

Ophthalmic Drug Delivery for Retinal Disorders

Delivery of therapeutics to the human eye is one of the most interesting endeavors a formulator can take on, but also one of the most challenging. The anatomy and chemical make-up of the eye make it highly resistant to therapeutic penetration. Successfully circumventing these protective barriers requires intimate knowledge of the constraints of ophthalmic delivery as well as specialized formulation and development expertise. Drug delivery to the back of the eye in particular is expected to experience the largest growth in the next five years and 55% of debilitating ocular diseases affect this segment¹. Therefore, in this paper, we will primarily explore the constraints of posterior ocular drug delivery and applicable routes of administration. We will also dive into considerations for developing and manufacturing ophthalmic drug products.

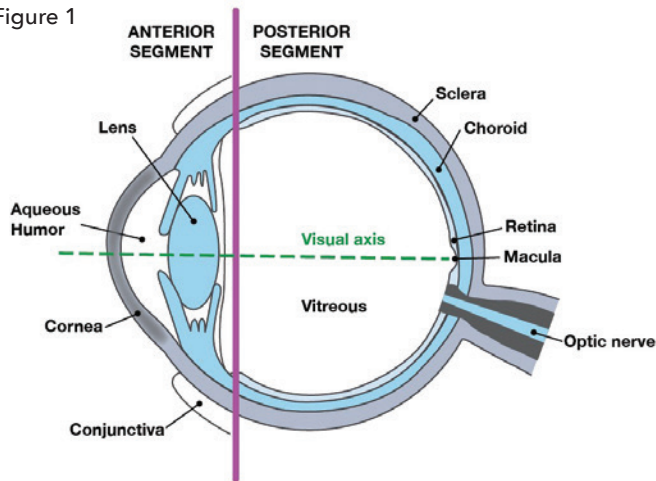
Types of Ocular Drug Delivery

Anterior Drug Delivery

Ocular drug delivery can be classified into two categories, posterior and anterior drug delivery, each of which possesses its own unique obstacles. Anterior drug delivery pertains to the front portion of the eye and deals mostly with penetrating the cornea. The cornea is the transparent layer covering the visible portion of the eye and aids in focusing light (see Figure 1). It is commonly targeted with topical formulations such as eye drops, including solutions, suspensions, and emulsions, and ophthalmic gels. Topical drug administration has been the standard of care for treating ocular ailments for decades, yet it still presents challenges formulators have not fully overcome.



Figure 1



Typically, only 1-5% of a topically administered drug is absorbed at the site of action, mostly due to the difficult path a drug must take to effectively penetrate the target tissue². The first obstacle in permeating the cornea begins with several precorneal loss factors. These include lacrimation (tearing up), solution drainage, blinking, and non-productive absorption in other tissue, among others. As a result, frequent administration of a drug is often needed to maintain an efficacious drug level. However, high concentrations of drug administered to a sensitive organ such as the eye can cause side effects or even tissue damage. Additionally, repeated administration can become costly when dealing with an expensive active pharmaceutical ingredient (API).

The small amount of drug that remains will then encounter the three main layers of the cornea: the epithelium, stroma, and endothelium. The epithelium is very lipophilic and selective to only very small molecules. The stroma is highly hydrophilic and makes up the largest portion of the cornea. The endothelium keeps the rest of the cornea hydrated and is also lipophilic. Developing a drug product that can easily pass through these layers is a significant challenge to formulators.

Posterior Ocular Drug Delivery

Posterior drug delivery refers to the back segment of the eye, which primarily consists of the choroid, vitreous, and retina (see Figure 1). The retina is a primary focus of many posterior treatments and is comprised of a thin layer of tissue lining the back of the eye. This tissue receives light, which it then converts into neural signals and sends to the brain for recognition. The retina is therefore a critical component of the eye; disorders affecting this area are one of the leading causes of vision loss.

Despite the significance, there are still limited treatment options available for posterior segment diseases. The back of the eye is considered one of the most difficult areas to effectively treat. Compared to the front portion, the posterior segment generally cannot be accessed via a topical route due to the natural impermeability of the eye exterior and the distance a therapeutic agent would have to travel to reach the site of action. Despite this, more than 90% of ophthalmic therapeutics on the market in 2010 were topical². Additionally, systemic delivery via oral or intravenous administration is also not practical method of treating the posterior segment. High concentrations must be achieved in the blood stream for a drug to pass through the retinal artery and achieve therapeutic levels inside the eye. Since it exposes the whole body to the drug, systemic administration would require a very high dose to be administered and would likely include significant side effects as a result.

Treatment Methods

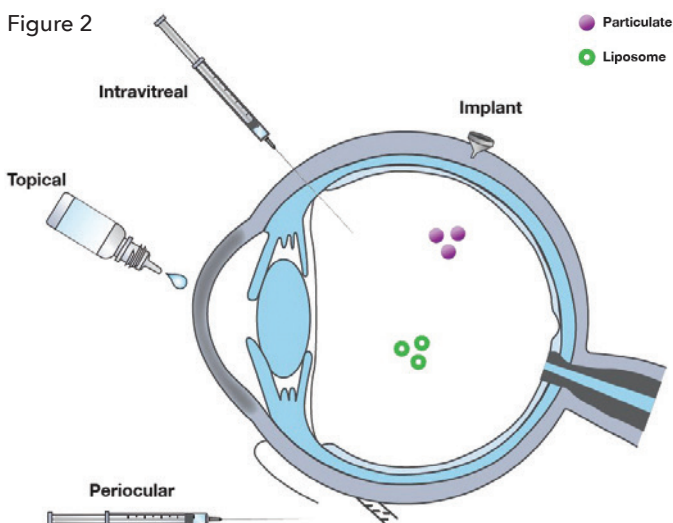
Traditional methods to treat posterior disorders overcome the challenges experienced in topical or systemic applications with administration closer to the site of action. Typical drug delivery for back-of-the-eye application include sustained release systems, such as implants and drug-eluting particulates, and injections into the vitreous or closely surrounding tissue.



Ocular Injectables

Ocular injectables can be broken down into periocular and intravitreal (IVT) injections (see Figure 2). IVT injections involve inserting a therapeutic agent directly into the vitreous humor via a needle and syringe. The vitreous is a gelatinous fluid that fills the eyeball and serves to keep the retina in place as well as help light flow through the eye. Injections into this fluid have the significant advantage of bypassing typical ocular obstacles like the highly-resistant blood-retinal barrier (BRB). Groundbreaking products within the last decade like Eylea® and Lucentis® for the treatment of macular degeneration helped make IVT injections the most recommended method of targeting the retina. However, these products still experience challenges, such as the fact that drug distribution in the vitreous can be non-uniform, maintaining an effective drug concentration over time is difficult, and elimination is highly dependent on the molecular weight of the compound. One way around these issues is frequent administration, but multiple invasive procedures are neither ideal for a patient nor cost effective.

Periocular injections are administered in the tissue closely surrounding the eyeball, such as the conjunctiva (see Figure 1) or sub-tenon's space. The conjunctiva is a membrane that lines the front of the eye and inside of the eyelids, whereas sub-tenon's space or capsule is thin tissue that envelops the eyeball and forms the socket in which the eye rotates. Periocular injections are considered safer than IVT injections but can be less effective as they still must penetrate the eyeball to reach



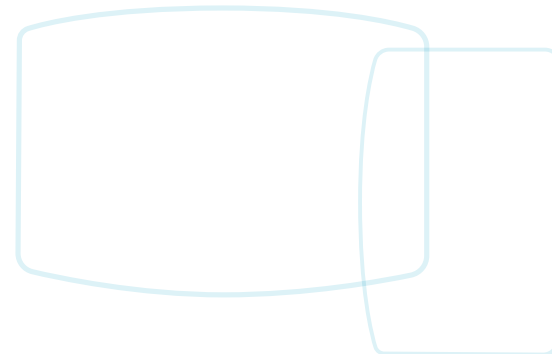
the diseased tissue for retinal disorders and struggle to attain sustained release. Periocular injections are commonly utilized for the treatment of uveitis, an inflammation of the eye that can affect both anterior and posterior segments, and macular edema, which is swelling in the center of the retina.

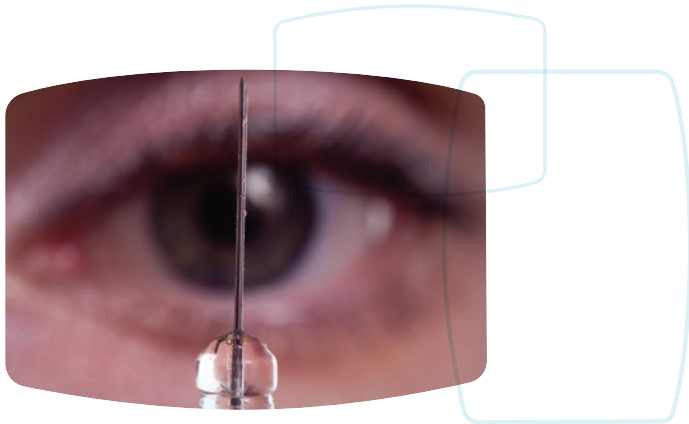
Sustained-Release Systems

A sustained release system is a vehicle designed for the release of a drug at a predetermined rate to maintain a constant therapeutic concentration for a defined period of time.

Liposomes and Particulates

Obstacles experienced in some standard injectable drug products have led many to investigate alternative drug delivery systems. Controlled and sustained drug delivery continues to be a major area of interest, especially with the development of newer and more potent ocular drugs with shorter half-lives on the rise. One controlled release approach that also aids in containing potent APIs is combining a drug with lipid vesicles, known as liposomes. Liposomes consist of a phospholipid bilayer, which are naturally attracted to cell membranes and can therefore bind easily to facilitate effective drug transfer when loaded with an API. They also have the unique advantage of being able to deliver both hydrophobic and hydrophilic drugs. Another method is encapsulating or combining a drug with a polymeric compound to form micro- or nanoparticulates. These can be of a reservoir or matrix composition, meaning a drug is either encapsulated with or distributed evenly within a polymer. One of the most commonly investigated polymers for this application is poly(lactic-co-glycolic acid) (PLGA) due to its ability to break down safely in the body and release drug at a controlled rate when injected. Both liposomes and polymer particulates can improve bioavailability, slow drug clearance, and stabilize the active form of the drug.





Drug-Eluting Ocular Implants

Ocular implants are minute devices designed for localized drug delivery and come in both biodegradable and non-biodegradable forms. These implants are inserted into the vitreous humor of the eyeball (see Figure 1), suprachoroidal space, or the closely surrounding tissue to release drug for up to several years. Approved products include Ozurdex[®] and Iluvien[®], both intravitreal implants for macular edema, and Yutiq[™], an implant for non-infectious uveitis, among others. Polymers used in non-biodegradable systems include materials such as polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA). Though these materials offer longer-lasting release, they are considerably less popular than biodegradable implants, such as those made with PLGA, due to the dangers and inconvenience associated with additional procedures needed to remove and replace the implant once it has become depleted.

Regardless, the advantage of continual release has caused implants to gain significant momentum in recent years. Ocular implants make up approximately one-third of all FDA-approved implants on the market and have almost double the number in clinical development³. They have been found effective in the treatment of several retinal disorders where drug delivery over several months to years without additional intervention can be life-changing. Sustained release is key when treating retinal disorders as they are typically considered treatable but not curable - meaning, once developed, these conditions will require ongoing care.

Retinal Disease States & Sterility in Ophthalmic Products

The enduring nature of retinal disorders is unfortunate for patients but opens a large market for developers to create therapies that slow disease progression and ease debilitating symptoms. Treatments for retinal diseases,

such as Age-related Macular Degeneration (AMD) and Diabetic Retinopathy (DR), are expected to experience larger growth over the next five years than any other ocular disease area. Due to an increasingly aging population and a surge in obesity, the prevalence of retinal disorders is on the rise. Both AMD and DR are principal causes of blindness, with AMD being the leading cause of permanent sight loss in the elderly and DR taking first place for those of working age^{4,5}. AMD is caused by deterioration of the center of the retina, called the macula, and DR results from high blood sugar damaging retinal blood vessels. However, despite high rates of occurrence, there are only four approved therapies on the market for the treatment of AMD and two for DR³.

Treatment options are lacking for many reasons, ranging from the significant drug product expertise needed in developing these complex formulations to the strict level of sterility required to manufacture them. The human eye is highly susceptible to bacteria and other irritants, making product sterility critical. There are two main methods of manufacturing a sterile drug product: terminal sterilization and aseptic processing. Terminal sterilization involves filling and sealing a product under high-quality environmental conditions, then sterilizing the final product in its container. Terminal sterilization is the preferred method, but the complex components increasingly found in ocular drug products, such as biologics and nanoparticulates, cannot always be safely sterilized with this method. Interestingly, and important to consider, a developer must prove their drug product cannot be terminally sterilized before FDA-approval for aseptic processing can be received⁶. Aseptic processing involves a drug product and its container being sterilized separately and then brought together as a finished product under sterile conditions.

Regardless of which method a drug product may require, it is critical sterile products be handled by an organization with the proper equipment and a proven track record of successfully manufacturing sterile products. As ophthalmic drug products come into direct contact with tissue crucial to a person's sight, product developers should expect significant FDA scrutiny when it comes to sterility. However, formulators should not be steered away from pursuing sight-saving therapies, as patient need is at an all-time high. Exciting innovations are possible with the right tools and partners.

Conclusion

The human eye has unique processes and functionality from the rest of the body and plays a significant role in everyday life. Therefore, special considerations must be taken when choosing to develop and manufacture ocular drug products. There are several treatments for disorders affecting the posterior segment of the eye available today, and even more in clinical development, as formulators increasingly innovate in this rapidly growing field. From increasing bioavailability to deciding whether to utilize a pre-filled syringe and assuring its sterility, trusting the right people to support you in the drug product development process can help mitigate your risk and expedite your product successfully to market. With an increasing population of diabetics and the elderly coupled with improved diagnostic tools, the need for ocular therapeutics will only continue to grow in the years to come. Developers should therefore position themselves to meet this growing need.

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9911 Brecksville Road
Cleveland, OH 44141-3201 USA

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