

The Renaissance of Drug Delivery Systems for the Posterior Segment

BY ARON SHAPIRO; AND ELIOT LAZAR, MD

Drug delivery to the posterior segment is hampered by the anatomy of the eye due to its inherent design, which dilutes and removes foreign material. In topically administered treatments, more than 90% of the drug from an eye drop will be lost before making it past the tear film.¹ There is a considerable distance that a drug must travel to reach the posterior segment, and the journey is made more difficult by tear turnover and vascularized tissue absorption, with additional barriers such as the cornea, aqueous humor, and sclera. For years, the challenges in drug delivery to the posterior segment have proved difficult to overcome.

Although our column routinely discusses the immense and intricate undertaking of clinical research in retinal disease, this month we will take a hiatus from the “behind the scenes” of clinical trials to explore the heightened interest in posterior segment drug-delivery systems. This renaissance in ophthalmic drug delivery is no doubt a product of the need to fight the protective mechanisms of the eye in order to deliver effective treatment for debilitating retinal diseases. To widen the available treatment options, several new drug delivery systems are in development to help reach zero-order kinetics and other characteristics of a successful system (see “Characteristics of a Successful Drug Delivery System”). Although the list of drug delivery systems in development is extensive, for the purposes of this column we will focus on only a few.

CURRENT DRUG DELIVERY SYSTEMS

Implant technology has been known to achieve longer-lasting, highly localized drug delivery with more accurate concentration, although to date the technology is limited to 3 US Food and Drug Administration (FDA)-approved

devices. In early 1996, Bausch + Lomb (Aliso Viejo, CA) and its partner Control Delivery Systems (now pSivida, Watertown, MA) created Vitrasert, the prototype posterior segment drug delivery device, developed for the treatment of the blinding AIDS-related cytomegalovirus retinitis. The nonbiodegradable Vitrasert implant contains 4.5 mg of the antiviral drug ganciclovir embedded in a polymer-based system that slowly releases the drug over a 5 to 8 month period.² Following quickly on this success, Bausch + Lomb again teamed with Control Delivery Systems to begin clinical trials for Retisert, which contains the same polyvinyl alcohol polymer. This scleral-fixated implant for the treatment of uveitis releases 0.59 mg of fluocinolone acetonide and lasts approximately 30 months. Unfortunately, the lengthy duration of action of this implant may not offset its frequently seen ocular side effects, including the progression of cataracts, increased intraocular pressure (IOP), procedural complications, and pain.³

Newer biodegradable implants offer additional benefits, such as eliminating the need for removal and less potential for ocular toxicity. In 2001, Allergan, Inc. (Irvine, CA), partnered with and eventually bought Oculex (Sunnyvale, CA), the original developer of Ozurdex, formerly known as Posurdex, to continue development of the free-floating implant that delivers 0.7 mg of dexamethasone through a biodegradable polymer. Ozurdex is indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) and noninfectious uveitis affecting the posterior segment of the eye. It is associated with a lower rate of cataract formation (5%) and a lower rate of raised IOP and glaucoma requiring surgery (1%) at 6 months.⁴

CHARACTERISTICS OF A SUCCESSFUL DRUG DELIVERY SYSTEM

Delivery of drug must have zero-order kinetics

- Stable, consistent, reproducible

Cost to patient must be justified compared with conventional eye drop

- An increased cost must provide increased benefit

Should not damage or obstruct normal ocular functions

- Have minimal side effects

Consideration for patient population

- Older patients may have difficulty manipulating certain devices
- Easy for patients to insert and replace

Have the potential for extended drug delivery

- Be in an appropriate anatomic location
- Deliver multiple drugs for combination therapies
- Have controlled release

DRUG DELIVERY SYSTEMS IN CLINICAL DEVELOPMENT

The development of model drug delivery systems, such as those previously mentioned, has paved the way for additional treatment modalities. Several drugs are currently on the cusp of seeing FDA approvals. Illuvien (Alimera Sciences, Alpharetta, GA) is a free-floating nonerodable implant that delivers fluocinolone acetonide in a sustained and steady dose over an anticipated 24 to 36-month period. Illuvien is currently under review by the FDA for the treatment of diabetic macular edema (DME), but may be applicable to other diseases, including wet and dry age-related macular degeneration (AMD) and retinal vein occlusion (RVO).⁵

Encapsulated Cell Technology (ECT), developed by Neurotech Pharmaceuticals (Lincoln, RI), is one of the latest innovations targeted to deliver controlled, continuous biologics directly to the back of the eye. It involves the genetic engineering of human retinal pigment cells by plasmid transfection. ECT implants consist of cells that have been modified to produce a desired therapeutic factor, encapsulated in a section of a semipermeable hollow fiber membrane. Neurotech's current product, NT-501, contains human cells that have been modified to deliver ciliary neurotrophic factor (CNTF), a growth factor capable of rescuing dying photoreceptors

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and protecting them from degeneration.⁶ Neurotech is currently studying NT-501 in geographic atrophy (GA) associated with dry AMD and in retinitis pigmentosa. In May 2009, Neurotech announced positive results from a phase 2 study for GA. At 12 months, 96.3% of treated patients lost fewer than 3 lines of vision compared with 75% of patients in the control group. No serious events were reported and the implant was well tolerated.⁷

Additionally, Ocular Therapeutix (Bedford, MA) has a proprietary drug delivery system that uses polyethylene glycol (PEG) to encapsulate drug-loaded microspheres. The microspheres can be tailored to deliver sustained and therapeutic levels of drugs and are compatible with a surplus of ophthalmic medications. The depots can be inserted noninvasively through the punctum or injected between ocular tissues or intraocularly.⁸ In February 2011, Ocular Therapeutix announced that it would initiate a series of phase 3 clinical trials across a variety of therapeutic areas.⁹

Devices that have been traditionally used to treat diseases of the ocular surface are also being looked at for the posterior segment. Punctal plugs have been used to block the drainage of tears in patients with dry eye or those with dry eye components of various ocular surface diseases. L-PPDS (QLT, Vancouver, BC, Canada) is a minimally invasive punctal plug delivery system designed to deliver sustained release treatment to the eye and can be tailored to deliver a wide range of therapeutic agents over different time periods.¹⁰ Phase 2 studies are being completed to assess the efficacy of L-PPDS.¹¹

APPROACHES ON THE HORIZON

Innovation is key when thinking about expanding the drug-delivery technologies to the back of the eye, and the retinal drug-delivery pipeline has no shortage of prospective candidates. To fulfill the unmet need for sustainable and interactive therapies that effectively treat retinal disease, On Demand Therapeutics (Menlo Park, CA) has developed ODTx, a novel, biocompatible injectable implant made of multiple, sealed reservoirs to store and protect protein and macromolecular drugs until their desired release. The device is injected into the periphery of the vitreous in the region of the pars plana, and the segregated reservoirs are hermetically sealed to preserve protein stability for up to 1 year. The device is activated by a standard laser, using a slit lamp and mirrored lens to locate the ODTx implant. When the laser energy targets the selected reservoir, an opening is created, allowing the drug contained inside the reservoir to elute into the vitreous and diffuse to the retina. The unutilized reservoirs remain intact, and this enables the

ophthalmologist to release drugs from the additional reservoirs when required.¹²

Additional cutting-edge technology designed to be implanted under the skin of the eye includes the MicroPump (Replenish, Pasadena, CA), a microelectromechanical system that can dispense nanoliter-sized doses of drugs on an as-needed basis to either the anterior or posterior segment of the eye. The device consists of a refillable drug reservoir, flexible cannula, and check valve with a 31-gauge needle used to refill the reservoir.¹³

Transscleral drug delivery with microneedles, solid or hollow needles of micron dimension that penetrate into tissue for targeted delivery, is also an area in development. A hollow microneedle device may enable delivery into other regions of the eye with superior targeting, and, although this concept certainly requires further investigation, studies have shown that microneedles can infuse solutions containing soluble molecules, nanoparticles, and microparticles into the sclera in a minimally invasive manner.^{14,15}

At this year's Association for Research in Vision and Ophthalmology meeting, Euclid Systems (Herndon, VA) presented data on in situ polymerizing collagen gel formulations and collagen wafer depots. Such depots produced sustained in vitro release of drug for more than 30 days.¹⁶ These results show potential for collagen depots to be injected or implanted in the subconjunctival space to provide sustained release of active ingredients for a period of months to the posterior pole.

Treatments for some types of retinitis pigmentosa are also evolving. PRO-001 (ProRetina, Madrid, Spain) is a neuroprotective agent designed for slow release and is currently in preclinical studies for the treatment of retinitis pigmentosa.¹⁶

Other work on groundbreaking technologies includes that from the University of British Columbia (UBC) in Vancouver and the University of Utah. UBC has been investigating a device to be implanted behind the eye that releases drugs when triggered by an external magnet. Researchers at the University of Utah are exploring uncharted territory with their capsule drug ring (CDR), a device with a refillable reservoir designed to be implanted in the peripheral lens capsule during or after cataract surgery without sutures for sustained drug release. Additional experiments will entail implantation of the CDR in a rabbit model to assess the feasibility of this device in humans.¹⁷ Further, SurModics has provided Genentech and Roche an exclusive license to use its proprietary biodegradable microparticle drug delivery system to develop a sustained drug delivery formulation of ranibizumab (Lucentis).¹⁸

Although finding treatments for multifactorial retinal

diseases is a lengthy journey involving time, patience, and undoubtedly a little luck, the intriguing approaches of many of the aforementioned devices have piqued the interest of those in the field. With the retinal drug delivery renaissance in full force, practitioners may soon see improved drug delivery technologies that provide optimal pharmacokinetics, dose intervals, greater durability, and less invasive routes of administration to add to their armamentarium. While the ideal posterior pole drug-delivery system remains elusive, the pipeline is replete with intriguing devices, suggesting that durable and effective delivery of therapeutics through sustained-release devices will play an active role in the future of ophthalmology. ■

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