Drug Delivery for Posterior Segment Eye Disease

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In recent years, significant advances have been made in optimizing the delivery of drugs to target tissues within the eye and in maintaining effective drug doses within those tissues. Most pharmacologic management of ocular disease, however, continues to use the topical application of solutions to the surface of the eye as drops. Factors that can limit the usefulness of topical drug application include the significant barrier to solute flux provided by the corneal epithelium and the rapid and extensive precorneal loss that occurs as the result of drainage and tear fluid turnover. After the instillation of an eyedrop (maximum of 30 μl) into the inferior fornix of the conjunctiva, the drug mixes with the lacrimal fluid, and drug contact time becomes a function of lacrimation, tear drainage and turnover, and to some extent the composition of the precorneal tear film itself. It has been estimated that typically less than 5% of a topically applied drug permeates the cornea and reaches intraocular tissues. The major portion of the instilled dose is absorbed systemically by way of the conjunctiva, through the highly vascular conjunctival stroma and through the lid margin vessels. Significant systemic absorption also occurs when the solution enters the nasolacrimal duct and is absorbed by the nasal and nasopharyngeal mucosa. Despite the relatively small proportion of a topically applied drug dose that ultimately reaches anterior segment ocular tissues, topical formulations remain effective, largely because of the very high concentrations of drugs that are administered.

Recent advances in topical drug delivery have been made that improve ocular drug contact time and drug delivery, including the development of ointments, gels, liposome formulations, and various sustained and controlled-release substrates, such as the Ocusert, collagen shields, and hydrogel lenses. The development of newer topical delivery systems using polymeric gels, colloidal systems, and cyclodextrins will provide exciting new topical drug therapeutics. The delivery of therapeutic doses of drugs to the tissues in the posterior segment of the eye, however, remains a significant challenge. Approximately 1.7 million Americans over the age of 65 suffer from age-related macular degeneration (AMD) and as the nation ages, this number will grow by an estimated 200,000 new cases per year. Severe vision loss from AMD and other diseases affecting the posterior segment, including diabetic retinopathy, glaucoma, and retinitis pigmentosa accounts for most cases of irreversible blindness world wide.

Currently, the treatment of posterior segment disease is to a significant extent limited by the difficulty in delivering effective doses of drugs to target tissues in the posterior eye (Fig.1). Four approaches may be used to deliver drugs to the posterior segment—topical, systemic, intraocular, and periocular (including subconjunctival, sub-Tenon’s, and retrobulbar). Topically applied drugs may enter the eye by crossing the conjunctiva and then diffusing through the sclera, but for reasons previously cited, this approach typically does not yield therapeutic drug levels in the posterior vitreous, retina, or choroid, and although systemic administration can deliver drugs to the posterior eye, the large systemic doses necessary are often associated with significant side effects. An intravitreal injection provides the most direct approach to delivering drugs to the tissues of the posterior segment, and therapeutic tissue drug levels can be achieved. Intravitreal injections, however, have the inherent potential side effects of retinal detachment, hemorrhage, endophthalmitis, and cataract. Repeat injections are frequently required, and they are not always well tolerated by the patient. Further, drugs injected directly into the vitreous are rapidly eliminated. Intravitreal sustained-release devices have been used to avoid repeated injections. The best known of these devices is the Vitrasert ganciclovir implant, used in the treatment of cytomegalovirus retinitis. These and other intravitreal sustained release systems, including other implant devices, microspheres, and liposomes, are exciting new modalities of drug delivery that offer effective treatment of visually devastating diseases. The devices, however, do require intraocular surgery, must be replaced periodically, and have potential side effects similar to those associated with intravitreal injection.

Periocular drug delivery using subconjunctival or retrobulbar injections or placement of sustained-release devices provides another route for delivering drugs to the posterior tissues of the eye. This approach to drug delivery is safer and less invasive than intravitreal injection and also offers the exciting potential for localized, sustained-release drug delivery. Drug delivery by this vector ideally would be transscleral and thus could take advantage of the large surface area of the sclera. The average 17-cm² surface area of the human sclera accounts for 95% of the total surface area of the globe and provides a significantly larger avenue for drug diffusion to the inside of the eye than the 1-cm² surface area of the cornea. Also, regional differences in scleral thickness could be used to further optimize transscleral drug diffusion if sustained-release delivery devices or systems could be placed in regions where scleral permeability was greatest. The sclera, for example, is 1.0 mm thick near the optic nerve and an average of 0.53 mm thick at the corneoscleral limbus and thins to an average of 0.39 mm at the equator, where it can be as thin as 0.1 mm in a significant number of eyes. Further, an increasing body of evidence suggests that the sclera is quite permeable to a wide

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range of solutes and holds significant potential for posterior segment drug delivery.

Initial studies by Bill7 demonstrated that both albumin and dextran, when injected into the suprachoroidal space of the rabbit eye, will diffuse across the sclera and accumulate in the extraocular tissues. Subsequent animal studies in rabbits clearly established that drugs do enter ocular tissues after subconjunctival or retrobulbar injections.8,9 Ahmed and Patton3 have documented that topical timolol and inulin can penetrate the sclera to enter intraocular tissues after topical application in rabbits, if the corneal absorption route is blocked. This group first suggested that it might be possible to exploit the scleral absorption route to promote site-specific delivery of drugs to intraocular tissues in the back of the eye. Additional studies have demonstrated that after a peribulbar or subconjunctival injection, significant levels of dexamethasone can be measured in the vitreous and that these levels are achieved by direct diffusion of dexamethasone through the sclera, although some delivery by systemic absorption does occur.3 Care must be exercised when performing subconjunctival injections, because significant ocular drug absorption can occur via the corneal route if the injected solution is allowed access to the tears through the injection site.10

In vitro flux studies have shown the sclera to be quite permeable to a wide molecular weight range of solutes, both in bovine11 and in human12 tissue. For these studies, small pieces of sclera are isolated, typically from the superior temporal quadrant of the globe to avoid the anterior and posterior ciliary perforating vessels. The tissue is mounted between two chambers of a Ussing-type perfusion apparatus, and steady state transscleral fluxes are measured using radiolabeled or fluorescein labeled solutes. Scleral hydration and ultrastructure have been shown to be normally preserved over the course of the in vitro studies. Such studies, thus, indicate that normal scleral physiology can be maintained over the course of short-term and longer-term perfusion periods and that scleral flux is not altered by the experimental setup. The results of these studies have shown that the permeability constant ($K_{\text{TRANS}}$) for transscleral solutes (molecular weight range: 285–70,000) is inversely related to solute molecular weight.

In vitro flux studies are typically performed in the absence of any pressure across the isolated scleral tissue. Because transscleral pressure might be expected to affect scleral hydration and/or scleral thickness by compressing the tissue and this in turn could alter scleral solute permeability, it becomes important to document potential effects of pressure on scleral permeability. To this end, a perfusion chamber has been developed that permits the imposition of pressure across the tissue, to simulate intraocular pressure.13 The simulated intraocular pressure can be controlled by varying the height of the water column in the outflow tubing. The tissue is mounted between two hemichambers. The choroidal hemichamber, representing the choroidal tissues, is perfused at a slow rate, whereas the episcleral hemichamber is held static, modeling the situation in which a drug is added to Tenon’s space and exposed directly to the sclera. The results of experiments using this system show that both human and rabbit sclera remain quite permeable to low-molecular-weight compounds under the influence of a simulated intraocular pressure, and although the results indicate that pressure can affect scleral permeability for small molecules ranging in size from 18 to 392 Da, the effect is small. Scleral permeability to small molecules is thus a weak function of transscleral pressure, over the range of 0 to 60 mm Hg, and a strong function of molecular weight. It is likely that these effects are synergistic when the diffusion of macromolecules across the sclera in the presence of a transscleral pressure is considered. Pressure would be expected to reduce scleral permeability by compressing collagen fibers within the sclera.
Narrowing the intercollagen pathways should affect the diffusion of macromolecules more than small molecules because of the molecular size of the pathways; thus, a narrowing of the spaces between collagen fibers within the sclera slows the diffusion of small molecules and might completely block the transport of macromolecules. The permeability of the sclera to larger molecules as a function of pressure has not yet been investigated.

Results of in vitro permeability studies indicate that scleral solute permeability is comparable to that of the corneal stroma. Passive solute diffusion through an aqueous pathway is the primary mechanism of drug permeation across the sclera. The sclera is an elastic and microporous tissue composed of proteoglycans and closely packed collagen fibrils, containing approximately 70% water. The most reasonable diffusion pathway for drugs is through the interfibrillar aqueous media of the gel-like proteoglycans. A fiber matrix–predictive model of sclera has been developed to describe flux across the tissue. This model is novel in that all the parameters used correspond to geometrical and physicochemical properties of the tissue (such as water, collagen, GAG, noncollagenous protein, and salt content) and of the solutes themselves. These values were obtained from independent measurements reported in the literature and are not derived or fitted. The predicted scleral permeabilities provided by this model show very good agreement with reported experimental data. The model provides further insight into the flux of solutes and the delivery of drugs across the sclera. Changes in the physicochemical parameters of the sclera have rather small effects on the permeabilities of small compounds, such as most conventional drugs. The tissue is quite permeable to these small compounds, and transscleral delivery would be expected to occur rather rapidly. For larger molecules, however, such as proteins, DNA, virus vectors, and other new products of biotechnology, the model indicates that transscleral delivery could be significantly improved by taking advantage of thinner regions of the tissue, by increasing scleral hydration, or by transient modification of the scleral extracellular matrix.

Drug delivery across the sclera or cornea is governed in part by transient diffusion across the tissue that typically occurs over a time course of minutes unless some type of controlled release formulation or device is used. Experimental measurements of scleral permeability are, however, based on determinations of steady state flux. It is important to note that in the absence of a sustained-release system, drug–sclera contact times would be expected to be too brief to permit the attainment of steady state flux. Thus, in vitro flux measurements can be expected to over predict transscleral drug delivery. The utilization of some type of sustained-release delivery system would appear to be necessary for successful utilization of transscleral drug delivery. The ideal sustained-release system would provide controlled, long-term drug release, specific scleral site delivery and prolong drug–sclera contact time. This would permit improved drug flux through thinner areas of the tissue, potentially permit treatment to specific posterior segment regions, and minimize systemic drug absorption by the conjunctival vasculature. A wide variety of sustained-release drug delivery systems exist, including various gel formulations, erodible polymers, microspheres, liposomes, and various types of inserts, including miniosmotic pumps and combinations of these technologies. Two currently available technologies show exciting potential for transscleral application. In situ forming polymeric gels are viscous liquids that on exposure to physiologic conditions will shift to a gel phase. Pluronic F-127 is a polycylic compound that exhibits the phenomenon of reverse thermal gelation, remaining in the liquid state at refrigerator temperatures and gelling on warming to ambient or physiologic temperatures. Bioadhesive compounds such as fibrin glue also hold great promise. Both Pluronic F-127 and fibrin glue have been used widely in medical and pharmaceutical systems. These compounds have excellent tissue compatibility. Drugs can be incorporated into them, and the formulation can be applied to a scleral site, where it will quickly gel or solidify. Preliminary in vitro perfusion studies with F-127 and fibrin glue have demonstrated that they can provide slow, uniform sustained release of dexamethasone across human sclera.

The sclera, by virtue of its large surface area, accessibility, and relatively high permeability may indeed provide a useful vector for delivering drugs to tissues in the posterior of the eye. Significant questions that will ultimately determine the feasibility of this therapeutic approach have yet to be answered. To what extent will choroidal blood flow limit drug delivery across the sclera? Will the pharmacokinetics of transscleral delivery be compatible with long-term sustained release drug delivery? How will intraocular pressure affect the diffusion of proteins and larger molecules across the tissue? Can regional differences in scleral thickness be taken advantage of to enhance drug delivery? To what extent will binding of drugs to the scleral extracellular matrix affect drug delivery or sustained release? Can sustained release delivery systems be developed that will permit site-specific drug delivery?

In this issue of Investigative Ophthalmology and Visual Science, Ambati et al. show that the rabbit sclera in vitro is permeable to higher molecular weight dextrans, up to 150 kDa, as well as to the proteins IgG and bovine serum albumin. This extends the molecular weight range of scleral permeability described in previous studies that have reported scleral permeabilities to solutes up to 70 kDa in molecular weight. An accompanying study by Ambati et al., also appearing in this issue, shows that in vivo transscleral delivery is capable of maintaining significant levels of biologically active protein in the choroid and retina of the rabbit eye. This vector provides selective delivery with no measurable systemic absorption. Furthermore, and significantly, the protein retains its biological activity. The authors demonstrate that therapeutic levels of such agents can clearly be achieved in the posterior segment using transscleral delivery.

Experimental evidence currently shows that transscleral delivery of drugs can be accomplished and suggests great promise that this approach will provide new therapeutic approaches for treating visually devastating diseases of the posterior segment of the eye. Future studies will further define the feasibility of this approach.

References


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