OCULAR DRUG DELIVERY: TARGETING THE POSTERIOR SEGMENT

Many efforts are under way to improve drug delivery to the back of the eye.

BY ARON SHAPIRO

One inch or less. That is the short distance an ocular drug must travel to reach a target site at the back of the eye. Research has come a long way over the past 4 decades in efforts to make this inch-long journey more successful.

Delivering ocular drugs to their target tissues often requires them to traverse the fat-water-fat structure of the corneal barrier while ensuring minimum wastage through tear washout and systemic absorption. This is why delivering drugs effectively to the posterior of the eye is a challenge that many companies have aimed to overcome. This installment of the Innovations in Retina column describes recent developments in methods of ophthalmic drug delivery to the posterior segment of the eye.

ROUTES OF DELIVERY

Topical, systemic, and intraocular delivery are the three main routes through which ophthalmic medications are administered to the back of the eye.

The easiest of these methods is topical application of ophthalmic preparations in the form of solutions, suspensions, ointments, gels, or emulsions. Unfortunately, only about 5% of the applied dose may enter the internal structures of the eye, either through the cornea—which is ideal for small lipophilic drugs—or through the conjunctiva and sclera, a route that is better suited for large, hydrophilic drugs.

Most of the dose that is not washed out is systemically absorbed through the conjunctiva and nasal fluids and also through lacrimal drainage, pharynx, gastrointestinal tract, skin, aqueous humor, and inner ocular tissues, ultimately to be eliminated by metabolic processes.1

For effective systemic delivery, a relatively high drug concentration must circulate in the plasma to achieve a therapeutic dose within the eye. Oral drugs can be suitable for posterior segment treatment, although their use exposes the whole body to the drug, often giving rise to undesired side effects.2

In order to ensure that the required dose of a drug reaches its target tissues, it may have to be administered by subconjunctival injection, intravitreal injection, or sub-Tenon injection. Besides being invasive and carrying a degree of risk of infection, these routes require multiple visits to the doctor’s office and can greatly inconvenience patients.3

Patient-centered research has called for improved and easier methods of drug delivery. Several strategies have been proposed.

ENHANCING DELIVERY

Refining ocular drug delivery calls for different approaches based on the target area and treatment requirements of the disease to be treated. One practical approach involves increasing the solubility and penetration capacity of a drug; molecules with low aqueous solubility can be made more water-soluble by the addition of hydrotropic solubility enhancers to the formulation, thus increasing the bioavailability of the active ingredient. A drug formulation containing penetration enhancers such as gelucires and cyclodextrine microparticles can improve drug partitioning into the corneal epithelium, thus allowing better penetration.
of the drug through the cornea for more efficient delivery to the posterior segment of the eye.1

Designing a drug that stays in contact with ocular tissues for a longer time could ensure less precorneal loss and better penetration to the target site. There are several ways of increasing the retention time of a drug. Viscosity-enhancing polymers—such as derivatives of cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, carbomers, and hyaluronic acid and its modified forms—absorb water to form viscoelastic gels that are suitable vehicles for drug delivery.6 Liquid formulations that transition to gels upon instillation, called in situ gelling systems, are typically triggered by changes in temperature, pH, or electrolyte interaction. Some compounds or polymers have mucoadhesive properties that can increase the residence time of a drug due to interaction between the formulation and the mucus-covered ocular surface. Here, the residence time is governed by the slower turnover of mucus rather than the rapid turnover of the aqueous tear component.4

Nanoparticles, which are sub–micron-sized particles ranging from 10 nm to 1000 nm, can provide versatile drug delivery systems. Drugs can be loaded into these particles by attachment to the matrix, or the drug can be dissolved, encapsulated, or entrapped within their structures.6 Recently, sub–micron-sized liposomes have shown potential as topical drug delivery systems in the form of eye drops for the treatment of posterior segment diseases.1

Another strategy involves the use of drug-loaded devices placed in the upper or lower conjunctival cul-de-sac or even directly on the cornea. Such ocular inserts, whether formulated to be removable or biodegradable, can function as controlled-release drug reservoirs. Contact lenses have also been used for ocular drug delivery, and their drug-loading capacity can be enhanced by the inclusion of so-called container molecules that can accommodate the molecules in their cavities.1

One way of overcoming all external barriers involves the use of ocular implants, designed either to penetrate ocular membranes or to reside entirely within the eye. These can be formulated to provide short-term medication or to deliver medication for several years for chronic ocular conditions.

SUSTAINED-RELEASE PRODUCTS

Four decades of research have resulted in the availability of only four intraocular sustained-release drug delivery products with regulatory approval either globally or in Europe. They include the fluocinolone acetonide intraocular implant 0.19 mg (Retisert, Bausch + Lomb), indicated for chronic noninfectious posterior uveitis; the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) for macular edema secondary to branch or central retinal vein occlusion (RVO), diabetic macular edema (DME), and posterior uveitis; the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences), which uses pSivida’s Durasert technology for delivery in patients with DME who have been previously treated with corticosteroids without intraocular pressure (IOP) elevation; and the ganciclovir intravitreal implant 4.5 mg (Vitrascert, Bausch + Lomb) for cytomegalovirus retinitis.

Numerous innovative ocular drug delivery products are now in development. Several sustained-release formulations of dexamethasone are in clinical development. A dexamethasone depot (Dextenza, Ocular Therapeutix) is undergoing phase 3 clinical evaluation for treatment of postoperative inflammation and pain.7 The sustained-release dexamethasone formulation EGP-437 (EyeGate) is delivered noninvasively by the EyeGate II Delivery System for treatment of noninfectious anterior uveitis and macular edema. In a phase 1/2 clinical trial, positive responses were seen with EGP-437 compared with dexamethasone intravitreal implant 0.7 mg control in patients with macula edema, and dosing evaluation studies are continuing.8 Taiwan Liposome Company is developing another sustained-release dexamethasone treatment (ProDex), delivered by the company’s BioSeizer platform; this implant is in phase 2 studies for macular edema.9 Sustained-release formulations of prostaglandin analogs are also in development for the treatment of glaucoma or ocular hypertension. In a phase 2 study, a travoprost depot (OTX-TP, Ocular Therapeutix) showed average IOP reduction over 3 months similar to that induced by topical travoprost.10 In a separate phase 2 study, ENVS15 (travoprost XR, Envisia) demonstrated statistically significant and clinically meaningful reduction in IOP with results comparable to topical once-daily travoprost ophthalmic solution (Travatan Z, Alcon).11

These same anterior segment delivery systems may also be used intravitreally for treatment of posterior segment conditions, according to the companies. Ocular Therapeutix is also developing a 6-month sustained-release anti-VEGF hydrogel injection for retinal diseases such as age-related macular degeneration, RVO, and DME. Such an
implant could significantly reduce the dosing frequency for anti-VEGF therapies and the likelihood of side effects associated with monthly intravitreal injections.\textsuperscript{12}

Two advanced delivery systems mentioned in this article can now deliver sufficient doses of drugs to the retina over prolonged periods. The EyeGate II Delivery System uses a low-level electrical current to deliver a specified amount of drug for each treatment. This noninvasive method, powered by iontophoresis, can transfer high drug concentrations across ocular tissues to the posterior segment.\textsuperscript{13} The BioSeizer platform is a lipid-based technology that can carry a therapeutic agent and enable significantly prolonged retention time at the target site, thereby reducing the frequency of drug administration.\textsuperscript{14}

Cyclodextrins are circular sugar compounds that have the property of forming water-soluble inclusion complexes to enhance the aqueous solubility of lipophilic compounds. Oculis is developing a nanoparticle technology that would use \(\gamma\)-cyclodextrin nanoparticle/microparticle eyedrops to deliver drugs to the anterior and posterior segments. The technology has been used successfully to deliver dexamethasone and dorzolamide, and is currently being explored to deliver other drugs to the back of the eye.\textsuperscript{15,16}

Replenish has developed the MicroPump, a refillable implant that dispenses nanoliter-size doses as required.\textsuperscript{17} pSivida’s Durasert technology is a miniaturized, injectable sustained-release drug delivery system in use in the fluorocinolone acetate implant 0.19 mg.\textsuperscript{18} DSM Biomedical is developing customized polymeric delivery systems, adding to this range of products.

**FUTURE DELIVERY SYSTEMS**

Studies are under way to develop improved drug delivery systems for various ocular conditions. Retinal therapies usually involve significant challenges for effective drug delivery, and recent studies are attempting to address these concerns.

Evolving novel delivery systems include cell-penetrating peptide constructs that can be fused to a therapeutic protein transduction domain to transport microgram-size quantities of large-molecule monoclonal VEGF inhibitors in a topical eyedrop that penetrates to the posterior segment.

Slow-release depots of VEGF inhibitors are another area of study. In vitro pharmacokinetic work is being done on controlled-release polymer reservoirs of ranibizumab (Lucentis, Genentech). A noninvasive electrosomotic method of delivery of bevacizumab (Avastin, Genentech) was shown to be successful and analogous to the efficacy of intravitreal bevacizumab. A polymer nanoparticle system with conjugation of bevacizumab was shown to reduce leakage of the drug into the bloodstream and to prolong its retention in the vitreous, making it potentially safer and more effective than intravitreal injection. In vitro and in vivo pharmacokinetics in rabbits of solid-state microparticles of bevacizumab within sustained-release hydrogel matrices are also being investigated.\textsuperscript{19}

Steroid therapy is still very useful for retinopathy. A dexamethasone intravitreal implant 0.7 mg together with macular grid laser was found effective for treatment of RVO, allowing the lengthening of time between injections. The proprietary PRINT technology (Envisia) was used to create biodegradable implants and microparticle suspensions of steroids for 6-month slow-release depots for intravitreal delivery. Release kinetics of loteprednol in a nanoparticle gel are being studied. Topical dexamethasone \(\gamma\)-cyclodextrin nanoparticle eyedrops were found to improve visual acuity and decrease macular thickness in patients with DME.\textsuperscript{19}

**CONCLUSION**

This article described just a few promising studies from among the plethora being conducted in the realm of sustained-release and alternative delivery methods for posterior segment drugs. Although it may be some time before many or any of these technologies are available, this review may provide a sense of hope, to know that so much change is taking place in the field of ocular drug delivery.

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**Aron Shapiro**

vice president of retina at Ora in Andover, Mass.