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EDITORIAL

Drug delivery in ocular diseases: Barriers and strategies

Deep Kwatra, Ashim K Mitra

Deep Kwatra, Ashim K Mitra, Department of Pharmaceutical Sciences, School of Pharmacy, University of Missouri-Kansas City, Kansas, MO 64108-2718, United States
Deep Kwatra, Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas, KS 66160, United State
Author contributions: Both authors contributed equally to the document.
Correspondence to: Ashim K Mitra, PhD, Professor, Chairman, Department of Pharmaceutical Science, School of Pharmacy, University of Missouri-Kansas City, 2464 Charlotte Street, Kansas, MO 64108-2718, United State. mitraa@umkc.edu
Telephone: +1-816-2351615 Fax: +1-816-2355779
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Abstract

The eye is a complex organ made up of diversified cells with specified functions. Presence of anatomical, physiological and physiochemical barriers make it difficult to deliver drugs in therapeutic amounts at intended sites. To overcome these, drug delivery scientists have followed two distinct yet complimentary approaches. The first involves using alternate delivery routes to conventional ones allowing for more direct access to intended target sites. Second approach involves development of novel drug delivery systems providing better permeability, treatability and controlled release at target site. Combination of both these approaches are being utilized and optimized in order to achieve optimal therapy with minimal adverse effects.

Key words: Ocular diseases; Drug delivery; Optimal therapy; Barrier; Strategy

Core tip: The eye is a complex organ where combinations of various anatomical and physiological barriers work together to make it difficult to deliver drugs in the right amounts at the intended sites. To circumvent these barriers and to achieve desired levels ophthalmologists, ocular pharmacologists and pharmaceutical scientists have developed various drug delivery strategies with appropriate mode of administration.

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INTRODUCTION

The eye presents a complex assembly of diverse cells resulting in a very intricate structural organization with a specified function. Hence, subject of eye diseases is in itself very diverse. Ocular diseases of the eye include those that effect the entire globe of the eye as a whole to those that affect the different types of tissues involved in vision process. The transparent refractive structures of eye, *i.e.*, lens and cornea are essential for proper channeling of the light to sensory components. The eye contains multiple types of neurons essential for the communication of the sensory function performed by the light sensitive retinal cells along with the pigmented epithelial cells in the choroid and its capillaries. These sensory components need to complement each other and function in tandem to result in proper vision.

In 1909, Duane[1] wrote a comprehensive classification of eye diseases for the first time. Anatomically these can be classified as those affecting the anterior segment of the eye *vs* those involving the posterior segment of the eye. Anatomical location within the globe plays an important role in the selection of potential therapeutic regimens. Though various therapeutic entities have been identified over the years for various ocular diseases, achieving sufficient ocular bioavailability still remains the foremost challenge for ophthalmic drug delivery scien-

tists. This is because of the presence of multiple ocular barriers. Unlike the diseases of the lens, where corrective equipment's such as eye ware or surgery is the primary mode of treatment, diseases such as age related macular degeneration, diabetic retinopathy and cytomegalovirus (CMV) retinitis require therapies for the back of the eye. In order to achieve appropriate drug levels at the target site, two major approaches have been undertaken. One of the approaches consists of the exploration of better, non-invasive and therapeutically more efficient routes for ocular drug delivery. The second approach involves investigating novel drug delivery systems or devices capable of better targeted and controlled therapy.

BARRIERS TO OCULAR DRUG DELIVERY

The reason why it is difficult to achieve relevant therapeutic doses within the eye is primarily due to the presence of multiple barriers. When a dosage form is either administered topically or systemically, it faces multiple obstacles before it reaches its site of action. As a result ocular bioavailability from topically administered drug is usually only 1%-7% of the applied dose. These barriers can be broadly classified as anatomical barriers and physiological barriers.

Anatomical barriers

When a dosage form is topically administered there are two routes of entry, either through the cornea or *via* the non-corneal route. The cornea is a very tight multilayered tissue that is mainly composed of five sections: epithelium, bowman's membrane, stroma, descemet's membrane and endothelium. Out of these it's the epithelium which acts as the principal barrier. These 5-6 layers of columnar epithelial cells with very tight junctions create high paracellular resistance of 12-16 kΩ.cm[2]. It acts as a major barrier to hydrophilic drug transport through intercellular spaces. On the other hand stroma, which consists of multiple layers of hexagonally arranged collagen fibers containing aqueous pores or channels allow hydrophilic drugs to easily pass through but it acts as a significant barrier for lipophilic drugs. Thus for a drug to have optimum bioavailability, it should have the right balance between lipophilicity and hydrophilicity. The remaining layers are leaky and do not act as significant barriers.

Non-corneal route bypasses the cornea and involves movement across conjunctiva and sclera. This route is important especially for large and hydrophilic molecules such as peptides, proteins and siRNA[3]. The conjunctiva is more permeable than cornea especially for hydrophilic molecules due to much lower expression of tight junction proteins relative to corneal epithelium. High vascularity of the limbal area renders this route not suitable for drug delivery as the blood vessels remove a large fraction of absorbed dose[4]. Only a small fraction of the dose reaches the vitreous.

Physiological barriers

The eye's primary line of defense is its tear film. Bioavailability of topically administered drugs is further reduced by precorneal factors such as solution drainage, tear dilution, tear turnover, and increased lacrimation[5]. The lacrimal fluid is an isotonic aqueous solution containing a mixture of proteins (such as lysozyme) as well as lipids. Following topical application, lacrimation is significantly increased leading to dilution of administered dose. This in turn lowers drug concentration leading to diminished drug absorption. Rapid clearance from the precorneal area by lacrimation and through nasolacrimal drainage and spillage further reduces contact time between the tissue and drug molecules. This in turn lowers the exact time for absorption leading to reduced bioavailability. The average tear volume is 7-9 μL with a turnover rate of 16% per minute[6]. Thus drugs administered as eye drops need to be isotonic and nonirritating to prevent significant precorneal loss.

Drug and dosage form related factors

Christopher Lipinski's[7] rule of five give a general consideration to what physical properties a molecule should have to show favorable ADME characteristics. The physicochemical properties of the drug molecule become even more important in the case of ocular drug delivery because of the complex anatomical and physiological constrains. The rate of absorption from the administered site depends highly on the physical properties of drug molecule (solubility, lipophilicity, degree of ionization and molecular weight) and ocular tissue structure.

Solubility: Solubility is dependent on the pKa of the drug and pH of the solution. With these parameters one can determine the ratio of ionized to unionized molecules. Usually unionized molecules can readily permeate biological membranes. As previously shown by our group that the permeability of unionized pilocarpine is almost two fold greater than that of its ionized form[8]. In case of ionized species, their charge can also affect permeability across the cornea. The corneal epithelium bears a negative charge at the pH of lachrymal fluid and hence cationic species tend to penetrate at a faster rate to their anionic counterparts.

Lipophilicity: Lipophilicity and corneal permeability display sigmoidal relationship[9]. This is because of the differential permeability of the different layers of cornea towards lipophilic drugs. As previously mentioned, lipophilic drug tend to permeate easily through the epithelial layers of cornea. But the hydrophilicity of the inner layer of cornea (stroma) requires higher hydrophilicity for optimal permeation. Partition coefficient (Log P) value ranging from 2-4 is found to result in optimum corneal permeation[10].

Molecular weight and size: The weight and size of a molecules play a critical role in deciding its overall permeability through paracellular route. The diameter of the tight junctions present on corneal epithelium is less than 2 nm. Thus, molecules having molecular weight

less than 500 Dalton are able to permeate readily[11]. The paracellular permeability is further limited by the pore density ($4.3 \times 10^6/cm^2$) of corneal epithelium. The conjunctiva has larger paracellular pore diameter thus allowing permeation of larger molecules such as small and medium size peptides (5000-10000 Daltons)[12]. Permeation across sclera occurs through the aqueous pores and molecular size of the solute can be the determining factor[13,14]. Sucrose (molecular weight-342 Daltons) permeates 16 times faster than inulin (molecular weight-5000 Daltons)[2]. Scleral permeability is approximately half of conjunctiva but much higher than cornea.

DRUG DELIVERY BY NOVEL ROUTES

Drug delivery through topical or systemic route faces a number of challenges limiting their success. Advancements in drug design, drug formulation and devices have led to successful products. But the scientists have experimented with alternate routes of drug delivery that can overcome barriers presented by the more conventional routes. Injections through visible portions of the sclera targeting various sections of ocular structures are routinely carried out by a trained specialist.

Intravitreal injection

Intravitreal injection (IVI) involves delivering of the drug formulation directly into the vitreous humor through pars plana. This method provides direct access to the vitreous and avoids both the cornea and also the scleral blood vessels. Formulations such as solution, suspension or a depot formulation can be administered through this route. Drug elimination occurs either through the retina or the anterior chamber through the aqueous humor following a first order rate of decline[15]. This rate of elimination has a linear correlation with the molecular weight of the drug. Larger molecules tend to have longer half-lives as high as several weeks as compared to less than 3 d for low molecular weight compounds[16].

IVI administration is associated with adverse effects such as retinal detachment, cataract, hyperemia and endophthalmitis[17]. Sustained release drug delivery systems can help by lowering frequency of administration thus allowing for better patient compliance.

Subconjunctival injections

This injection delivers the drug beneath the conjunctival membrane that lines the inner surface of eyelid. It allows for circumvention of both cornea and conjunctiva allowing the drug direct access to the sclera. It is much less invasive with lesser side effects when compared to intravitreal injections[18]. The method is an excellent route for delivering hydrophilic drugs as it bypasses their rate-limiting barriers allowing more drugs to enter into the vitreous. It is an excellent route for delivering both depot forming formulations as well as for the delivery of macromolecular drugs such as avastin (bevacizumab: a recombinant monoclonal antibody against VEGF) and insulin[19-23].

Retrobulbar and peribulbar route

Retrobulbar injection is given through eyelid and orbital fascia and it places the drug into retrobulbar space. This mode administers the drug to the back of the eye ball and is used to deliver drugs such as antibiotics and corticosteroids. This route is especially applicable for the delivery of anesthetic agents as it causes minor or no change in IOP though in certain orbital diseases the reverse is also possible[24-26]. Yet, it is a very delicate procedure as it may damage the optic nerve and thus requires proper expertise and equipment[17,27].

Peribulbar route for drug delivery involves injections above and/or below the globe. It is also a viable route for the delivery of anesthesia especially in cases of cataract surgery, It is a safer route compared to the retrobulbar route with reduced risk of injury[28,29]. Though it a safer method unlike retrobulbar injection multiple cases of elevated intraocular pressure after peribulbar injections have been reported[24,30,31].

Sub-tenon injections

Sub-tenon injections are administered into a cavity between tenon's capsule and sclera using a blunt cannula. Pre-operative deep sedation is also not a requirement for this procedure[32]. Sub-tenon route appears to be a better and safer route for delivering anesthesia relative to retrobulbar and peribulbar administration since it does not require sharp needles[33]. Steroids injected through this route have also been shown to be effective in the treatment of uveitis, cystoid macular edema, complicating uveitis and non-necrotizing scleritis[34,35].

Intracameral injections

Intracameral route is similar to intravitreal injections but this injection delivers drug to the anterior chamber. Drugs administered through this route are limited to anterior chamber with very limited access to the posterior segment. It is generally employed for anterior segment procedures such as cataract surgery[17]. Clinical studies have reported that intracamerally delivered dexamethasone is effective in reducing post-operative inflammation in glaucomatous and non-glaucomatous patients[36]. It is an efficient and often a more cost-effective method of delivering antibiotics relative to topical antibiotics and antifungal agents[37-39].

CONTROLED DRUG DELIVERY

Along with advances in methods of delivering dosage forms through various routes, significant progress has been made in the design of dosage forms allowing better targeting and controlled release.

Implants

Implants are devices that control drug release kinetics by utilizing various degradable or non-biodegradable poly-

meric membranes. These are usually surgically implanted at the pars plana[40-43]. Polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA), and polysulfone capillary fiber (PCF) are most commonly used non-biodegradable implant polymers. PVA and EVA implants are usually employed for delivering lipophilic drugs whereas PCF implants can be applied for both hydrophilic and lipophilic molecules. These non-biodegradable implants provide an advantage, *i.e.*, low burst effects, However due to their non-biodegradable nature, the implants need to be surgically removed[41,43].

Biodegradable polymers such as poly lactic acid (PLA), poly glycolic acid (PGA), poly lactic-co-glycolic acid (PLGA) and polycaprolactones undergo enzymatic and/or non-enzymatic hydrolysis. It leads to bulk erosion of encapsulated drug rather than surface erosion which are limited to polymeric matrix surface[41,44]. Burst release thus is an issue with these implants.

Gel systems

Gel formulations usually incorporate various phase changing polymers, *i.e.*, after administration, polymer phase changes into semi-solid or solid matrix in order to achieve sustained drug delivery. This change in polymer phase maybe, ion concentration, pH or temperature dependent[45]. Fluids showing viscoelastic nature are preferred for the usage in gel forming systems. Such systems containing hyaluronic acid, polyacrylic acid and/or chitosan are able to maintain high viscosity under conditions of low shear and low viscosity under high shear rate allowing ease of formulation and application along with sustained delivery. Chitosan formulation shows prolonged drug residence on ocular tissues by not only increasing the viscosity of solution but also improving mucoadhesive properties[46].

Hydrogels are the polymeric networks that are hydrophilic in nature. These polymers can incorporate large quantities of water and biological fluids into a swollen cross-linked gel system. The hydrogels have the ability to retain hydrophobic and hydrophilic agents both small as well as macromolecules. The polymer network regulates permeation and diffusion characteristics. These polymers can be biodegradable or non-biodegradable and also biocompatible based on the gelling material. Polysaccharides have been widely used in hydrogels and are considered to be more advantageous over synthetic polymers[45].

Micro and nano formulations

Micro particles: These particles are formulated with biodegradable and biocompatible polymers such as polylactide and PLGA. The particles are usually administered by intravitreal injection and are known to sustain drug release for several weeks or even months. Various advantages of this delivery system include high *in vivo* stability, biocompatibility, and controlled as well as sustained drug release[47]. These formulations can be used for delivering both small and macro molecules, and release of both hydrophilic and lipophilic molecules can be sustained by altering the block polymer ratios.

Nanoparticles: Nanoparticles can be formulated with biodegradable polymers: natural or synthetic polymers, lipids, phospholipids and even metals. As the name suggests diameter of these particles is less than 1 μm. Bioactive molecule are either encapsulated or attached to the surface of nanoparticles. PLA, PLGA and other natural polymers like chitosan, gelatin, sodium alginate and albumin are biodegradable polymers that are usually employed for the formulation of nanoparticles. Nanoparticles administered by intravitreal injection appear to sustain the release for up to 4 mo[48-50].

Liposomes: These are biodegradable and amphiphilic delivery systems usually formulated with phospholipids and cholesterol. Lipid composition, size, surface charge and method of preparation for the liposomes are modified based on their application. Liposomal formulations can be utilized for both improving the permeability as well as sustaining the release of the entrapped hydrophilic drugs[51]. Liposome encapsulated phosphodiester (16-mer oligothymidylate) (pdT16) oligonucleotides has been utilized for CMV retinitis. Liposomes sustain the release of therapeutic agents into the vitreous and retina-choroid and avoids non-targeted tissues (sclera, lens)[48,52,53].

Niosomes: These are bilayer structures which can entrap both hydrophilic and lipophilic drugs. These nonionic surfactant bilayers exhibit low toxicity and are chemically stable. Niosomes are also used in their modified form, *i.e.*, discosomes (12-16 μm) in ophthalmology. Discosomes contains non-ionic surfactant, *i.e.*, Solulan C24. These vesicles fit better in the cul-de-sac of the eye and are not drained into systemic circulation because of their large size. Higher entrapment efficiency of timolol maleate was observed in discosomes relative to niosomes[48,54,55].

Dendrimers: These drug delivery systems contain an inner core surrounded by successive series of branches. Dendrimers have the ability to display multiple copies of surface groups for biological recognition. These molecules are easy to prepare and functionalize, which make them very attractive for drug delivery. Addition of acrylic acids during formulations render them more bioadhesive leading to prolonged contact time with the absorbing area which ultimately results in longer residence time thereby lowering dosage frequency.

CONCLUSION

The eye is a complex organ where combinations of various anatomical and physiological barriers work together to make it difficult to deliver drugs in the right amounts at the intended sites. To circumvent these barriers and to achieve desired levels ophthalmologists, ocular pharma-

cologists and pharmaceutical scientists have developed various drug delivery strategies with appropriate mode of administration. Further improvements are needed to achieve effective and highly patient compliant therapies.

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