KJ, Chiang CH (2000) Acyclovir-containing liposomes for potential ocular delivery. Corneal penetration and absorption. J Control Release 63(1–2):135–140

Lee VH (1983) Esterase activities in adult rabbit eyes. J Pharm Sci 72(3):239–244

Lee VH, Robinson JR (1986) Topical ocular drug delivery: recent developments and future challenges. J Ocul Pharmacol 2(1):67–108

Lee JH, Pidaparti RM, Atkinson GM, Moorthy RS (2012) Design of an implantable device for ocular drug delivery. J Drug Deliv 2012:527516

Li N, Zhuang C, Wang M, Sun X, Nie S, Pan W (2009) Liposome coated with low molecular weight chitosan and its potential use in ocular drug delivery. Int J Pharm 379(1):131–138

Lo R, Li PY, Saati S, Agrawal RN, Humayun MS, Meng E (2009) A passive MEMS drug delivery pump for treatment of ocular diseases. Biomed Microdevices 11(5):959–970

Losa C, Calvo P, Castro E, Vila-Jato JL, Alonso MJ (1991) Improvement of ocular penetration of amikacin sulphate by association to poly(butylcyanoacrylate) nanoparticles. J Pharm Pharmacol 43(8):548–552

Losa C, Marchal-Heussler L, Orallo F, Vila Jato JL, Alonso MJ (1993) Design of new formulations for topical ocular administration: polymeric nanocapsules containing metipranolol. Pharm Res 10(1):80–87

Lu C, Yoganathan RB, Kociolek M, Allen C (2013) Hydrogel containing silica shell cross-linked micelles for ocular drug delivery. J Pharm Sci 102(2):627–637

Luo Q, Zhao J, Zhang X, Pan W (2011) Nanostructured lipid carrier (NLC) coated with Chitosan Oligosaccharides and its potential use in ocular drug delivery system. Int J Pharm 403 (1–2):185–191

Mac Gabhann F, Demetriades AM, Deering T, Packer JD, Shah SM, Duh E et al (2007) Protein transport to choroid and retina following periocular injection: theoretical and experimental study. Ann Biomed Eng 35(4):615–630

Macha S, Mitra AK (2003) Overview of ocular drug delivery. In: Mitra AK (ed) Ophthalmic drug delivery systems, 2nd edn. Marcel Dekker, New York, pp 1–12

Mainolfi N, Powers J, Amin J, Long D, Lee W, McLaughlin ME et al (2013) An effective prodrug strategy to selectively enhance ocular exposure of a cannabinoid receptor (CB1/2) agonist. J Med Chem 56(13):5464–5472

Maiti S, Paul S, Mondol R, Ray S, Sa B (2011) Nanovesicular formulation of brimonidine tartrate for the management of glaucoma: in vitro and in vivo evaluation. AAPS PharmSciTech 12 (2):755–763

Majumdar S, Nashed YE, Patel K, Jain R, Itahashi M, Neumann DM et al (2005) Dipeptide monoester ganciclovir prodrugs for treating HSV-1-induced corneal epithelial and stromal keratitis: in vitro and in vivo evaluations. J Ocul Pharmacol Ther 21(6):463–474

Mannermaa E, Vellonen KS, Urtti A (2006) Drug transport in corneal epithelium and blood-retina barrier: emerging role of transporters in ocular pharmacokinetics. Adv Drug Deliv Rev 58 (11):1136–1163

Matsuo T, Masuda I, Yasuda T, Matsuo N (1996) Gene transfer to the retina of rat by liposome eye drops. Biochem Biophys Res Commun 219(3):947–950

Mehanna MM, Elmaradny HA, Samaha MW (2010) Mucoadhesive liposomes as ocular delivery system: physical, microbiological, and in vivo assessment. Drug Dev Ind Pharm 36 (1):108–118

Mishima S (1981) Clinical pharmacokinetics of the eye. Proctor lecture. Invest Ophthalmol Vis Sci 21(4):504–541

Mitra AK, Velagaleti PR, Grau UM (2010) Topical drug delivery systems for ophthalmic use. Google Patents

Mohammadi S, Jones L, Gorbet M (2014) Extended latanoprost release from commercial contact lenses: in vitro studies using corneal models. PLoS One 9(9), e106653

Molokhia SA, Jeong EK, Higuchi WI, Li SK (2008) Examination of barriers and barrier alteration in transscleral iontophoresis. J Pharm Sci 97(2):831–844

Molokhia SA, Jeong EK, Higuchi WI, Li SK (2009) Transscleral iontophoretic and intravitreal delivery of a macromolecule: study of ocular distribution in vivo and postmortem with MRI. Exp Eye Res 88(3):418–425

Molokhia SA, Sant H, Simonis J, Bishop CJ, Burr RM, Gale BK et al (2010) The capsule drug device: novel approach for drug delivery to the eye. Vision Res 50(7):680–685

Molokhia SA, Thomas SC, Garff KJ, Mandell KJ, Wirostko BM (2013) Anterior eye segment drug delivery systems: current treatments and future challenges. J Ocul Pharmacol Ther 29 (2):92–105

Monem AS, Ali FM, Ismail MW (2000) Prolonged effect of liposomes encapsulating pilocarpine HCl in normal and glaucomatous rabbits. Int J Pharm 198(1):29–38

Moosa RM, Choonara YE, du Toit LC, Kumar P, Carmichael T, Tomar LK et al (2014) A review of topically administered mini-tablets for drug delivery to the anterior segment of the eye. J Pharm Pharmacol 66(4):490–506

Muchtar S, Almog S, Torracca MT, Saettone MF, Benita S (1992) A submicron emulsion as ocular vehicle for delta-8-tetrahydrocannabinol: effect on intraocular pressure in rabbits. Ophthalmic Res 24(3):142–149

Nagarsenker MS, Londhe VY, Nadkarni GD (1999) Preparation and evaluation of liposomal formulations of tropicamide for ocular delivery. Int J Pharm 190(1):63–71

Nair KL, Vidyanand S, James J, Kumar GSV (2012) Pilocarpine-loaded poly(DLlactic-co-glycolic acid) nanoparticles as potential candidates for controlled drug delivery with enhanced ocular pharmacological response. J Appl Polym Sci 124:2030–2036

NeurotechUSA. Available from: http://www.neurotechusa.com/cntfrenexus.html

Nicoli S, Ferrari G, Quarta M, Macaluso C, Santi P (2009) In vitro transscleral iontophoresis of high molecular weight neutral compounds. Eur J Pharm Sci 36(4–5):486–492

Normand N, Valamanesh F, Savoldelli M, Mascarelli F, BenEzra D, Courtois Y et al (2005) VP22 light controlled delivery of oligonucleotides to ocular cells in vitro and in vivo. Mol Vis 11 (21):184–191

Olsen TW, Aaberg SY, Geroski DH, Edelhauser HF (1998) Human sclera: thickness and surface area. Am J Ophthalmol 125(2):237–241

Paasonen L, Laaksonen T, Johans C, Yliperttula M, Kontturi K, Urth A (2007) Gold nanoparticles enable selective light-induced contents release from liposomes. J Control Release 122 (1):86–93

Parkinson TM, Ferguson E, Febbraro S, Bakhtyari A, King M, Mundasad M (2003) Tolerance of ocular iontophoresis in healthy volunteers. J Ocul Pharmacol Ther 19(2):145–151

Pascolini D, Mariotti SP (2012) Global estimates of visual impairment: 2010. Br J Ophthalmol 96 (5):614–618

Patel SR, Berezovsky DE, McCarey BE, Zarnitsyn V, Edelhauser HF, Prausnitz MR (2012) Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. Invest Ophthalmol Vis Sci 53(8):4433–4441

Pearce W, Hsu J, Yeh S (2015) Advances in drug delivery to the posterior segment. Curr Opin Ophthalmol 26(3):233–239

Pederson J (2006) Fluid physiology of the subretinal space. In: Rayan SJ (ed) Retina, 4th edn. Elsevier Inc., Philadelphia, pp 1909–1920

Pehlivan SB, Yavuz B, Calamak S, Ulubayram K, Kaffashi A, Vural I et al (2015) Preparation and in vitro/in vivo evaluation of cyclosporin A-loaded nanodecorated ocular implants for subconjunctival application. J Pharm Sci 104(5):1709–1720

Peng CC, Burke MT, Carbia BE, Plummer C, Chauhan A (2012) Extended drug delivery by contact lenses for glaucoma therapy. J Control Release 162(1):152–158

Pepic I, Jalsenjak N, Jalsenjak I (2004) Micellar solutions of triblock copolymer surfactants with pilocarpine. Int J Pharm 272(1–2):57–64

Pepic I, Hafner A, Lovric J, Pirkic B, Filipovic-Grcic J (2010) A nonionic surfactant/chitosan micelle system in an innovative eye drop formulation. J Pharm Sci 99(10):4317–4325

Peyman GA, Schulman JA, Khoobehi B, Alkan HM, Tawakol ME, Mani H (1989) Toxicity and clearance of a combination of liposome-encapsulated ganciclovir and trifluridine. Retina 9 (3):232–236

Phan CM, Subbaraman L, Jones L (2014) Contact lenses for antifungal ocular drug delivery: a review. Expert Opin Drug Deliv 11(4):537–546

Pignatello R, Bucolo C, Ferrara P, Maltese A, Puleo A, Puglisi G (2002) Eudragit RS100 nanosuspensions for the ophthalmic controlled delivery of ibuprofen. Eur J Pharm Sci 16 (1–2):53–61

Prabhu P, Nitish KR, Koland M, Harish N, Vijayanarayan K, Dhondge G et al (2010) Preparation and evaluation of nano-vesicles of brimonidine tartrate as an ocular drug delivery system. J Young Pharm 2(4):356–361

Quintana-Hau JD, Cruz-Olmos E, Lopez-Sanchez MI, Sanchez-Castellanos V, Baiza-Duran L, Gonzalez JR et al (2005) Characterization of the novel ophthalmic drug carrier Sophisen in two of its derivatives: 3A Ofteno and Modusik-A Ofteno. Drug Dev Ind Pharm 31(3):263–269

Rafie F, Javadzadeh Y, Javadzadeh AR, Ghavidel LA, Jafari B, Moogooee M et al (2010) In vivo evaluation of novel nanoparticles containing dexamethasone for ocular drug delivery on rabbit eye. Curr Eye Res 35(12):1081–1089

Raghava S, Hammond M, Kompella UB (2004) Periocular routes for retinal drug delivery. Expert Opin Drug Deliv 1(1):99–114

Ranta VP, Mannermaa E, Lummepuro K, Subrizi A, Laukkanen A, Antopolsky M et al (2010) Barrier analysis of periocular drug delivery to the posterior segment. J Control Release 148 (1):42–48

Reimondez-Troitino S, Csaba N, Alonso MJ, de la Fuente M (2015) Nanotherapies for the treatment of ocular diseases. Eur J Pharm Biopharm 95(Pt B):279–293

Reimondez-Troitino S, Csaba N, Alonso MJ, de la Fuente M (2015b) Nanotherapies for the treatment of ocular diseases. Eur J Pharm Biopharm 95:279–293

Rodriguez-Aller M, Kaufmann B, Guillarme D, Stella C, Furrer P, Rudaz S et al (2012) In vivo characterisation of a novel water-soluble cyclosporine A prodrug for the treatment of dry eye disease. Eur J Pharm Biopharm 80(3):544–552

Rowe-Rendleman CL, Durazo SA, Kompella UB, Rittenhouse KD, Di Polo A, Weiner AL et al (2014) Drug and gene delivery to the back of the eye: from bench to bedside. Invest Ophthalmol Vis Sci 55(4):2714–2730

Ruponen M, Urtti A (2015) Undefined role of mucus as a barrier in ocular drug delivery. Eur J Pharm Biopharm 96:442–446

Saati S, Lo R, Li PY, Meng E, Varma R, Humayun MS (2010) Mini drug pump for ophthalmic use. Curr Eye Res 35(3):192–201

Sachinkumar P, Atul K, Sandip B, Shitalkumar P (2015) Formuation and evaluation of an in situ gel for ocular drug delivery of anticonjunctival drug. Cellul Chem Technol 49(1):35–40

Saha P, Yang JJ, Lee VH (1998) Existence of a p-glycoprotein drug efflux pump in cultured rabbit conjunctival epithelial cells. Invest Ophthalmol Vis Sci 39(7):1221–1226

Sanders DR, Goldstick B, Kraff C, Hutchins R, Bernstein MS, Evans MA (1983) Aqueous penetration of oral and topical indomethacin in humans. Arch Ophthalmol 101(10):1614–1616

Santipharp P, Laman LA (2008) Ophthalmic nanoparticulate formulation of a cyclooxygenase-2 selective inhibitor. Patent US20080145430 A1

Schoenwald RD (1990) Ocular drug delivery. Pharmacokinetic considerations. Clin Pharmacokinet 18(4):255–269

Sedlacek J (1965) Possibility of the application of ophthalmic drugs with the use of gel contact lenses. Cesk Oftalmol 21(6):509–512

Shell JW (1985) Ophthalmic drug delivery systems. Drug Dev Res 6(3):245–261

Shen Y, Tu J (2007) Preparation and ocular pharmacokinetics of ganciclovir liposomes. AAPS J 9 (3):E371–E377

Shen J, Deng Y, Jin X, Ping Q, Su Z, Li L (2010) Thiolated nanostructured lipid carriers as a potential ocular drug delivery system for cyclosporine A: improving in vivo ocular distribution. Int J Pharm 402(1–2):248–253

Shen J, Gan L, Zhu C, Zhang X, Dong Y, Jiang M et al (2011) Novel NSAIDs ophthalmic formulation: flurbiprofen axetil emulsion with low irritancy and improved anti-inflammation effect. Int J Pharm 412(1-2):115–122

Shukla A, Fuller RC, Hammond PT (2011) Design of multi-drug release coatings targeting infection and inflammation. J Control Release 155(2):159–166

Sigurdsson HH, Kirch J, Lehr CM (2013) Mucus as a barrier to lipophilic drugs. Int J Pharm 453 (1):56–64

Sjoquist B, Stjernschantz J (2002) Ocular and systemic pharmacokinetics of latanoprost in humans. Surv Ophthalmol 47(Suppl 1):S6–S12

Spataro G, Malecaze F, Turrin CO, Soler V, Duhayon C, Elena PP et al (2010) Designing dendrimers for ocular drug delivery. Eur J Med Chem 45(1):326–334

Spraul CW, Lang GE, Grossniklaus HE, Lang GK (1999) Histologic and morphometric analysis of the choroid, Bruch's membrane, and retinal pigment epithelium in postmortem eyes with age-related macular degeneration and histologic examination of surgically excised choroidal neovascular membranes. Surv Ophthalmol 44(Suppl 1):S10–S32

Steuer H, Jaworski A, Elger B, Kaussmann M, Keldenich J, Schneider H et al (2005) Functional characterization and comparison of the outer blood-retina barrier and the blood-brain barrier. Invest Ophthalmol Vis Sci 46(3):1047–1053

Stratford RE Jr, Lee VH (1985) Ocular aminopeptidase activity and distribution in the albino rabbit. Curr Eye Res 4(9):995–999

Sznitowska M, Zurowska-Pryczkowska K, Janicki S, Jarvinen T (1999) Miotic effect and irritation potential of pilocarpine prodrug incorporated into a submicron emulsion vehicle. Int J Pharm 184(1):115–120

Taban M, Chen B, Perry JD (2006) Update on punctal plugs. Compr Ophthalmol Updat 7 (5):205–212, discussion 213–214

Talluri RS, Katragadda S, Pal D, Mitra AK (2006) Mechanism of L-ascorbic acid uptake by rabbit corneal epithelial cells: evidence for the involvement of sodium-dependent vitamin C transporter 2. Curr Eye Res 31(6):481–489

Thrimawithana TR, Young S, Bunt CR, Green C, Alany RG (2011) Drug delivery to the posterior segment of the eye. Drug Discov Today 16(5-6):270–277

Ticho U, Blumenthal M, Zonis S, Gal A, Blank I, Mazor ZW (1979) A clinical trial with Piloplex--a new long-acting pilocarpine compound: preliminary report. Ann Ophthalmol 11(4):555–561

Tirucherai GS, Dias C, Mitra AK (2002) Corneal permeation of ganciclovir: mechanism of ganciclovir permeation enhancement by acyl ester prodrug design. J Ocul Pharmacol Ther 18(6):535–548

Tong YC, Chang SF, Liu CY, Kao WW, Huang CH, Liaw J (2007) Eye drop delivery of nano-polymeric micelle formulated genes with cornea-specific promoters. J Gene Med 9(11):956–966

Trivedi R, Kompella UB (2010) Nanomicellar formulations for sustained drug delivery: strategies and underlying principles. Nanomedicine (Lond) 5(3):485–505

Trivedi R, Redente EF, Thakur A, Riches DW, Kompella UB (2012) Local delivery of biodegradable pirfenidone nanoparticles ameliorates bleomycin-induced pulmonary fibrosis in mice. Nanotechnology 23(50):505101

Tyagi P, Barros M, Stansbury JW, Kompella UB (2013) Light-activated, in situ forming gel for sustained suprachoroidal delivery of bevacizumab. Mol Pharm 10(8):2858–2867

Vadlapudi AD, Vadlapatla RK, Kwatra D, Earla R, Samanta SK, Pal D et al (2012a) Targeted lipid based drug conjugates: a novel strategy for drug delivery. Int J Pharm 434(1-2):315–324

Vadlapudi AD, Vadlapatla RK, Mitra AK (2012b) Current and emerging antivirals for the treatment of cytomegalovirus (CMV) retinitis: an update on recent patents. Recent Pat Antiinfect Drug Discov 7(1):8–18

Vadlapudi AD, Cholkar K, Vadlapatla RK, Mitra AK (2014) Aqueous nanomicellar formulation for topical delivery of biotinylated lipid prodrug of acyclovir: formulation development and ocular biocompatibility. J Ocul Pharmacol Ther 30(1):49–58

Valls R, Vega E, Garcia ML, Egea MA, Valls JO (2008) Transcorneal permeation in a corneal device of non-steroidal anti-inflammatory drugs in drug delivery systems. Open Med Chem J 2:66–71

Vandamme TF, Brobeck L (2005) Poly(amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. J Control Release 102(1):23–38

Vega E, Egea MA, Valls O, Espina M, Garcia ML (2006) Flurbiprofen loaded biodegradable nanoparticles for ophthalmic administration. J Pharm Sci 95(11):2393–2405

Vinogradov SV, Batrakova EV, Kabanov AV (2004) Nanogels for oligonucleotide delivery to the brain. Bioconjug Chem 15(1):50–60

Vooturi SK, Kadam RS, Kompella UB (2012) Transporter targeted gatifloxacin prodrugs: synthesis, permeability, and topical ocular delivery. Mol Pharm 9(11):3136–3146

Wadhwa S, Paliwal R, Paliwal SR, Vyas SP (2010) Hyaluronic acid modified chitosan nanoparticles for effective management of glaucoma: development, characterization, and evaluation. J Drug Target 18(4):292–302

Wong VG (1989) Biodegradable ocular implants. Google Patents

Wu J, Zhang JJ, Koppel H, Jacob TJ (1996) P-glycoprotein regulates a volume-activated chloride current in bovine non-pigmented ciliary epithelial cells. J Physiol 491(Pt 3):743–755

Xiang CD, Batugo M, Gale DC, Zhang T, Ye J, Li C et al (2009) Characterization of human corneal epithelial cell model as a surrogate for corneal permeability assessment: metabolism and transport. Drug Metab Dispos 37(5):992–998

Xu X, Weng YH, Xu L, Chen H (2013) Sustained release of avastin (R) from polysaccharides cross-linked hydrogels for ocular drug delivery. Int J Biol Macromol 60:272–276

Yavuz B, Pehlivan SB, Vural I, Unlu N (2015) In vitro/in vivo evaluation of Dexamethasone--PAMAM dendrimer complexes for retinal drug delivery. J Pharm Sci 104(11):3814–3823

Yellepeddi VK, Sheshala R, McMillan H, Gujral C, Jones D, Raghu Raj Singh T (2015) Punctal plug: a medical device to treat dry eye syndrome and for sustained drug delivery to the eye. Drug Discov Today 20(7):884–889

Yenice I, Mocan MC, Palaska E, Bochot A, Bilensoy E, Vural I et al (2008) Hyaluronic acid coated poly-epsilon-caprolactone nanospheres deliver high concentrations of cyclosporine A into the cornea. Exp Eye Res 87(3):162–167

Yu J, Xu X, Yao FL, Luo ZC, Jin L, Xie BB et al (2014) In situ covalently cross-linked PEG hydrogel for ocular drug delivery applications. Int J Pharm 470(1–2):151–157

Yuan XB, Yuan YB, Jiang W, Liu J, Tian EJ, Shun HM et al (2008) Preparation of rapamycin-loaded chitosan/PLA nanoparticles for immunosuppression in corneal transplantation. Int J Pharm 349(1–2):241–248

Zhang T, Xiang CD, Gale D, Carreiro S, Wu EY, Zhang EY (2008) Drug transporter and cytochrome P450 mRNA expression in human ocular barriers: implications for ocular drug disposition. Drug Metab Dispos 36(7):1300–1307