LUBRIZOL LIFE SCIENCE

Key Considerations for Ocular Drug Development & Solubility Enhancement Techniques

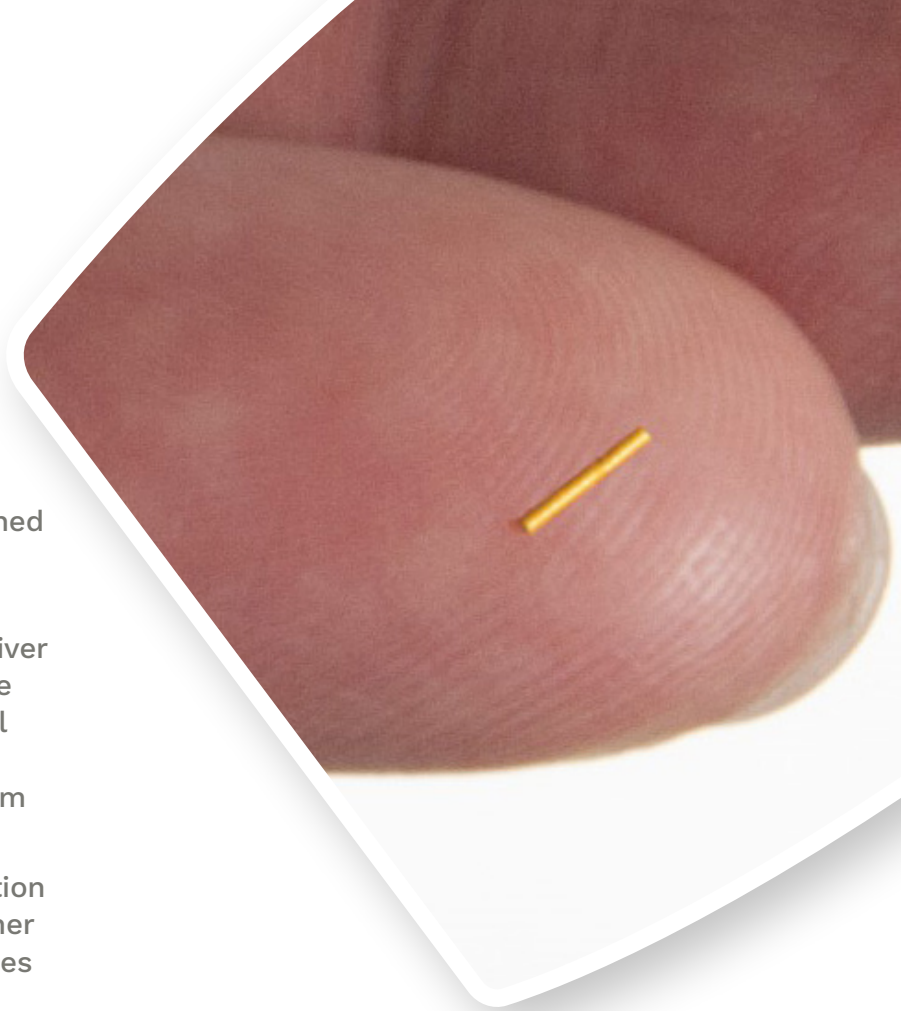
The ocular drug delivery market has grown significantly in recent years and will continue to do so for the foreseeable future. In fact, the global ocular drug delivery system market is forecasted to rise at a compound annual growth rate (CAGR) of 6.8% between 2021 and 2031[1].

This strong performance is principally due to an aging population, resulting in more patients suffering from the degeneration of their eyesight. For instance, the projected number of people worldwide with age-related macular degeneration is expected to grow from 196 million in 2020 to 288 million in 2040[2].

The eye's anatomy is highly resistant to penetration of therapeutic agents, and successfully bypassing its protective barriers requires in-depth knowledge of ocular delivery, as well as specialized formulation and development expertise.

In this guide, we will discuss how new and existing technologies can be employed to optimize ophthalmic formulations. We will then review the top considerations for an ocular drug delivery project to maximize the probability of success.

Drug Delivery systems



Patient compliance and convenience are key drivers for ocular drug development and innovation. Properties such as sustained release are important for patients as this reduces dosing frequency.

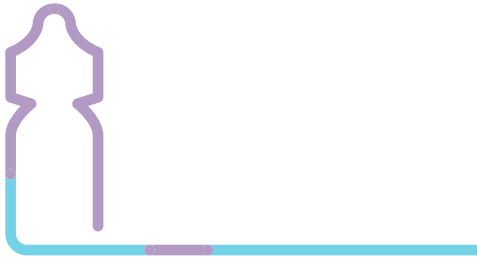
New technologies are also evolving to deliver agents more effectively to parts of the eye that are unreachable by traditional topical formulations, such as the retina. These innovations have the potential to transform the way many eye diseases are treated.

There are many examples of next-generation ocular treatments harnessing this and other technologies, offering exciting opportunities for market innovation:

- **Drug-eluting intraocular devices –** drug-eluting contacts and intraocular lenses provide a new avenue for convenient administration and controlled release of drugs to treat ocular surface conditions. They provide a number of benefits over traditional topical dosage forms, such as no leakage and reduced instances of dosage errors.
- **Topical microdosing devices –** innovative devices, such as Optejet®, can enable low and precise dosing of topical ophthalmic drug formulations. The device can dispense the formulation as a mist, which gently hits the eye and can be retained on the eye surface. As a result, such devices can minimize eye irritation and mitigate against issues such as reflexive blinking, which can lead to irregular dosing.
- **Long-acting injectables –** to treat conditions not pertaining to the surface of the eye, injectable drug formulations are often utilized. A new generation of long-acting injectable drugs offers the possibility of minimized dosage frequency, optimizing convenience and compliance.
- **Ocular implants –** new implantable drug delivery devices are offering opportunities for extended release of drug formulations. Implantables can be broken down into two broad categories. These include bioresorbable implants, which are inserted into the patient's eye and safely absorbed by the body over time, or biodurable implants, which do not break down over time and may be removed or refilled once the treatment is complete. Implants are particularly beneficial for targeting retinal disorders which otherwise would need to be treated using injectable formulations. By reducing dosage frequency, implantables free patients from having to visit a doctor's office regularly for treatment.

These innovations all give pharmaceutical companies the opportunity to create better drug products that are effective and align with what patients need from their ocular treatments.

Top considerations for ocular drug delivery



Stringent requirements for sterility

The eye is highly sensitive, so products intended for ophthalmic administration must be sterile to protect from infection.

With preservatives to maintain formulation sterility falling out of favour due to their potential to irritate the eye, the integrity of sterile manufacturing processes is particularly crucial.

Regulations are in place in many countries that require even more stringent sterility standards for ocular products compared to some other administration routes, such as oral. Sterile processing from the production of the formulation all the way to the secondary packaging is crucial to ensure compliance with such legislation.

Dosage form

When selecting a dosage form, it is important to consider the specific portion of the eye that the active pharmaceutical ingredient (API) must target, as well as the desired dosage frequency.

For treatments designed to target ophthalmic surface issues, such as dry eye or conjunctivitis, it is recommended to opt for topical formulations, including solutions, suspensions and emulsions, or even intraocular lenses. Conditions affecting the interior of the eye, including the retina, are better treated using injections or implants.

API issues

When developing an ocular drug product, the physical characteristics of the API itself also need to be considered. For instance, the water solubility of the active can have a significant impact on the bioavailability of the drug, which can determine the therapeutic effect and its duration. Poor water solubility is an increasing problem worldwide, affecting 40% of marketed drugs and up to 90% of APIs currently in the discovery pipeline.

One common approach for enhancing the solubility of an API is to use excipients or an advanced technology, such as nanomilling. However, few excipients are generally recognized as safe for ocular drug delivery, particularly for intravitreal administration.

Optimizing formulation performance for ocular drug delivery

Optimizing the performance of the final formulation often requires expert support from an organization experienced in ocular drug development. Lubrizol Life Science Health (LLS Health) has extensive experience in this area and can help determine the appropriate approach for overcoming API issues, such as low solubility.

Without modification or enhancement, poorly soluble APIs fail to be absorbed properly by the human body, limiting their bioavailability. As such, it is crucial to take measures to address the issue during the formulation development process.

There is a wide range of techniques that can be harnessed to increase the solubility of APIs and improve their delivery:

- **Encapsulation Techniques:** amphiphilic lipid- and polymer-based compounds are used to encapsulate poorly soluble APIs. The hydrophilic component of the compound is then able to strongly interact with water, allowing the API to combine with the hydrophobic segment of the compound and for the formulation to be created.

- **Chemical Modification:** this includes approaches such as pH modification, which uses acidic or basic excipients to enhance the solubility of ionizable APIs, or salt formation – turning the API into a soluble salt. PEGylation using polyethylene glycol chains to form a conjugate with the API is another approach.
- **Inclusion Complexes:** entrapping APIs within β-cyclodextrins – water-soluble torus-shaped cyclic oligosaccharides with a hydrophilic surface and a hollow hydrophobic core – can allow them to be carried across biological membranes. Serum albumin can also be complexed with APIs to form bioresorbable nanoparticles with improved solubility and dissolution rate.
- **Particle Size Reduction:** physical modification can be used to physically improve the solubility of an API. Reducing the size of the individual particles increases the surface-to-area volume ratio, thereby enhancing its dissolution rate. The most common size reduction approaches include:
  - **Micronization:** this entails the reduction of average particle diameters to the micrometer range. Micronized API particles are typically generated through jet milling, which uses pressurized air to reduce particle sizes to the required micron scale.
  - **Nanomilling:** this approach is designed to produce particle sizes even smaller than those achieved via micronization – in the nano range. This is achieved by putting the API in a liquid vehicle (typically aqueous), then grinding them into smaller particles using polymeric or ceramic milling media. The even greater surface area-to-volume ratios offered by nanoparticles mean that the approach is ideal for APIs that are particularly poorly soluble, enabling them either to be dissolved or to be held in suspension. Nanoparticulate suspensions can then be formulated into stabilized liquids, lyophilized powders, solid dosage forms, or a variety of other form factors for multiple routes of administration.

Working with ocular drug delivery experts to develop better products

To stand out in a competitive and fast-growing ocular drug market, formulators need to consider new ways of delivering products. Not only do they need to think about harnessing the benefits of new ocular dosage forms, they need to explore how to tackle the challenges unique to ocular delivery.

By working closely with a knowledgeable partner, such as a CDMO, that has extensive experience developing and manufacturing ocular products, a formulator can effectively address all considerations unique to ophthalmic delivery.

How LLS Health can help

LLS Health's longstanding history of supplying polymers, developing ophthalmic drug delivery systems, and carrying out aseptic production means it is well placed to help its partners overcome many of the challenges of ocular drug products.

To find out more about how LLS Health can support your ophthalmic project, **contact us today.**

References:
1 - https://www.fmiblog.com/global-ocular-drug-delivery-system-market-to-rise-at-6-8-cagr-between-2021-and-2031/
2 - https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(13)70145-1/fulltext