Review Article

Theme: Established Drug Delivery Technologies: Successes and Challenges

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Ocular Drug Delivery

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Abstract. Ocular drug delivery has been a major challenge to pharmacologists and drug delivery scientists due to its unique anatomy and physiology. Static barriers (different layers of cornea, sclera, and retina including blood aqueous and blood–retinal barriers), dynamic barriers (choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution), and efflux pumps in conjunction pose a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment. Identification of influx transporters on various ocular tissues and designing a transporter-targeted delivery of a parent drug has gathered momentum in recent years. Parallely, colloidal dosage forms such as nanoparticles, nanomicelles, liposomes, and microemulsions have been widely explored to overcome various static and dynamic barriers. Novel drug delivery strategies such as bioadhesive gels and fibrin sealant-based approaches were developed to sustain drug levels at the target site. Designing noninvasive sustained drug delivery systems and exploring the feasibility of topical application to deliver drugs to the posterior segment may drastically improve drug delivery in the years to come. Current developments in the field of ophthalmic drug delivery promise a significant improvement in overcoming the challenges posed by various anterior and posterior segment diseases.

KEY WORDS: nanoparticles; retina; transporter.

INTRODUCTION

Designing a drug delivery system to target a particular tissue of the eye has become a major challenge for scientists in the field. The eye can be broadly classified into two segments: anterior and posterior. Structural variation of each layer of ocular tissue can pose a significant barrier following drug administration by any route, i.e., topical, systemic, and periocular. In the present work, we attempted to focus on various drug absorption barriers encountered from all three routes of administration. Structural characteristics of various ocular tissues and their effectiveness as barriers for the delivery of drugs and their colloidal dosage forms have been discussed. The role of efflux pumps and strategies to overcome these barriers utilizing the transporter-targeted prodrug approach have also been touched upon. Current developments in ocular dosage forms, especially colloidal dosage forms, and their applications in overcoming various static and dynamic barriers have been elucidated. Finally, various developments in noninvasive techniques for ocular drug delivery have also been emphasized.

MODES OF ADMINISTRATION, BARRIERS, AND THEIR SIGNIFICANCE IN OCULAR DRUG DELIVERY

Compared with drug delivery to other parts of the body, ocular drug delivery has met with significant challenges posed by various ocular barriers. Many of these barriers are inherent and unique to ocular anatomy and physiology making it a challenging task for drug delivery scientists. These barriers are specific depending upon the route of administration *viz.* topical, systemic, and injectable. Most of these are anatomical and physiological barriers that normally protect the eye from toxicants. Moreover, various preformulation and formulation factors need to be considered while designing an ophthalmic formulation. Table I summarizes various routes of administration, their benefits, and challenges in ocular drug delivery. Figure 1 represents important parts of the eye along with different routes of drug administration represented in italics.

Topical administration. Topical administration, mostly in the form of eye drops, is employed to treat anterior segment diseases. For most of the topically applied drugs, the site of action is usually different layers of the cornea, conjunctiva, sclera, and the other tissues of the anterior segment such as the iris and ciliary body (anterior uvea). Upon administration, precorneal factors and anatomical barriers negatively affect the bioavailability of topical formulations. Precorneal factors include solution drainage, blinking, tear film, tear turn over, and induced lacrimation (1). Tear film, whose composition

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Table 1. Summary of Routes of Administration, Benefits, and Challenges in Ocular Delivery

Route	Benefits	Challenges	Application in the treatment of diseases
Topical	High patient compliance, self-administrable and noninvasive	Higher tear dilution and turnover rate, cornea acts as barrier, efflux pumps, BA <5%	Keratitis, uveitis, conjunctivitis, scleritis, episcleritis, blepharitis
Oral/Systemic	Patient compliant and noninvasive route of administration	BAB, BRB, high dosing causes toxicity, BA <2%	Scleritis, episcleritis, CMV retinitis, PU
Intravitreal	Direct delivery to vitreous and retina, sustains drug levels, evades BRB	Retinal detachment, hemorrhage, cataract, endophthalmitis, patient incomppliance	AMD, PU, BRVO, CRVO, DME, CME, UME, CMV retinitis
Intracameral	Provides higher drug levels in the anterior chamber, eliminates usage of topical drops, reduces corneal and systemic side effects seen with topical steroid therapy	TASS, TECDS	Anesthesia, prevention of endophthalmitis, inflammation and pupil dilation
Subconjunctival	Delivery to anterior and posterior segment, site for depot formulations	Conjunctival and choroidal circulation	Glaucoma, CMV retinitis, AMD, PU
Subtenon	High vitreal drug levels, relatively noninvasive, fewer complications unlike intravitreal delivery	RPE, chemosis, subconjunctival hemorrhage	DME, AMD, RVO, uveitis
Retrolbulbar	Administer high local doses of anesthetics, more effective than peribulbar, minimal influence on IOP	Retrolbulbar hemorrhage, globe perforation, respiratory arrest	Anesthesia
Posterior juxtascleral	Safe for delivery of depot formulations, sustain drug levels up to 6 months to the macula, avoids risk of endophthalmitis and intraocular damage	Requires surgery and RPE acts as barrier	AMD

BA bioavailability, BAB blood–aqueous barrier, BRB blood–retinal barrier, AMD age-related macular degeneration, DME diabetic macular edema, BRVO branched retinal vein occlusion, CRVO central retinal vein occlusion, RVO retinal vein occlusion, CME cystoid macular edema, UME uveitic macular edema, CMV cytomegalovirus, IOP intraocular pressure, TASS toxic anterior segment syndrome, TECDS toxic endothelial cell destruction syndrome, RPE retinal pigmented epithelium, PU posterior uveitis

and amount are determinants of a healthy ocular surface, offers the first resistance due to its high turnover rate. Mucin present in the tear film plays a protective role by forming a hydrophilic layer that moves over the glycocalyx of the ocular surface and clears debris and pathogens (2). Human tear volume is estimated to be 7 μ l, and the cul-de-sac can transiently contain around 30 μ l of the administered eye drop. However, tear film displays a rapid restoration time of 2–3 min, and most of the topically administered solutions are washed away within just 15–30 s after instillation. Considering all the precorneal factors, contact time with the absorptive membranes is lower, which is considered to be the primary reason for less than 5% of the applied dose reaching the intraocular tissues (3).

In addition, various layers of the cornea, conjunctiva, and sclera play an important role in drug permeation. The cornea, the anterior most layer of the eye, is a mechanical barrier which limits the entry of exogenous substances into the eye and protects the ocular tissues. It can be mainly divided into the epithelium, stroma, and endothelium. Each layer offers a different polarity and a potential rate-limiting structure for drug permeation. The corneal epithelium is lipoidal in nature which contains 90% of the total cells in the cornea and poses a significant resistance for permeation of topically administered hydrophilic drugs. Furthermore, superficial corneal epithelial cells are joined to one another by desmosomes and are surrounded by ribbon-like tight junctional complexes (zonula occludens) (4,5). Presence of these tight junctional complexes retards paracellular drug permeation from the tear film into intercellular spaces of the epithelium as well as inner layers of the cornea.

The stroma, which comprises 90% of the corneal thickness, is made up of an extracellular matrix and consists of a lamellar arrangement of collagen fibrils. The highly hydrated structure of the stroma poses a significant barrier to permeation of lipophilic drug molecules. Endothelium is the innermost monolayer of hexagonal-shaped cells. Even though endothelium is a separating barrier between the stroma and aqueous humor, it helps maintain the aqueous humor and corneal transparency due to its selective carrier-mediated transport and secretory function (6). Furthermore, the corneal endothelial junctions are leaky and facilitate the passage of macromolecules between the aqueous humor and stroma (7). Thus, corneal layers, particularly the epithelium and stroma, are considered as major barriers for ocular drug delivery. It is vital to understand that the permeant should have an amphipathic nature in order to permeate through these layers. A schematic of the corneal layers that a permeant needs to cross is presented by Barar *et al.* (6).

Compared to cornea, conjunctival drug absorption is considered to be nonproductive due to the presence of conjunctival blood capillaries and lymphatics, which can cause significant drug loss into the systemic circulation thereby lowering ocular bioavailability. Conjunctival epithelial tight junctions can further retard passive movement of hydrophilic molecules (8). The sclera, which is continuous with the cornea originates from the limbus and extends posteriorly throughout the remainder of the globe. The sclera mainly consists of collagen fibers and proteoglycans embedded in an extracellular matrix. Permeability through the sclera is considered to be comparable to that of the corneal stroma. Recent reports

Fig. 1. Routes of drug administration to eye

indicate that the permeability of drug molecules across the sclera is inversely proportional to the molecular radius (9). Dextrans with linear structures were less permeable as compared to globular proteins (9). Furthermore, the charge of the drug molecule also affects its permeability across the sclera. Positively charged molecules exhibit poor permeability presumably due to their binding to the negatively charged proteoglycan matrix (10).

Systemic (parenteral) administration. Following systemic administration, the blood–aqueous barrier and blood–retinal barrier are the major barriers for anterior segment and posterior segment ocular drug delivery, respectively. Blood–aqueous barrier consists of two discrete cell layers located in the anterior segment of the eye *viz.* the endothelium of the iris/ciliary blood vessels and the nonpigmented ciliary epithelium. Both cell layers express tight junctional complexes and prevent the entry of solutes into the intraocular environment (6) such as the aqueous humor. Blood–retinal barrier restricts the entry of the therapeutic agents from blood into the posterior segment. It is composed of two types of cells, *i.e.*, retinal capillary endothelial cells and retinal pigment epithelium cells (RPE) known as the inner and outer blood–retinal barrier, respectively. RPE, located between the neural retina and the choroid, is a monolayer of highly specialized cells. RPE aids in biochemical functions by selective transport of molecules between photoreceptors and choriocapillaris. Furthermore, it maintains the visual system by uptake and conversion of retinoids (11). However, tight junctions of the RPE efficiently restrict intercellular permeation. Following oral or intravenous dosing, drugs can easily enter into the choroid due to its high vasculature compared to retinal capillaries. The choriocapillaris are fenestrated resulting in rapid equilibration of drug molecules present in the bloodstream with the extravascular space of the choroid. However, outer blood–retinal barrier (RPE) restricts further entry of drugs from the choroid into the retina. Even though it is ideal to deliver the drug to the retina via systemic administration, it is still a challenge due to the blood–retinal barrier, which strictly regulates drug permeation from blood to the retina. Hence, specific oral or intravenous targeting systems are

needed to transport molecules through the choroid into deeper layers of the retina (12).

Recent advancements in nanotechnology encouraged researchers to find ways to overcome blood–retinal barrier. In one such study using C57BL/6 mice, the researchers demonstrated that intravenously administered 20-nm gold nanoparticles could pass through the blood–retinal barrier and distribute in all the retinal layers without cytotoxicity. The viability of retinal endothelial cells, astrocytes, and retinoblastoma cells was also not affected. In contrast, larger 100-nm nanoparticles were not detected in the retina (13). A few attempts have also been made for gene delivery to the eye by intravenous route of administration. A diffuse expression of SV40/ β -galactosidase gene in mouse inner retina, RPE, iris, as well as conjunctival epithelium, was observed upon intravenous administration of polyethylene glycol (PEG) conjugated immunoliposomes (14). A more recent report demonstrates the utility of intravenous administration of transferrin, arginine–glycine–aspartic acid peptide, or dual-functionalized *poly*(lactide-co-glycolide) (PLGA) nanoparticles. These functionalized PLGA nanoparticles were successful in targeted delivery of antivascular endothelial growth factor intraceptor plasmid to choroidal neovascularization (CNV) lesions. The delivery of nanoparticles to the neovascular eye was attributed to the leaky blood–retinal barrier as a result of CNV in the laser-treated rat eye (15).

Pharmacokinetic studies involving various drugs such as micafungin (16), marbofloxacin (17), and amphotericin B (18) demonstrated that these drugs are distributed in ocular tissues upon intravenous administration. One marketed intravenously administered formulation is visudyne, which is used in photodynamic therapy for the treatment of wet age-related macular degeneration (AMD). However, owing to the toxicity and delivery concerns, intravenous administration is not very common in treating ocular disorders.

Oral administration. Oral delivery (19–21) or in combination with topical delivery (22) has been investigated for different reasons. Topical delivery alone failed to produce therapeutic concentrations in the posterior segment. Also, oral delivery was studied as a possible noninvasive and patient preferred route to

treat chronic retinal diseases as compared to injectable route. However, limited accessibility to many of the targeted ocular tissues limits the utility of oral administration which necessitates high dosage to observe significant therapeutic efficacy. This can result in systemic side effects. Hence, parameters such as safety and toxicity need to be considered when trying to obtain a therapeutic response in the eye upon oral administration. For example, in glaucoma therapy, oral carbonic anhydrase inhibitors, such as acetazolamide and ethoxzolamide, have been discontinued in most of the cases due to their systemic toxicity (23,24). The oral route is not predominant, and only a limited number of compounds were investigated for ocular drug delivery. These include various classes of drugs such as analgesics (25), antibiotics (21,26–28), antivirals (29), antineoplastic agents (30), and omega-6 fatty acids (31). A major prerequisite of the oral route for ocular applications is high oral bioavailability of the drug. Following oral absorption, molecules in systemic circulation must also cross the blood–aqueous and blood–retinal barriers. The function and barrier property of these protective ocular structures was previously discussed.

Periocular and intravitreal administration. Although not very patient compliant, these routes are employed partly to overcome the inefficiency of topical and systemic dosing to deliver therapeutic drug concentrations to the posterior segment. Moreover, systemic administration may lead to side effects making it a less desirable delivery route for geriatric patients. The periocular route includes subconjunctival, subtenon, retrobulbar, and peribulbar administration and is comparatively less invasive than intravitreal route (See Fig. 1 for anatomical location of the sites of administration in the eye, represented in italics). The drug administered by periocular injections can reach the posterior segment by three different pathways: transscleral pathway; systemic circulation through the choroid; and the anterior pathway through the tear film, cornea, aqueous humor, and the vitreous humor (32).

Subconjunctival injection obviates the conjunctival epithelial barrier, which is rate-limiting for permeation of water-soluble drugs. Thus, the transscleral route bypasses cornea–conjunctiva barrier. Nevertheless, various dynamic, static, and metabolic barriers limit drug access to the posterior segment. Dynamic barriers include conjunctival blood and lymphatic circulation. Various authors reported rapid drug elimination via these pathways following subconjunctival administration (33–35). As a result, the formulation is drained into systemic circulation thereby lowering ocular bioavailability. Thus, drug elimination from the subconjunctival space becomes a major determinant of the vitreous drug levels following subconjunctival administration. The molecules that escape conjunctival vasculature permeate through sclera and choroid to reach the neural retina and photoreceptor cells. The sclera is not a major barrier as it is more permeable than the cornea. Moreover, permeability across the sclera is independent of lipophilicity unlike corneal and conjunctival layers but depends primarily on the molecular radius (12,36). However, choroid is a significant barrier as high choroidal blood flow can also eliminate a considerable fraction of drug before it can reach the neural retina. Furthermore, blood–retinal barriers limit drug availability to the photoreceptor cells.

Unlike periocular injections, the intravitreal injection offers distinct advantages as the molecules are directly

inserted into the vitreous. However, drug distribution in the vitreous is non-uniform. Small molecules can rapidly distribute through the vitreous, whereas the diffusion of larger molecules is restricted. This distribution also depends on the pathophysiological condition and molecular weight of the administered drug (37). The vitreous also acts as a barrier for retinal gene delivery following an intravitreal injection. Hyaluronan, a negatively charged glycosaminoglycan present in the vitreous, can interact with cationic lipid, polymeric, and liposomal DNA complexes (38). This interaction can lead to severe aggregation and complete immobilization of DNA/cationic liposome complexes (39). Similarly, mobility of nanoparticles in the vitreous depends on their structure and surface charge. Polystyrene nanospheres do not diffuse freely into the vitreous due to their adherence to collagen fibrillar structures (39). Hence, surface modification of nanospheres with hydrophilic PEG chains has been performed. A recent study using human serum albumin nanoparticles also demonstrated that anionic nanoparticles with a zeta potential of -33.3 mV diffused more freely in the vitreous than cationic particles with a zeta potential of 11.7 mV (40).

The inner limiting membrane (ILM), the cell layer separating the retina and the vitreous, is a barrier for retinal delivery following intravitreal administration of gene-based therapeutics. For example, the ILM poses a barrier for penetration of the adeno-associated virus into the retina from the vitreous. Mild digestion of ILM enhanced transduction of multiple retinal cell types from the vitreous indicating its high barrier property (41). Moreover, drug transport from vitreous to the outer segments of retina and choroid is more complex due the presence of RPE.

The half-life in the vitreous is another factor that can determine the therapeutic efficacy. Following intravitreal injection, the drug is eliminated either by the anterior route or posterior route. The anterior elimination route involves drug diffusion across the vitreous into the aqueous humor through zonular spaces followed by elimination through aqueous turnover and uveal blood flow. The posterior elimination pathway involves drug permeation across the blood–retinal barrier and requires optimum passive permeability or active transport mechanisms. As a result, hydrophilicity and large molecular weight tend to increase the half-life of the compounds in the vitreous humor (12).

MELANIN BINDING

The presence of melanin may alter ocular drug disposition. Interaction with this pigment may alter the availability of free drug at the targeted site. Thereby, melanin binding may significantly lower pharmacological activity (42). In ocular tissues, melanin is present in uvea and RPE. It binds to free radicals and drugs by electrostatic and Van der Waals forces or by simple charge transfer (43). Based on available information, it may be concluded that all basic and lipophilic drugs bind to melanin (44). Even though drug binding to melanin is not necessarily predictive of ocular toxicity, it has significant pharmacological consequences and requires careful consideration in ocular drug delivery. Melanin binding in the iris–ciliary body affects drug concentrations in anterior

ocular tissues and drug response (45). A melanin-bound drug is not usually available for receptor binding necessitating the administration of larger doses (46). Likewise, melanin present in choroid and RPE affects the extent of drug uptake into the retina and vitreous following transscleral or systemic drug administration. As a result of melanin binding, permeation lag-time of lipophilic beta-blockers through bovine choroid-RPE is much longer than more hydrophilic beta-blockers (11). Similarly, binding of lipophilic compounds to the bovine choroid-Bruch's membrane was demonstrated to be higher due to the presence of melanin. Consequently, there is a greater resistance to solute permeation across choroid-Bruch's membrane than the sclera, which is devoid of melanin (47).

TRANSPORTERS IN EYE

The traditional approach to improve ocular bioavailability is to modify the drug chemically to achieve the desired solubility and lipophilicity. However, a more rational approach would be a transporter-targeted modification of the drug. Transporters are membrane-bound proteins that play an important role in active transport of nutrients across biological membranes. The presence of transporters has been reported on various ocular tissues. However, in the present article, we have focused on the transporters that are localized in the epithelia of the cornea, conjunctiva, and retina. These transporters may be amenable to bind and transport specific-targeted ligands attached to drug moieties.

Two types of transporter systems are of interest in ocular drug delivery: efflux transporters and influx transporters. Widely studied efflux transporters belong to the ATP binding cassette superfamily, whereas influx transporters belong to the solute carrier (SLC) superfamily. Efflux transporters lower bioavailability by effluxing the molecules out of the cell membrane and cytoplasm. Prominent efflux transporters identified on ocular tissues include P-gp, multidrug resistance protein (MRP), and BCRP. Various authors reviewed the emerging role of transporters in ocular drug delivery (48–50). P-gp has an affinity to efflux lipophilic compounds in normal as well as in cancerous cells, possibly leading to emergence of drug resistance. Expression and functional activity of P-gp was identified on various ocular cell lines and tissues such as the cornea (51–53), conjunctiva (54,55), and RPE (56–58). However, some authors recently indicated that the expression of P-gp on human corneal epithelium may be negligible or absent (59,60). MRP works in a similar manner but effluxes organic anions and conjugated compounds. Out of nine known isoforms of the MRP family, only three were identified in ocular tissues. MRP2 and MRP5 were identified in corneal epithelium (61,62), whereas MRP1 was identified in rabbit conjunctival epithelial cells (63). RPE expresses MRP1 (64). The presence of BCRP was also reported on the corneal epithelium (65). Expression patterns of these transporter proteins in the cell lines may vary based on its origin and culture condition (58–60). Some of the recent reports highlighted the expression of pharmaceutically relevant transporters using cultured human ocular cell models and human ocular tissues (59,60,66). Urti *et al.* (59) reported that only MRP1, MRP5, and BCRP were expressed in the freshly

excised human corneal epithelial tissue, whereas cell models overexpressed many other efflux transporters compared to that of the normal corneal epithelium.

Influx transporters facilitate the translocation of essential nutrients and xenobiotics across biological membranes. These include carriers for amino acids, peptides, vitamins, glucose, lactate, and nucleoside/nucleobases. Stirred by the success of valacyclovir and the characterization of different influx transporters in ocular tissues, ophthalmic drug delivery scientists investigated various prodrugs targeting these influx transporters. Transporter-targeted prodrugs offer multiple advantages. The prodrugs or analogues designed to target the influx transporters can significantly enhance the absorption of poorly permeating parent drugs, as these conjugates become substrates for the influx transporters and simultaneously evade the efflux pumps. Furthermore, physicochemical properties of the drug such as solubility and stability can be improved compared to the parent drug.

The most commonly applicable influx transporters for ocular drug delivery are amino acid and peptide transporters. These proteins may have a putative role in ocular drug delivery along with their physiological role of transporting various amino acids and nutrients into ocular tissues. Amino acid transporters that belong to SLC1, SLC6, and SLC7 gene families were identified at the molecular level in ocular tissues, and their functional role was examined as well. The SLC1 family consists of five high affinity glutamate transporters (EAAT1–EAAT5) and two neutral amino acid transporters (ASCT1 and ASCT2). Few of these transporters were identified so far in ocular tissues. mRNA expression of ASCT1 (SLC1A4) has been detected in rabbit cornea and in rabbit primary corneal epithelial cells (rPCEC) (67). Functional activity of ASCT1 on rabbit cornea was also demonstrated by studying the saturable, Na⁺-dependent uptake of L-alanine in rPCEC cell line and by determining its permeability across isolated rabbit cornea. Molecular evidence for ASCT2 (SLC1A5) expression was confirmed in retinal Muller cells, and it was suggested that the amino acid D-serine, synthesized in Muller cells, is effluxed through this transporter system (68). B⁰⁺ (SLC6A14) is a neutral and cationic amino acid transporter with broad substrate specificity. Blisse and coworkers carried out a real-time quantitative polymerase chain reaction (RT-PCR) on total RNA isolated from rabbit cornea, rabbit corneal epithelium, and human cornea. This report confirmed the expression of the amino acid transporter B(0,+) on cornea (69). This study also concluded that primary carrier involved in L-arginine transport across corneal epithelium is the B⁰⁺ system. This carrier system is also attributed to L-arginine transport in pigmented rabbit conjunctiva (70). Identification and functional characterization of an Na⁺-independent large neutral amino acid transporter, LAT1 (SLC7A5), was reported in human and rabbit cornea (71). Presence of this transporter system along with LAT2 (SLC7A8) was also confirmed in the posterior segment with an *in vitro* human model using RPE cell line (hTERT-RPE) at mRNA level (72). mRNA expression of LAT2 was also shown in ARPE-19 cells, and its role in Na⁺-independent transport of L-phenylalanine was emphasized (73).

Peptide transporters have been widely investigated for ocular drug delivery. Using excised rabbit cornea, Anand *et al.* reported functional evidence for the presence of the oligopeptide transporter system akin to the peptide trans-

porters present in the intestine (74). Recent reports also indicate the detection of both PEPT1 and PEPT2 on the newly introduced clonetics human corneal epithelium (cHCE) cell line and on human cornea with RT-PCR (60,75). Furthermore, the difference in the transporter expression in various species was studied (60). The extent to which mRNA levels correlate with protein expression and transporter activity needs to be studied in greater detail. Existence of a proton-coupled dipeptide transport system has been reported on conjunctival epithelial cells by demonstrating its role in mediating the uptake of model dipeptide L-carnosine (76). Peptide transporter expression was also studied in the back of the eye tissues. Berger *et al.* reported expression of PepT-2 mRNA on retinal Muller cells (77). Expression of peptide transporters across retina was also shown by using ocular microdialysis technique. This study involved vitreous clearance of cephalosporins, which are substrates of this transporter system (78).

Other than amino acid and peptide transporters, organic cation/anion (SLC22), monocarboxylate (SLC16), and nucleoside transporters (SLC 28 and 29) have been identified on various ocular tissues. Moreover, various vitamin transporters were studied for their functional role in ocular tissues (79–82).

Transporter-targeted prodrugs were developed following the identification and characterization of various influx and efflux transporters on ocular tissues. These studies are clinically very significant since transporter-targeted prodrugs have the potential of improving ocular absorption of poorly permeating parent drug. Improvement in ocular bioavailability upon prodrug administration was attributed to the involvement of various ocular transporters, change in physicochemical properties, or a combination of these two factors. Prodrugs are recognized by the membrane transporters as substrates resulting in their translocation across the epithelia. A schematic representation of efflux evasion by the prodrug and concomitant cellular entry mediated by the influx transporter is depicted in Fig. 2. Table II provides a summary of various transporter-targeted prodrugs investigated for drug delivery to various ocular tissues such as cornea, conjunctiva, and RPE.

COLLOIDAL DOSAGE FORMS FOR OCULAR DRUG DELIVERY

Colloidal dosage forms have been widely studied and employed in the field of ocular drug delivery (48). These dosage forms include liposomes, nanoparticles, microemulsions, and nanoemulsions etc. Barriers to ocular drug delivery have already been described earlier in the context of structure and function of various ocular tissues and how each tissue can act as a barrier. The chronic nature of many ocular diseases necessitates frequent drug administration.

Advantages of colloidal dosage forms include sustained and controlled release of the drug at the targeted site, reduced frequency of administration, ability to overcome blood–ocular barriers, and efflux-related issues associated with the parent drug (83). Further, these carriers can also bypass or overcome various stability-related problems of drug molecules, e.g., proteins and peptides. Designing an ideal delivery system for any ocular disease depends on molecular

Fig. 2. Circumvention of efflux proteins by prodrug approach

properties of the drug such as size, charge, and affinity towards various ocular tissues and pigments.

For successful transcorneal delivery with colloidal dosage form, nature and characteristics of each layer of the cornea should be understood. Corneal epithelium and stroma are formidable barriers for hydrophilic and hydrophobic drugs, respectively. Corneal epithelial mucosa possesses an overall negative charge, thus permeability of positively charged molecules is favored at physiological pH (84). While designing a liposome-based formulation, selection of the lipid plays an important role. Investigators have compared transcorneal permeation using cationic, anionic, and neutral liposomes. Mostly, cationic liposomes containing various drug molecules such as penicillin G, tropicamide, and acetazolamide appear to provide maximum drug transport across the cornea relative to the anionic and neutral liposomes (85–87). Similar charge behavior is also expected for other colloidal dosage forms such as nanoparticles and microemulsions. Chitosan-coated nanoparticles appear to exhibit higher permeation relative to uncoated nanoparticles. Table III summarizes available literature on various formulations developed to sustain drug release via both the transcorneal and transscleral pathways. Apart from transcorneal absorption, transscleral and conjunctival absorption also play an important role following topical administration.

Transscleral permeability of a compound depends on various parameters such as molecular weight, molecular radius, hydrophilicity, and charge of the molecule. Furthermore, the *in vivo* performance of colloidal dosage forms can be affected by size, dynamic barriers such as blood and

Table II. Transporter-Targeted Prodrugs for Ocular Drug Delivery

Transporter system-targeted tissue/cell line	Drug/prodrugs employed	Observation	Reference
B(0,+) on the cornea	L-aspartate ACV	Fourfold higher transcorneal permeability of L-aspartate ACV compared to ACV	(109)
B(0,+) on the cornea	Gamma-glutamate-ACV (EACV)	Higher aqueous solubility of the prodrug along with the transporter recognition	(110)
B(0,+) on the cornea	Phenylalanine-ACV and gamma-glutamate-ACV	The prodrugs inhibited the transport of L-arginine ^d across the cornea implied that they are substrates of B(0,+)	(69)
OPT system on the cornea	L-valine ACV	Threefold higher transcorneal permeability of L-valine ACV compared to ACV	(74)
OPT system on the cornea	Gly-Val-GCV, Val-Val-GCV, and Tyr-Val-GCV	Significant transcellular passive diffusion and transporter recognition resulted in higher AUC and C _{max}	(111,112)
OPT system on rPCEC cells and the cornea	Val-quinidine and Val-Val-quinidine	Prodrugs were not recognized by P-gp efflux pump and further found to be substrates of peptide transporters	(113)
OPT system on the retina	Gly-Val-GCV, Val-Val-GCV, and Tyr-Val-GCV	Twofold higher RCS tissue permeability than that of GCV due to higher lipophilicity and translocation mediated by OPT across RPE	(114)
SMVT on the retina	Biotin-GCV	Higher biotin-GCV permeability into the retina-choroid and slower elimination from vitreous	(115)
GLUT1 on the HRPE cells	Glu-dopamine	Transporter recognizes prodrug, not the parent drug	(116)

OPT oligopeptide transporter, SMVT sodium-dependent multiple vitamin transporter, B(0,+) amino acid transporter, GLUT glucose transporter, rPCEC rabbit primary corneal epithelial cells, HRPE human retinal pigment epithelium cells, RCS retina-choroid-sclera, ACV acyclovir, GCV ganciclovir, RPE retinal pigment epithelium

^d A substrate of B(0,+)

lymphatic flow, affinity of the encapsulated drug towards melanin, and surface conjugation of nanoparticles with various endogenous molecules. Following periocular administration of nanoparticles, size plays a crucial role in determining the fate of the particles and the entrapped drug. Studies inferred that clearance of 20 nm particles by blood and lymphatic circulation was significantly higher, while 200-nm particles could be found at the injection site for over 2 months. Also, the study concluded that 20-nm particles were able to cross the scleral tissue to a very low extent, while 200-nm particles could not cross the sclera (88,89). Affinity of drug molecules towards melanin pigment present in the choroid-RPE also plays an important role in ocular disposition. Molecules having a higher affinity for melanin can bind to the pigment, and hence delivery to the inner retinal layers and the vitreous humor can be delayed (90). Drug targeting by functionalization with some of the endogenous carrier molecules, which are natural substrates for a particular receptor or transporter such as luteinizing hormone-releasing hormone agonist and transferrin, was successful. Disease conditions can also affect drug availability into the inner retinal tissues including Muller and photoreceptor cells (92).

In diabetes, disruption of the blood-retinal barrier can result in significant drug transport to the target site (92). Following intravitreal injection of a dosage form, the fate of colloidal carriers depends on numerous critical parameters. Vitreous humor is a colloidal fluid containing small amounts of solutes, ions, and low-molecular weight compounds. It mainly contains collagen (40–120 µg/ml) and hyaluronic acid (100–400 µg/ml). Due to negative charge of vitreal hyaluronan, positively charged molecules tend to aggregate in the vitreous humor. This was observed initially with the DNA lipoplex. Hence, it is very crucial to estimate the zeta potential of a colloidal dosage form under physiological condition (38). PEGylation of particles can significantly

minimize or avoid this problem to a large extent (93). ILM is also known to restrict the movement of particles from vitreous humor to inner retinal layers. Achieving sustained drug levels from periocular administration is necessary for treating AMD, diabetic macular edema, and diabetic retinopathy. After subconjunctival administration, colloidal dosage forms (size up to 20 nm) and released drug molecules can be rapidly cleared by conjunctival, choroidal, and lymphatic circulations. Table IV summarizes available literature in this field.

Various strategies have been employed to avoid clearance from these vasculatures. One such strategy is the development of a fibrin sealant containing the drug for posterior segment diseases such as retinoblastoma, wet AMD, macular edema, and proliferative vitreoretinopathy. Fibrin sealant has been approved by the US Food and Drug Administration. Once injected along with the drug solution, this sealant immediately forms a gel-based semisolid structure, which sustains drug release over a longer period (94). Table V summarizes recent advances in the use of fibrin sealant for ocular drug delivery. This approach was successfully studied for delivery of tobramycin (keratitis), topotecan, carboplatin (retinoblastoma), and insulin (diabetic retinopathy).

MICRONEEDLE-, ULTRASOUND-, AND IONTOPHORESIS-BASED OCULAR DRUG DELIVERY SYSTEMS

All these delivery systems are noninvasive methods designed to deliver drugs to intraocular regions, mainly for the treatment of posterior segment diseases. Researchers have developed drug-coated microneedles with a length of 500 to 750 µm. The drug to be delivered can be coated on the solid metal. Following administration, coated molecules

Table III. Drugs Formulated in Colloidal Dosage Form for Ocular Delivery

Formulation	Characteristic of the formulation	Reference
Liposome	Liposomal formulation of diclofenac was coated with low-molecular weight chitosan which resulted in higher corneal permeation and better sustained drug release without any toxicity	(117)
Liposome	Liposomal hydrogel formulation of gatifloxacin has sustained the drug release and enhanced transcorneal permeation	(118)
Liposome	Liposomal formulation of sparfloxacin lactate has increased transcorneal permeation and antibacterial activity against <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , and <i>Bacillus subtilis</i> compared to free drug	(119)
Liposome	Transcorneal permeation and intraocular distribution of GCV liposomal formulation was 3.9-fold and two- to tenfold higher, respectively, than GCV solution	(120)
Liposome	Transcorneal permeation of demeclocycline was substantially higher, and intraocular pressure was lowered for longer period of time	(121)
Nanoparticles	Polymeric nanoparticles of PLGA and polyepsilon-caprolactone enhanced transcorneal permeability of flurbiprofen	(122)
Liposome and nanoparticles	Both liposomal and nanoparticulate formulations sustained doxorubicin release across sclera. Drug release from liposomes was slower than nanoparticles	(123)
Microparticles	Following subconjunctival administration of PLGA microparticles, celecoxib levels were sustained, and inhibition of diabetes-induced retinal oxidative damage was observed	(124)
Microparticles and nanoparticles	Following subconjunctival administration of PLGA nano- and microparticles containing budesonide, drug levels were sustained in the retina for longer period of time	(125)
Collagen matrix	Upon subconjunctival injection in rabbits, collagen matrix provided sustained release of cisplatin and resulted in a higher concentration in intraocular tissues	(126)

dissolve rapidly, and subsequently, microneedles are removed from the tissue. This delivery system generates a much higher concentration compared to a free drug solution (95). Sodium fluorescein and pilocarpine were coated and delivered using a similar technique. In the case of sodium fluorescein, permeation was found to be 60 fold higher, and in the case of pilocarpine, rapid constriction of pupil was observed. Similarly, intrascleral hollow microneedles have also been developed. This delivery system is able to deliver microparticles, nanoparticles, and drugs in a solution with minimal invasion. To deliver microparticles, concomitant administration of spreading enzymes such as hyaluronidase

and collagenase is also necessary. These enzymes rapidly hydrolyze the collagenous and extracellular matrix structure of the sclera making the delivery of microparticles feasible (96).

Similarly, ultrasound-mediated drug delivery has also received attention in recent years. Delivery of beta-blockers such as atenolol, carteolol, timolol, and betaxolol, was attempted with ultrasound application (20 kHz for 1 h) across cornea in the treatment of glaucoma. Corneal permeability of these compounds has been significantly enhanced with ultrasound. Recently, researchers have attempted to deliver a hydrophilic molecule, sodium fluorescein, at an ultrasound

Table IV. Factors Affecting Transport of Drug Molecule or Its Colloidal Dosage Form

Factors affecting <i>in vivo</i> fate of drug	Important features and conclusions of the study	Reference
Size of NPs	20 nm NPs could not retain in the periocular site due to rapid elimination, while 200 nm and 2 μ m particles were detected after 2 months at the site of periocular injection in rats	(88)
Melanin pigment	Transscleral transport of celecoxib was significantly higher in the Sprague–Dawley rats (nonpigmented) than Brown Norway rats (pigmented)	(90)
Blood and lymphatic circulation	Transport of 20 nm NPs across sclera was minimal due to rapid disposition in the presence of both blood and lymphatic circulations. Higher size (200 nm) is required to avoid clearance via both circulations	(89)
Diseases condition (diabetes)	In diabetic rats, transscleral retinal and vitreal levels of celecoxib were significantly higher than nondiabetic rats. Transscleral delivery in pigmented rats was higher than nonpigmented rats	(92)
Functionalization of NPs	Transport across cornea was enhanced due to functionalization of polystyrene NPs (20 nm) with deslorelin, a luteinizing hormone-releasing hormone (LHRH) agonist and transferrin	(91)
Charge on the NPs	Positive and negatively charged NPs were shown to distribute to the inner ocular tissues such as retina and vitreous humor following application of iontophoresis technique. Positively charged NPs have shown higher penetration than negatively charged NPs	(127)
Charge on NPs	Following intravitreal injection, anionic NPs were shown to distribute to the subretinal space and RPE in higher extent than cationic NPs. Endocytosis of NPs in Muller cells was also shown in the study	(40)
Charge and PEGylation	After intravitreal injection of NPs, neural retina restricts the movement of NPs into RPE, which can be overcome by application of ultrasound	(93)

Table V. Strategies to Sustain the Drug Release Using Fibrin Sealant and Gel

Name of drug molecule	Strategy to sustain the drug release using fibrin sealant and gel	Reference
Tobramycin	Fibrin-enmeshed tobramycin liposomes have shown significant inhibition of <i>Pseudomonas keratitis</i> following topical application of drug compared to the control group	(128)
Carboplatin	Following subconjunctival administration, fibrin sealant provided sustained release of carboplatin (till 2 weeks) and higher drug concentrations in choroid-retina as compared to free carboplatin administration	(129)
Carboplatin	Following subconjunctival administration of a low dose of carboplatin in fibrin sealant, drug release was sustained for a longer period of time, and thus tumor regression was achieved in ten out of 11 rabbits suffering from retinoblastoma	(130)
Dexamethasone and methotrexate	Sustained release was achieved via transscleral delivery of both the drugs in sealant compared to administration of free drug solutions	(131)
Topotecan	Subconjunctival administration of topotecan in fibrin sealant resulted in inhibition of transgenic murine retinoblastoma. Investigators also observed significant inhibition of tumor in contralateral eye and thus concluded that major route of drug delivery is hematogenous rather than transscleral	(132)
Insulin	Following subconjunctival implantation of thermosensitive hydrogel, sustained release was achieved for the treatment of diabetic retinopathy and other retinal diseases	(133)
Hydrophilic model drugs (methylene blue and bovine serum albumin)	Biodegradable thermoresponsive hydrogels provided controlled release of both the molecules	(134)
Bovine serum albumin, immunoglobulin G, bevacizumab, and ranibizumab	Intravitreal injection of biodegradable hydrogel can sustain the release of macromolecules for a longer period of time	(135)

frequency of 880 kHz and intensities of 0.19–0.56 W/cm² with an exposure duration of 5 min. This study reported a tenfold enhancement in corneal permeation with minor changes in the epithelium (97).

Ocular iontophoresis has received a lot of attention in recent years particularly to deliver drugs across cornea and sclera. Transcorneal iontophoresis of ciprofloxacin hydrochloride (ocular infection), gentamicin (pseudomonas keratitis), and antisense oligonucleotides (treatment of angiogenesis in cornea) appeared to produce encouraging results (98–100). Dexamethasone phosphate, methylprednisolone (posterior segment inflammation), carboplatin (retinoblastoma), and methotrexate

(inflammatory diseases and intraocular lymphoma) were also successfully delivered using this technique (101–104).

TOPICAL DELIVERY OF DRUGS FOR POSTERIOR SEGMENT EYE DISEASES

Drug delivery to posterior segment tissues following topical administration remains a challenging task. In the earlier section, we have briefly described the barriers which restrict drug movement to the posterior segment. Barring a few, most molecules cannot reach the posterior segment tissues upon topical administration. In some cases, signifi-

Table VI. Summary of Drugs Which Can Be Delivered to Posterior Segment Tissues Following Topical Administration

Drug molecule	Critical benefit or proposed mechanism/route of drug entry into posterior segment	Reference
ESBA105, an anti-TNF-alpha single-chain antibody	After topical application, ESBA105 was observed to distribute to all the ocular tissues including retina and vitreous humor. ESBA105 has shown 25,000-fold less systemic exposure than IV administration	(136)
Dexamethasone	After topical administration of dexamethasone-cyclodextrin eye drops, drug was found in posterior segment tissues as well. Both topical penetration and redistribution after systemic delivery were probable routes for drug entry into posterior segment tissues	(137)
Dexamethasone	Topical application of dexamethasone/gamma-cyclodextrin (gammaCD) microparticulate suspension provided higher dexamethasone concentration into the retina without any side effect	(138)
Nepafenac	Topically applied nepafenac can reach retina and thus can be used to treat choroidal and retinal neovascularization	(107)
Memantine HCL	After administration of topical drops, drug was distributed in choroid and retina. Desired physicochemical properties and higher melanin binding capacity of drug was shown to be the main reason for this distribution	(108)
Dorzolamide	Following topical administration, drug reaches the posterior segment tissues in 30 min and inhibits the function of carbonic anhydrase in all the tissues including retina	(139)
Brimonidine	Following topical application, drug is rapidly absorbed by conjunctiva and cornea. Accumulation in pigmented tissues was higher than nonpigmented tissues. Retinal drug level was sufficient to provide neuroprotection	(106)
Betaxolol	Topically applied drug was largely distributed into posterior segment tissues because of higher drug permeability across cornea and conjunctiva	(105)

cantly higher permeation of drug molecules across cornea, sclera, or conjunctiva followed by topical administration resulted in significant distribution into intraocular tissues, e.g., brimonidine, betaxolol, and nepafenac (105–107). Higher affinity of memantine hydrochloride towards melanin pigment also played an important role in the distribution to the posterior segment (108). Table VI summarizes a list of molecules for which topical application resulted in significant levels in posterior segment tissues such as the retina, choroid, and vitreous humor. In one such approach, our laboratory has developed a novel platform technology consisting of mixed nanomicellar formulation of a drug molecule to deliver it to the posterior segment upon topical application (US patent application 20090092665). Vitamin E-TPGS and octoxynol 40 were used as surfactants to prepare a mixed nanomicellar clear aqueous formulation of a lipophilic compound. Selection of a surfactant having the HLB difference greater than three was very crucial for this formulation. Hydrophobic drugs such as voriconazole and dexamethasone were successfully incorporated in the micellar-based formulation. Upon topical application of micellar formulation (≈ 10 – 20 nm), the researchers were able to deliver drugs to the retina in therapeutic levels. Another important benefit of this approach was the absence of drug levels in the lens or vitreous. This distribution pattern can be crucial to avoid or delay the development of major side effects of steroids such as cataract formation and intraocular pressure elevation, which often result in discontinuation of the therapy.

CONCLUSION

Effective treatment of ocular diseases is a formidable task because of the nature of diseases and presence of the ocular barriers. Challenges in drug delivery to ocular tissues have been partially met by the identification of transporters and modification of drug substances to target these transporters. The specificity of transporters aids in targeting specific tissues thereby lowering side effects and improving bioavailability. Development of noninvasive delivery techniques will revolutionize ocular drug delivery. The potential for the growth of sustained drug delivery systems involving polymeric systems is limitless, and newer polymers would serve the purpose of controlled and sustained delivery for treating vision-threatening diseases. Advances in nanotechnology and noninvasive drug delivery techniques will remain in the forefront of new and novel ophthalmic drug delivery systems.

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