

CONSIDERATIONS FOR OPHTHALMIC DRUG DELIVERY AND DEVELOPMENT

In this article, Robert Lee, PhD, President of the CDMO Division of Lubrizol Life Science Health, discusses recent advances in ophthalmic dosage forms and how companies are meeting these challenges to better serve their customers.

There has been a rise in the incidence of ocular conditions due to an ageing population, an increase in diabetes and other diseases, and improved diagnoses of many serious eye disorders. Companies have been discovering innovative drugs to treat these conditions, but the development of effective ophthalmic formulations can be challenging. These obstacles arise from the increasingly common bioavailability and solubility issues with new drugs, as well as stability, sterility and patient concerns.

OPHTHALMIC DOSAGE FORMS

While topicals are the most popular dosage form on the market for the treatment of eye conditions, there is a growing need for injectables and implantables for some serious, hard-to-treat ophthalmic conditions. The main dosage forms include the following:

- Topicals, which can be delivered as eye drops (emulsions, suspensions or solutions), gels or ointments. A common example is Restasis® (Allergan, Dublin, Ireland), a topical ophthalmic emulsion for the treatment of dry eye.
- Injectables often come in two forms:
 - Periocular (administered to tissue closely surrounding the eye)
 - Intravitreal (injected into the fluid within the eye). Notable developments in the past several years include Regeneron's Eylea® (aflibercept) and Roche's Lucentis® (ranibizumab), both of which are biologics
- Implants and inserts, which can be bioabsorbable or non-bioabsorbable and can be used to release drug for up to several years. They can be injected, surgically inserted or placed beneath the eyelid or in the lacrimal punctum. For example, Allergan's Ozurdex® (dexamethasone intravitreal implant) is implanted in the retina to treat macular oedema.

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INDUSTRY TRENDS

The ocular market is continually growing – an eight-fold increase was seen in the number of NDAs and biologics license applications (BLAs) between 2015 and 2018.

The market is also increasingly focused on select disease states, primarily:

- Dry eye
- Post-op pain and inflammation following cataract surgery
- Glaucoma
- Diabetic retinopathy
- Wet and dry age-related macular degeneration.

Among the treatments available for these disease states, retinal disorder therapies, such as biologics and gene therapies, have contributed to much of the market growth. These therapies are trending toward longer-acting products, such as intravitreal injections, especially with poly(lactic-co-glycolic acid) (PLGA) microparticles. Additional trends include formulations with multiple APIs, improved delivery devices for topicals, and preservative-free options such as sterile multidose eye-drop bottles.

ANTERIOR AND POSTERIOR DRUG DELIVERY

The administration site of ocular drugs can be divided into two categories, anterior and



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posterior drug delivery. Anterior delivery, or “front” of the eye, includes the surface of the eye and primarily involves penetrating the cornea. Posterior delivery, or “back” of the eye, mainly targets the retina.

Topical drug administration to the front of the eye has been the standard of care for the treatment of ocular diseases for decades. However, low drug penetration – usually less than 5% of a drug is absorbed¹ – limits the effectiveness of topical treatments. Additionally, topical therapies cannot be used to treat back-of-the-eye disorders; the necessary diffusion distance to the site of action and the viscosity of the vitreous render topicals ineffective. As a result, the posterior segment of the eye is typically the most difficult area to treat, and ocular injections and implants are the only viable treatment options.²

In addition to eye anatomy, other considerations for effective ocular treatments include:

- Solubility and bioavailability issues with APIs
- API and product stability
- Product sterility
- Packaging and product containment needs.

ENHANCING BIOAVAILABILITY

Low aqueous solubility and poor stability of many APIs mean that 70–90% of new drugs suffer from bioavailability issues.^{3,4}

However, with the right development partner, this does not have to be a deal-breaker. Indeed poor aqueous solubility can be viewed as an opportunity for innovation, as there are multiple methods that can be used to increase drug solubility or dissolution rate and, therefore, bioavailability.

One solution to this issue is to choose the correct drug delivery technology. Below are a few options drawn from our experience.

NANOPARTICLES

One method is particle size reduction, mainly with nanoparticulates, which increases the surface area of the drug particles and enhances the rate of dissolution. There are many nanoparticulate systems, which work in a variety of dosage forms:

- Pure API
- Solid lipid nanoparticles (SLNs) with API contained in a lipidic matrix
- Polymeric nanoparticles, which are similar to SLNs but with a polymer *in lieu* of lipids
- Nanocapsule systems, such as:
 - Liposomes, which are comprised of an aqueous core and a lipid bilayer shell
 - Emulsions, which are an oil core with a surfactant shell.

Below, we discuss in more detail some of these nanoparticle systems.

Solid lipid nanoparticles

SLNs are comprised of a solid matrix core that can solubilise lipophilic compounds, which are then dispersed and stabilised by an emulsifier. They improve stability and can protect a drug from chemical degradation. These systems can be used for a wide variety of APIs. Some SLNs can be terminally sterilised – which is a great benefit – although this does not apply to biologics.

Liposomes

Liposomes are constructed to deliver a drug inside a phospholipid bilayer, which is naturally attracted to cell membranes and facilitates effective drug transfer. These systems can deliver both hydrophobic drugs, dissolved in the bilayer, and hydrophilic drugs, dissolved in the aqueous core. This is a viable option for oligonucleotides used in gene therapies, which are on the rise in ophthalmics.

Liposomes can also improve biodistribution of a drug *in vivo* by mimicking cells; they are good at containing potent APIs (e.g. steroids); and are suitable for topical, sprayable and injectable systems.

MICROPARTICLES

Microparticle systems are an option for improving stability by protecting an API from enzymatic degradation in the body. They offer controlled and sustained release and can be used in topicals to aid muco-adhesion or as injectable depots.

For biodegradable systems, PLGA is the most common polymer used to encapsulate a drug due to its ability to break down safely in the body and release drug at a controlled rate.

IMPROVING END-PRODUCT STABILITY

Many APIs are sensitive to environmental conditions such as light, humidity, temperature and pH, which can affect product shelf life and stability. Shelf life refers to changes in the physicochemical properties of a drug product in its primary packaging when under typical storage conditions. Long-term storage conditions and the materials used in bottles and vials can greatly impact stability, for example, semipermeable ophthalmic bottles need to be stored at lower humidity conditions.

The stability of a drug product is also affected when introduced to a biological system. Many ocular drugs are subject to enzymatic and hydrolytic stresses present on the surface of the eye or within the vitreous, resulting in a shorter half-life.

Stability can be improved with several methods, including cold storage and lyophilisation. Refrigeration is required for most ophthalmics, especially for temperature-sensitive biologics. Nearly all intravitreal injections on the market are stored at refrigerated temperatures (2–8°C).

Lyophilisation, or freeze-drying, is used to preserve or stabilise materials and can be done aseptically. It may also preserve the integrity of water-sensitive products.

THE NEED FOR STERILITY

As with any parental product, sterility is a critical quality attribute of all ophthalmics as the human eye is highly susceptible to bacteria and irritants. The US FDA has issued many warnings concerning sterility over the years to some developers and contract development manufacturing organisations (CDMOs) manufacturing ophthalmics, creating a clear demand for partners that can provide sterile, expertly run facilities.

The two methods of sterilising drug products are terminal sterilisation and aseptic processing. Terminal sterilisation involves filling and sealing a product under high-quality environmental conditions, then sterilising the final product in its primary container using:

- Heat
- Radiation (gamma rays, e-beam)
- Sterile filtration followed by aseptic fill-finish
- Ethylene oxide gas.

Terminal sterilisation is the preferred method, but the complex components increasingly found in ocular drugs, such as biologics and nanoparticles, cannot always tolerate this process. The FDA requires aseptic processing to be used only when terminal sterilisation is not possible.

Aseptic processing involves a drug product and its container being sterilised separately then brought together as a finished product under sterile conditions. This may require sterilising excipients and API separately.

The formulator must be careful with the selection of the sterilisation methods as this can affect the physicochemical properties (e.g. the stability and viscosity) of the final drug product. It is imperative to find a partner with a lot of experience of sterilisation, along with a proper facility and equipment for the required drug delivery methods.

CONTAINMENT

Many ocular drugs on the market and in development are highly potent compounds and need to be handled appropriately to protect employees and customers, adding complexity to the development process. This often includes corticosteroids and biologics (e.g. vascular endothelial growth factor [VEGF] inhibitors), two common API types in ophthalmics. Containment efforts may include:

- Isolator technology, in which the negative pressure differential minimises the potential for contamination
- Cleanrooms that maintain negative pressure compared with adjacent areas
- Facility-wide high efficiency particulate air (HEPA) filtration of incoming air and exhaust.

PACKAGING

Depending on the dosage form, ensure your development partner can fill your bottle, vial or tube at the proper volume and batch size. Injectables can be filled into vials, ampoules or prefilled syringes. Topicals can use single-use droppers, such as a blow-fill-seal, or a multidose bottle.

For topicals, the market is increasingly moving away from preservatives in formulations due to potential irritation and toxicity.⁵ However, it can be challenging to dose ophthalmics sterilely when the

bottle holds multiple doses and the seal is broken during initial use. Many innovations have emerged as a result, including sterile multidose bottles made by Aptar Pharma (IL, US), Nemera (La Verpillière, France) and Aero Pump (Hochheim am Main, Germany), among others.

For injectables, many formulations traditionally filled into vials are now being considered for prefilled syringes. Prefilled syringes have significant advantages, such as simplified, more convenient drug administration, reduced likelihood of improper dosing and less opportunity for contamination. Considerations when determining good candidates for prefilled syringes include whether your manufacturer has the proper capabilities, glass versus plastic syringe, precipitation of the drug product and the potential for modified degradation induced by adsorption and/or absorption of API or excipients by the syringe.

CONCLUSION

Special considerations must be taken when developing and manufacturing ocular drugs to ensure that treatments are safe, sterile and effective.

As the industry moves towards more complex APIs, dosage forms and delivery vehicles, those who do not have the capabilities to develop or manufacture an ocular product in-house should evaluate partners skilled in a wide variety of applications and highly adaptive to the evolving market.

Ophthalmics consistently encounter bioavailability, solubility and stability issues, while patient compliance and sterility should also be considered when developing new products. Developers should not be discouraged by these challenges, however, as success is possible with the right partner.

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Robert Lee, PhD, President, Lubrizol Life Science Health, CDMO Division, is responsible for product and business development along with providing strategic direction. Before joining Lubrizol, Dr Lee held senior management positions at Novavax, Lyotropic Therapeutics and Imcor Pharmaceutical Co. He holds BS degrees in Biology and Chemistry from the University of Washington, US, and a PhD in Physical Bioorganic Chemistry from the University of California, Santa Barbara, US. Dr Lee has published more than three dozen articles and five book chapters, as well as holding 11 issued patents and 15 provisional or PCT patent applications. He has over 30 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. Dr Lee maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas, US, in the early 1990s, serving as a reviewer for both the International Journal of Pharmaceutics and Journal of Pharmaceutical Sciences, and serving on the Editorial Board for the Journal MOJ Bioequivalence & Bioavailability, The Scientific Pages of Nanotechnology and the Journal of Analytical and Pharmaceutical Research.

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