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Ocular drug delivery

Deepta Ghate & Henry F Edelhauser†
†*Emory University Eye Center, 1365B, Clifton Road, Atlanta, GA 30322, USA*

Drug delivery to the eye is hampered by anatomical factors, including the corneal epithelium, the blood–aqueous barrier and the blood–retinal barrier. This review aims to outline the major routes of ocular drug delivery, including systemic, topical, periocular and intravitreal. The pharmacokinetics, the disadvantages and the clinical relevance of these drug delivery routes have been emphasised. Recent advances in surgical techniques, therapeutic approaches and material sciences have produced exciting new therapies for ocular diseases. The role of ophthalmic drug formulation in targeting the desired ocular tissue and enhancing drug delivery by the chosen route whilst minimising side effects is also discussed.

Keywords: intravitreal injection, ocular drug delivery, ocular pharmacokinetics, posterior subtenon injection, topical drug delivery

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1. Introduction

Ocular drug delivery is an extremely important topic, especially with the recent development of new drugs for age-related macular degeneration. Drug delivery to the eye can vary in ease from the simple topical eye drop, which rapidly penetrates to the anterior chamber, to the complicated engineering skills required to develop intravitreal implants. This review aims to outline the major routes of ocular drug delivery, the science behind drug delivery by these routes, and the newer techniques developed to enhance drug delivery to the eye. The anterior segment and the posterior segment are two entirely different ocular regions and the challenges faced in delivering therapeutic drugs to each of these areas are unique; hence, they are dealt with separately.

2. Anterior segment drug delivery

The anterior segment of the eye consists of the cornea, conjunctiva, iris, ciliary body and the lens with its zonules. The major routes for anterior segment drug delivery are topical delivery and subconjunctival injection.

Drug delivery to the anterior segment following systemic administration is limited due to the blood–aqueous barrier, formed by the nonpigmented layer of the epithelium of the ciliary body, and the endothelium of the blood vessels of the iris. This is similar to the blood–brain barrier and limits the drug concentration reached in the aqueous. Drugs such as ofloxacin, however, do penetrate the blood–aqueous barrier [1], especially in an inflamed eye, but there is a simpler way to get to the anterior chamber; the eye drop.

2.1 Topical drug delivery to the eye

Topical drug delivery is the most convenient and efficacious method of ocular drug delivery to the anterior segment. The advantages of this route are obvious: it avoids first-pass metabolism of drugs in the liver; it allows the drug to selectively target the anterior chamber and it is noninvasive. However, on a practical note, only 1 – 7% of the instilled drug reaches the aqueous humor (Figure 1). The inefficiency of this route stems mainly from the precorneal tear clearance mechanism, the highly selective corneal–epithelial barrier, drug loss through the conjunctival–scleral route and

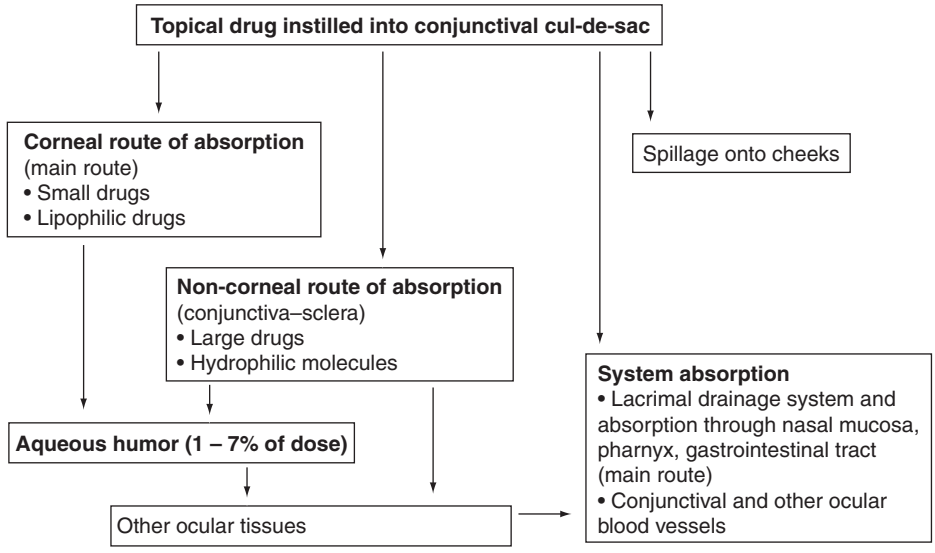

Figure 1. Profile of a topically applied drug.

the difficulty that the elderly have with dosing eye drops to the eye [2].

2.2 Precorneal tear drainage

Under normal conditions, the tear volume is 7 – 9 µl in humans with a turnover rate of 0.5 – 2.2 µl/min. The typical volume delivered by commercial eyedroppers is 35 – 56 µl; this sudden increase in the tear volume causes rapid reflex blinking. Irritant drugs also cause increased tear secretion, which dilutes the drug. Most of the drug is pumped through the lacrimal drainage system and some is spilled onto the cheeks. The corneal surface area for drug absorption is ~ 1 cm^2, whereas the conjunctival surface area is nearly 17 cm^2 [3]. Therefore, a topical drug to the cornea is spread over a large surface area, which limits the direct diffusion across the cornea. The drug resides in the conjunctival cul-de-sac for ~ 3 – 5 min; therefore, only a small fraction of the drug actually makes it through the cornea [2,4].

2.3 The corneal barrier

The epithelium (Figure 2) in the human cornea provides maximum resistance to penetration by drugs. It is comprised of five layers and has tightly adherent cells with gap and tight junctions. Drugs penetrate this layer by either partitioning through the cells (intracellular) or bypassing between the cells (paracellular). The epithelium is a lipophilic tissue, which contributes 90% of the barrier to hydrophilic drugs and 10% of the barrier to lipophilic drugs. The paracellular route predominates for hydrophilic drugs or ions of small molecular weight (< 350 MW), whereas the intracellular route predominates for lipophilic drugs [2]. The presence or absence of an epithelium is thus an important factor to consider in drug absorption. Diseased corneas often have a compromised epithelial surface allowing for better drug penetration.

The stroma, as a barrier, can be considered an aqueous environment interspersed with glycosaminoglycans and collagen fibrils. Drugs diffuse through the stroma with relatively minor resistance. If the stroma is isolated, there is no dependence on lipophilicity but a strong dependence on molecular radius, reflecting the aqueous intercellular route of drug diffusion [5]. If a molecule is sufficiently lipophilic to rapidly cross the epithelium, it is the stroma that becomes rate limiting.

The Bowman's and Descemets membrane do not provide significant resistance to drug penetration. The endothelium is a monolayer of cells with large intercellular junctions, which presents a leaky lipophilic barrier. The endothelium is definitely not rate limiting for hydrophilic compounds but it may play a small role in determining the permeability for lipophilic compounds [2,5].

3. Drug properties affecting absorption

In an intact cornea, drug penetration depends primarily on the partitioning properties of the therapeutic agent. For example, let us consider the often debated question of which prednisolone formulation is most effective. Phosphate preparations are hydrophilic solutions and, thus, penetrate the epithelium poorly. This is in contrast to the hydrophobic alcohol-base and acetate suspensions that should theoretically be more adept to penetrate all layers of the cornea. The experimental data comparing the prednisolone phosphate and prednisonole acetate permeability does not demonstrate this fact clearly. Leibowitz *et al.* concluded that prednisolone acetate 1%

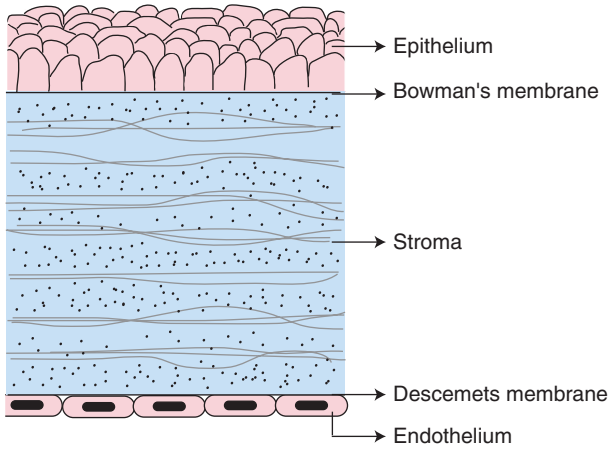

Figure 2. Anatomy of the cornea.

suspension was the most effective in getting across the cornea and in suppressing corneal inflammation [6]. Other studies showed that, despite the theoretical advantage the acetate formulation had, in clinical situations the two medications are probably equally effective [7]. The acetate formulation is a suspension and needs shaking to reach the dosing level required, decreasing the patient compliance and varying the drug delivered to the eye [8]. Thus, there is a good rationale for preferring phosphate solutions that provide more consistent dosage of the drug.

Increasing the drug concentration and dosage frequency should theoretically increase the drug delivered to the anterior chamber. Using the example of topical prednisonole, Liebowitz *et al.* have shown that although increasing the concentration of prednisolone acetate by > 1% did not increase the anti-inflammatory effect [9], increasing the dosing frequency did increase the efficacy of the drug [10]. The limiting factor, however, was decreased patient compliance.

Drug solubility affects ocular absorption in two ways. The presence of insoluble deposits of the drugs in the cul-de-sac, commonly seen with topical ciprofloxacin, leads to a sustained effect, which in turn produces altered permeability parameters for different esters of the drug. Poorly soluble drugs such as steroids can be delivered to the eye in suspension. For maximum drug bioavailability, a suspension needs to have a rapid rate of dissolution of the suspended particles in the tear film during the contact time. Ocular bioavailability is related to particle size [11], as is the dissolution rate and the potential for irritation. Any size < 10 µl minimises ocular irritation and reflex tearing [12]. Drugs in suspension also have the added disadvantage of poor patient compliance because they need to be resuspended before each use by shaking, as previously mentioned.

Cyclodextrins are used to solubilise complex drugs that are poorly soluble, unstable or difficult to formulate. The cyclodextrin–drug complex has improved wettability, dissolution, solubility and stability in solution. The cyclodextrin–drug complex preserves the intrinsic ability of the drug to penetrate biological membranes, thus improving drug absorption [13]. Cyclodextrin formulations have been shown to improve the penetration of pilocarpine [14] and carbonic anhydrase inhibitors [15].

The pH of a drug determines its degree of ionisation. A higher proportion of the nonionised species results in higher transcorneal permeability, as shown by Mitra *et al.* [16] for pilocarpine and Brechue *et al.* [17] for topical carbonic anhydrase inhibitors. Variations in osmolality of 220 – 640 mOsm/kg in the tears seem to be tolerated; beyond these values, irritation occurs causing reflex tearing and blinking. In general, the eye tolerates hypotonic solutions (which increase epithelial permeability) better than hypertonic solutions, which cause an immediate dilution as the drug draws out water from the conjunctiva and cornea by osmosis [4].

Solutions in multiple-dose containers must have a preservative to prevent the growth of microorganisms. Benzalkonium chloride (BAC), the most commonly used preservative, also enhances corneal permeability of various drugs [18,19]. On the other hand, this same effect results in epithelial toxicity when the dosing schedule requires multiple administrations in one day [20,21]. In fact, after the topical administration of one drop of 0.01% BAC in rabbit eyes, significant BAC amounts could be found in all ocular surface tissues ≤ 168 h after application [22]. A new multi-dose bottle has been introduced for an artificial tear formulation, which uses an Airless Antibacterial Dispensing System (AADS ™; Pfizer, Inc.). It uses a valve system and an airless pump with a silver antibacterial coil that allows for preservative-free eye drops.

4. Non-corneal route of absorption

Although the corneal route is assumed to be the principle route of entry for topical drugs into the eye, studies have conclusively proved that the conjunctiva–scleral layer also plays a role in the drug absorption of large hydrophilic molecules such as inulin [23] and timolol maleate, carbonic anhydrase inhibitors, and of peptides and proteins that can be used as drug carriers. The permeability of the conjunctiva to large hydrophilic molecules is in fact twice that of the sclera and higher than the cornea [24,25]. The drug reaches the anterior chamber either by vessel uptake, lateral diffusion into the cornea or by direct diffusion through the conjunctiva, sclera and ciliary body into the anterior chamber. This route is generally less productive as the limbal area is full of blood vessels, which dissipate the drug into the systemic circulation [4].

Thus, the amount of drug that diffuses across the cornea depends on more than just the drug formulation. The presence or absence of an epithelium, the wastage of the drug due to tear drainage and, the factor over which we have minimal control, patient compliance, all play a role in affecting drug absorption in the clinical setting.

5. Improving drug absorption by topical drug delivery

5.1 Patient compliance

Patient adherence to topical drug regimens has mostly been studied for glaucoma patients who need lifelong medications. All the studies prove that the lesser the number of drops, the better the adherence. In a recent compliance study, the proportion of patients who deviated from the prescribed regimen ranged from 5 – 80% [26]. Poor adherence is often mistaken for poor efficacy of the drug. Drugs with local or systemic side effects have poorer patient compliance.

5.2 Reducing drug drainage

As shown in Figure 1, nearly 50 – 100% of a topically applied drug ends up in the systemic circulation. Reducing the volume of the drop instilled to 5 – 15 µl [27] improves the local/systemic effect balance. Punctal occlusion helps to reduce drug absorption by the large nasal mucosa and to decrease side effects [28].

5.3 Increasing drug penetration through the epithelium

The epithelium is the major barrier for most ocular drugs, as previously mentioned. The penetration enhancers are a class of drugs that transiently change the permeability of the cornea.

Preservatives such as BAC are known to increase the permeability of the epithelium to various drugs [18,19]. BAC is one of the most common preservatives used in the ophthalmic drug formulation; however, multiple drops of BAC do cause epithelial accumulation and, eventually, epithelial toxicity [20,21]. The calcium chelators such as EDTA are reported to loosen the tight junctions between the superficial epithelial cells and increase paracellular transport [29]. Surface enhancers are another class of drugs that are incorporated into the lipid bilayer and change the membrane properties, that increases transcellular transport. Numerous classes of surfactants have been described in the literature, including nonionic surfactants, bile salts and acids, lysophosphatidyl lipids and others [30]. Other penetration enhancers that are used include the glycosides with surface activity (Saponin, Digitonin), and fatty acids that affect both the cell membranes and the tight junctions. Azones, cytochalasins and ionophores have also been shown to effectively enhance transcorneal penetration [30].

Iontophoresis is a technique of introducing drugs into tissues noninvasively, by imposing electric currents across the cornea or sclera. Transcorneal iontophoresis has shown enhanced drug penetration into the aqueous [31]. Recent studies in human volunteers have demonstrated that iontophoresis works for anti-inflammatory drugs [32]. However, this technique can also result in corneal epithelial and endothelial damage [33]. Further studies are needed to establish the safety and efficacy profile of this technique.

6. Increasing retention time in the conjunctival cul-de-sac

6.1 Ointments and emulsions

Ophthalmic ointments are emulsions of aqueous drugs and ointment bases (e.g., white petroleum). The major advantage is their tendency to serve as a drug depot in the conjunctival sac, resulting in enhanced and sustained drug absorption. The disadvantages include blurring of vision on instillation, difficulty in applying the exact dose, and sensitivity of the base to temperature. Most drugs are not soluble in petroleum ointments and exist as solid microcrystals that have to diffuse through the petroleum to reach the surface. Thus, although ointments are useful for prolonged drug delivery, especially at night, they are not necessarily better than solutions.

Interest in emulsions has been renewed by the submicron emulsion (0.1 – 0.3 µm) with nonionic surfactants for stability [34]. Increased ocular–retention time and increased bioavailability of indometacin, timolol and other drugs have been reported with submicron–emulsion formulations [35,36]. Ciclosporin is available commercially as an ophthalmic emulsion (RESTASIS®, Allergan, Inc.).

6.2 Increasing viscosity of solutions

The viscosity of ophthalmic solutions can be increased by methylcellulose, hydroxypropylmethycellulose, hydroxyethyl cellulose and poly(vinyl alcohol) (PVA) among others. They increase the residence time of the drug and slow clearance, resulting in enhanced absorption [2]. Patton and Robinson suggested that the optimal viscosity of solutions should be 12 – 15 cps [37]. Higher viscosity ranges caused ocular surface irritation, increased blinking and higher drainage. A more viscous solution also causes visual blurring and may block the puncti and canaliculi.

PVA is particularly useful as a drug component because it reduces the surface tension of water, reduces the interfacial tension at an oil–water interface and enhances tear–film stability. A PVA–tropicamide solution combination was found to be 3.7-fold more effective than ophthalmic solutions and 2-fold more effective than other polymers [38]. This property has resulted in the incorporation of PVA in many artificial tear formulations.

6.3 Mucoadhesive formulations

Mucoadhesion refers to the process of attachment of the drug carrier system to the mucin coat. In the eye, the drug system will bind to the mucin coat covering the conjunctiva and cornea. Mucoadhesives increase the residence time and, in addition, provide intimate contact between the drug and the absorbing tissue, which results in a high drug concentration in the local area and a high drug flux through the absorbing tissue. The most commonly used mucoadhesives are macromolecular hydrocolloids that cannot cross biological membranes [30].

Hyaluronic acid is a mucoadhesive biological polymer that also has the advantages of having a high water binding capacity, non-irritancy, increased viscosity and pseudoplastic behaviour. Other mucoadhesives include carboxymethycellulose, polyacrylic derivatives, xanthane and carrageenan [30]. Lubricant eye drops for dry eye treatment often use mucoadhesives for longer drug retention periods (e.g., Refresh Liquigel™ with carboxymethycellulose; Allergan, Inc.).

Chitosan is a polymer with good ophthalmic potential. It is biodegradable, non-toxic and biocompatible, besides being pseudoplastic and viscoelastic in solution. Chitosan microspheres have been used to deliver acyclovir through rabbit corneas [39], and have been shown to enhance ocular delivery of ofloxacin from erodible inserts based on poly(ethylene oxide) [40].

6.4 Gels and inserts

Gels are semisolid systems with particles or macromolecules distributed in a liquid, which increase retention time. Gel formulations of pilocarpine have proven to be more efficacious with lower dosing frequency than solutions [41].

In situ gel-forming systems are formulations that undergo gellation on contact with the ocular system. They combine the advantages of dispensing an aqueous solution with increased retention time of a high-viscosity formulation. Gels that are activated by ions [42], pH [43] and temperature [44] have also been developed. They have been shown to increase the bioavailability of the drugs under experimental conditions and represent an exciting approach to ophthalmic drug delivery.

Ophthalmic inserts are solid devices that are placed in the conjunctival cul-de-sac. These devices are designed to release the drug at a constant rate for a prolonged duration of time whilst minimising systemic absorption through the nasal mucosa and improving patient compliance. The pilocarpine Ocusert® (ALZA Corp.) was the first marketed device to achieve zero-order kinetics. The drug is contained in a reservoir enclosed by two release-controlling membranes made of ethylene vinyl acetate copolymer and surrounded by a ring to aid in the positioning and placement. It has been shown to maintain a therapeutic effect with a smaller amount of drug and, thus, lesser side effects [45].

Other inserts include medicated contact lenses and collagen shields. These have been shown to provide a prolonged drug delivery with minimal systemic absorption. Hyaluronic acid derivative corneal shields have been shown to provide continuous methylprednisolone drug delivery to the rabbit anterior chamber for 48 h [46]. Another potential advantage of insert therapy is the possibility of promoting non-corneal penetration, especially of hydrophilic drugs that are poorly absorbed through the cornea.

6.5 Microparticles

Liposomes are microscopic structures (0.01 – 10 µm) consisting of spheres (vesicles) of lipid bilayers separated by water or an aqueous buffer compartment. The major advantage ascribed to liposomal formulations is the ability to circumvent cell membrane barriers and protect the delivered drug from metabolic or immune attack, reduce drug toxicity, and enhance the therapeutic effect. Almost every class of topically or subconjunctivally applied ophthalmic drug has been studied in liposomal form, including antibiotics, antifungals and steroids [47] with promising penetration and pharmacokinetics, although these results are preliminary. Therefore, there are a limited number of topical ophthalmic drugs using liposomes on the market.

Liposomal formulations are preferentially taken up by phagocytes. Liposomal antirejection drugs have been shown to delay graft rejection in animal models [48]. This may be an extremely useful tool in the corneal graft surgeon's repertoire.

Liposomal photosensitisers that can be activated by lasers [49] have been used to treat corneal neovascularisation and anterior segment tumours. Heat-releasable liposomal formulations have also been devised [50], possibly for focal application of toxic drugs.

Nanoparticles are polymeric colloidal particles ranging in size from 10 to 1000 nm. They consist of macromolecular materials in which the drug is dissolved, entrapped, encapsulated, and/or to which the drug is adsorbed or attached. Nanosperes are solid matricial spheres with the drug in the matrix or adsorbed on the surface of the colloidal carrier. Nanocapsules are small capsules with a central cavity surrounded by a polymeric membrane.

Nanoparticle formulations of several ophthalmic drugs have been studied, and have demonstrated increased corneal permeability [51]. The proposed mechanism is an enhanced retention time in the cul-de-sac, possibly due to the bioadhesive properties. Chitosan nanoparticles in particular show a great deal of promise because of the mucoadhesive properties of chitosan [52]. In a recent study De Campos *et al.* proved that fluorescent chitosan nanoparticles penetrated into the conjunctival and corneal epithelium, and did not affect the viability of the cells [53]. Nanoparticle suspensions of insert polymer resins have also been used to enhance drug delivery to the anterior chamber [54,55].

7. Subconjunctival drug delivery

The subconjunctival route is an attempt to minimise dosing frequency while maintaining a sustained drug delivery to the anterior and posterior segment over a prolonged duration of time. However, the morbidity of repeated subconjunctival injections, particularly in inflamed eyes, has reduced the popularity of this route for anterior segment drug delivery. In a corneal ulcer study comparing the subconjunctival and the topical application for gentamicin and cefazolin, subconjunctival injections produced high but transient peaks, followed by persistent low troughs [56]. In contrast, eye drops produced moderate but sustained concentrations throughout the treatment period. This study reported equal efficacy for both routes. Other studies have demonstrated a sustained therapeutically effective drug concentration after subconjunctival

gentamicin [57]. In general, hydrophilic drugs, which penetrate through the sclera, are more effective when given by the subconjunctival route because they are shielded from the culde-sac. A drug given by this method is not required to penetrate the conjunctival epithelium, a significant rate-limiting barrier for water-soluble drugs.

The conjunctiva–cornea barrier is bypassed in the subconjunctival injection, permitting direct transcleral drug delivery. Subconjunctival implants represent an easy and minimally invasive (compared with intravitreal) route for sustained transcleral drug delivery to the posterior segment. Kompella *et al.* have demonstrated retinal delivery of budenoside using subconjunctival nanoparticles [58]. Edelhauser *et al.* have demonstrated that collagen matrix–cisplatin [59] and fibrin sealant–carboplatin [60] formulations provide better release of the drug in several ocular tissues including the retina as compared with a drug solution, and may be a useful adjunct to the treatment of retinal tumours.

8. Posterior segment drug delivery

Delivering drugs to the posterior segment of the eye is a greater challenge than to the anterior segment. The most common modes are topical delivery, systemic administration, periocular and intravitreal injections. The approach varies depending on the target tissue.

Drug delivery to the anterior sclera or episclera can be achieved through topical medications or subconjunctival injections. Bilateral and posterior scleral diseases such as scleritis are generally treated by systemic medications. Periocular injections can be risky with associated scleral disease and scleral thinning. Scleral diseases are often immunological in nature; they are usually caused by systemic rheumatological illnesses, which need long-duration systemic immunosuppresives or steroids.

Drug delivery to the retina and vitreous is another matter. The major limitation to transcleral and systemic administration is the blood–ocular barrier.

8.1 The blood–ocular barrier

The blood–ocular barrier is comprised of an outer and an inner component. The outer component is formed by the junctional complexes of the retinal pigment epithelial cells (RPE) cells and the pigment epithelial cells of the pars plana, and the inner barrier component is formed by the tight junctions between the endothelial cells of the retinal capillaries. This effectively limits the perfusion of the drug from the highly vascular choroid, with its high rate of blood flow and permeable capillaries, into the retina and vitreous; posing similar pharmaceutical challenges as the blood–brain barrier.

To achieve a therapeutic concentration in the vitreous, the drug must pass through the blood–retinal barrier (BRB). Lipid-soluble drugs, such as minocycline and chloramphenicol, do penetrate the BRB but the β-lactams (cefazolin) and aminoglycosides (amikacin), which are used in the treatment of endophthalmitis, do not reach adequate vitreous concentrations after systemic administration [61]. However, newer drugs such as gatifloxacin (which have a lower MIC_{90}) do seem to achieve therapeutic drug levels in the vitreous in the phakic noninflamed eye after systemic administration [62]. Other factors affecting penetration through the BRB include pH (which affects drug ionisation and, therefore, polarity), molecular weight, and protein binding (it is generally believed that only unbound drugs can pass through the BRB [63]).

Inflammation and trauma also have important roles in breaking the BRB by disrupting tight junctions, increasing transendothelial vesicles, increasing pinocytosis and the formation of microvilli. These factors are extremely important for both the treatment and prophylaxis of inflamed and traumatised eyes. Ciprofloxacin, administered systemically, reaches therapeutic concentrations in the vitreous of eyes following trauma and inflammation [63,64]. However, as the eye heals and the inflammation decreases, the drug concentration may become difficult to predict.

Other factors that affect drug delivery to the posterior segment are anatomical. The aphakic and vitrectomised eye is essentially converted to one single chamber, enhancing the distribution of the drug. Ciprofloxacin does reach therapeutic levels in the vitreous of silicone oil-filled eyes after oral administration [65], and cefazolin levels were higher in vitrectomised eyes than normal eyes after intravenous injection [66], particularly if the eyes were inflamed.

9. Periocular injections

Another major method of drug delivery to the posterior segment is the periocular route, which includes subconjunctival, retrobulbar, peribulbar and posterior subtenon injections. These methods are far less invasive than the intravitreal. The drug delivered by periocular injection can reach the posterior segment by three main routes: transcleral; systemic circulation through the choroid; and the anterior route through the tear film, cornea, aqueous and the vitreous.

The sclera has a large surface area (16.3 cm^2) [67] and scleral permeability shows no dependence on lipophilicity but a dependence on molecular radius [5]. As with the corneal stroma, the sclera is composed of collagen and proteoglycan fibres with few protein binding sites. Drugs permeate through the aqueous intercellular media of the sclera occupying the pores between the collagen fibres [68,69]. Thus, pore diameter and the intracellular space are important determinants of transcleral drug delivery, particularly for drugs such as large hydrophilic peptides and oligonucleotides. The cornea is relatively impermeable to solutes with a molecular size of > 1 kDa; however, dextran (40 kDa) and albumin (69 kDa) readily penetrate the sclera [70,71]. Scleral permeability is affected by an increase in intraocular pressure, but the effect seems to be minimal at 15 mmHg [72]. Scleral hydration, however, seems to be independent of intraocular pressure [73].

Transcleral diffusion of various molecules of different molecular weight and therapeutic importance has been studied. The scleral permeability constant (K_{trans}) of fluorescent-labelled vancomycin, polymyxin B and penicillin G were $6.66 \pm 1.46 \times 10^{-7}$, $3.90 \pm 0.59 \times 10^{-7}$ and $50.8 \pm 4.8 \times 10^{-7}$ cm/s, respectively [74]. A recent study demonstrated that triamcinolone acetonide could diffuse transclerally with a K_{trans} of $1.47 \pm 0.17 \times 10^{-5}$ cm/s [75]. The K_{trans} for the transcleral diffusion of a naked, single-stranded, fluorescein-labelled oligonucleotide has been reported to be $7.67 \pm 1.8 \times 10^{-7}$ cm/s [76].

Weijtens *et al.* studied the intraocular dexamethasone concentration in the unoperated human eye after different routes of administration. They found that subconjunctival injection of dexamethasone diphosphate 2.5 mg resulted in an estimated vitreous dexamethasone concentration (peaked at 3 h) that was three-times higher than a 5-mg peribulbar injection (peaked at 6 – 7 h) and 12-times higher than a 7.5-mg p.o. dose [77,78]. Systemic absorption after both the peribulbar and subconjunctival injections is of the same order of magnitude as an oral dose. They hypothesise that after a peribulbar injection, the drug reaches the vitreous through both the haematogenous and the transcleral route. After a subconjunctival injection, in addition to the haematogenous and transcleral route, the transcorneal (via leakage through the puncture wound in the conjunctiva) route is believed to provide a significant contribution. Similarly, the same group found that subretinal fluid concentrations of dexamethasone in patients with retinal detachments were higher with subconjunctival injections than peribulbar injections or oral administration [79]. On the other hand, Lee *et al.* injected radiolabelled mannitol subconjunctivally in rabbits and concluded that, after subconjunctival injection, direct penetration through the sclera is the predominant pathway for drug delivery to the posterior segment with minimal contribution from the recirculation pathway and the transcorneal pathway [80].

10. Enhancement of transcleral drug delivery

10.1 A transcleral depot

The human eye is remarkably tolerant of foreign bodies on the sclera, the most obvious example being the scleral buckle used in retinal-detachment surgery. A transcleral depot would fulfil the demands for a nondestructive, minimally invasive method for sustained drug delivery. Scleral implants of indometacin have been reported to be effective in animal studies [81], and an intrascleral betamethasone depot has been shown to provide sustained drug release [82]. The hurdles are the orbital clearance, uveoscleral outflow, choroidal blood flow and the BRB. Collagen matrix and fibrin sealant have proven effective in promoting sustained drug delivery across the sclera [59,60]. Microspheres and other nanoparticles have been used to deliver the anti-VEGF aptamer EYE-001, budesonide and other angiostatic factors across the sclera to the retina [83-85]. Anecortave acetate is a novel angiostatic cortisone being evaluated clinically for the treatment of exudative age-related macular degeneration. It is delivered as a posterior juxtascleral depot using a specially designed curved cannula and is currently undergoing clinical trials as Retaane™ (Alcon).

10.2 Increasing scleral permeability

Scleral permeability is increased by scleral thinning, increasing tissue hydration and temperature. Age, cryotherapy and diode laser photocoagulation do not seem to affect scleral permeability [86]. There have been studies that demonstrate that prostaglandins improve scleral permeability. This increased permeability is accompanied by increased expression of matrix metalloproteases and could be used to enhance transcleral delivery of peptides into the posterior segment [87-89]. A recent study proposed that 0.01 and 0.05% BAC could be used to increase transcleral penetration of drugs with minimal toxicity [90].

10.3 Iontophoresis

Iontophoresis has been proven to increase transcleral delivery of various drug classes, including fluorescein, antibiotics and steroids [31]. Unfortunately, it may also result in retinal damage: retinal oedema, disruption of the normal retinal architecture, haemorrhagic necroses and retinal pigment epithelial hyperplasia [91]. Further studies are needed to develop a viable iontophoresis method. Low frequency ultrasound (20 kHz) has been shown to increase transdermal permeability to drugs [92]. This technique has not yet been reported in the eye.

11. The intravitreal injection

Introducing drugs into the eye by direct injection through the pars plana is the most efficient mode of drug delivery to the posterior segment. It is also the most invasive and the route with the most serious complications. In the case of intravitreal triamcinolone, rates of endophthalmitis varying from 0.15% to as high as 0.87% have been reported [93-95].

These drugs can be introduced into the vitreous in solution, in a depot formulation or dispersed in microparticles. In solution, the drugs diffuse through the vitreous and the aqueous at the rate they would diffuse in a free solution [96]. Of the intravitreal drug transport, 30% is by convective currents in the vitreous [97]. After the initial equilibrium, the drug concentration decreases by first-order kinetics, either across the anterior hylaloid surface via the aqueous, or across the retinal surface [98]. Aminoglycosides, streptomycin, vancomycin and sulfacetamide are believed to be eliminated anteriorly, whereas the cephalosporins, clindamycin and dexamethasone are believed to be eliminated posteriorly [61]. Increasing the molecular weight of the drug increases the retention time in the vitreous. Most drugs have a molecular weight of < 500 Da and the half-life is likely to be < 3 days with frequent reinjections necessary [96]. The internal limiting membrane is impermeable to linear molecules > 40 kDa and globular molecules > 70 kDa [99]. Thus, larger macromolecules will have a longer

retention time, possibly weeks, but their effect on the retina after an intravitreal injection is limited.

Liquefaction of the vitreous, after vitrectomy or due to age, changes the pharmacokinetics of an intravitreal injection. Vitrectomy and lensectomy results in the formation of one intraocular compartment. The vitreous has an important role in retaining the intravitreal antibiotic and many antibiotics, including amikacin and cefazolin, have a reduced half-life after vitrectomy [61].

Intraocular inflammation has significant effects on drug delivery; it decreases the active transport of the drugs through the retinal surface, but increases the permeability of the posterior retinal and anterior hyaloid surface structures. Both amikacin and gentamicin (cleared through the anterior route) have reduced half-life in the vitreous of the inflamed eye [61]. Intravitreal drugs that are removed posteriorly have, in general, a shorter half-life in the vitreous than anteriorly eliminated drugs because active transport may be involved in posterior clearance. Probenecid has been proven to increase the half-life of intravitreal carbenecillin and cefazolin in the monkey [100]. Inflammation increases the half-life of intravitreal cefazolin, probably by interfering with active transport [101].

A drug delivery depot introduced into the vitreous should provide a long-lasting and steady drug delivery technique. The depot mass and the duration of drug release will vary if the vitreous is liquefied, or if the drug has to be delivered to the retinal surface rather than to the vitreous [98]. Vitreous implants, either tethered or free, consist of a core of drugs (ganciclovir, steroids, ciclosporin and others) surrounded by layers of polymers. The implants omit the need for repeated intravenous or intravitreal injections and thus improve patient compliance. They provide steady drug delivery, which may be important for the treatment of chronic ocular conditions. However, implants have disadvantages. There may be a risk of drug toxicity and risks associated with the surgical placement of implants. Intravitreal implants have been used to deliver ganciclovir, steroids and ciclosporin to the posterior segment [102-104]. Current ganciclovir implants (Vitrasert™, Chiron Vision) deliver the drug for ~ 8 months and achieve intravitreal levels higher than maintenance intravenous therapy; they have also been shown to decrease the progression of cytomegalovirus retinitis. However, these implants do not affect cytomegalovirus retinitis in the other eye and do not prevent or treat systemic infection. The fluocinolone acetonide intravitreal implant (Retisert ™, Bausch and Lomb) has been developed to last for 30 months. Complications such as retinal detachments, endophthalmitis, cataract and vitreous haemorrhage have been reported with these implants but the number of these complications is small. The implants essentially deliver the same drug concentration to all patients, and individual drug adjustments based on clinical response are not possible.

Drugs can be administered into the vitreous as microparticles or liposomes. Other than loss of drug from the vitreous and release of drug from the particles, the clearance of the microparticles from the vitreous must also be considered. The largest solute shown to diffuse out of the vitreous is hyaluronic acid (molecular weight of 1,000,000 Da). Molecules larger than this are assumed to have no diffusion out of the vitreous [98]. However, vitreous currents into the optic nerve sheath and phagocytosis [105,106] in the vitreous also have to be considered. The possibility of nondegradable particles, especially liposomes, accumulating in the vitreous after repeated injections is high, a possibility that can only be treated by vitrectomy.

As the diameter of particles rises to 50 nm, the light scattering interferes with vision [98]. There is also a risk of sedimentation under gravity that may result in toxic concentrations where the particles accumulate on the retina. No sedimentation was observed for 50-nm spheres; its influence having been eliminated by Brownian motion. Presumably the optical effects will restrict the size of the particle before sedimentation has an effect.

An important consideration when injecting intravitreal drugs is toxicity. Aminoglycosides, in particular, are known to be toxic to the photoreceptors and RPE with relative sparing of the inner retina. The relative toxicities established by D'Amico were gentamicin > netilimicin = tobramycin > amikacin = kanamycin [107]. Other drug formulations have vehicles that could be toxic to the retina. Intravitreal triamcinolone acetonide has benzyl alcohol as the vehicle. Benzyl alcohol has been implicated in cases of sterile endophthalmitis after intravitreal injection, and aseptic meningitis after intrathecal injection [108,109]. Therefore, a cleansing technique has to be followed to decrease the solvent before triamcinolone injection [110].

12. Expert opinion

Intravitreal implants, which provide sustained-release drug delivery, have been described above. Liposomes have also been described previously in the review. They have several properties that make them ideal for intravitreal drug delivery; the ability to incorporate precise drug amounts over varied concentrations, the ability to prevent metabolic degradation of the drug and the ability to slowly release the drug into the vitreous. Several drugs have been evaluated for delivery with liposomes including amikacin, ciclosporin and ganciclovir [47].

Liposomes have been injected into the subretinal space and vitreous for gene transfer to the retina and choroid. DNA, histones and proteins are fused with the liposomes, which are then incorporated into envelopes of vector viruses. This allows the liposome to enter the cell cytoplasm directly without being digested by the liposomal system of the cell [111]. In a rat model, this method of gene transfer has been used to overexpress enzymes in RPE cells and inhibit experimental choroidal neovascularisation [112]. Heat-sensitive liposome drug preparations have also been formulated. A light source will release the drug [113]. This system could eventually be used to treat choroidal diseases.

Gene transfer to the posterior segment has also been extensively studied. Viral vectors or viral envelopes are the most commonly used means to transfer DNA, histones or proteins to the retina cells [114,115]. Nonviral modes of gene transfer include electroporation or lipofection to evaluate tissue-specific promoter fragments, or to evaluate the effects of transgene expression in the retina [116].

Microspheres loaded with drugs as doxorubicin, retinoic acid and ganciclovir have been proven to be more effective than regular intravitreal drug delivery in solution [114]. They have the advantage of lasting longer than a single injection but do not need a large sclerotomy as most current implants do.

Biodegradable scleral plugs containing different drugs (e.g., 5-fluorouracil [5-FU], corticosteroids, fluconazole and tacrolimus) used to close the ports made during pars plana vitrectomy are an interesting approach [115]. They may be very useful at combating proliferative vitreoretinopathy and other postoperative complications.

Berger *et al.* studied the intravitreal injection of covalently linked 5-FU with dexamethasone and 5-FU with triamcinolone [116]. Individually, these drugs have a short half-life in the vitrectomised eye but binding the drugs covalently increases their half-life and limits the active drug released.

The study of ocular-drug pharmacokinetics is exciting with novel approaches to drug delivery being developed all the time. The drugs have to overcome the natural anatomical barriers in the eye, including the blood–aqueous and blood–retinal barriers but the drug delivery technique has to be as free from complications as possible. The drug delivery route thus has to be individualised to the drug formulation and the therapeutic drug effect desired, and multidisciplinary research, involving experts from pharmacology, biomaterials, ophthalmology, pharmaceutics and biology, is required to develop newer drug delivery devices.

Declaration

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Affiliation

Deepta Ghate[1] MD &
Henry F Edelhauser[†2] PhD
[†]Author for correspondence
[1]Research Fellow, Emory University Eye Center, 1365B, Clifton Road, Atlanta, GA 30322, USA
[2]Ferst Professor of Ophthalmology and Director of Ophthalmic Research,
Emory University Eye Center, 1365B,
Clifton Road, Atlanta, GA 30322, USA
Tel: +1 404 778 5853; Fax: +1 404 778 4143;
E-mail: ophthfe@emory.edu