

Ocular Iontophoresis for Drug Delivery

Could this method work for dosing posterior segment therapeutics?

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Posterior segment ocular diseases, including age-related macular degeneration (AMD), diabetic retinopathy and diabetic macular edema (DME), retinal vein occlusion, uveitis, and endophthalmitis, are responsible for causing visual impairment and blindness worldwide.¹ To treat these diseases effectively, therapeutic levels of drug must be delivered to the targeted ocular tissues while systemic and local effects are minimized.²

In clinical practice, accessing the posterior segment of the eye with therapeutics presents significant challenges. Oral medications are one option for treating these diseases. To date, however, no orally delivered drug has been approved for an ophthalmic indication in the United States. This may be related to the overwhelming obstacle presented by the blood-retina barrier as well as significant development and regulatory costs. Topically applied drops do not sufficiently penetrate through the natural protective ocular barriers.³

Hence, the only approved posterior segment treatments require invasive delivery methods, including intravitreal injections, sustained release delivery systems, or surgical procedures. Invasive procedures, however, pose safety risks such as infection, retinal detachment, and vitreous hemorrhage. As more products using these dosing approaches are approved, the absolute number of adverse reactions may also increase.

The regulatory approval of pharmacologic products such as pegaptanib sodium (Macugen, Eyetech) and ranibizumab (Lucentis, Genentech) has revolutionized ophthalmic medicine for patients suffering from posteri-

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or segment degenerative diseases such as AMD. However, these treatments, delivered as intravitreal injections, present risk/benefit questions that patients and ophthalmologists must consider. Generally, the benefits significantly outweigh the risks; however, more patient-friendly, lower-risk dosing approaches clearly are desirable.

The inherent safety concerns with frequent and invasive drug delivery have served as the impetus for many investigators to seek innovative dosing alternatives that may require less frequent injections such as implants or controlled-release formulations. Alternatives such as iontophoresis can circumvent the need for injections entirely. Research efforts may yield products that expand ophthalmologists' arsenal of treatment options while enhancing the risk/benefit profile for patients.

To overcome the inherent shortcomings of available ophthalmic treatments such as low ocular bioavailability, limited depth of drug penetration, high dosing frequency, and injection-related complications, researchers have investigated a wide variety of drug delivery approaches over the



Figure 1. EyeGate II Delivery System.



Figure 2. Ocular Applicator Placement on Eye.

past 50 years. These advances include cationic emulsions, suspensions, inserts, injections, and nanoparticles. Additionally, as part of the quest to find alternative ocular dosing paradigms, ocular iontophoresis has been studied.

BACKGROUND AND MECHANISM OF ACTION

The process of iontophoresis involves applying an electrical current to an ionizable substance to increase its mobility across a surface, a concept which dates back to the 18th century. The first transscleral iontophoretic appli-

cation for vitreal drug delivery was reported in 1943.⁴ Later, David Maurice played a pivotal role in advancing the use of iontophoresis to enhance ocular drug delivery,^{5,6} but techniques for ophthalmic iontophoresis have taken decades to evolve. Although scientists, engineers, and ophthalmologists have experimented with a broad variety of ocular iontophoresis devices and drugs, no product has been approved, nor have there been data published from carefully controlled clinical trials addressing the efficacy and safety of this delivery method. During the past decade, however, the technology has advanced significantly, and devices can quickly and safely deliver high drug concentrations into ocular tissues.⁷

Many reports describe examples of ocular iontophoresis delivering substantially higher ocular drug concentrations than traditional topical applications.

A novel ocular iontophoresis system, the EyeGate II Delivery System (EGDS; Eyegate Pharmaceuticals, Inc., Waltham, MA) has been designed to achieve optimal therapeutic levels of drug in the anterior and posterior segments of the eye, while simultaneously minimizing systemic distribution. The EGDS (Figures 1 and 2) utilizes an inert electrode, which electrolyzes water to produce the hydroxide or hydronium ions required to propel charged drug molecules. The iontophoretic delivery of an anionic drug at physiologic pH requires cathodic electrolysis with the EyeGate inert electrode. This process generates hydroxide ions that promote movement of the anion into the ocular tissues while concurrently raising the pH of the drug solution. With the converse strategy, the iontophoresis delivery of a cationic drug at physiologic pH requires anodic electrolysis with the EyeGate

inert electrode. This process generates hydronium ions that promote movement of the cation into the ocular tissues, while concurrently lowering the pH of the drug solution. In both strategies, the drug product solution contains ample buffering capacity to accommodate the generation of hydroxide or hydronium ions.

CLINICAL STUDIES FOR DRY EYE AND ANTERIOR UVEITIS

The EGDS has been studied with a dexamethasone phosphate ophthalmic solution (EGP-437) that is tailored

for delivery via iontophoresis in patients who have dry eye or anterior uveitis. Two clinical studies demonstrate product safety and therapeutic response, and they support the potential use of the product for treating patients with these diseases.^{8,9} The system is currently being tested with EGP-437 in a phase 3 study, entitled ALLUVION, for dry eye patients.

In the anterior uveitis study, which was sponsored by EyeGate, patients received a single iontophoretic dose with EGP-437. The treatment was simple, rapid, well-tolerated, and efficacious. Among the 40 patients who were treated in the study, most had a complete response, indicating that there was an anterior cell score reduction from greater than 1.5 to 0. Across all treated subjects, no noteworthy safety concerns were observed; intraocular pressure remained unchanged for 28 days, and very low systemic dexamethasone levels were detected (mean Cmax <5 ng/mL). Thus, given the drug-device combination, if EGP-437 meets regulatory approval requirements for anterior uveitis, dry eye, or other indications, it will be a useful therapeutic option for treating these ocular conditions.

PRECLINICAL STUDIES ON DELIVERY TO THE POSTERIOR SEGMENT

In addition to EyeGate's ongoing clinical work surrounding ocular surface and anterior segment conditions, the platform also offers significant potential for addressing posterior segment diseases such as AMD and DME. Through a recently established research collaboration, EyeGate and RXi Pharmaceuticals Corporation will explore the noninvasive delivery of novel RNAi therapeutics. Evidence exists suggesting a potential role for RNAi in the management of neovascular AMD.¹⁰ Combining RNAi molecules with EGDS provides an opportunity to develop truly innovative treatments for many ocular diseases. Teams are now exploring the ability of EGDS to deliver RXi's sd-rxRNA compounds to the eye in preclinical models. Once inside the eye, it is believed that RXi's sd-rxRNA compounds will have access to retinal cells and, by virtue of their self-delivering properties, enter these cells and silence disease-related genes.

UNMET NEEDS IN DRUG DELIVERY

Although patients with selected ocular conditions have benefited from significant advancements in procedures, medical devices, and therapeutics for the posterior segment, there remains substantial unmet medical need. Physicians and patients seek more predictable, safe, effective treatments. The limitations inherent in currently available drug-delivery methods and the increasing number of patients affected by ocular medical conditions underscore the growing importance of

pursuing innovative drug delivery methods through meticulous biomedical research. Ocular iontophoresis appears to offer significant benefits; it can safely and effectively deliver substantial drug levels in a controlled manner without the disadvantages of repeated intraocular injections or surgical implants. Thus far, the results from clinical studies demonstrate that the iontophoresis of a corticosteroid (EGP-437) may capably treat patients with clinically significant anterior segment diseases. Future research will focus upon evaluation of EGP-437 in other ocular conditions, including potentially blinding posterior segment diseases such as AMD. The use of EGDS with novel therapeutics, such as RXi's sd-rxRNA molecules, represents an exciting new frontier in posterior segment ophthalmic pharmacotherapeutics.

To view a video demonstrating how the EGDS functions, go to: www.eyetube.net/video/eyegate-ii-delivery-system. ■

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