Challenges and solutions in topical ocular drug-delivery systems

Maryam Ali and Mark Edward Byrne[†]

Vision significantly affects quality of life and the treatment of ocular disease poses a number of unique challenges. This review presents the major challenges faced during topical ocular drug administration and highlights strategies used to overcome the natural transport barriers of the eye. The circulation of tear fluid and aqueous humor decrease the residence time of topically delivered drugs, while ocular barriers in the corneal and conjuctival epithelia and the retinal pigment epithelium limit transport. Successful treatment strategies increase the residence time of drugs in the eye and/or enhance the ability of the drug to penetrate the ocular barriers and reach the target tissue. In this review, we discuss several drug-delivery strategies that have achieved clinical success or demonstrate high potential. We also draw attention to a number of excellent reviews that explore various ocular drug-delivery techniques in depth. Finally, we highlight cutting-edge drug-delivery technologies that improve the efficacy of current drug-delivery methods or use proven techniques to deliver novel therapeutics.

Expert Rev. Clin. Pharmacol. 1(1), 145–161 (2008)

CONTENTS

Ocular diseases & impact

Barriers to ocular drug delivery

Strategies to overcome drug removal at the ocular surface

Strategies for permeation enhancement through ocular membranes

Strategies to delivery drugs to the posterior of the eye

Expert commentary

Five-year view

Key issues

Financial & competing interests disclosure

References

Affiliations

[†]*Author for correspondence*
Auburn University, Biomimetic & Biohybrid Materials, Biomedical Devices, and Drug Delivery Laboratories, Department of Chemical Engineering, Auburn, AL 36849, USA
Tel.: +1 334 844 2862
Fax: +1 334 844 2063
byrneme@eng.auburn.edu

KEYWORDS:
drug delivery, extended drug delivery, noninvasive, ocular bioavailability, ophthalmic, permeation enhancer, residence time, topical delivery

Recent advances in genetics, neuroscience and molecular biology are leading to unprecedented discovery of mechanisms underlying ocular disease and new therapeutics for treatments that increase quality of life [1]. Equally important is the optimal delivery of therapeutics, which has been the subject of intense R&D that is continually pushing the boundaries currently delineated by traditional topical formulations. Topical formulations, such as solutions and suspensions in the form of eye drops, have been in use for centuries [2] and are still the most common treatment approach currently used [3].

Effective drug administration rests on delivering a sufficient amount or concentration of drug to the site of action within a given time period. For the eye, the majority of drugs are administered topically and the remaining are administered in a systemic manner. For anterior or front-of-eye therapy, the majority of treatments require noninvasive, topically applied drugs. For posterior or back-of-eye therapy, drugs are typically administered via systemic routes and also by intravitreal injection [4]. All of these treatments have their own limitations, which primarily involve the body's natural mechanisms and barriers that impede the transport of molecules. However, it should be distinctly understood that quality of vision, being crucial to our evolutionary survival, translates to the eye performing an excellent job in preventing foreign materials from crossing its barriers. Therefore, any drug-delivery mechanism we use needs to effectively deliver medication without permanently weakening these protective barriers.

The rates at which drugs pass through or interact with the different ocular barriers is of significant interest to the field of ocular drug administration. Systemic delivery of drugs to the eye is impeded by the blood–ocular barriers, which prevent transport from the blood to the eye interior [5]. These barriers, along with liver metabolism, significantly limit the bioavailability of orally or intravenously administered drugs. Drugs delivered topically to the ocular surface also face reduced drug transport, which is influenced by lacrimation and tear turnover, nasolacrimal drainage, spillage from the eye, metabolic degradation and nonproductive adsorption/absorption. These protective mechanisms lead to poor drug absorption on the surface of the eye, despite it being a

10.1586/17512433.1.1.145

ISSN 1751-2433

very accessible organ to treat topically. As a result, ocular bioavailability of drugs applied topically to the eye is typically very poor, with less than 1–7% of the applied drug being absorbed and the rest entering the systemic circulation [6,7].

From a clinical perspective, the challenge is to provide medication conveniently, noninvasively and in therapeutically significant concentrations for long periods of time with minimal transfer of drug to the systemic circulation – providing topical, targeted therapy to the eye. This can be best achieved by extending the residence time or duration of drugs on the surface of the eye and/or by increasing drug transport through ocular barriers, such as the cornea, sclera and conjunctiva. The concentration of drug reaching the desired site of action can be significantly improved by altering the kinetics of drug administration, removal and/or absorption. Therefore, this review focuses on an overview of topical administration challenges and strategies, and presents a number of excellent technologies and papers in the field. We also direct the reader to a number of ocular administration and delivery review articles, book chapters, as well as ocular pharmacokinetics texts [3,6–12].

Ocular diseases & impact

The USA prescription ophthalmic drug market is valued at approximately US$4.5 billion and is growing annually at an average of 7% [13]. This is due to a number of factors, such as an increase in the overall aging population and subsequent eye issues encountered, an increase in the incidence of disease and required disease prevention due to an increase in surgical procedures and contact lens use, and an increase in the number of medicines prescribed since optometrists in most US states can now directly prescribe most medications [301].

Highly debilitating diseases, such as cataracts, retinal degenerative maladies (e.g., macular degeneration and retinitis pigmentosa), diabetic retinopathy, glaucoma and uveitis, affect a large number of the population and have significant economic impact [14]. While the aforementioned diseases can lead to partial and complete blindness, other diseases, such as dry eye, bacterial conjunctivitis, ocular allergy and ocular inflammation, do not typically lead to complete loss of vision, but significantly affect quality of life for a larger number of people and also have a considerable economic impact. Posterior drug candidates with a smaller target market have primarily been the work of specialty pharmaceutical companies with subsequent licensing, codevelopment and manufacturing from large pharmaceutical companies. In certain respects, many reports highlight that this has led to a lack of ocular drug therapies, especially for posterior eye disease [302]. TABLE 1 outlines the major diseases of the eye, the proportion of the US population affected, as well as the treatment location within the eye.

Barriers to ocular drug delivery

The eye is pharmacokinetically isolated from the rest of the anatomy and the site of drug action ultimately determines the strategy for successful topical delivery. Tear drainage and, to some extent,

Table 1. Major diseases of the eye.

Disease	General ocular location affected	Potential to severely limit vision/blindness	Number of USA population affected (% of population*) and/or 2007 ocular market financials
Refractive error	Anterior	High	75 million (25% of general population)
Cataracts	Anterior	High	20.5 million (54% of people aged over 65 years)
Dry or wet age-related macular degeneration	Posterior	High	1.7 million people aged over 50 years‡
Retinal degenerative disease or retinitis pigmentosa	Posterior	High	5.3 million (2.5% of people aged 18 years and older)
Diabetic macular edema	Posterior	High	500,000
Diabetic retinopathy	Posterior	High	4.1 million
Glaucoma	Anterior	High	2.2 million (2% of people aged 40 years and older)
Uveitis	Anterior/posterior	High	346,000
Dry eye	Anterior	Low	50 million (15% of general population)
Infection or risk of infection§	Anterior	Moderate	US$740 million
Allergy	Anterior	Low	75 million (25% of general population); US$630 million
Inflammation§	Anterior	Moderate	US$500 million

*Assuming a USA population of approximately 301 million (July 2007 estimate).
‡Only cases of late age-related macular degeneration are included.
§For infection and inflammation, which are prescribed after surgery (e.g., cataract and laser-assisted *in situ* keratomileusis) and for prophylactic measures, financial estimates for the ocular drug market in each sector for the year 2007 are presented [13].
Data compiled from [1,13,15,109,303].

the absorption through the eyelids lead to less drug on the surface of the eye available to transport through ocular barriers, such as the cornea, conjunctiva and sclera. The cornea is a transparent, dome-shaped structure covering the front of the eye. It is contiguous with the conjunctiva, a delicate mucous membrane with a highly vascularized stroma that covers the sclera (the tough, opaque, white of the eye) and lines the inner surface of the eyelids.

The human eye surface holds a tear volume that ranges from 7.0 to 30.0 µl, with a tear turnover rate of 0.5–2.2 µl/min [6,15]. This translates to a therapeutically relevant drug residence time of under 5 min with complete exchange of tear volume in approximately 14 min, assuming normal lacrimation and blinking rates since blinking aids in contaminant removal and promotes a well-mixed tear fluid. If the topical medication or the mechanical forces of the instilled drop irritate the eye, lacrimal secretion will increase and further dilute the dosage.

The ocular tear system and the tear film play a crucial role in maintaining an optically clear surface in the front of the eye. The bulk of the tear fluid is a 6–7-µm thick aqueous layer with dissolved oxygen, nutrients and proteins [16]. The interface between this layer and the air comprises a 0.1-µm thick layer of lipids that limits evaporative loss of the aqueous film [17]. Between the aqueous layer and the ocular epithelia (which are hydrophobic) exists a layer of hydrophilic mucins that maintains the integrity of the surface by trapping and removing foreign matter and lubricate against the shearing force applied by blinking [18]. The movement of fluid in the eye depends on the flow of the aqueous phase, which is secreted by the lacrimal glands above the eye, spread over the eye surface through surface tension and blinking, and drains out of the eye through the lacrimal puncta with the aid of a pumping mechanism [19]. Up to 95% of topically applied drug can be washed away from the eye surface within minutes [11].

The rate-determining barriers for transport through the cornea to the aqueous humor are the corneal epithelium, the stroma and the endothelium. FIGURE 1 presents ocular anatomy and highlights the transport of drugs through the ocular surface. When a drug reaches the corneal or conjunctival epithelium, it must find a path through the layers of cells. For a drug to take a transcellular path (i.e., through the cells), it needs to enter the cell either by facilitated transport or by diffusion through the lipid bilayer. The former requires particular chemical interactions with transporters native to the cells, while the latter requires lipophilicity and depends on the drug solubility, degree of ionization and size, and on the cell membrane thickness. Both depend on the drug concentration gradient and the effective area. Lipophilic drugs can transport quickly through the transcellular pathway but hydrophilic drugs, especially those larger than 20,000 Da, have difficulty [20]. The paracellular path (i.e., around the cells) is impeded by the presence of tight junctions. Stromal transport is approximately equivalent for all ocular drugs and relatively independent of drug partitioning, and the endothelium is only one cell layer in thickness with transport depending on partitioning behavior as in the epithelium. We refer the reader to an excellent review that compiles ocular tissue permeability measurements [21].

Hydrophilic drugs have been demonstrated to transport through the outer layers of the conjunctiva more quickly than through the corneal epithelium. After conjunctival absorption, transport may include lateral diffusion into the corneal stroma and, to a limited extent, arterial vessel uptake [22]. The drug may also be secreted back to the surface via efflux proteins in the epithelia [5,20].

After passing through the ocular surface barriers, the drug reaches the anterior segment between the cornea and the lens (FIGURE 2). Typically, 3% of the instilled drug reaches this point [6]. The aqueous humor is a clear filtrate of blood that is produced by the ciliary body, circulates through the anterior chamber at approximately 1% per minute [23] and drains out via the trebecular meshwork. It delivers nutrients and antioxidants to the cornea and lens without interfering with visual clarity. The aqueous humor poses an additional impediment to topical drugs targeting the posterior of the eye. Any drug that diffuses through the cornea will be at risk of dilution and flushing away via the aqueous humor. By this point, drugs delivered via the corneal route can bediluted to the point of inefficacy, even before moving into the posterior segment. FIGURE 2 demonstrates the movement of aqueous humor through the anterior segment.

Drug that reaches the sclera has another pathway at its disposal: it may diffuse laterally through the highly permeable sclera and reach the posterior segment of the eye [24]. FIGURE 3 shows the transport of drugs through the posterior segment. The tissues here support the retina and encase the vitreous humor, a highly viscous fluid. Inside the sclera is a layer of vascularized tissue known as the choroid and inside that is the retina, the tissue on which light falls to produce images. The retina consists of several layers of tissue that, relating to their importance to drug delivery, can be classified as neural tissue and the retinal pigmented epithelium (RPE). The choroid nourishes the outermost layers of the retina, including the outer third of the neural tissue and the RPE. Bruch's membrane is the innermost layer of the choroid. It also provides the basement membrane of the RPE. The RPE is a significant barrier to the transport of drug from the sclera (or systemically delivered drugs from the choroid) into the neural tissue and the vitreous humor. Another barrier is the endothelial cells of the retinal capillaries that are located among the retinal neural tissue. They prevent drugs from the circulatory system reaching the neural retina. The RPE and endothelial cells also bear efflux proteins that actively remove drugs from the retina. Together, the RPE and retinal endothelial cells form the blood–retinal barrier [5,25].

The common alternatives to reach the posterior segment involve injecting the drug or inserting a drug-delivery device into the vitreal cavity of the eye, or using a periocular route of delivery – applying the drug, carrier or device within the eye surface barriers and relying on trans-scleral transport. Noninvasive methods are generally preferred because of the relative lack of patient discomfort and surgical complications, such as endophthalmitis, hemorrhage, retinal detachment and cataracts [8].

In addition to the ocular barriers, ocular tissues contain metabolic enzymes to break down xenobiotics that manage to penetrate into the tissue. Thus, any drugs that reach the

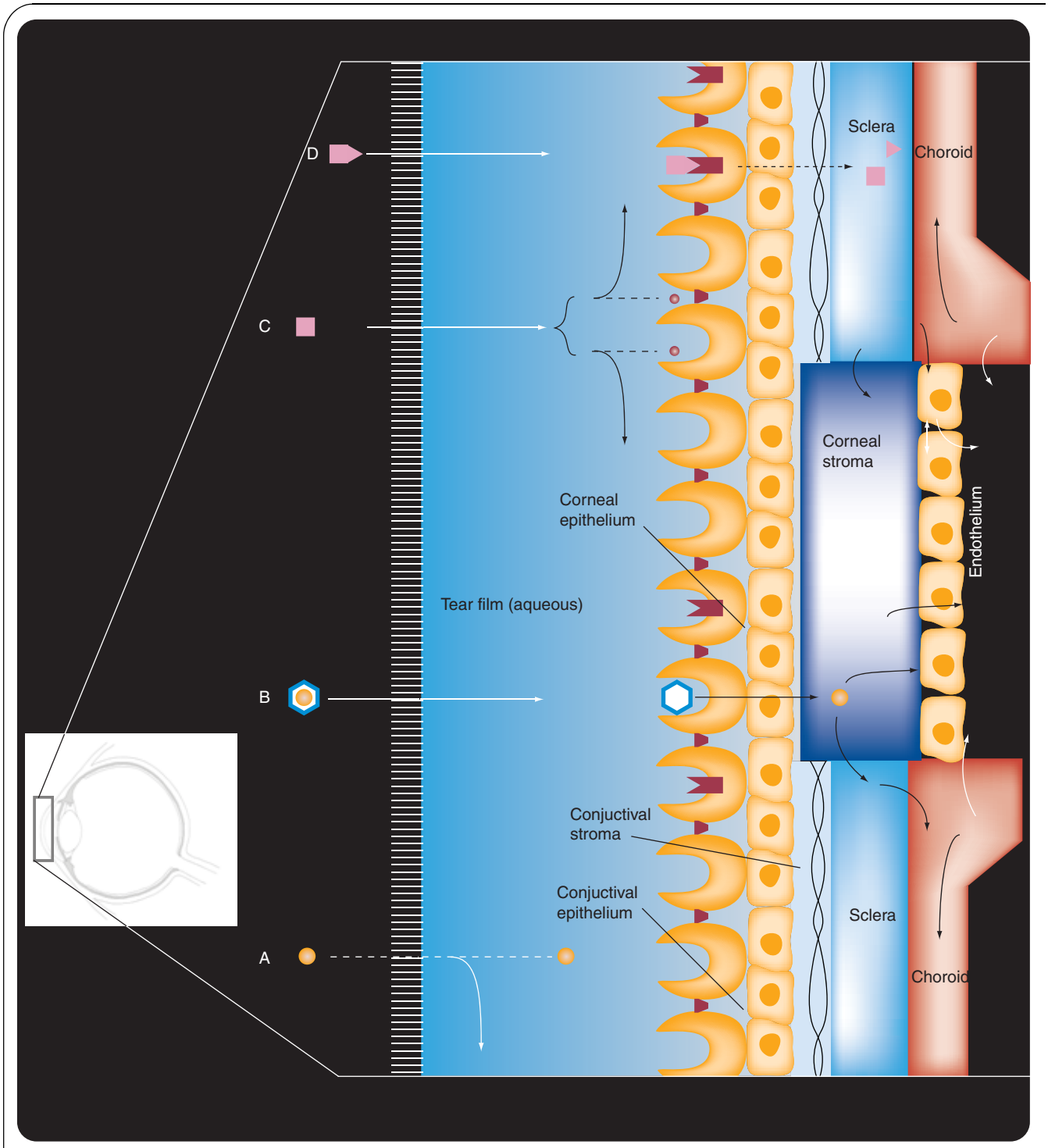

Figure 1. Transport of drugs through the ocular surface. (A) A lipophilic drug that cannot easily penetrate the tear film is washed away. (B) A lipophilic drug in the central cavity of a cyclodextrin molecule. The cyclodextrin solubilizes in the tear film and reaches the ocular epithelium. The lipophilic drug partitions out of the cyclodextrin and into the lipid membrane of the epithelium. (C) A hydrophilic drug that solubilizes in the tear film and reaches the epithelium; it cannot cross the epithelium transcellularly (because of the lipid membrane) or paracellularly (because of tight junctions) and eventually washes away from the eye surface. (D) A hydrophilic prodrug that penetrates the epithelium transcellularly with the aid of a membrane transporter. Once in the ocular tissue, it is converted into the drug by enzymes. The corneal and conjunctival epithelia are contiguous and contain several layers of cells (not shown), the outermost layer features microvilli that interact with tear film mucins. Drugs that penetrate the epithelia can move easily between ocular tissues, such as the corneal and conjunctival stroma, the sclera beneath the conjunctiva, the vascularized choroid and the leaky endothelium. From there, they can diffuse into the anterior chamber or laterally through the sclera to the eye posterior.

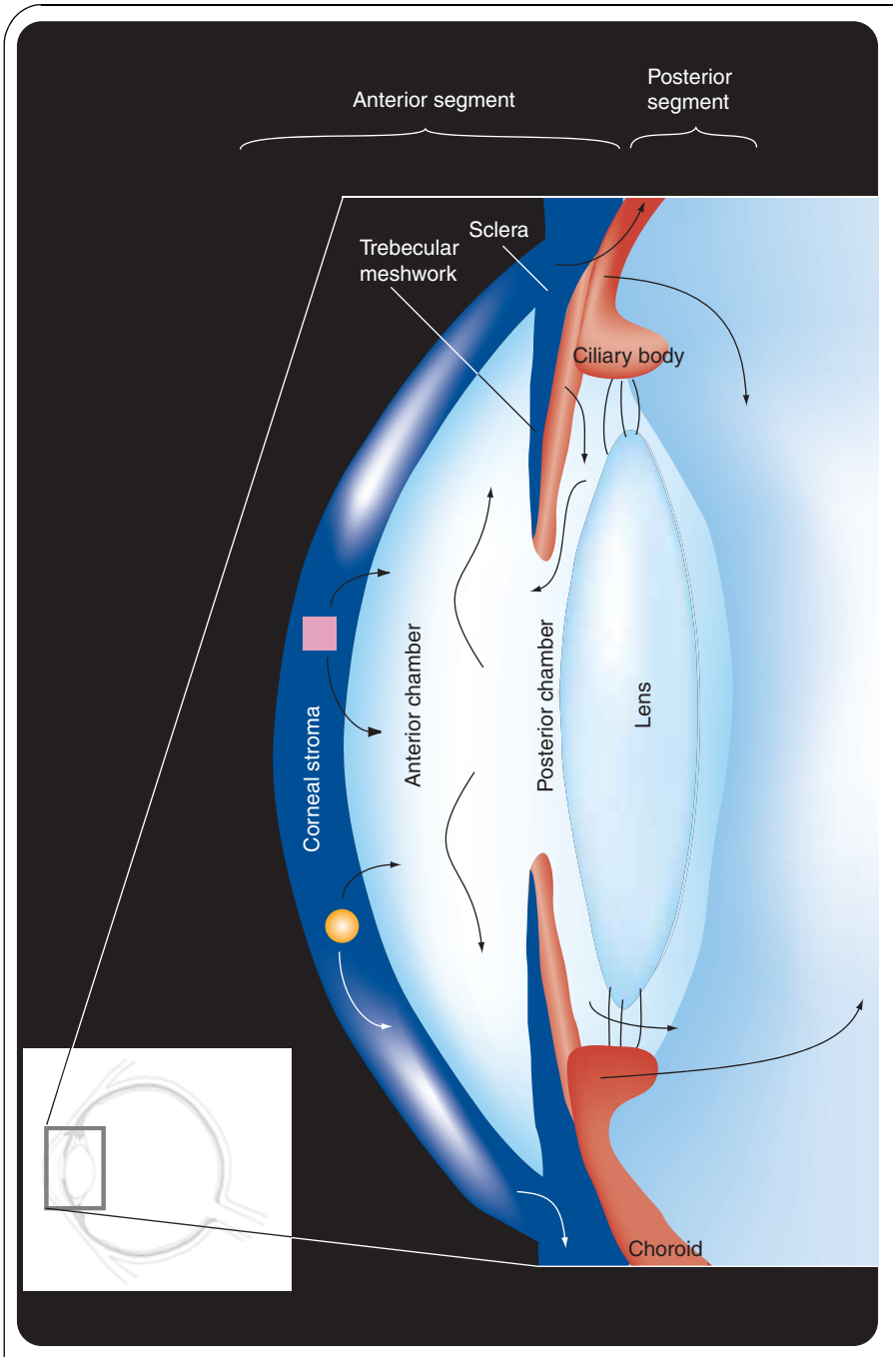

Figure 2. Transport of drugs through the anterior segment. Hydrophilic and lipophilic drugs pass from the permeable stroma and sclera into the anterior segment, the choroid and the posterior segment. They also penetrate into the ciliary body, transfer to the secreted aqueous humor and circulate around the anterior and posterior chamber before draining away through the trebecular meshwork.

interior of the eye are further depleted by the action of enzymes, including, among others, esterases, aldehyde and ketone reductases [26].

Strategies to overcome drug removal at the ocular surface

The most common method for delivering drugs to the eye is through eye-drop solutions administered to the eye surface. They are relatively simple to apply and are noninvasive, and most solutions are easy to prepare, with low manufacturing costs. There are over 100 topical eye-drop formulations on the market today.

Patient compliance remains one of the biggest drawbacks of topical drop administration, with evidence suggesting a large percentage of patients with significant periods of ineffective drug concentration levels. The volume of instilled dose is also highly variable from application to application, which depends on the squeeze or pressure force, the angle of administration and the ability to resist blinking [27]. These issues compound quick drug loss along with tear flow rate, which washes the instilled dose from the eye within approximately 14 min. Also, the tear drainage rate has been show to linearly increase with instilled volume [6,8]. FIGURE 4 highlights these effects on the concentration profile of topically instilled drug in the eye

Eye-drop formulations typically contain preservatives to prevent pathogenic contamination, guarantee sterility and, in some cases, stabilize the drug. Most multiple-use drops last for approximately 1 month and the longer the duration of use, the higher the probability for contamination. Preservatives can be toxic to ocular tissue and providers attempt to optimize the contamination protection:toxicity ratio. In certain cases, preservatives have been shown to have ancillary benefits with antibiotic medications [28], as well as in other formulations acting as permeation enhancers [29]. In preservative-free, single-use containers, the risk for contamination is great and good manufacturing practices must be assured. Typically, preservative-free formulations are single-dose containers suited for patients with allergies or those with significant surgical concerns where preservative toxicity may interfere with healing.

The physiochemical properties of drugs, such as hydrophilicity/lipophilicity, degree of ionization, shape and size, affect their ability to transport through ocular barriers. Typically, lipophilic drug properties increase the speed of the molecule through cell membranes, an increased degree of ionization of the drug decreases lipid solubility and subsequent membrane transport, and decreased drug radius or particle size increases transport.

While hydrophilic drugs are formulated in solutions, lipophilic drugs are formulated in suspensions, which typically require resuspension prior to use. Suspensions have a much

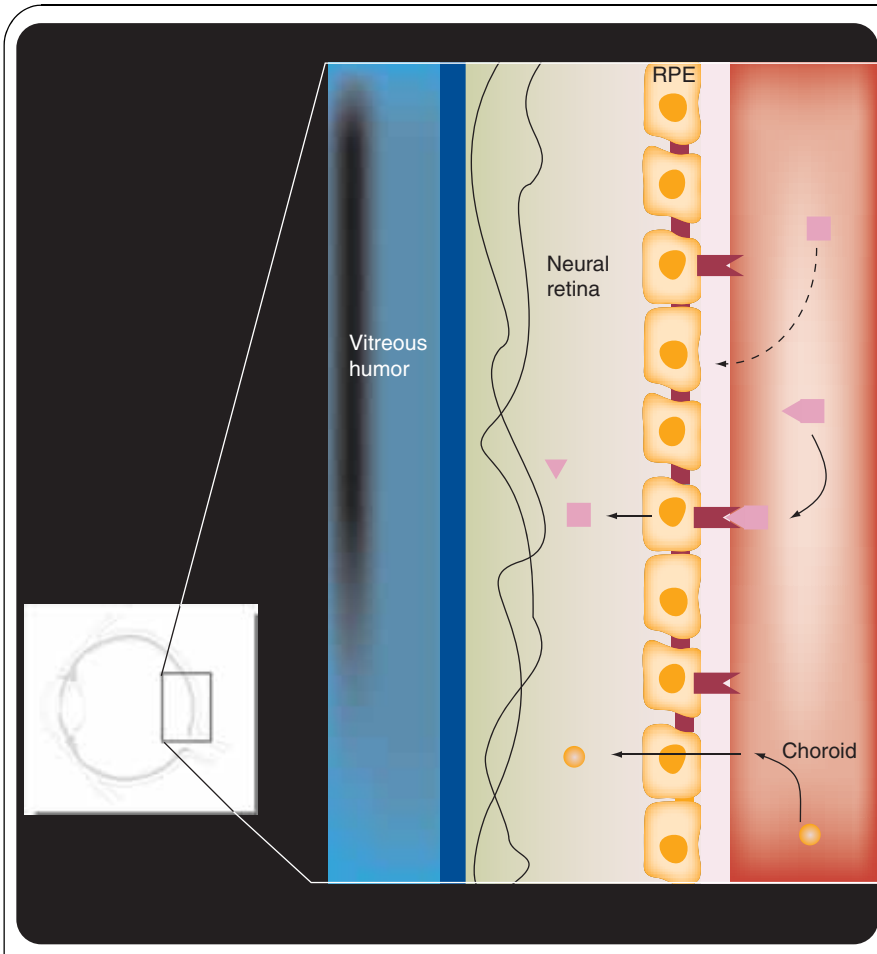

Figure 3. Transport of drugs through the posterior segment. Topically delivered drugs diffuse through the sclera and systemically delivered drugs diffuse from the choroid vasculature in the posterior segment of the eye. The outermost layer of the retina is known as the RPE, a layer of tight-junctioned cells that prevents drugs from penetrating into the retina. Small lipophilic drugs penetrate the lipid membrane easily but large hydrophilic drugs require assistance either from permeation enhancers or transporters. When the drug reaches the neural retina, it acts upon the target cells. The retinal vasculature is lined with endothelial cells bound by tight junctions to prevent blood-borne drugs and pathogens from reaching the neural retina. Together, the retinal vascular endothelium and the RPE form the blood–retinal barrier.
RPE: Retinal pigmented epithelium.

lower market share compared with solutions and face additional hurdles, such as drug precipitation and resuspension, as well as particle size and polydispersity issues, which can limit the amount of drug applied to the eye or the transport through ocular barriers.

In recent years, smaller sized particles within topical formulations have been studied for their ability to increase transport. These systems will be presented in this section since they have also been hypothesized to increase residence time. Micro- or nanoemulsions are highly stable systems containing hydrophobic organic phases, often in droplet form, dispersed within an aqueous continuous phase with amphiphilic interfacial films [30,31]. The dispersed phase contains lipophilic drug and the aqueous phase enables the microemulsion to effectively mix with tear fluid. By contrast, a lipophilic formulation would wash out of the eye rapidly without reaching the epithelial tissue. Additionally, it is theorized that the lipophilic droplets adhere to the epithelium and increase their residence time [32,33]. Particle sizes should be under 10 µm in diameter for maximum comfort [34]. Also, it has been reported that submicron emulsions decease the susceptibility of drug to degradation [35].

Liposomes are microscopic vesicles made of concentric phospholipid bilayers with alternating lipophilic and aqueous compartments. Based on their structure, they can be categorized as small unilamellar vesicles, large unilamellar vesicles and large multilamellar vesicles. The cavities within the liposomes, lined by the polar 'heads' of the phospholipids, can carry hydrophilic drugs. Lipophilic drugs can be solubilized within the bilayer among the hydrophobic 'tails'. The hydrophilic outer surface allows effective dispersion in the tear film. Liposomes also protect the drug from enzymatic degradation and may have an increased residence time by binding to the epithelium [36,37].

Nanosuspensions or colloidal suspensions are submicron colloidal dispersions of pure drug particles stabilized by surfactants, and have been used in order to increase the solubility of poorly soluble drugs and increase dissolution rates via increased surface area [38]. Recent work highlights nanosuspensions of glucocorticoid drugs in comparison to solutions and microcrystalline suspensions. In a rabbit model, nanosuspensions exhibited higher intensity of glucocorticoid action and a higher extent of absorption with the viscosity of the nanosuspension playing an important role in increasing duration of action [39].

Nano- and microspheres are submicron- and micron-sized solid particles containing drug dispersed within a polymer. The spheres are suspended in an aqueous solution to form eye drops. In one study, biodegradable poly(lactide-co-glycolide) (PLGA) microsphere carriers for vancomycin were dispersed in the topical formulation. *In vivo* results in rabbits measuring the aqueous humor concentration indicated a twofold increase in bioavailability over eye drops. Interestingly enough, increasing the viscosity of the formulation by adding hydroxypropyl methylcellulose did not increase bioavailability [40]. PLGA microspheres have also been used as carriers for gene delivery, for *in vitro* studies with human RPE cells and for *in vivo* studies with rats. In the latter, gene expression was observed in the RPE within 4–7 days [41]. Ganciclovir was loaded into albumin protein nanoparticles for intravitreal injection, and no autoimmune response was noted [42].

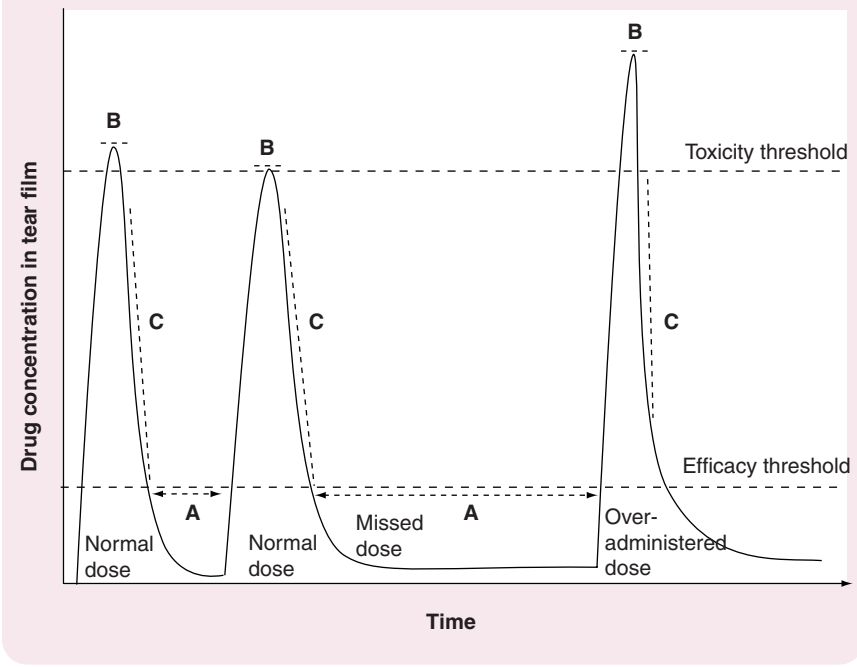

Figure 4. Hypothetical plot of drug concentration from an eye drop in the ocular tear film over time. The concentration of drug delivered by eye drop to the tear film varies with time. When a drop is placed in the eye, the concentration spikes to its maximum level. The concentration eventually decreases as lacrimation, drainage and (to a lesser degree) absorption deplete the drug. The concentration drops below the level considered therapeutic before the next dose is applied. (A) If a dose is missed, the eye tissues spend excessive time without therapeutic levels of drug. (B) The maximum drug concentration in the eye from one application to another varies owing to factors such as squeeze force on dropper and angle of dropper position. Patients may also accidentally overadminister the drug. These variations in application can push the tear concentration to toxic levels. (C) An excessive volume of drug solution can increase the spillage and drainage from the eye (it is well documented that the drainage rate increases linearly with instilled volume).

To overcome low drug bioavailability, topical formulations have remained marginally effective to a large extent by the administration of small volumes of very high concentrations of drug multiple times on a daily basis. Thus, many formulations attempt to deliver more drug and increase the driving force of the flux by delivering highly concentrated drug. This produces only a minor improvement and can lead to toxic side effects if improperly managed. Various improved methods have focused on increasing the residence time the drug spends on the surface of the eye before it is washed away by normal protective mechanisms.

Viscosity enhancers, such as methylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose, polyvinylalcohol and polyvinylpyrrolidone, have been added to topical formulations to retain the drug on the eye surface for longer periods of time by increasing the viscosity of the tear fluid and decreasing the tear drainage rate. These types of formulations are typically rated more comfortable compared with less viscous or saline-based solutions and act as wetting agents, lowering surface tension and increasing tear break-up time. Polysaccharides, such as chitosan, that are mucoadhesive with the negatively charged mucin layer, have also been used, increasing corneal residence time threefold [43]. A considerable increase in viscosity leads to ointments that invoke the smallest rate of drug loss but significantly interfere with vision. They are also difficult to apply and can be quite noncosmetic. Thus, ointments are used to a much smaller extent than solutions and are typically used at night.

Mucoadhesive polymers interact with the mucin layer of the tear film and adhere to the ocular surface. Hyaluronan and other polymers have been used in this context but their weak interactions prevent true mucoadhesive behavior. A novel set of polymers known as thiomers are synthesized by modifying polymers with thiol moieties [44]. Through disulfide linkages with the native mucins of the epithelium, they become covalently anchored to the ocular surface. Mucoadhesive polymers can be applied directly to the eye as a drug vehicle, or they can be used to attach inserts to the eye. A thiolated polyacrylate insert has been shown to deliver fluorescein for 8 h [45]. *In situ* gels and mucoadhesive polymers have both been designed to incorporate microspheres and liposomes for extended release. Timolol maleate encapsulated in chitosan was compared with timolol gel in rabbit eyes and demonstrated similar ability to lower the intraocular pressure at half the drug concentration [46]. We direct the reader to the following mucoadhesive reviews [47,48].

In situ gel-forming systems are liquid for ease of application, but undergo phase transitions and acquire a gel-like consistency when they encounter the physiological environment of the eye. They are mixed with the desired drug and instilled into the culde-sac (i.e., the pocket underneath the lower eye lid), where they gel into a substance that withstands removal by tear circulation without interfering with vision. Currently, they can deliver a fairly uniform dosage over the course of approximately 6 h [49].

Gellation can be triggered by a change in pH (e.g., Carbopol® with methylcellulose [50]), by the presence of mono- or divalent ions (Gelrite®, a gellan-gum polysaccharide [51,52]) and by a change in temperature (e.g., Pluronic® F127 with Pluronic® F68 [53], poly[*N*-isopropylacrylamide] and chitosan [54]). Research has focused on combinations of the aforementioned triggering mechanisms to decrease liquid viscosities, to optimize the phase transition and gain better control over gellation times, to extend drug release and to decrease the proportion of polymer needed in a dosage [55,56]. We direct the readers elsewhere [57–59].

Recently, soft hydrogel contact lenses have been demonstrated as extended drug-delivery carriers for the eye. New methodologies, greater understanding of polymeric structural properties and network formation have produced a number of developments that are considerably different from past efforts that involved taking a conventional lens and soaking it within a concentrated drug solution. Delivering medications via contact lenses has been a prevailing notion since the inception of using hydrophilic, crosslinked polymer gels on the surface of the eye. In fact, the first patent in the field from Otto Wichterle in 1965 states that "medicinally active substances such as antibiotics may be dissolved in the aqueous constituent of the hydrogels to provide medication over an extended period … via diffusion" [201]. The biggest obstacle to this rationale is maintaining a significant concentration of drug within the fluid to have a therapeutically relevant effect, which is ultimately limited by the solubility of the drug. This has been the primary reason why drug release from contact lenses has not become a clinical or commercial success. One promising technique to create contact lenses with therapeutically relevant drug loading and extended release is to produce a macromolecular framework with memory for the drug during polymer synthesis. This technology has roots to a field termed molecular imprinting, which has primarily concentrated on highly crosslinked polymer matrices for separation and sensing.

For molecularly imprinted hydrogel contact lenses, it has been shown that the extension of release for weakly crosslinked systems has a strong dependence on the monomer:template (M:T) ratio [60], as well as the diversity and number of interactions of the recognition site [61]. Drugs such as timolol [62], ketotifen fumarate [61] and antibiotics [63] have demonstrated *in vitro* extension of release using these methods. For example, biomimetic hydrogel contact lenses have been developed for the enhanced loading and extended release of the antihistamine ketotifen fumarate [61], which exhibited an extended-release profile for duration of 5 days with three distinct rates of release. Multiplicity of M:T interactions was achieved with four functional monomers chosen from an analysis of histamine ligand-binding pockets, which led to significantly enhanced loading and duration of release compared with less functionalized systems at a constant M:T ratio. Considering these systems maintain the mechanical and optical properties of contact lenses, there is high potential for therapeutic contact lenses based on these types of technology to deliver a number of ocular therapeutics without the need for multiple eye drops. *In vivo* validation of the most recent systems is currently under study, and the imprinting process is not as effective with lipophilic drugs owing to solubility constraints during hydrophilic gel formation. For reviews on hydrogel imprinting see elsewhere [64–66].

Increasing the drug reservoir within contact lenses has also included nanoparticulate and liposomal laden lenses [67] and ion exchange hydrogels [68], with duration of drug release during *in vitro* and *in vivo* experiments shown to be less than 1 day. Nanoparticulate-laden lenses have shown promise within *in vitro* studies and demonstrate 55% of drug released in 3 days. These techniques have concerns, such as inadequate drug loading at therapeutically relevant concentrations for long release times; and, for lens-dispersed nanoparticles, decreased mechanical stability induced by grain boundaries, reduced optical clarity, and longer and more costly production schemes. Recently, lenses have been demonstrated to deliver polyvinyl alcohol chains as a moisturizing agent to counteract ocular discomfort [69].

Ocular inserts can also deliver drug to the eye while avoiding the need for repeated eye drops. Soluble inserts, such as collagen shields, have been used as corneal bandages and drug-delivery carriers and are produced from porcine scleral tissue. Typically, they are soaked in solutions of drug and dissolve in the eye at characteristic rates, but they have had poor control over release and poor comfort since they are not individually fitted for patients. They also interfere with vision and cannot be inserted or removed by the patient, and they have self-expelled from the eye in many cases. Collagen shields release drug for hours and modification of the collagen film has been shown to produce longer release rates up to several days [70].

Ocular inserts are placed in the eye, deliver drug until depleted and (unless they are biodegradable) are removed at the end of the release period. Ocusert® (Alza Corp., US FDA approved in 1974) consists of a small wafer of drug reservoir enclosed by two diffusion-controlling membranes, which is placed in the corner of the eye and provides extended release of an antiglaucoma agent for approximately 7 days with an increased release rate in the first 7 h [71,72]. It must be removed at the end of the release period. Lacrisert® (Merck), which is also placed in the lower eyelid, is a cellulose-based polymer insert used to treat dry eyes [73]; it is administered once a day and is degradable. However, inserts have not found widespread use due to increased price over conventional treatments, occasional noticed or unnoticed expulsion from the eye [12] and potential for fragmentation and membrane rupture with a burst of drug being released [4].

Gel-forming inserts have also been produced from high-molecular-weight poly(ethylene oxide) (PEO) with drug release controlled by surface erosion. For the delivery of ofloxacin in rabbits, inserts were placed in the lower eyelid and demonstrated a twofold increase in drug residence time in the aqueous humor, a 3.8-fold increase in aqueous humor drug concentration, and approximately a tenfold increase in bioavailability over Exocin® eyedrops. The increases were attributed to PEO-enhanced permeability and/or increased tear viscosity [74].

Bioadhesive ophthalmic drug inserts (BODI®) are homogenous extruded mixtures of polymer and drug, shaped into rods 5 mm long and 2 mm in diameter and placed in the cul-de-sac. Animal tests have been conducted in canines [75], delivering the antibiotic gentamicin over 7 days. The bacteriological cure rate was similar to that from eye drops, with the added advantage of ease of use – one deposition of the insert as opposed to 21 instillations of eye drops.

Another ocular insert under development is the OphthaCoil, a thin, coiled, stainless steel wire coated with a drug-containing hydrogel. The coiled structure is intended to provide shape and

flexibility, the ends are capped to protect the eye from the wire edges and the coil interior can be used as a drug reservoir. Release of ciprofloxacin has been measured *in vitro* for over 5 h. The release time can potentially be increased by modifying the hydrogel coating and the polymer in the drug reservoir [76].

The anatomy of the eye has also been altered to increase residence time. For example, a mechanical technique for increasing drug residence time in the eye is to block the lacrimal puncta with punctal plugs. The tears produced in the eye cannot drain and thus accumulate in the eye, so any instilled drug is not washed away. This technique has demonstrated results when used with the drug timolol in glaucoma patients [77].

TABLE 2 summarizes various strategies for increasing the residence time of drugs on the ocular surface.

Strategies for permeation enhancement through ocular membranes

Drugs that reach the ocular surface need to penetrate the ocular epithelium, but the epithelium presents barriers that few drugs can easily overcome. For hydrophilic drugs, transcellular transport is difficult unless facilitated by a limited range of transporters present on the corneal and conjunctival epithelial cells. The intercellular spaces have tight junctions that resist paracellular transport.

Lipophilic drugs can diffuse through the cell membranes with relative ease. However, as mentioned previously, they cannot pass through the tear film and reach the epithelium as easily as hydrophilic drugs. Here we have a dilemma – drugs that reach the epithelium with ease have trouble penetrating it, and vice versa. Very few drugs have a high solubility in water as well as good partitioning in lipids. It would be useful if we could use a hydrophilic vehicle to bring the drug to the cell membrane and then have it diffuse through the membrane through a lipophilic vehicle.

Pairing an ionic drug with its counter ion has been shown to improve ocular penetration. The cationic timolol, when paired with anionic sorbic acid, has a twofold higher penetration into the aqueous humor than when delivered alone [78].

Cyclodextrins are ring-shaped oligosaccharides that can sequester lipophilic drugs within their central hydrophobic cavities [79]. The hydrophilic shells solubilize in the tear film and carry the drug to the epithelium, where the drug partitions into the cell membrane and penetrates the epithelium. This strategy has been demonstrated successfully with a number of drugs, including pilocarpine, which demonstrated a fourfold increased permeation in rabbit corneas after the addition of hydroxypropyl β-cyclodextrin [80]. Novel methylated cyclodextrins have lipophilic properties that allow them to diffuse through the cell membranes in addition to their action as solubilizers of lipophilic drugs in aqueous environments. Dexamethasone has been delivered to the eye posterior as a topical eye drop by complexation with randomly methylated cyclodextrins [81]. Cyclodextrins also have anti-irritant properties.

Table 2. Strategies to increase residence time on the eye surface.

General topical administration strategy	Subclassification	Measure of invasiveness and difficulty of application	Market penetration
Topical eye drops with viscosity enhancers	Solutions Suspensions	Low	FDA approved
Topical eye ointments		Moderate	FDA approved
Mucoadhesive polymers/particles in formulation	Polymers Micro/nanoemulsions Liposomes Colloidal suspensions	Low	FDA approved
Imprinted soft contact lenses		Low	Demonstrated *in vitro*; marginal *in vitro* work completed
Particulate-containing soft contact lenses		Low	Demonstrated *in vitro*
In situ gel forming	Δ pH gelation Δ Temperature gelation Δ Ionic strength gelation Combination	Moderate	FDA approved
Inserts	Degradable Nondegradable	High	FDA approved
Punctal plugs		High	FDA approved

High: Physician must apply; Moderate: Not easy for patient to apply; Low: Patient can apply.

Another option is to chemically modify the drug into a less therapeutic but more penetrable form, so that after it penetrates the cornea it can be converted into the therapeutic form by enzymes in the eye. The modified form is known as a prodrug. A water-soluble prodrug of ciclosporin A is produced by esterification of the drug with a moiety containing a phosphate group. The prodrug has improved bioavailability and penetration, and conversion in the eye back to the drug is approximately 6% in 3 min [82].

Aside from modifying the drug, researchers have increased permeation by modifying the epithelial cells. The cell membranes can be made more porous by disrupting the lipid bilayers with surfactants, such as polyoxyethylene 20 stearyl ether [83]. Chelating agents, such as ethylenediamine tetra-acetic acid (EDTA), sequester calcium ions and consequently loosen the tight junctions, opening up the paracellular pathway [84]. Recently, studies have indicated a cytotoxic effect from many permeation enhancers and absorption promoters, but the use of fetal bovine serum can ameliorate this [85]. An interesting fact is that absorption promoters have been shown to promote penetration of peptide drugs through the corneal epithelium more than through the conjunctival epithelium. This may allow control over the pathway and extent of drug penetration through the epithelia [86].

A third option is to transiently modify the structure of the epithelium so that its permeability increases just long enough to deliver the drug. Iontophoresis, which can be transcorneal or trans-scleral, delivers drug to the eye close to an electrode with potential equal to the charge of the drug [87,88]. The circuit is completed by touching the grounded electrode to another part of the body. The resulting electric field forces the drug through the epithelium. Gentamicin has recently been delivered to rabbit eyes through a drug-loaded hydrogel probe [89,90].

Sonophoresis is a similar technique that uses ultrasound to transiently increase the porosity of the epithelial membranes. It has been used to enhance the permeability of the drug betaxolol 4.4-times through rabbit corneas *in vitro* [91].

TABLE 3 summarizes various strategies for enhancing permeation of drug through the ocular membranes.

Strategies to delivery drugs to the posterior of the eye

Drugs delivered to the posterior of the eye can follow a number of routes [7]. While topically applied drug may penetrate the conjunctiva and sclera, it will generally be diluted and eliminated to a subtherapeutic dosage. The more common topical alternatives to reach the posterior segments involve either injection of a drug, a drug-delivery carrier or a drug-delivery device into the vitreal cavity of the eye, or by periocular delivery (following a trans-scleral route to the back of the eye and allowing it to penetrate the RPE). Additionally, some drugs are delivered through systemic circulation with oral or intravenous sources. Most systemically delivered drugs reach the ocular posterior in minute amounts, and there is a risk of systemic toxicity [92].

Noninvasive methods are generally preferred because of the relative lack of patient discomfort and surgical complications, such as endophthalmitis, hemorrhage, retinal detachment and cataracts [93]. The least invasive method would be delivery to the ocular surface with eye drops. While there is a tremendous challenge involved in overcoming all the ocular barriers from the tear film to the aqueous humor or RPE, progress is being made in delivering increasing amounts of drug to the posterior from surface-delivered sources. A likely drug candidate would have high partitioning in both water and lipids. Methylated cyclodextrins solubilize in both phases and could potentially improve the penetration of any drug sequestered in their central cavities. Their action has been demonstrated for dexamethasone [81].

More often, intraocular delivery involves repeated injections of the drug directly into the vitreal cavity. The wet form of age-related macular degeneration (AMD) and diabetic macular edema (DME) are commonly treated through intravitreal injections of anti-VEGF antibody fragments, such as ranibizumab or pegaptanib [94,95]. As the procedure is invasive, there may be side effects, such as infection at the injection site, intraocular pressure increase [96], cataract formation [97] or retinal detachment [98]. In addition, the injections are needed as often as once a month. This not only causes discomfort and inconvenience to the patient, but also increases the chances of developing side effects.

Newer developments include sustained-release implants that are inserted into the vitreal cavity, such as ganciclovir (Vitrasert®) for cytomegalovirus retinitis. While this technique is also surgically invasive, the implant may only need to be inserted once every few years. This dramatically reduces the risk of side effects and limits patient discomfort to one surgical procedure or less. Other implants in the market or in late-stage clinical trials are Retisert® (Bausch & Lomb), delivering fluocinolone acetonide to treat chronic noninfectious uveitis [99], and Medidur™ (Alimera Sciences), delivering the same drug for DME [100].

While the challenges for delivery to the posterior of the eye are greater than for other parts of the eye, researchers are making progress. One significant area of research is the study of RPE membrane transporters to facilitate penetration through this barrier. The RPE, similarly to the conjunctiva, consists of cell layers bounded by tight junctions. The paracellular transport route is difficult to bypass so, for delivering nonlipophilic drugs transcellularly, it can be advantageous to use native membrane transporters. RPE transporters exist for amino acids, peptides, monocarboxylic acids, nucleosides, folate and organic cations [5]. Studies are currently being performed in animal models.

Iontophoresis and sonophoresis are also used to penetrate the sclera near the back of the eye. Coulomb-controlled iontophoresis (CCI) delivers specific dosages of drug more accurately. Research on probes has been carried out to improve efficacy and safety. A probe coated with a hydrogel containing gentamicin is being developed and has been tested on rabbits [89]. In addition to drugs and proteins, iontophoresis can be used to delivery nucleic acids for gene therapy [88].

Subconjunctival injections can deliver drug into the sclera while bypassing the epithelial barriers. The drug can diffuse laterally through the sclera and reach the choroid and retina.

Table 3. Strategies for permeation enhancement through ocular membranes.

General topical administration strategy	Example(s)	Type of transport enhancement	Measure of invasiveness and ease of application	Market penetration
Particle size	Micro/nanoemulsions, liposomes, colloidal suspensions	Lipophilic drugs in tear film	Low	FDA approved
Noncovalent modification: biphasic solubility	Counter-ion pairing	Hydrophilic drugs through corneal epithelium	Low	FDA approved
Noncovalent modification: hydrophobic interior/hydrophilic exterior vehicles	Cyclodextrins	Lipophilic drugs in tear film	Low	In clinical trials
Functionalized hydrophobic interior/hydrophilic exterior vehicles	Functionalized cyclodextrins	Lipophilic drugs in tear film and through corneal epithelium	Low	Demonstrated *in vivo* animal studies
Covalent drug modification	Prodrug mechanisms	Hydrophobic/hydrophilic drugs through corneal epithelium	Low	FDA approved
Modifying the corneal epithelium or tight junctions	Surfactants	Hydrophilic drugs through corneal epithelium	Low	Found in existing formulations
	Chelating agents	Hydrophilic drugs through corneal epithelium	Low	Found in existing formulations
	Iontophoresis	Trans-scleral or transcorneal	High	In clinical trials
	Sonophoresis	Trans-scleral or transcorneal	High	Demonstrated *in vivo* animal studies

High: Significant – requires a physician in a medical setting; Low: Formulation issue – patient can apply in similar manner to most topical solutions.

Cisplatin has been delivered to rabbit retinas successfully by this mechanism. Better results were achieved when the drug was delivered within a collagen matrix rather than in a buffer solution [101].

A new technique involves delivering drug systemically and using light energy to localize the drug in the target tissue. Known as light-targeted delivery, the procedure begins with liposome-encapsulated drug injected intravenously. The encapsulation reduces systemic toxicity. As the liposomes circulate through the body, a light beam is directed into the pupil and directed at ocular tissue, such as the choroid neovasculature (CNV) in cases of AMD. The light beam gently warms the RPE, the CNV and the choroid capillaries to 40°C, prompting the liposomes to melt and release the drug to the local area. We suggest a good review discussing the procedure and its applications [102].

Scleral plugs are devices that are surgically implanted into the sclera and deliver drug to the sclera for extended periods of time. They have the advantage over injections of having a higher capacity, but the implantation procedure is more invasive. There have been successful animal studies involving this device, including the treatment of uveitis in rabbits with a plug that delivered tacrolimus [103].

Expert commentary

The administration of topical ocular medication can treat diseases on eye surfaces, such as the conjunctiva and cornea, or transfer to regions within the inner eye and treat front-of-eye diseases, such as glaucoma or anterior uveitis.

Topical eye drops in the forms of solutions and suspensions are the workhorse of ophthalmic drug administration. Together with ointments, they capture over 90% of currently administered ocular drugs. Evidence for topical administration of 'therapeutics' dates back to ancient times, where pharmacopoeic tablets from Babylonia and Assyria list remedies made of herbs, honey and minerals. Treatments were applied as powders, or dissolved in milk or wine to make pastes and washes. Egyptians used aloe, antimony and animal liver extracts to treat various eye disorders. The Greeks and Romans mixed copper and lead compounds with spices and biological extracts into 'collyria', which were cakes of solid medication that could be dissolved in water or saliva and applied topically. The first 'modern' topical eye medication is difficult to identify, but the origin of ophthalmology as a science rooted in pathology can be traced to the 18th Century. Despite the long history of topically applying medication, what have been the major contributions of industry, engineering and science producing technological improvements and innovations with topical administration?

In many regards, the industry has been focusing on two ways of achieving more efficient and efficacious delivery: extending the residence time of drugs on the eye surface and increasing drug transport through ocular barriers. Drug residence time has been increased by viscosity enhancers, mucoadhesive particles, and formulations and systems where the drug diffuses slowly from a gel into the tear film (e.g., *in situ* gelling systems and collagen shields). However, most gel systems and shields account for less than 1% of ocular administration methods [104]. As a whole, these methods have been effective at increasing the amount of drug delivered at the eye surface and the amount of drug that reaches the aqueous humor. Improved ocular penetration in these types of systems is due to increased surface contact. Inherently coupled is a decreased systemic absorption. However, the recent improvements in efficacy and bioavailability are relatively small in comparison to the length of time topical drops have been on the market.

In significant contrast, the last three decades have seen tremendous improvements in our understanding and development of extended or controlled drug-delivery systems, as well as their entry in the clinical marketplace. The return on investment in R&D has been staggering. In the early 1970s, controlled-release systems were nonexistent from a clinical perspective. In 2005, 100 million people worldwide were using drug-delivery systems with annual sales in the USA alone at approximately US$30 billion [105]. Of these numbers, very few controlled drug-delivery devices have found their way to the clinic to treat ocular disease, even considering one of the first controlled-release products was for the ophthalmic market. In 1974, Ocusert became the first FDA-approved product from ALZA Corp.; Lacrisert from Merck and Co. was FDA approved in 1981. These two products, which are still used today to treat front-of-eye issues (namely glaucoma and dry eye), have had considerable success in treating disease for extended periods of time with decreased toxicity.

A significant investment in devices has not been achieved for eye disease. This could be because the eye is easily accessed for localized targeted delivery in the form of eye drops, the cost of such systems is typically much more than conventional drop formulations, and significantly increased efficacy of such devices has not been adequately proven to shift investment by industry. Ultimately, the size of each market also plays a big role. It may be argued that topical drops are effective and well tolerated by patients, despite the inconvenience of multiple daily drops. However, all patients go through periods of decreased drug concentrations due to the peaks and valleys, and the majority of patients experience significant lag periods with ineffective drug concentrations when doses are missed. For surface eye issues, such as anti-inflammatory, anti-infective and anti-allergy medications, which are large topical markets all surpassing US$600 million per year, there has been little research creating more controlled or extended devices or vehicles. The increased efficacy associated with controlled or extended delivery of these types of therapeutics from devices has not been demonstrated. When this is achieved and efficacy is proven far superior, there will be a number of products moving into the market.

There are many underlying issues in creating successful topical devices on the eye surface. Devices must not create the feeling of a foreign object within the eye, which is difficult considering the limited space to place a device. Also, the device should not be difficult to insert and not require significant dexterity or training. It should also not be easily expelled by the eye. To exploit the significant area of the eye, it must not interfere with vision. For example, new R&D in therapies based on contact lens platforms is currently underway. Progress in polymer science and engineering has led to these improvements in the understanding of network formation and drug interaction.

For other disease within the anterior anatomy, the causes of cataracts are currently being studied and no drug therapy exists that is proven to prevent the formation of cataracts. Thus, the only device to date for anterior issues has been to treat glaucoma.

The rationale for drug-delivery devices for posterior eye diseases is even more pronounced since it is harder to deliver therapeutics to these regions without systemic delivery or invasive procedures, such as periocular injection (i.e., into tissue surrounding the eye), intracameral injection (i.e., into the anterior chamber) or intravitreal injection (i.e, into the vitreal cavity). The complications associated with injections can be great and can outweigh most benefits. Also, retinal degenerative disease, retinitis pigmentosa, macular degeneration and diabetic retinopathy affect a significant extent of the population. Finally, patient apprehension with ocular injections and repeated injections is significant. Thus, for posterior eye disease, it is hard to believe the first intravitreal implant, Vitrasert, was developed in the 1990s and FDA approved in 1996. In 2005, another vitreal implant, Retisert, was approved by the FDA. Controlling the delivery of therapeutics to the back of the eye can produce steady doses for 30 months without the need for repeated injections. Medidur is the newest intravitreal device, designed to have a duration of 18–36 months. Comparing these devices with systemic therapy is important as well as the degree to which the drugs' side effects can be controlled. For example, cataract formation and glaucoma are documented side effects of the corticosteroid released from Retisert. With systemic administration, ocular side effects may be managed better by tailoring the medication dosage or type of medication to prevent side effects. This may be the reason it has taken so long to develop these extended-release carriers. The other reason may be that big pharmaceutical companies have not invested in discovering new drug candidates for the back of the eye.

Periocular routes of delivery with trans-scleral transport has been demonstrated with inserts as well as nanoparticles and microparticles, with retention at the particle site related to a cut-off particle size [106]. Intravitreal degradable particle injections have promise but particles must not interfere with vision and the number of injections must be limited and carefully examined to outweigh potential side effects.

Increasing drug transport through ocular barriers has tremendous potential. Counter-ion pairing, cyclodextrins, prodrug mechanisms and permeation enhancers are making significant progress, increasing the permeation of drugs through the

ocular barriers. Iontophoresis and sonophoresis are not expected to yield as high market penetration compared with other methods of delivery, although probe design has improved considerably since the earliest demonstrations. The key to permeation-enhancing mechanisms is to transiently open the tight junctions without significantly affecting the barrier properties of the eye. These methods are beginning to significantly increase the applicability of topical drops to more effectively treat inner eye disease.

The last few years have seen more combination agents in topical form and multitherapy approaches. It is clear that therapies that increase drug residence time on the surface of the eye and increase the transport through ocular barriers are enhancing topical drug delivery. Future formulations or devices will see heightened emphasis on both these issues to maintain market share.

Five-year view

The outlook for topical drug delivery is strong. There is still a rather large unmet need to treat back-of-eye disorders and developments in drug candidates and delivery mechanisms will increase. Commercialization of novel R&D of noninvasive technologies will be key to sustaining the efficient treatment of posterior eye disease without significant side effects. In the long term, methods to control or modulate release profiles of the drug-delivery carrier will be the ultimate key to success, limiting side effects of extended-therapy release from carriers that cannot be removed. A major question that will remain in 5 years is can we transfer drugs to the back of the eye noninvasively via topical methods applied to the eye surface?

Within the topical drop segment, combination products and products with emphasis on permeation enhancement and transporters will increase. This will increase bioavailability and efficacy and decrease the multiplicity of eye-drop administration. This emphasis will lead to increased R&D to achieve similar delivery for posterior drugs.

As additional drug-delivery systems are demonstrated to work *in vivo*, coordination of absorption and delivery rates will decrease the major contribution of drug loss via tear turnover. This will also limit systemic drug loss via the nasal lacrimal route and the conjunctiva. If a significant concentration of drug can transport to the inner anterior eye, there is the increased potential to use this pathway to reach the posterior segment. However, a significant hurdle remains, with the aqueous humor circulation posing a barrier. It is more likely that the scleral route will be preferred for topically delivering drugs for the posterior segment.

Regarding topical inserts, for techniques to translate to the clinic even within 5 years, they must fit well into existing manufacturing techniques and not contain molecules/monomers or entities that would require significant preclinical studies. Much beyond this time, with significant increases in micro- and nanotechnology R&D, we may see very comfortable inserts easily applied by the patient for a variety of ocular diseases. For example, *in vivo* validation of release and efficacy from imprinted contact lens delivery systems, as well as integration with current manufacturing techniques, are key for successful commercialization. Beyond 5 years, new carriers will be studied and developed that provide multiple drug release and/or on-demand release.

Some newer strategies are unlikely to be in clinical use within 5 years but will demonstrate increasing effectiveness in the lab. Some techniques focus on eliminating the side effects of current drug-delivery techniques. Light-targeted delivery ensures localized delivery to the choroidal neovascularization in AMD while minimizing systemic side effects by encapsulating the drug in liposomes. Encapsulation techniques are also being applied to genetic material for gene delivery to treat problems such as photoreceptor loss [107].

In terms of new drugs, for a 5-year timeline, one must look at the clinical development pipeline. There are a number of new drug candidates in clinical trials and we direct the reader elsewhere [108].

In certainty, it is clear that the next 5 years will require multidisciplinary integration and cooperation from the fields of ophthalmology, materials science, polymer science, and engineering and biomedical engineering to develop the best strategies for preserving vision and quality of life.

Key issues

- Ophthalmic drugs preserve vision and improve quality of life in people of all ages.
- Traditional topically delivered drugs have low bioavailability because of ocular surface and retinal barriers, and circulation of tear fluid and aqueous humor.
- New strategies increase the residence time of drug in the eye and enhance permeation through ocular barriers.
- Drug residence time on the eye surface is increased with drug-delivery devices and polymeric materials.
- Permeation is enhanced by modifying the drugs' physicochemical properties and exploiting membrane transporters.
- Drugs are delivered to the eye posterior by lateral diffusion through the sclera or by inserting a drug-delivery device into the vitreal cavity.
- Future directions of research include combined strategies that increase residence time and drug penetration.

Financial & competing interests disclosure

The authors have a US patent pending on imprinted contact lenses (Contact Drug Delivery System, US Patent, pending US20060177483 A1). The authors have founded OcuMedic, Inc., a drug-delivery technology company based in Auburn, AL, USA. M Byrne is founder, CTO, and has a financial interest in this company.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

1 National Eye Inst. *Progress in Eye and Vision Research 1999–2006*. National Institute of Health, US Department of Health and Human Services, MD, USA (2006).

2 Albert DM. *The History of Ophthalmology*. Blackwell Science, MA, USA (1996).

3 Lang JC. Ocular drug delivery: conventional ocular formulations. *Adv. Drug Deliv. Rev.* 16(1), 39–43 (1995).

• 10-year view of patents from 1985 to 1995 and summary of PDR for ocular medicines.

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

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

• Excellent discussion of the future of transporters.

6 Schoenwald RD. Ocular pharmacokinetics. In: *Textbook of Ocular Pharmacology.* Zimmerman TJ, Kooner K, Sharir M *et al.* (Eds). Lippincott-Raven Publishers, PA, USA 119–139 (1997).

7 Geroski DH, Edelhauser HF. Drug delivery for posterior segment eye disease. *Invest. Ophthalmol. Vis. Sci.* 41(5), 961–964 (2000).

8 Bartlett JD, Jaanus SD. *Clinical Ocular Pharmacology.* Butterworth-Heinemann Publishers, MA, USA (1984).

• Excellent introductory text on clinical pharmacology.

9 Clark AF, Yorio T. Ophthalmic drug discovery. *Nat. Rev. Drug Discov.* 2(6), 446–459 (2003).

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

11 LeBourlais C, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems-recent advances. *Prog. Retinal Eye Res.* 17(1), 33–58 (1998).

12 Saettone MF. Progress and problems in ophthalmic drug delivery. *Pharmatech* 1–6, (2002).

• Excellent review article and introduction to ocular barriers.

13 Elder M. US market for prescription ophthalmic drugs, devices, diagnostics, and surgical equipment. *Business Communications Research* (2006).

14 Friedman DS, Congdon N, Kempen J, Tielsch JM. *Vision Problems in the US: Prevalence of Adult Vision Impairment and Age-Related Eye Disease in America.* National Eye Institute and Prevent Blindness America, IL, USA (2002).

15 Glasson MJ, Stapleton F, Keay L, Willcox MDP. The effect of short term contact lens wear on the tear film and ocular surface characteristics of tolerant and intolerant wearers. *Cont. Lens Anterior Eye* 29(1), 41–47 (2006).

16 Holly FJ, Lemp MA. Tear physiology and dry eyes. *Surv. Ophthalmol.* 22(2), 69–87 (1977).

17 Sharma A, Ruckenstein E. Mechanism of tear film rupture and its implications for contact lens tolerance. *Am. J. Optom. Physiol. Opt.* 62(4), 246–253 (1985).

18 Holly FJ. Tear film physiology. *Am. J. Optom. Physiol. Opt.* 57(4), 252–257 (1977).

19 Doane MG. Blinking and the mechanics of the lacrimal drainage system. *Ophthalmology* 88(8), 844–851 (1981).

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

21 Prausnitz MR, Noonan JS. Permeability of cornea, sclera, and conjunctiva: a literature analysis for drug delivery to the eye. *J. Pharm. Sci.* 87(12), 1479–1488 (1998).

•• Excellent compilation and comprehensive database of ocular tissue permeability measurements.

22 Lee VHL. Precorneal, corneal and postcorneal factors. In*: Ophthalmic Drug Delivery Systems.* Mitra AK (Ed.). Marcel Dekker Publishers, NY, USA 59–81 (1993).

23 Robinson JC. Ocular anatomy and physiology relevant to ocular drug delivery. In: *Ophthalmic Drug Delivery Systems.* Mitra AK (Ed.). Marcel Dekker Publishers, NY, USA 29–57 (1993).

24 Jiang J, Geroski DH, Edelhauser HF, Prausnitz MR. Measurement and prediction of lateral diffusion within human sclera. *Invest. Ophthalmol. Vis. Sci.* 47(7), 3011–3016 (2006).

25 Urtti A. Challenges and obstacles of ocular pharmacokinetics and drug delivery. *Adv. Drug Deliv. Rev.* 58(11), 1131–1135 (2006).

26 Duvvuri S, Majumdar S, Mitra AK. Role of metabolism in ocular drug delivery. *Curr. Drug Metab.* 5(6), 507–515 (2004).

27 Sklubalova Z, Zatloukal Z. Systemic study of factors affecting eye drop size and dosing variability. *Pharmazie* 60(12), 917–921 (2005).

28 Blondeau JM, Hedlin P, Borsos SD. The antimicrobial activity of gatifloxcin (GAT) with or without benzalkonium chloride (BAK) against ocular bacterial pathogens. Presented at: *Association for Research in Vision and Ophthalmology Annual Meeting.* Fort Lauderdale, FL, USA, 1–5 May 2005.

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

30 Zurowska-Pryczkowska K, Sznitsowska M, Janicki S. Studies on the effect of pilocarpine incorporation into a submicron emulsion on the stability of the drug and the vehicle. *Eur. J. Pharm. Biopharm.* 47(3), 255–260 (1999).

31 Naveh N, Muchtar A, Benita S. Pilocarpine incorporated into a submicron emulsion vehicle causes an unexpectedly prolonged ocular hypotensive effect in rabbits. *J. Ocul. Pharmacol.* 10(3), 509–520 (1994).

32 Vandamme TF. Microemulsions as ocular drug delivery systems: recent developments and future challenges. *Prog. Retin. Eye Res.* 21(1), 15–34 (2002).

33 Fialho SL, da Silva-Cunha A. New vehicle based on a microemulsion for topical ocular administration of dexamethasone. *Clin. Experiment. Ophthalmol.* 32(6), 626–632 (2004).

34 Zimmer A, Kreuter J. Microspheres and nanoparticles used in ocular delivery systems. *Adv. Drug Deliv. Rev.* 16, 61–73 (1995).
- Thorough discussion of the various classes of colloidal carriers.

35 Prankerd RJ, Stella VJ. The use of oil-in-water emulsions as a vehicle for parenteral drug administration. *J. Parenter. Sci. Technol.* 44, 139–149 (1990).

36 Ebrahim S, Peyman GA, Lee PJ. Applications of liposomes in ophthalmology. *Surv. Ophthalmol.* 50(2), 167–182 (2005).
- Discussion of liposomes applied to novel ophthalmic therapies.

37 Mainardes RM, Urban MC, Cinto PO *et al.* Colloidal carriers for ophthalmic drug delivery. *Curr. Drug Targets* 6(3), 363–71 (2005).
- Thorough discussion of the various classes of colloidal carriers.

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

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

40 Gavini E, Chetoni P, Cossu M, Alvarez MG, Saettone MF, Giunchedi P. PLGA microspheres for the ocular delivery of a peptide drug, vancomycin using emulsification/spray-drying as the preparation method: *in vitro*/*in vivo* studies. *Eur. J. Pharm. Biopharm.* 57(2), 207–212 (2004).

41 Bejjani RA, BenEzra D, Cohen H *et al.* Nanoparticles for gene delivery to retinal pigment epithelial cells. *Mol. Vis.* 11, 124–132 (2005).
- Uses nanoparticles as gene-delivery vectors in retinal pigmented epithelium (RPE) cell cultures.

42 Merodio M, Irache JM, Valamanesh F, Mirshahi M. Ocular disposition and tolerance of ganciclovir-loaded albumin nanoparticles after intravitreal injection in rats. *Biomaterials* 23(7), 1587–1594 (2002).

43 Felt O, Furrer P, Mayer JM, Plazzonet B, Buri P, Gurny R. Topical use of chitosan in ophthalmology: tolerance assessment and evaluation of precorneal retention. *Int. J. Pharm.* 180(2), 185–193 (1999).

44 Bernkop-Schnerch A. Thiomers: a new generation of mucoadhesive polymers. *Adv. Drug Deliv. Rev.* 57(11), 1569–1582 (2005).
- Novel mucoadhesive polymers are modified to covalently bond with ocular mucins.

45 Hornof M, Weyenberg W, Ludwig A, Bernkop-Schnurch A. Mucoadhesive ocular insert based on thiolated poly(acrylic acid): development and *in vivo* evaluation in humans. *J. Control. Release* 89(3), 419–428 (2003).

46 Aggarwal D, Kaur IP. Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system. *Int. J. Pharm.* 290(1–2), 155–159 (2005).

47 Greaves JL, Wilson CG. Treatment of diseases of the eye with mucoadhesive delivery systems. *Adv. Drug Deliv. Rev.* 11(3), 349–383 (1993).

48 Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. *Adv. Drug Deliv. Rev.* 57(11), 1595–1639 (2005).

49 Lin H, Sung KC. Carbopol/pluronic phase change solutions for ophthalmic drug delivery. *J. Control. Release* 69, 379–388 (2000).

50 Sultana Y, Aqil M, Ali A, Zafar S. Evaluation of carbopol-methyl cellulose based sustained-release ocular delivery system for pefloxacin mesylate using rabbit eye model. *Pharm Dev. Technol.* 11(3), 313–319 (2006).

51 Rozier A, Mazuel C, Grove J, Plazonnet B. Gelrite®: a novel, ion-activated, *in-situ* gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. *Int. J. Pharm.* 57(2), 163–168 (1989).

52 Sultana Y, Aqil M, Ali A. Ion-activated Gelrite®-based *in situ* ophthalmic gels of pefloxacin mesylate: comparison with conventional eye drops. *Drug Deliv.* 13(3), 215–219 (2006).

53 Wei G, Ding P, Zheng J, Lu W. Pharmacokinetics of timolol in aqueous humor sampled by microdialysis after topical administration of thermosetting gels. *Biomed. Chromatogr.* 20, 67–71 (2006).

54 Cao Y, Zhang C, Shen W, Cheng Z, Yu LL, Ping Q. Poly(*N*-isopropylacrylamide)-chitosan as thermosensitive *in situ* gel-forming system for ocular drug delivery. *J. Control. Release* 120(3), 186–194 (2007).

55 Lin H, Sung KC, Vong W. *In situ* gelling of alginate/pluronic solutions for ophthalmic delivery of pilocarpine. *Biomacromolecules* 5(6), 2358–2365 (2004).

56 Wu C, Qi H, Chen W *et al.* Preparation and evaluation of a carbopol/HPMC-based *in situ* gelling ophthalmic system for puerarin. *Yakugaku Zasshi* 127(1) 183–191 (2007).

57 Ruel-Gariepy E, Leroux J. *In situ*-forming hydrogels – review of temperature sensitive systems. *Eur. J. Pharm. Biopharm.* 58, 409–426 (2004).

58 Sultana Y, Jain R, Aqil M, Ali A. Review of ocular drug delivery. *Curr. Drug Deliv.* 3, 207–217 (2006).

59 Gokulgandhi MR, Modi DM, Parikh JR. *In situ* gel systems for ocular drug delivery: a review. *Drug Deliv. Technol.* 7(3), 30–37 (2007).

60 Hiratani H, Mizutani Y, Alvarez-Lorenzo C. Controlling drug release from imprinted hydrogels by modifying the characteristics of the imprinted cavities. *Macromol. Biosci.* 5(8), 728–733 (2005).

61 Venkatesh S, Sizemore SP, Byrne ME. Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics. *Biomaterials* 28(4), 717–724 (2007).

62 Alvarez-Lorenzo C, Hiratani H, Gómez-Amoza JL, Martínez-Pacheco R, Souto C, Concheiro A. Soft contact lenses capable of sustained delivery of timolol. *J. Pharm. Sci.* 91(10), 2182–2192 (2002).
•• First paper demonstrating imprinted weakly crosslinked lenses for drug delivery.

63 Alvarez-Lorenzo C, Yañez F, Barreiro-Iglesias R, Concheiro A. Imprinted soft contact lenses as norfloxacin delivery systems. *J. Control. Release* 113(3), 236–244 (2006).

64 Byrne ME, Park K, Peppas NA. Molecular imprinting within hydrogels. *Adv. Drug Deliv. Rev.* 54(1), 149–161 (2002).
•• First paper highlighting the potential for imprinting within hydrogel drug-delivery carriers.

65 Hilt JZ, Byrne ME. Configurational biomimesis in drug delivery: molecular imprinting of biologically significant molecules. *Adv. Drug Deliv. Rev.* 56(11), 1599–1620 (2004).

66 Alvarez-Lorenzo C, Concheiro A. Molecularly imprinted polymers for drug delivery. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 804(1), 231–245 (2004).

67 Gulsen D, Chauhan A. Dispersion of microemulsion drops in HEMA hydrogel: a potential ophthalmic drug delivery vehicle. *Int. J. Pharm.* 292(1–2), 95–117 (2005).

68 Uchida R, Sato T, Tanigawa H, Uno K. Azulene incorporation and release by hydrogel containing methacrylamide propyltrimenthylammonium chloride, and its application to soft contact lens. *J. Control. Release* 92(3), 259–264 (2003).

69 Winterton LC, Lally JM, Sentell KB, Chapoy LL. The elution of poly (vinyl alcohol) from a contact lens: the realization of a time release moisturizing agent/artificial tear. *J. Biomed. Mater. Res. Part B Appl. Biomater.* 80(2), 424–432 (2007).
- First long-chain comfort molecule release from contact lens platform.

70 Vasantha R, Sehgal PK, Rao KP. Collagen ophthalmic inserts for pilocarpine drug delivery system. *Int. J. Pharm.* 47(1–3), 95–102 (1988).

71 Armaly MF, Rao KR. The effect of pilocarpine Ocusert with different release rates on ocular pressure. *Invest. Ophthalmol.* 12(7), 491–496 (1973).

72 Urquhart J. Development of the Ocusert pilocarpine ocular therapeutic systems, a case history. In: *Ophthalmic Delivery Systems.* Robinson J (Ed.). American Pharmaceutical Association, Washington DC, USA 105–118 (1980).

73 Prause JU. Treatment of keratoconjunctivitis sicca with Lacrisert. *Scand. J. Rheumatol.* 61(Suppl.), 261–263 (1986).

74 Di Colo G, Burgalassi S, Chetoni P, Fiaschi MP, Zambito Y. Saettone MF. Gel-forming erodible inserts for ocular controlled delivery of ofloxacin. *Int. J. Pharm.* 215, 101–111 (2001).

75 Baeyens V, Felt-Baeyens O, Rougier S, Pheulpin S, Boisrame B, Gurny R. Clinical evaluation of bioadhesive ophthalmic drug inserts (BODI) for the treatment of external ocular infections in dogs. *J. Control. Release* 85(1–3), 163–168 (2002).

76 Pijls RT, Cruysberg LP, Nuijts RM, Dias AA, Koole LH. Capacity and tolerance of a new device for ocular drug delivery. *Int. J. Pharm.* 341(1–2), 152–161 (2007).

77 Bartlett JD, Boan K, Corliss D, Gaddie IB. Efficacy of silicone punctal plugs as adjuncts to topical pharmacotherapy of glaucoma – a pilot study. Punctal Plugs in Glaucoma Study Group. *J. Am. Optom. Assoc.* 67(11), 664–668 (1996).

78 Higashiyama M, Inada K, Ohtori A, Tojo K. Improvement of the ocular bioavailability of timolol by sorbic acid. *Int. J. Pharm.* 272(1–2), 91–98 (2004).

79 Kaur IP, Chhabra S, Aggarwal D. Role of cyclodextrins in ophthalmics. *Curr. Drug Deliv.* 73(3), 189–192 (2004).

80 Aktas Y, Unlu N, Orhan M, Irkec M, Hincal AA. Influence of hydroxypropyl β-cyclodextrin on the corneal permeation of pilocarpine. *Drug Dev. Ind. Pharm.* 29(2), 223–230 (2003).

81 Loftsson T, Sigurdsson HH, Hreinsdottir D, Konradsdottir F, Steffansson E. Dexamethasone delivery to posterior segment of the eye. *J. Incl. Phenom. Macrocycl. Chem.* 57, 585–589 (2007).
- Novel cyclodextrin is chemically modified to enable penetration through lipid bilayers.

82 Lallemand F, Felt-Beeyens, Rudaz S *et al.* Conversion of cyclosporine A prodrugs in human tears vs rabbits tears. *Eur. J. Pharm. Biopharm.* 59(1), 51–56 (2005).

83 Saettone MF, Chetoni P, Cerbai R, Mazzanti G, Braghiroli L. Evaluation of ocular permeation enhancers: *in vitro* effects on corneal transport of four β-blockers and *in vitro*/ *in vivo* toxic activity. *Int. J. Pharm.* 142, 103–113 (1996).

84 Grass GM, Wood RW, Robinson JR. Effects of calcium chelating agents on corneal permeability. *Invest. Ophthalmol. Vis. Sci.* 26(1), 110–113 (1985).

85 Burgalassi S, Chetoni P, Monti D, Saettone MF. Cytotoxicity of potential ocular permeation enhancers evaluated on rabbit and human corneal epithelial cell lines. *Toxicol. Lett.* 122(1), 1–8 (2001).

86 Sasaki H, Yamamura K, Mukai T *et al.* Modification of ocular permeability of peptide drugs by absorption promoters. *Biol. Pharm. Bull.* 23(12), 1524–1527 (2000).

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

88 Myles ME, Neumann DM, Hill JM. Recent progress in ocular drug delivery for posterior segment disease: emphasis on transscleral iontophoresis. *Adv. Drug Deliv. Rev.* 57(14), 2063–2079 (2005).
- Comprehensive discussion of iontophoresis in its current state, including probe design and therapeutic avenues.

89 Eljarret-Binstock E, Raiskup F, Stepensky D, Domb AJ, Frucht-Pery J. Delivery of gentamicin to the rabbit eye by drug-loaded hydrogel iontophoresis. *Invest. Ophthalmol. Vis. Sci.* 45(8), 2543–2548 (2004).

90 Frucht-Pery J, Raiskup F, Mechoulam H, Shapiro M, Eljarret-Binstock E, Domb AJ. Iontophoretic treatment of experimental pseudomonas keratitis in rabbit eyes using gentamicin-loaded hydrogels. *Cornea* 25(10), 1183–1186 (2006).

91 Zderic V, Vaezy S, Martin RW, Clark JI. Ocular drug delivery using 20-Hz ultrasound. *Ultrasound Med. Biol.* 28(6), 823–829 (2002).

92 Tamesis RR, Rodriguez A, Christen WG, Akova YA, Messmer E, Foster CS. Systemic drug toxicity trends in immunosuppressive therapy of immune and inflammatory ocular disease. *Ophthalmology* 103(5), 768–75 (1996).

93 Kurz D, Ciulla TA. Novel approaches for retinal drug delivery. *Ophthalmol. Clin. North Am.* 15(3), 405–410 (2002).

94 Schmidt-Erfurth UM, Pruente C. Management of neovascular age-related macular degeneration. *Prog. Retin. Eye Res.* 26(4), 437–451 (2007).

95 Ng EW, Adamis AP. Anti-VEGF aptamer (pegaptanib) therapy for ocular diseases. *Ann. NY Acad. Sci.* 1082, 151–171 (2006).

96 Frenkel RE, Mani L, Toler AR, Frenkel MP. Intraocular pressure effects of pegaptaib (Macugen) injections in patients with and without glaucoma. *Am. J. Ophthalmol.* 143(6), 1034–1035 (2007).

97 Thompson JT. Cataract formation and other complications of intravitreal triamcinolone for macular edema. *Am. J. Ophthalmol.* 141(4), 629–637 (2006).

98 Nicolo M, Ghiglione D, Calabria G. Retinal pigment epithelial tear following intravitreal injection of bevacizumab (Avastin). *Eur. J. Ophthalmol.* 16(5), 770–773 (2006).

99 Mohammad DA, Sweet BV, Elner SG. Retisert: is the new advance in treatment of uveitis a good one? *Ann. Pharmacother.* 41(3), 449–454 (2007).

100 Ogden J. Addressing drug delivery challenges using versatile controlled and targeted systems. *Drug Deliv. Report* (2006).

101 Gilbert JA, Simpson AE, Rudnick DE, Geroski DH, Aaberg TM, Edelhauser HF. Transscleral permeability and intraocular concentrations of cisplatin from a collagen matrix. *J. Control. Release* 89(3), 409–417 (2003).

102 Zeimer R, Goldberg MF. Novel ophthalmic therapeutic modalities based on noninvasive light-targeted drug delivery to the posterior pole of the eye. *Adv. Drug Deliv. Rev.* 52(1), 49–61 (2001).

103 Sakurai E, Nozaki M, Okabe K, Kunou N, Kimura H, Ogura Y. Scleral plug of biodegradable polymers containing tacrolimus (FK506) for experimental uveitis. *Invest. Ophthalmol. Vis. Sci.* 44(11), 4845–4852 (2003).

104 *Physicians' Desk Reference (36th Edition)*, Thompson Healthcare, Inc., MI, USA (2007).

105 Langer R. Biomaterials for drug delivery and tissue engineering. *MRS Bull.* 31, 477–485 (2006).

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

107 Liu X, Brandt CR, Rasmussen CA, Kaufman PL. Ocular drug delivery: molecules, cells, and genes. *Can. J. Ophthalmol.* 42, 447–454 (2007).

108 Abelson MB, Chapin M, Plumer A. Ophthalmic drugs: what's in the pipeline? *Ophthalmology Times/Special Report.* 30(9), 16–18 (2005).

109 Moss SE, Klein R, Klein BEK. Prevalence of and risk factors for dry eye syndrome. *Arch. Ophthalmol.* 118(9), 1264–1268 (2000).

Patent

201 Wichterle O. Cross-linked hydrophilic polymers and articles made therefrom: US3220960 (1965).

Websites

301 Murphy J. You're only in upto your knees. Review of optometry online www.revoptom.com/archive/FEATURES/RO1100f6uptoknees.htm#optometric

302 Pagnini F. Ocular drugs: light at the end of the tunnel www.imshealth.com/web/content/0,3148,64576068_63872702_70261000_71056319,00.html

303 Ophthalmology Psivida www/psivida.com/application/Ophthalmology.asp

Affiliations

- *Maryam Ali, MS*
Auburn University, Biomimetic & Biohybrid Materials, Biomedical Devices, and Drug Delivery Laboratories, Department of Chemical Engineering, Auburn, AL 36849, USA
Tel.: +1 334 844 8059
Fax: +1 334 844 2063
alimary@auburn.edu
- *Mark Edward Byrne, PhD*
Auburn University, Biomimetic & Biohybrid Materials, Biomedical Devices, and Drug Delivery Laboratories, Department of Chemical Engineering, Auburn, AL 36849, USA
Tel.: +1 334 844 2862
Fax: +1 334 844 2063
byrneme@eng.auburn.edu