

# OPTIMISING OPHTHALMIC DRUG DELIVERY FOR THERAPEUTIC EFFECTIVENESS

In this article, Barbara Morgan, PhD, General Manager of CDMO Services at Lubrizol Life Science Health, offers a fresh take on one of today's most challenging ophthalmic drug delivery issues as well as trends in the industry. She discusses how eye physiology impacts product formulation and choice of dosage form, and how advanced delivery technologies are providing new options for formulators seeking to improve the bioavailability or stability of their ophthalmic treatments.

Delivery of therapeutics to the human eye is one of the more challenging projects a drug developer can take on. The anatomy and chemical composition of the eye make it highly resistant to pharmaceutical penetration. Successfully circumventing these protective barriers requires extensive knowledge and experience of ocular drug delivery, as well as specialised formulation, development and manufacturing expertise.

## TRENDING TOWARDS COMPLEXITY

Dosage form options are diverse, ranging from topical emulsions, suspension, and solutions to injectables and implants, as are the formulation options and delivery considerations for each.

Pharma innovators across the board are increasingly engaging outsourced service providers to develop and manufacture their ophthalmic formulations. This is largely due to the fact that complex formulations and dosage forms – such as long-acting intravitreal injections and biodegradable ocular implants – have become increasingly prevalent. Additionally, overall trends in healthcare and the pharma industry are prompting development of increasingly potent and hard-to-manufacture formulations. The advanced expertise and equipment

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required for these products has made in-house development more challenging.

## INCREASE IN DRUG APPROVALS

The ocular pharma industry is experiencing an unprecedented surge in venture capital investment, innovation and new drug and biologic approvals, facilitated by a fundamental shift in how the US FDA handles new drug applications.

In 2012, the FDA Safety and Innovation Act (FDASIA) was enacted, creating the “breakthrough therapy” designation to identify promising new drugs and boost their development.<sup>1</sup> The programme is proving to be quite successful – in 2018, the FDA approved 61 novel drugs.<sup>2</sup> For ophthalmics, in particular, between 2015 and 2018 there was an 800% increase in new ocular drug approvals. In addition, in 2017, two novel therapies for glaucoma were approved – an indication that had not seen a new treatment option for more than 20 years.<sup>3</sup> Only a few months later, the first-ever gene therapy for ophthalmic use was approved to treat mutation-associated retinal dystrophy.<sup>4</sup>

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**Dr Barbara Morgan**  
General Manager of CDMO Services  
T: +1 610 861 4701

**Lubrizol Life Science Health**  
3894 Courtney St  
Bethlehem  
PA 18017  
United States

[www.lubrizol.com/life-sciences](http://www.lubrizol.com/life-sciences)

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## TOPICALS FOR THE FRONT OF THE EYE

Ocular drug delivery is classified into two categories – posterior and anterior – each of which possesses unique barriers. Anterior drug delivery focuses primarily on penetrating the cornea, which is commonly targeted with topical solutions, suspensions and emulsions in the form of drops, gels or ointments. Topical drug administration has been the standard of care in ophthalmics for decades, yet it still presents challenges formulators have not fully overcome. For instance, only 1-5% of a topically administered drug is absorbed at the site of action.<sup>5</sup>

Permeating the cornea is challenging because of several precorneal loss factors, including lacrimation (tearing), solution drainage, blinking and non-productive absorption in areas that are not the target tissue. As a result, more frequent dosing is often required, which is wasteful of the drug or may result in side effects.

## POSTERIOR OCULAR DRUG DELIVERY

Posterior drug delivery refers to the back segment of the eye, which consists of the choroid, vitreous and retina. The retina, in particular, is a primary focus of many posterior treatments and comprises a thin layer of tissue critical for sight. The back of the eye is considered one of the most difficult areas to treat effectively. The posterior segment is generally inaccessible via topical routes due to the natural impermeability of the eye's exterior and the time and distance therapeutic agents would have to travel to reach the site of action.

Systemic delivery via oral or intravenous administration is also not practical for treating the posterior segment. High concentrations of the drug need to be in the bloodstream for it to pass through the retinal artery and achieve efficacious levels inside the eye. Despite these shortcomings, more than 90% of ophthalmic therapeutics on the market in 2010 were topical.<sup>5</sup>

Obstacles experienced in some standard ocular drug products have led many to investigate alternative drug delivery systems. Back-of-the-eye drug developers are increasingly turning to controlled or sustained release systems, such as implants, drug-eluting particulates and injections into the vitreous or closely surrounding tissue. These dosage forms incorporate additional technologies that facilitate effective drug release.

## OPHTHALMIC INJECTABLES

### Liposomes and Particulates

One controlled release approach that can help contain potent APIs involves combining a drug with lipid vesicles, known as liposomes. Liposomes consist of a phospholipid bilayer, which is naturally attracted to cell membranes and can therefore bind easily to facilitate effective drug transfer when loaded with an API. They have the unique advantage of being able to deliver both hydrophobic and hydrophilic drugs.

### Micro and Nano Particulates

Another delivery approach combines 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 within or distributed evenly throughout a polymer. One of the most commonly investigated polymers for this application is polylactico-glycolic acid due to its ability to break down safely in the body and release drug at a controlled rate when injected.

Particle size reduction has proven to successfully aid in delivering drugs because it increases the surface area for the API to be exposed for absorption by adjacent tissues.

## OCULAR IMPLANTS

Ocular implants are often inserted into the vitreous humour, the suprachoroidal space or the closely surrounding tissue and have been developed in both biodegradable and non-biodegradable forms. They can sustain localised drug delivery for up to several years. The advantage of sustained release has caused the development of ocular implants to gain significant momentum in recent years.

Ocular implants make up approximately one-third of all FDA-approved implants on the market with numerous additional products hot on their heels in clinical development. They have been found effective in the treatment of several retinal disorders, where sustained release is key. Retinal

disorders are typically considered treatable but not curable – meaning, once developed, these conditions will require ongoing care.

## ABOUT THE COMPANY

The health business team at Lubrizol Life Science partners with customers to speed their innovative medical devices and differentiated pharma products to market. Its team provides high-quality polymers and excipients, along with state-of-the-art product design, development and manufacturing services, with the ultimate goal of creating solutions that improve patient outcomes.

## REFERENCES

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## ABOUT THE AUTHOR

Barbara Morgan has worked with LLS Health, a Lubrizol Life Science Company, since 2014 and was named General Manager in 2018. In addition, she has a larger global role serving as the Global Business Director for all of Lubrizol Life Science's pharma businesses, facilitating a strong relationship between the different business units. With a PhD in Organic Chemistry from the University of Pennsylvania (US), Dr Morgan has more than 15 years' experience in both drug development and business development in the pharma industry. She has published numerous articles in peer-reviewed journals and holds patents, including one on the treatment of cancer stem cells.