OPHTHALMIC DRUG DELIVERY

ON drugDELIVERY

MARCH 15TH 2022 • ISSUE N° 130

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OPHTHALMIC DRUG DELIVERY

This edition is one in the ONdrugDelivery series of publications. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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Front cover image, eyedropper and eye, courtesy Unither Pharmaceuticals. See this issue, p 17. Reproduced with kind permission.

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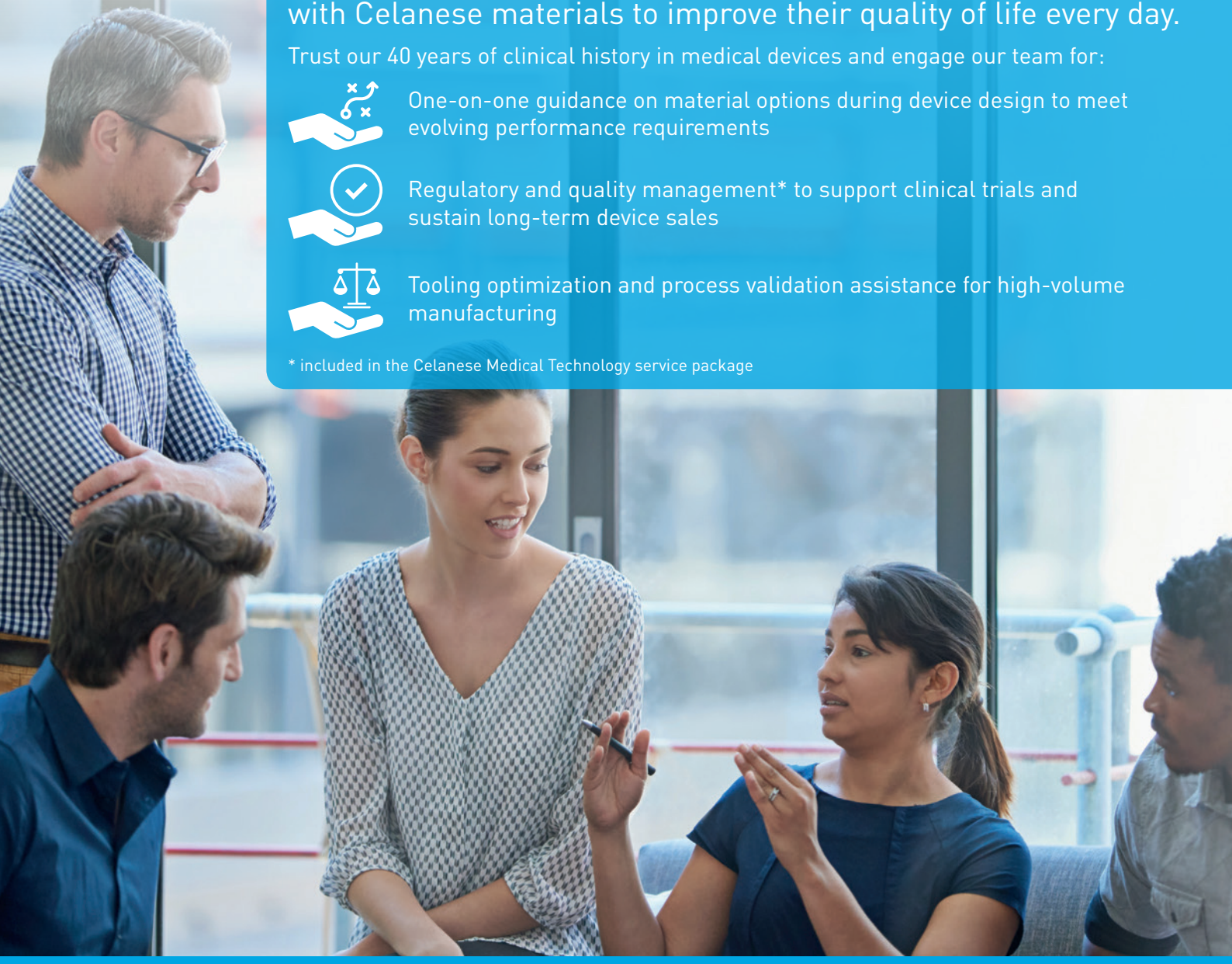

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ENVISIONING NEW HORIZONS IN OCULAR DRUG DELIVERY

In this article, Jay S Duker, MD, Chief Operating Officer at EyePoint Pharmaceuticals, discusses the history and future of ocular drug delivery, with a special focus on posterior segment diseases and the battle to overcome significant patient and caregiver burdens.

A BRIEF HISTORY OF OCULAR DRUG DELIVERY

In the ophthalmic space, practitioners are lucky to have a wide range of quality medications at their disposal. Topical drop-based medications have long been characterised by strong efficacy and tolerability profiles. Relevant examples include antibiotic drops for conjunctivitis, intraocular pressure modulators for glaucoma and steroidal agents for the treatment of dry eye disease. These medications have played a pivotal role in making positive care outcomes more predictable, safe and accessible around the world.

Unfortunately, no drug delivery system is perfect. Eye drops, for instance, present clear challenges and trade-offs. For example, although drops are generally effective, safe and tolerable, many patients consider them inconvenient and consider self-administration of them burdensome. This is especially true for products that require twice- or thrice-daily dosing, which represent a large share of the popular and affordable options on the market today.

Additionally, because the human eye possesses so many anatomical defence mechanisms, drug penetration is difficult. As a result, eye drops are primarily effective only in the eye's anterior segment, making them less viable for treating pathologies of the posterior segment, which houses the retina, macular, choroid and other structures that facilitate sight. Unfortunately, diseases that manifest here, including age-related macular degeneration (AMD), diabetic retinopathy and diabetic macular oedema, have a significant, often devastating, impact on patient vision.

In light of these factors, ophthalmologists sometimes turn to systemic drugs to mitigate posterior segment disease progression. These drugs can be delivered intravenously or orally. These modalities slow disease progression and can preserve visual acuity longer but can also incur systemic side effects – an unacceptable cost for many patients.

> "The advent of intraocular injections, which allow practitioners to deliver compounds directly to tissues at the back of the eye, represented a watershed moment in ophthalmology."

INTRAOCULAR INJECTIONS – BENEFITS, LIMITATIONS AND EMERGING IMPERATIVES

The advent of intraocular injections, which allow practitioners to deliver compounds directly to tissues at the back of the eye, represented a watershed moment in ophthalmology. For the first time, retinal specialists could deliver sight-preserving therapies in a relatively safe, controlled manner to the target tissues. Today, intraocular injection-based products – specifically, anti-vascular endothelial growth factor (anti-VEGF) agents – are considered the gold standard of care for treating these diseases, including the "wet" variety of AMD, which is characterised by new blood vessel growth and subsequent leakage in the centre of the retina and, fortunately, can be slowed with prompt medical intervention.

Still, in the world of medicine, few (if any) solutions are perfect. Although this drug delivery method provides distinct advantages, it also presents real limitations. First, the window of therapeutic action for these drugs is relatively short, requiring patients to return to their doctor each or every other month, often indefinitely. Additionally, contemporary evidence suggests that, for wet AMD and diabetic retinopathy, just one or two missed doses can cause vision loss. This was made

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"Ophthalmic researchers and clinical leaders have set their sights on an urgent imperative in drug delivery – facilitating safe and effective posterior segment therapy while reducing logistical burdens for our most vulnerable patients and their caregivers."

especially clear during the early covid-19 pandemic, when societal disruption led to decreased treatment compliance and, subsequently, adverse outcomes for thousands of vulnerable patients.

Accordingly, ophthalmic researchers and clinical leaders have set their sights on an urgent imperative in drug delivery – facilitating safe and effective posterior segment therapy while reducing logistical burdens for our most vulnerable patients and their caregivers. If this vision can be made a reality, we can theoretically improve patient compliance, preserve vision for longer periods of time, positively impact patient quality of life and minimise the burdens on caregivers, healthcare systems and the economy at large.

NOVEL APPROACHES FOR INTRAOCULAR DRUG DELIVERY

To meet this important imperative and overcome significant and costly limitations, drug manufacturers are approaching the problem from diverse developmental angles. One conceptually straightforward approach involves increasing medication dosage fourfold at the initial injection in order to reduce the number of total injections required (EYLEA® – Regeneron, NY, US). Phase II trial data presented in February 2022 indicates that this may be a viable approach.

Figure 1: An implantable ophthalmic drug delivery device on a dime to show size.

Another approach involves a surgical procedure wherein a refillable port device is surgically placed in the wall of the eye; the port is loaded with anti-VEGF, releases it slowly over the course of six months and is then refilled at the doctor's office (SUSVIMO™ and LUCENTIS® – Roche, Basel, Switzerland). Intraocular injections are still required but at a reduced frequency. The US FDA approved this first-of-its-kind device in October 2021.

Gene therapy, which could theoretically induce ocular cells to endogenously create and deploy anti-VEGF proteins, represents another interesting avenue of innovation. Early efficacy data appears promising but, as an industry, we are very much in the early stages of gene therapy, and concerns about associated ocular inflammation need to be explored and addressed.

"For years now, ophthalmic research has also focused on the concept of sustained drug delivery, which may unlock new avenues for controlling therapeutic results and increasing patient compliance."

For years now, ophthalmic research has also focused on the concept of sustained drug delivery, which may unlock new avenues for controlling therapeutic results and increasing patient compliance. Sustained drug delivery's proof of concept has been validated in the treatment of several ocular diseases, such as sustained delivery of ganciclovir for cytomegalovirus (CMV) retinitis; fluocinolone acetonide for chronic non-infectious uveitis (RETISERT® – Bausch + Lomb, NY, US; YUTIQ® – EyePoint Pharmaceuticals, MA, US); and, in 2020, bimatoprost for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension (DURYSTA™ – Allergan, Dublin, Ireland).

In recent years, a novel, implant-based methodology has been in development for releasing anti-VEGF medication at a slow, steady rate over a long period of time (Figures 1 & 2). This technology is being developed both to extend the time between patient visits and to facilitate steady-state medication release, which may help physicians control disease progression in a more even, predictable way.

Figure 2: Injector used to insert the ophthalmic implants.

EXPLORING FACTORS FOR TECHNOLOGY SELECTION

Taken together, these research initiatives offer practitioners several distinct and valuable options when it comes to drug delivery. Implants, sustained-release therapies, gene therapies and other delivery technologies will all likely have an eventual role to play in ophthalmic care, and individual clinicians will undoubtedly choose based on their patients' specific situations, needs and constraints.

There is also an inherent cost-benefit analysis to be made regarding each approach. Gene therapy, for instance, represents a fascinating avenue of pursuit but its novelty makes it expensive to implement, at least until uptake becomes more widespread across pathologies. Additionally, because gene therapy works at an endogenous level, adverse events can be costly and difficult, if not impossible, to remediate, whereas injections can be slowed or halted in response to problems that arise during the course of treatment.

A key cost-benefit question is "What is the ideal sweet spot for duration of therapy?" Research conducted by EyePoint Pharmaceuticals has indicated that most retinal physicians are looking for a six-month treatment option for wet AMD, with the feeling that treatment periods longer than six months may increase the risk of patients failing to make their follow-up visits. Additionally, six-month check-ins are beneficial for monitoring wet AMD progression in the patient's other eye and for detecting potential new ocular problems.

However, as previously stated, the reality on the ground is complex, rapidly evolving and best addressed by a diverse range of tools with distinct utilities and advantages. As with many domains in medicine, there will likely never be a "one-size-fits-all" solution, which is why the march of innovation carries on indefinitely.

FINAL THOUGHTS

The world of ophthalmic research is in a pivotal and transformative period. Although we have long had effective and efficient treatment options in the world of eye-drop-based therapy for anterior segment conditions, posterior segment drug delivery has been plagued with challenges for just as long. However, in the last decade, new technologies, discoveries and innovations – the result of, and testament to, the brilliance and hard work of researchers in the field – have created exciting new possibilities for superior drug delivery and, subsequently, improvements to standards of care. As new delivery methods are piloted, trialled and approved, we can finally look forward to a new era for the treatment of wet AMD and other serious diseases of the posterior segment. Unmistakably, a brighter future is in sight.

ABOUT THE COMPANY

EyePoint Pharmaceuticals is a pharmaceutical company committed to developing and commercialising therapeutics to help improve the lives of patients with serious eye disorders. The company's pipeline leverages its proprietary Durasert® technology for sustained intraocular drug delivery, including EYP-1901, a potential six-month intravitreal anti-VEGF treatment initially targeting wet AMD. The company has two commercial products: YUTIQ® (fluocinolone acetonide) for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye, and DEXYCU® (dexamethasone) for the treatment of postoperative inflammation following ocular surgery. DEXYCU is now sold in the US by ImprimisRx (Carlsbad, CA, US), a division of Harrow Health.

ABOUT THE AUTHOR

Jay Duker, MD, Chief Operating Officer at EyePoint Pharmaceuticals, is a leading retinal disease expert with more than 30 years' experience in the field of ophthalmology, focused on improving eyesight and preventing blindness. Dr Duker has held roles in clinical, research, business, start-ups and academic settings.

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The multidose eye dropper for preservative-free formulations

KEEPING UP WITH THE DEMAND FOR EFFECTIVE OPHTHALMIC DRUGS

In this article, Robert Lee, PhD, President of the CDMO Division of Lubrizol Life Science Health, explores the growth of the ophthalmic drug market and discusses the challenges that pharma companies may face when creating drugs to treat some of the most common ocular indications.

With rising public awareness of eye-related diseases and an ageing population, the demand for treatments for ocular conditions has dramatically increased. The global ophthalmic drug market has seen significant growth as a result. Its value was estimated to be US $28,400 million (£20,800 million) in 2020 and is expected to increase further to $36,300 million by 2025.[1–3] The rising incidence of glaucoma and age-related macular degeneration (AMD) in particular have been identified as key factors driving the predicted expansion.

Of the 2.2 billion people affected globally by ocular conditions, AMD (170 million), cataracts (94 million), glaucoma (7.7 million) and diabetic retinopathy (DR) (3.9 million) are the most common.[4] Some common ophthalmic conditions, including glaucoma, impact the front portion (anterior) of the eye, whereas others, such as DR and AMD, affect the rear portion (posterior) of the eye. Drugs used to treat these conditions will therefore need to reach the target area of the eye, resulting in different delivery requirements.

More and more pharma companies are keen to develop new ocular drugs as a result. However, developing effective ophthalmic products is no simple task; challenges often come in the form of formulation issues and the need to identify suitable delivery methods. Pharmaceutical companies will need to find a way to navigate these challenges throughout product development to ensure market success.

Fortunately for pharma companies seeking to take advantage of the growth in the sector, there is no need to face the challenges of ophthalmic drug development alone. One of the keys to success is identifying and partnering with contract development and manufacturing organisations (CDMOs) that have extensive ophthalmic drug development experience and expertise to support pharma companies on their manufacturing journey.

"Developing effective ophthalmic products is no simple task and challenges often come in the form of formulation issues and the need to identify suitable delivery methods."

UNDERSTANDING ANTERIOR EYE TREATMENT NEEDS

Drug delivery methods targeting the anterior section of the eye are often topical, commonly relying on dosage forms such as eye drops and topical ointments. Anterior delivery treatments are easy to administer and are the most widely available ophthalmic treatments. Despite their popularity, however, there are many challenges surrounding topical ophthalmic treatments, such as their ability to penetrate the cornea or stay on the eye long enough to achieve efficacy.

The bioavailability of APIs delivered in the form of eye drops has been reported to be as low as 5–10%.[5,6] One reason for this is that the conjunctival sac capacity is typically lower than the treatment volume, leading to a large proportion of the liquid running off from the eye area. Blinking and innate solution drainage also mean that the drug is often removed from the target area before it can be absorbed. The corneal and conjunctival epithelia additionally act as natural barriers, further limiting drug absorption.

Frequent administration to achieve the desired effect may be needed to compensate for low efficacy of the drug product. However, this has the potential to lead to toxicity, reduced patient compliance and increased costs. With careful formulation, residence time on the eye can be prolonged.

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"Compared with anterior eye treatments, drugs requiring delivery to the posterior of the eye are often even more challenging."

This can be achieved using delivery systems that offer muco- or bioadhesive properties, such as solid lipid nanoparticles, micelles and liposomes. Excipients such as carbomers, polycarbophil or sodium alginate can also establish bioadhesion.

INJECTIONS OR IMPLANTS FOR POSTERIOR EYE TREATMENT

Compared with anterior eye treatments, drugs requiring delivery to the posterior of the eye are often even more challenging. Posterior-targeting medicines generally need to reach the retina – a layer of cells critical for sight. As this currently cannot be achieved via topical administration, injections or implants are often used to deliver drugs to the back of the eye.

One of the main challenges associated with parenteral ophthalmic drugs is maintaining an effective concentration within the vitreous humor for a significant portion of time. Fluid clearance mechanisms limit the duration of the effect of drugs, necessitating further injections. However, treatments are invasive and uncomfortable for patients, so any method that can reduce frequency is highly desirable.

CONSIDERATIONS WHEN DEVELOPING IMPLANTS

Implantable drug delivery to the eye is highly attractive, due to sustained release potential, but can pose many challenges in development.[7] Implants can either be bioresorbable (absorbed by the body over time) or biodurable (do not break down and typically require removal and/or refilling following initial treatment). Careful consideration must be paid as to which polymers to use to provide these properties.

"The methods used to manufacture implantables vary considerably and include solvent-based methods, injection moulding and hot-melt extrusion."

The methods used to manufacture implantables vary considerably and include solvent-based methods, injection moulding and hot-melt extrusion. However, not all APIs are compatible with these methods. Throughout hot-melt and injection-moulding methods, APIs are often exposed to high temperatures and shear. Some drugs cannot tolerate these stresses without degradation occurring. Determining the best method for the API will require a thorough understanding of these manufacturing techniques.

Expert formulation could also allow for processing temperatures to be lowered to reduce API stress or switching to solvent-based processes to reduce degradation. However, solvent-based methods are not without their challenges and care must be taken to ensure that the API is compatible with the selected systems to minimise degradation.

THE BENEFITS OF EXPERT SUPPORT

The many challenges involved in designing both anterior and posterior ophthalmic treatments, and the rising complexity of their delivery systems, necessitate development and manufacturing by experts. Therefore, it is essential to partner with a CDMO with extensive experience of working with ophthalmic drug products. An ophthalmic drug development partner should be able to offer the expertise, capabilities and facilities necessary to help overcome the obstacles involved. A CDMO partner should also provide access to a portfolio of polymers, including implantable, biodurable polymers and mucoadhesive excipients, and have robust sterile manufacturing facilities.

ABOUT THE COMPANY

The Lubrizol Corporation, a Berkshire Hathaway Company, leverages its unmatched science to unlock immense possibilities at the molecular level, driving sustainable and measurable results. Founded in 1928, Lubrizol owns and operates more than 100 manufacturing facilities, and sales and technical offices around the world and has approximately 8,600 employees.

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ABOUT THE AUTHOR

Robert Lee, PhD, President, Lubrizol Life Science Health, CDMO Division, is responsible for product and business development along with providing the company's strategic direction. Before joining Lubrizol, Dr Lee held senior management positions at Novavax, Lyotropic Therapeutics and Imcor Pharmaceutical Co. He holds BSc degrees in Biology and Chemistry from the University of Washington (Seattle, WA, US) and a PhD in Physical Bio-organic Chemistry from the University of California (Santa Barbara, CA, 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 (Lawrence, KS, 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.

THE DEMAND FOR METERED DOSE EYE DROPS: A DOSE DELIVERY STUDY

In this article, Rouven Kraus, Head of Sales at Aero Pump, discusses a dose delivery study comparing various delivery technologies designed to meet the demand for metered dose eye drops.

The conjunctival sac of the human eye holds 7–10 µL of tears and has an overall capacity of 30 µL of fluid at a time.[1] To apply the right dose of medicine to the eye, drug delivery companies designed eye-drop devices that apply appropriate doses of 28–50 µL. Prescription drugs (e.g. prostaglandins for glaucoma treatment) usually come in delivery devices applying a dose of about 30 µL. The active ingredient is kept in the eye without any fluid spilling out. Moisturising eye drops containing, for example, sodium hyaluronate use dropper devices with a dose of about 30 µL or even about 50 µL if the product is intended to flush the eye. Especially for expensive APIs, drug manufacturers should turn their attention to prevent waste of the active and to avoid any overdosing risks. To do so, they are faced with using metered dose delivery technologies.

There are a multitude of different delivery technologies available on the market. Single-dose vials are designed to dispense a single amount of medicine and then will be discarded. Three-piece droppers are conventional multidose bottles for preserved medications. Regulatory bodies recommend the use of preservative-free delivery technologies to protect the ocular surfaces from any side effects caused by preservatives such as benzalkonium chloride. Squeeze dispensers (such as Aptar Pharma's OSD System or Nemera's Novelia®) are such preservative-free multidose bottles that protect the container content from microbial impurity.

Figure 1: Precise dose delivery of a metered dose pump.

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"Metered dose dropper pumps are unique in this field as they are the only preservative-free technology that is based on a purely mechanical pump system."

Metered dose dropper pumps (such as Aero Pump's 3K® pump or Ursapharm's (Saarbrücken, Germany) COMOD® system) are unique in this field as they are the only preservative-free technology that is based on a purely mechanical pump system. They always offer an accurate dose delivery with just one drop delivery per activation (Figure 1).

Aero Pump conducted a dosage size determination study with various delivery technologies that are available on the market. The study included several multidose eye-drop bottles.

The assay is based on the dose-uniformity requirements as set forth in the relevant Pharmacopeial chapters (USP Chapter <905> Uniformity of Dosage Units and Ph.Eur. <0676> Nasal Preparations). Ten samples per device are assayed individually by using calibrated balances. The whole study is performed by a single trained person to avoid any fluctuations. All devices are filled with a lubricating ophthalmic formulation available on the market. The assay is carried out on the amount of solution that is removed from an individual container in conditions of normal use, whereas the first 20 doses are discharged until a consistent dosage is achieved. For some devices it is necessary to prime the system to release the air from the device. The results are expressed as the delivered dosage units. Therefore, Pharmacopoeia foresees the following dose uniformity limits:

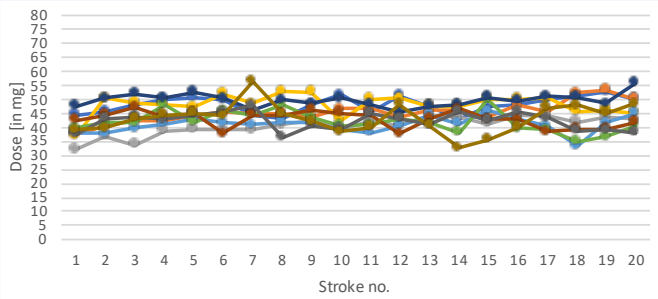
Maximum allowed acceptance value of mean dose = ± 15.0%

Maximum allowed acceptance value of each dosage unit = 80% of dispensed doses ±25.0% and 100% ±35.0%

The results of this dose delivery assay are shown in the diagrams in Box 1.

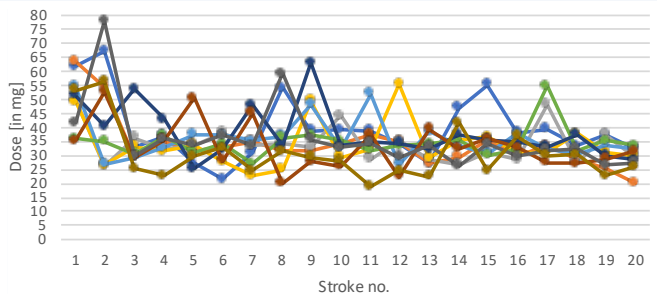
BOX 1: DOSE DETERMINATION RESULTS

Three-piece dropper



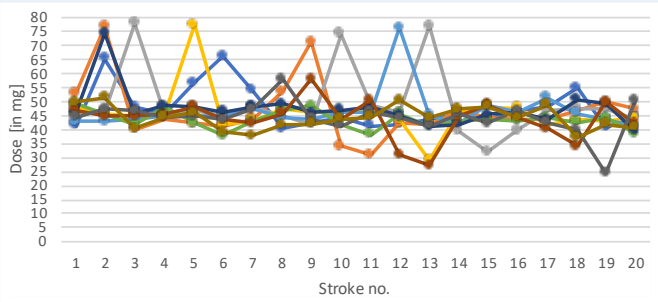
The mean delivered dose of the three-piece dropper is 44.4 mg. The device enables a consistent dose delivery of just one single drop per activation. The delivered dose is slightly fluctuating. All dispensed doses are in compliance with the relevant Pharmacopeial requirements regarding the dose delivery acceptance limits.

Ophthalmic squeeze dispenser



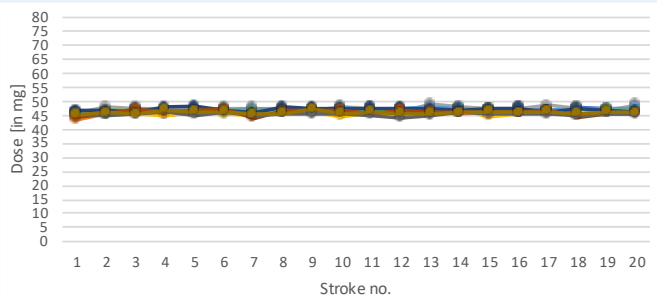
The ophthalmic squeeze dispenser (OSD) has a mean delivered dose of 35.0 mg. Several values do not comply with the acceptance limits of the single delivered doses. The output diagram shows that it was possible to dispense two drops within one single activation several times. There are several fluctuations of the delivered doses.

Novelia®



Novelia® has a mean delivered dose of 46.0 mg. The mean delivered dose is fully within the acceptance limits but several single values do not comply with the allowed dose delivery tolerances (80% of single doses ±25.0% and 100% of single values ±35.0%). The device enables a constant delivery of a uniformed drop but also carries the risk of accidentally dispensing two drops instead of one.

3K® pump



The 3K® pump shows the best dose delivery features out of all devices. It delivers a constant dose of 46.5 mg in the mean and all single dispensed doses 100% comply with the Pharmacopeial acceptance limits. The pump mechanism prevents any overdose risk for the patient.

"The results show that the pump-based mechanism used in the 3K® system achieved the best RSD value."

It is shown that all devices show good dose-uniformity results. But it is clearly visible that, except for the pump-based mechanism used in the 3K® technology, all other devices carry the risk of dispensing two drops per activation instead of just one. If the patient squeezes the bottle, they might instill two drops in their eye with the doubled active content. With some squeeze dispensers there is even the potential to create an extremely uncomfortable jet in the worst-case scenario.

The pump mechanism used in the 3K® pump avoids such overdosing reaction since the pump creates one defined dose per each activation, drop by drop (Figure 2).

During the assay the different devices were also compared with the relative standard deviation (RSD) by using the following formula:

$$RSD = \frac{(Standard\ Deviation)}{Mean} \times 100$$

The RSD value determines the deviation of all delivered drops in relation to the mean dispensed dose. The less the RSD rate, the more constant the dose uniformity. Table 1 shows the RSD results of all devices.

The results show that the pump-based mechanism used in the 3K® system achieved the best RSD value. All doses only fluctuate in a ratio of 2.0%. The minimum delivered dose out of all values is 43.5 mg and the maximum dose is 49.1 mg. The tested squeeze devices are more fluctuating in the dose uniformity. This is because the squeeze mechanism is controlled by pressure. Different pressure applied on the bottle may influence the delivered dose. And this is, in fact, the reality when looking at elderly patients with dexterity issues who may have less power to properly squeeze out the drops. Other patients may apply too much pressure and will squeeze out a higher dose – up to a doubled dose. Whereas the pump always works with the same activation force, which remains stable until the bottle is entirely emptied. This is user independent.

Device	Relative Standard Deviation
Three-piece dropper	10.5%
OSD	26.5%
Novelia®	17.1%
3K®	2.0%

Table 1: The RSD of every tested device.

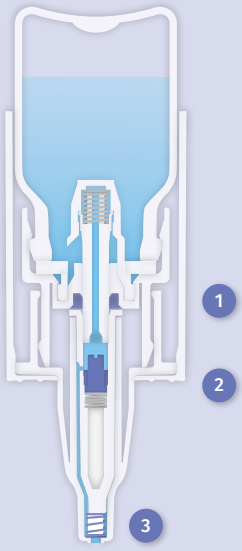
Figure 2: The risk of overdosing the eye.

"The pump always works with the same activation force, which remains stable until the bottle is entirely emptied."

From a previous usability study, one-third of subjects complained that "more than one drop came out". Improper delivery of drugs can lead to treatment failure, especially in the case of glaucoma patients. It increases the risk of potential side effects, such as burning or stinging, high blood pressure, fatigue, irregular heart rate, etc.

The 3K® pump ophthalmic system is designed in a way that the product chamber determines the output of the device. For a defined output of 45 mg, the pump will only release a drop size of 45 mg. The product chambers will be filled with the fluid again from the next activation of

Preservative-free 3K®-technology for microbiological safety



1. **The filter matrix** prevents ingress of contaminated air
2. **The valve** protects the content by stopping backflow of the product
3. **The oligodynamic nozzle** prevents microbiological growth in the tip

Figure 3: The principle of the 3K® technology with its triple protection barriers against microbiological contamination.

Figure 4: The Ophthalmic Multidose System in different sleeve designs.

the pump. The 3K® pump eyedropper is also available in lower dosage sizes such as 28 mg. The principle of the pump-based mechanism simply avoids overdosing.

ABOUT AERO PUMP'S PRESERVATIVE-FREE OPHTHALMIC MULTIDOSE SYSTEM

Aero Pump has developed a preservative-free multidose system with 3K® technology for ocular delivery. Special germ-reducing components inside the 3K® system ensure the microbiological safety of the device (Figure 3).

The pump system is available for use with plastic or glass containers in various fill sizes and, in terms of reducing container interaction with the product, this is a particular advantage. The 3K® system delivers an accurate dose over the whole lifecycle of the product, with one measured drop per actuation. The actuation force of Aero Pump's ophthalmic multidose system is stable, independent of the residual liquid inside the container.

Alongside the development of the ophthalmic multidose devices, Aero Pump has developed various customer-friendly actuation aids that enable a convenient application of the drop into the eye of the patient (Figure 4).

ABOUT THE COMPANY

Aero Pump is a leading manufacturer of high-precision application systems for the pharmaceutical and healthcare industry, focused on innovation, multi-functionality and contemporary design. Its spray pumps and dropper systems are widely established in the market and are primarily used in ophthalmic, pulmonary, nasal and dermal fields, suitable for preserved and preservative-free OTC and prescription drugs (Figure 5).

Figure 5: A brief view of Aero Pump's product range.

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ABOUT THE AUTHOR

Rouven Kraus has more than 10 years of experience in the ophthalmic drug market. He started his career in sales for a domestic iron foundry in Mainz, Germany, and joined Aero Pump in 2012 to augment the sales of its drug delivery device portfolio. In his role, he is managing global sales as well as the strategic approach to new ophthalmic developments and delivery technologies.

AERO PUMP

Ophthalmic 3K® Multidose System

Metered Dose for Preservative-free Solutions

The only available metered dose PFMD technology for ophthalmics

The metered dose and exact reproducability of the drop size, based on the mechanical functionality of the pump, is unique amongst eye droppers.

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ON drugDELIVERY

2022/23 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
April 2022	Pulmonary & Nasal Drug Delivery	Deadline passed
April/May	Drug Delivery & Environmental Sustainability	Mar 24, 2022
May	Delivering Injectables: Devices & Formulations	Apr 7, 2022
June	Connecting Drug Delivery	May 5, 2022
July	Novel Oral Delivery Systems	Jun 2, 2022
August	Industrialising Drug Delivery	Jul 7, 2022
September	Wearable Injectors	Aug 4, 2022
October	Prefilled Syringes & Injection Devices	Sep 1, 2022
Oct/Nov	Drug Delivery & Environmental Sustainability	Sep 15, 2022
November	Pulmonary & Nasal Drug Delivery	Oct 6, 2022
December	Connecting Drug Delivery	Nov 3, 2022
January 2023	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 1, 2022
February	Prefilled Syringes & Injection Devices	Jan 12, 2023
March	Ophthalmic Drug Delivery	Feb 2, 2023

INTERVIEW

In this interview, Natalia Servol speaks about Unither Pharmaceuticals' equipment for compounding and fill-finish of preservative-free products into multidose bottles, part of Unither's unique and innovative preservative-free multidose offering for partners.

NATALIA SERVOL, HEAD OF OPHTHALMIC BUSINESS, UNITHER

E: natalia.servol@unither-pharma.com

Natalia Servol holds a double master's degree in international business and education, and has more than 10 years' experience in the health industry. Her experience with brands such as Babymoov (Clermont-Ferrand, France) and Laboratoire TVM (part of Dômes Pharma Group, Pont-du-Château, France) gives her a 360-degree understanding of the health and care sector in her role as Head of Ophthalmic Business at Unither Pharmaceuticals.

Here, Ms Servol speaks about the company's equipment for compounding and fill-finish of preservative-free products into multidose bottles, part of Unither's unique and innovative preservative-free multidose offering for partners.

Q What equipment do you currently use for ophthalmic products?

A We have a considerable inventory of manufacturing equipment and versatile tank systems allowing us to work on industrial machines, under GMP conditions, with batch sizes from 3 L to 2,000 L. We additionally offer a variety of ophthalmic moulds going from 0.25 mL to 1.0 mL. We can compound and fill various types of formulation, including solutions, emulsions and gels.

Q How do you answer to your customers' needs such as regulatory and manufacturing requirements?

A I believe that the key to successfully creating relevant ophthalmological products lies in sharing ideas with partners.

Every Unither manufacturing plant has a dedicated R&D team and pilot workshop for the internal development of customer projects. If required, some works can be provided by or executed with the participation of our innovation and development centre in Bordeaux, France, or the back-up manufacturing plant. Our customers benefit from our international R&D and industrialisation footprint end to end, from early-stage work to commercial manufacturing.

"The key to successfully creating relevant ophthalmological products lies in sharing ideas with partners."

Unither has extensive experience of working in a truly international environment, both for project management with partners, and commercial supply. We meet international quality and regulatory standards and are approved by the EU EMA, the US FDA, Brazil's ANVISA, the Korean MFDS, China's MoH and many others.

"We meet international quality and regulatory standards and are approved by the EU EMA, the US FDA, Brazil's ANVISA, the Korean MFDS, China's MoH and many others."

Q What ophthalmic technologies does Unither offer?

A Unither's industrial engineering offering comprises three main technologies for sterile manufacturing of ophthalmic products: blow-fill-seal (BFS) in single-unit vials, preservative-free multidose (PFMD), and common multidose (MD) for products with preservatives.

We are always innovating solutions to meet our customers' requirements and we're always aware that ultimately this equates to meeting patients' needs. By building the industrial synergy between two main technologies for preservative-free ophthalmic products, BFS and PFMD, we believe we're truly providing our customers with tailored, sustainable solutions, and patients with products that will enhance their quality of life.

This has been the driving force for our creation and realisation of an innovative PFMD manufacturing line.

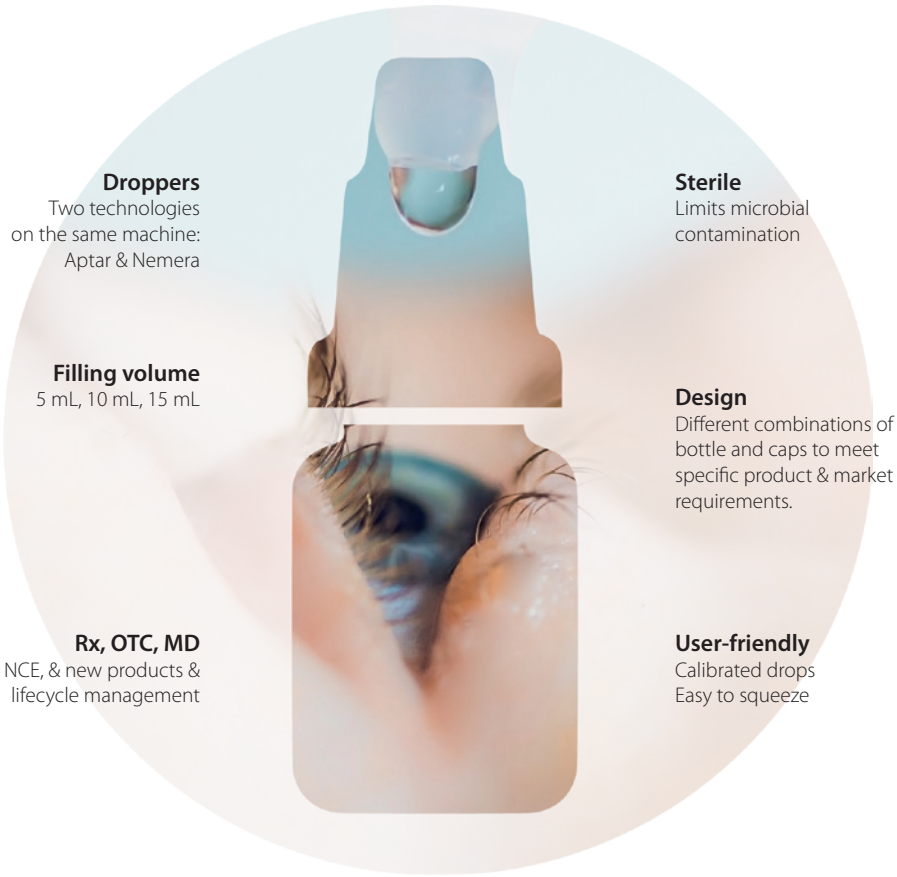

Figure 1: Unither's innovative PFMD manufacturing line is the embodiment of 25 years of know-how.

"Today, we are proud to introduce to you our innovative PFMD line for aseptic manufacturing of ophthalmic products."

Q **Can you tell us more about the PFMD manufacturing line?**

A Today, we are proud to introduce to you our innovative PFMD line for aseptic manufacturing of ophthalmic products (Figure 1).

We are especially proud and delighted with this achievement, a cutting-edge PFMD line that is the embodiment of more than 25 years of sterile know-how. It represents the result of uncountable hours of work by our teams together with external suppliers and customers.

By creating a synergy with unit-dose vials, the PFMD presentation acts as a complement to BFS and gives patients continuous security and product quality throughout their treatment period.

Q **How did you come up with this concept?**

A The new PFMD offering at Unither came about as a result of internally generated innovation and ideas, from our customers' feedback, and from our constant drive towards meeting patient needs.

As of today we work with technologies from two major players in the ophthalmic space: Aptar Pharma and Nemera. Looking to the near future, our patient-oriented philosophy means that we foresee novel tailored solutions being added to our offering in the near future.

Q **What is coming next for Unither?**

A We have plenty of exciting projects underway and on the horizon! We've recently taken a strategic decision to transform our Bordeaux R&D site into a Center of Excellence for Ophthalmology R&D, and the entire team is hard at work on this project.

We continue to create innovative solutions together with our partners. Among many novel initiatives we're supporting, one that I'd like to mention here is CureCall (Paris, France), a start-up specialising in the monitoring of chronic ocular diseases – a user-friendly solution for doctors and patients.

We foresee great challenges in the ophthalmic field and we do believe that vision science can overcome them by collaboration and free sharing of ideas within interdisciplinary teams. Our credo is be open-minded.

Unither will be attending numerous specialised events over the coming months, including the ARVO 2022 Annual Meeting (Denver, CO, US, May 1–4, 2022), and would welcome the opportunity to welcome new contacts to its booth.

ABOUT THE COMPANY

Unither Pharmaceuticals is a global pharmaceutical CDMO specialising in tailored dosage forms designed to simplify the lives of patients. Focused on R&D, key pharmaceuticals, niche product manufacturing and lifecycle management, Unither is best known for offering industrial solutions for the production of sterile and non-sterile liquids. It is a liquid stick-pack pioneer with an annual capacity of 500 million stick-packs, and a BFS leader with a 4 billion capacity for sterile vials.

Unither is a growing company working with an important number of customers whose products are sold in more than 100 counties worldwide. All this is possible due to Unither's industrial footprint on four continents: Europe (France), South America (Brazil), Asia (China) and North America (the US).

UNITHER PHARMACEUTICALS

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Ophthalmic Product Development

by Unither Pharmaceuticals

PREFORMULATION STUDY

- API characterization: Optical microscopy, assays, DRX, PSD, Log P, Log D, membrane permeability…
- Compatibility study
- Solubility study:
  - Solubility at saturation in different media
  - Solubility improvement: Cyclodextrin complexation, co-solvent, surfactants, micronization…
  - Modelization (software)
  - Early conservation study
- Preclinical batches manufacturing

ANALYTICAL METHODS DEVELOPMENT

- API assay
- Impurities assay and forced degradation study
- Preservative and antioxidant assays if necessary
- Sterility and microbiological controls
- Finished Product Photostability study

1

2

3

4

5

6

7

DEVELOPMENT CYCLE

FORMULATION STUDY

- Different forms: Solution, Gel, Emulsion, Micellar solution, Micro and nanoemulsion, Nanosuspension
- Formulation development by QBD (risk analysis and DoE on Jmp software)
- Rheology (viscoelastic behavior, gelation assessment, resistance under simulated eye blinking, viscosity behavior after tear contact...)
- Bioadhesion (mucoadhesive force)
- PSD by laser diffraction and DLS, Zeta potential if necessary
- Packaging choice: single or multiple use, glass or plastic
- Finished product characterization: Appearance, pH, Osmolality, Density, Drop size, Viscosity

STERILIZATION STUDY

- Steam sterilization impact
- Filtration study
- Filterability study

CONTAINER/CONTENTS INTERACTIONS

- Stressed studies
- Extractables and leachables (support of packaging supplier)

SCALE-UP STUDY

- Process robustness evaluation by QBD (risk analysis and DoE on Jmp software)
- Preliminary stability study
- Technical batches
- Analytical methods validation
- Cleaning verification (product cleanability) with LOQ method validation and recovery efficiency
- Clinical batches manufacturing

INDUSTRIALIZATION

- Small commercial batches
- Process validation
- Sterilization validation
- ICH stability studies and ongoing stability studies
- ICHQ3D and nitrosamines studies

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AN EYE ON THE FUTURE OF PRESERVATIVE-FREE DROPS

In this article, Alexandra Ritter, Head of Regulatory Affairs and Combination Products, and Matthias Birkhoff, Vice-President Business Development, both of Aptar Pharma, discuss the importance of the regulatory support the company offers to its customers for preservative-free ophthalmic platforms in the face of increasingly stringent regulatory requirements from both the EU EMA and US FDA, and describe new opportunities and growing demand for a wider range of multidose preservative-free ophthalmic drug-device combinations, including for indications such as dry-eye and glaucoma.

As the global population continues to live longer, vision care products are increasingly important, for both general vision care as well as quality of life, for those with various ocular disorders. Global sales of ophthalmic drugs represented approximately US$28.4 billion (£21.2 billion) in annual sales (2020),[1] with sales expected to grow to nearly $48 billion by 2030. Many new drugs are being developed and approved to treat ocular conditions such as dry eye syndrome, glaucoma, red eye and conjunctivitis (Figure 1). Furthermore, retinal disorders such as dry and wet forms of age-related macular degeneration (AMD) or diabetic retinopathy demonstrate clearly that ophthalmic treatments are a growing market segment.

> "Patients almost universally prefer to receive eye medication via topical drops, whenever the format is available."

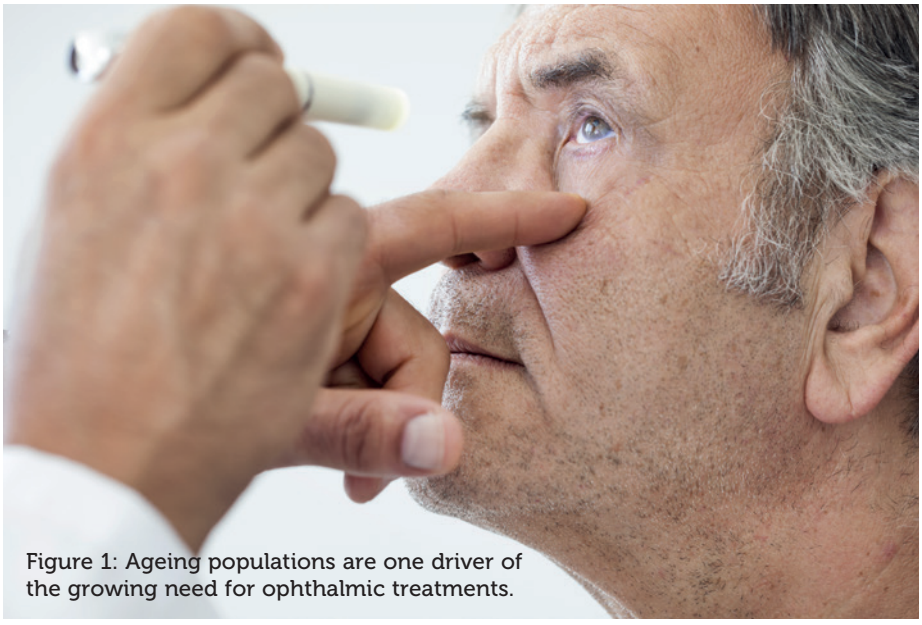

Figure 1: Ageing populations are one driver of the growing need for ophthalmic treatments.

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Most medications for treating retinal diseases and conditions are only available as invasive ocular injections. Typically, retinal diseases are chronic conditions requiring ongoing drug administration and, with many patients receiving regular injections into their eyes, this can result in reduced patient compliance and poorer patient outcomes overall.

Patients almost universally prefer to receive eye medication via topical drops, whenever the format is available, as opposed to having to go to a healthcare professional to receive repeated painful injections to the eye.[2] For a number of ocular diseases, eye drops provide a convenient and comfortable way to self-administer ocular medication.

So, what are the challenges to administering a wider range of medications via topical eye drops?

PRESERVATIVES

For one, multidose eye-drop formulations typically include preservatives to avoid micro-organisms contaminating the sterile eye-drop solution. This can occur when a normal eye-drop device is exposed to these contaminants by coming into contact with the eye or through other sources in the environment. The most common chemical preservative used in nasal and eye-drop formulations is benzalkonium chloride, which serves as a detergent, antiseptic, disinfectant, fungicide and bactericide.[3] Such preservatives have been shown to lead to undesirable side effects, particularly from long-term use, ranging from temporary irritation and discomfort to even more complex issues such as dissolution of the lachrymal film, apoptosis (cell death) and inflammation.[4,5] Studies have shown that long-term preservative use can lead to ocular hyperaemia, dotted keratitis or toxic keratopathy.

Another approach to maintaining eye-drop sterility is to apply silver ions or surface coatings to ophthalmic devices. These can provide antibacterial and antifungal protection of the formulation but can also present their own challenges as they may become less effective over time as the silver materials are consumed[6] or, more concerningly, could have accumulated health effects on the user.[7]

> "Studies have shown that long-term preservative use can lead to ocular hyperaemia, dotted keratitis or toxic keratopathy."

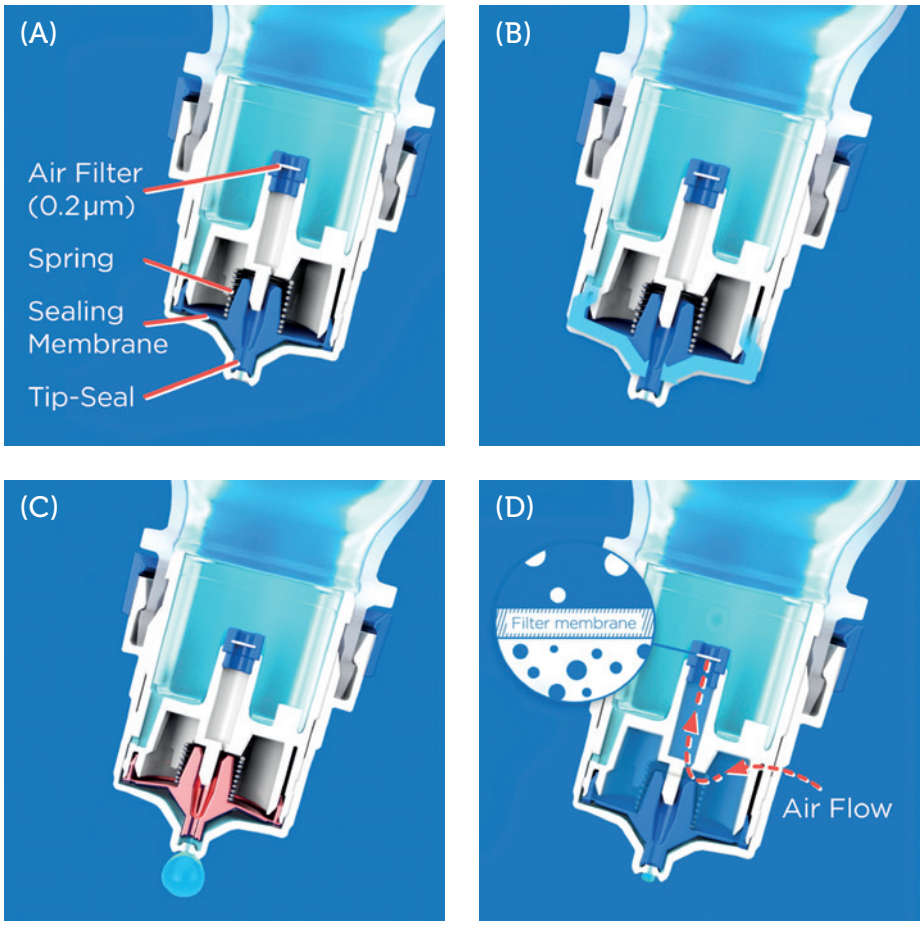

Figure 2: The patented Tip-Seal mechanism of the OSD. (A) Aptar Pharma's OSD Tip-Seal technology with a sealing membrane, spring mechanism and microbiological filter, protecting the formulation from any bacterial ingress via inflowing air. (B) By squeezing the bottle, the pressure inside the system rises, allowing the formulation to flow into the delivery channels. (C) The pressure rises until the sealing membrane of the Tip-Seal opens to release the drop. (D) After the drop has been released, the Tip-Seal closes again and any incoming air is filtered sterile through the 0.2 µm filter membrane.

THE PRESERVATIVE-FREE OPHTHALMIC DEVICE SOLUTION – APTAR PHARMA'S OSD

One way to enjoy the benefits of ophthalmic eye-drop delivery while avoiding the risks of using preservatives is to use a multi-use eye-drop device designed specifically to support preservative-free formulations. This requires a specialised ophthalmic eye-drop device that maintains the sterility of the liquid formulation, even with repeated use of the device throughout the treatment period.

Aptar Pharma manufactures the only ophthalmic device component that has been reviewed by the US FDA as part of the approval of a preservative-free multidose (PFMD) ophthalmic drug-device combination product. Aptar Pharma's Ophthalmic Squeeze Dispenser (OSD) uses a patented, purely mechanical Tip-Seal technology (Figure 2A) to maintain formulation sterility within the device. It also has a metal-free formulation pathway that avoids oxidative reactions between the formulation and metals.

This unique OSD device works as follows:

1. As the bottle is squeezed, the pressure inside the Tip-Seal rises until the spring-controlled sealing membrane opens and releases a single drop (Figure 2B and C).
2. The Tip-Seal then reseals the tip orifice, blocking potential contaminants from entering the tip.
3. To equilibrate the created pressure difference, air flows into the squeeze bottle through a microbiological filter, preventing contamination of the formulation (Figure 2D).

Due to its innovative design features, Aptar Pharma's OSD device allows consumers and patients to deliver a variety of preservative-free ophthalmic eye-drop formulations – solutions, emulsions or suspensions. From a technical perspective, the OSD is a viable solution to the preservative problem for both consumer products and prescription eye-care medications – and offers a proven track record of more than 300 market references worldwide.

But what about the regulatory environment? How do regulatory authorities view a device-driven preservative-free solution for ophthalmic eye-drop products, and what regulations must the applicant comply with?

DRUG-DEVICE COMBINATION PRODUCT REGULATORY REQUIREMENTS

Leading regulatory authorities have been supportive of the drive to reduce or eliminate the use of side-effect-inducing preservatives for ophthalmic products.

> "The ideal solution for administering preservative-free ophthalmic products is a multidose device that does not use any additives or preservatives."

The ideal solution for administering preservative-free ophthalmic products is a multidose device that does not use any additives or preservatives. Aptar Pharma's OSD technology platform offers a completely mechanical solution to meet these objectives. Products composed of both a device component (here, the OSD) and a drug product are viewed differently by regulatory authorities.

The FDA[8] and the European Medicines Agency (EMA)[9] have both continued to expand and clarify the requirements for these types of drug-device combination products (Figure 3). Aptar Pharma's OSD device has already been accepted by regulatory authorities worldwide, including the FDA, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) Germany, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) in France and the National Medical Products Administration (NMPA) China. With new, even stricter regulations around sterile product manufacturing and validation, such as the Annex I of the Medical Device Regulation (MDR) 2017/745, which now applies to drug-device combination products in the EU, the path for ophthalmic eye-drop combination products has changed.[10]

FDA Regulations

Under FDA regulations, therapeutic and diagnostic products that combine a drug or a biological product and a device are defined as combination products.[11] The division of the FDA that takes the lead on the evaluation and approval of the combination product is determined by the primary mode of action (PMoA) of the product. Other FDA divisions are selected for other secondary, yet relevant, aspects of the combination product.

The Genus decision issued on April 16, 2021[12] by the US Court of Appeals DC Circuit, held that articles that meet requirements of Section 201(h) of the FD&C act must be regulated as devices and not drugs. Taking this decision into consideration, eye cups, eye droppers and ophthalmic dispensers that have been regulated as drugs when packaged with a drug according to 21 CFR 200.50(c) now meet the "device" definition. The FDA might begin regulating ophthalmic drug-led combination products where the drug is PMoA with the Center for Drug Evaluation and Research (CDER) as the primary regulatory branch overseeing these products. As a result, such combination products would also be subject to 21 CFR Part 4, including cGMPs and post-marketing safety reporting requirements.

If the combination product's PMoA is a drug (not a device) then the combination product's submission may follow the condensed 21 CFR 4.4(b) filing.[13] This offers the benefit of requiring less information for the different constituent parts of the combination device, as outlined in option 2 below. For multidose (including preservative-free) eye-drop combination products, a drug manufacturer must now demonstrate compliance with cGMP regulations for each of the constituent parts (drug and device). There are two ways to achieve this requirement:

1. Full approach – demonstrate compliance with all cGMP regulations applicable to the device and drug (full application for each constituent).
2. Streamlined approach – with a condensed 21 CFR 4.4(b) filing for combination products, the drug manufacturer must demonstrate compliance with both the drug cGMPs (21 CFR parts 210 & 211) AND also demonstrate compliance with the following provisions of the device quality system (QS) regulation 21 CFR part 820:
   a. 21 CFR 820.20 Management responsibility
   b. 21 CFR 820.30 Design controls
   c. 21 CFR 820.50 Purchasing controls
   d. 21 CFR 820.100 Corrective and preventive action.

Figure 3: Regulations for combination products, such as ophthalmic eye-drop combination products, have evolved for the US and Europe.

Most likely, design controls are the most significant challenge for a drug manufacturer. Design controls, as defined in 21 CFR 820.30, are a systematic process to ensure that the product design meets the user needs, intended use and regulatory requirements. This results in a design history file, which has to be maintained over the product lifecycle.

EU Regulations

In the EU, "combination products" are not recognised by the same naming convention as would be applied by the FDA. However, they are still regulated based on their PMoA, either as a medicinal product or medical device. A drug product that contains a medical device as an integral part can be submitted to regulators as either a medicinal product for drugs or biologics – or as an advanced therapy medicinal product for cell therapies. Multidose eye-drop combination products typically fall under the medicinal product category.[14]

In May 2021, the EMA launched a new regulatory framework applying to medicinal products when used in combination with a medical device. The EMA has also published a final guideline on quality documentation requirements for medicinal products when used with a medical device[15] that took effect on January 1, 2022. Applicable eye-care products, such as those using Aptar Pharma's OSD, have to meet expanded requirements, including elements such as Annex 1 of the MDR 2017/745.[16] Most ophthalmic combination products would be reviewed as a medicinal product (drug) under Directive 2001(83/EC) or Regulation (EC) No 726/2004 and, in addition, would need to comply with the General Safety and Performance Requirements (GSPR) from MDR 2017/745, Annex I, in order to establish the safety and performance of the device, as well as the manufacturing requirements for sterile manufacturing.

If the product is to be marketed as a sterile "medicinal product" with an integral medical device, it would require the drug manufacturer to have a notified body opinion (NBOp). The NB would assess and confirm if the device meets the GSPR and would issue an NBOp, which must be submitted to the EMA in the MAA.

The drug manufacturer would need to provide comprehensive information to the NB to support the conformity assessment, such as data on risk management, safety, testing of performance, functionality and compatibility (accuracy of dosage, performance of device), usability, sterilisation validation and microbiology.[11]

RAISING THE BAR ON OPHTHALMIC EYE-DROP DEVICE COMBINATIONS

The outcome of these changes is that product owners of eye-drop combination products have to adapt to meet more comprehensive filing requirements that are focused on the device part. Partnering with a device manufacturer with proven experience of supporting applicants through the quality, regulatory and validation requirements, with both data and services, should be a critical consideration in every selection process.

APTAR PHARMA'S OSD DEVICE – REGULATORY SUPPORT

Having a well-designed and manufactured eye-drop device alone is not enough to provide a de-risked and confidence-inspiring pathway to regulatory approval for your drug-device combination product. Aptar Pharma did not stop at just designing and producing its innovative OSD system to meet market needs. It continues to develop data, support and services that help customers more easily navigate through the changing regulatory environment. With over 300 market references and millions of devices on the market, Aptar Pharma brings specialised experience with preservative-free eye-drop devices to every OSD project. For example, Aptar Pharma successfully supported the filing and FDA approval of a product for an ocular indication. The process benefited from the continued technical and regulatory support that Aptar Pharma was able to provide to the customer, including from its portfolio of stage-specific development packages. Aptar Pharma has enjoyed similar success in supporting product approvals with regulatory authorities in a number of markets around the world.

Aptar Pharma has developed data packages around the form and validation of its Tip-Seal technology. It also offers a range of analytical testing and services to support the validation of the OSD devices. For example, Aptar Pharma's Tip-Seal Integrity Test (TSIT) 2.0[17] challenges the mechanical tip closure system in worst-case scenarios against a number of bacteria and contaminants, including *Pseudomonas aeruginosa* (ATCC 9027), *Staphylococcus aureus* (ATCC 6538) and *Candida albicans* (ATCC 10231) (Figure 4).

Figure 4: Aptar Pharma's Tip-Seal Integrity Test TSIT 2.0 helps to define testing standards for PFMD devices.

These proprietary tests were designed to generate data supporting the integrity of the PFMD device suitable for submission to regulators while helping to define the testing standards for Aptar Pharma's customers. This is just another way that Aptar Pharma Services supports customers with regulatory filings.

Aptar Pharma has consciously adopted the strategy of providing a wide range of support and services that customers need to advance their drug-device combination products through the regulatory process (Table 1).

This includes topics such as design history files, design control documentation, verifications and custom performance evaluations of the devices, as well as the customer's intended use and formulations. With decades of experience working hand in hand with customers, Aptar Pharma provides input on aspects such as device selection, human factors study design and materials that help to de-risk the product. The company not only designs and manufactures the devices but also offers integrated testing services, formulation development expertise and material compatibility analysis in its laboratories, carried out by its team of industry-leading experts. Aptar Pharma can look at physical drop characteristics and formulation parameters to allow the customer

Ophthalmic Combination Device Support Documentation (related to Aptar Pharma device component)	Support from Aptar Pharma
Letter of Authorisation (LoA)	✓
Design Input (based on 21 CFR820.(c))	✓
Design Output (based on 21 CFR820.30 (d))	✓
Design Review (based on 21 CFR820.30 (e))	✓
Design Verification (based on 21 CFR820.30 (f))	✓
Design Validation (based on 21 CFR820.30 (g))	Product Owner
Design Transfer (based on 21 CFR820.30 (h))	✓
Design Changes (based on 21 CFR820.30 (i))	✓
Design History File (based on 21 CFR820.30 (j))	✓
Risk Management	✓
Supplemental (Human Factors etc.)	✓
Robustness Testing, Transport Studies	✓
Microbiology with Aptar Pharma Product and Support for Testing in Formulation	✓
Documentation of Sterilisation of Aptar Pharma Product	✓
Extractables Package for Aptar Pharma Product	✓
Additional Support Services with Customer Formulation, e.g.	
Device Formulation Acceptance Test services	✓
Device Performance with Product Formulation	✓
Pre-Support for PAI or US FDA inspection at Manufacturer	✓
CMC Consulting Support	✓
EU General Safety and Performance Requirements Support	✓

Table 1: Drug-device combination product documentation and service support considerations.

Figure 5: Aptar Pharma's broad expertise in analytical and regulatory services helps to advance drug-device combination products through the regulatory process.

formulation to work with the selected device. In doing all of this, Aptar Pharma also provides the data and documentation for inclusion in – or in support of – regulatory filings. This is so that customers do not have to invest in developing the same specialised knowledge and expertise themselves.

Aptar Pharma is a full-service organisation, with services and partners that can support clinical and commercial manufacturing at virtually any scale (Figure 5). Moreover, Aptar Pharma continuously strives to further develop and improve its analytical and regulatory support to deliver optimised, state-of-the-art procedures with patient safety in mind.

With increasing demand for PFMD eye-dropper technology, and more strict regulatory filing requirements for drug-device combination products, it is of critical importance to select a partner that not only provides a secure supply of high-quality and functional devices but can also provide the additional support, expertise and documentation on the device required to meet the filing and review requirements of regulatory authorities. Aptar Pharma continues to keep its eyes on a shared vision with its customers – that is "bringing new ophthalmic products to market that improve patient lives".

ABOUT THE COMPANY

For pharma customers worldwide, Aptar Pharma is the go-to drug delivery expert, from formulation to patient, providing innovative drug delivery systems, components and active material solutions across the widest range of delivery routes including nasal, pulmonary, ophthalmic, dermal and injectables. Aptar Pharma Services provides early-stage to commercialisation support to accelerate and de-risk the development journey. With a strong focus on innovation, it is leading the way in developing digital healthcare devices to help improve patient adherence and compliance. With a global manufacturing footprint of 14 manufacturing sites, Aptar Pharma provides security of supply and local support to customers. Aptar Pharma is part of AptarGroup, Inc.

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Clearly the world's favorite

The Ophthalmic Squeeze Dispenser from Aptar Pharma.
The global leader in preservative-free multidose eye care devices.

Anyone searching for a safe, stable, preservative-free and approved multidose eyecare device arrives at the same solution: Aptar Pharma.

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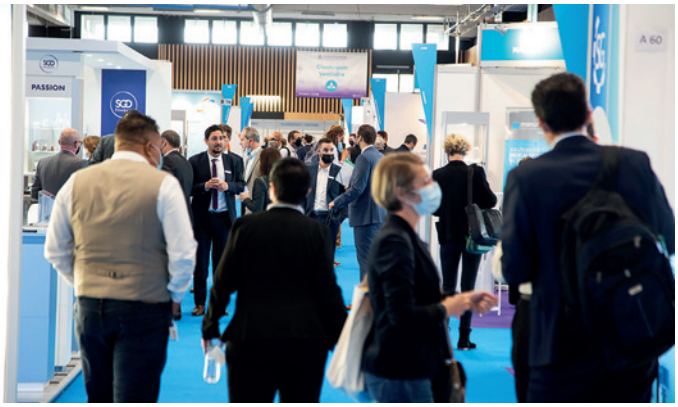

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SUSTAINED, CONTROLLED DRUG DELIVERY TO THE EYE

Here, Harsh Patel, PhD, Senior Scientist, Cyonna Holmes, PhD, Global Senior Manager, Marketing, and Brian Wilson, PhD, New Business Development Partner, all at Celanese, consider the challenges and advances in sustained-release ocular drug delivery.

Chronic eye diseases are the primary drivers of blindness and low vision, and the prevalence of these diseases is only expected to increase over the next five years due to an increased incidence of underlying conditions and the ageing population. Yet, there are still unmet needs in treating these diseases effectively. Innovative treatment approaches are needed to address the patient treatment burden and ineffective therapeutic delivery. As a result, improving efficacy and providing sustained delivery options for small molecules, biologics and RNA are critical for improving treatment options for chronic eye conditions. The ocular drug delivery market is expected to grow at a compound annual growth rate[1] of 6–9% as innovative approaches enter the market to address growing patient populations with glaucoma, chronic inflammation, diabetic retinopathy and macular degeneration.

> "Improving efficacy and providing sustained delivery options for small molecules, biologics and RNA are critical for improving treatment options for chronic eye conditions."

CHALLENGES WITH CURRENT DOSE FORMS AND TRENDS TOWARDS SUSTAINED DELIVERY

Traditional topical formulations and intravitreal injections dominate the ophthalmic drug market. However, topical formulations have been associated with a low estimated patient adherence rate of 40–50%[2] and poor bioavailability due to ocular barriers such as tear turnover, blinking and corneal and conjunctival barriers. Similarly, frequent intravitreal injections have negative side effects such as retinal toxicity, aggregation from injected materials, damage to the retina and lens, elevated intraocular pressure and inflammation due to repeated scleral puncturing.[3] To overcome these challenges, sustained, controlled delivery of small molecules and large biologics is needed, and these approaches are gaining traction over current dose forms when treating chronic eye diseases.[4] Successful application of such systems can significantly reduce the treatment burden to patients and, in turn, facilitate lower overall cost to the healthcare system.[5]

POLYMERIC IMPLANT FOR OCULAR DRUG DELIVERY

Polymeric implantable drug delivery systems remain a promising option for sustained, controlled delivery of therapeutics in the eye. The controlled, continuous release of therapeutic (Figure 1) from a polymeric implant removes the variability of patient compliance,

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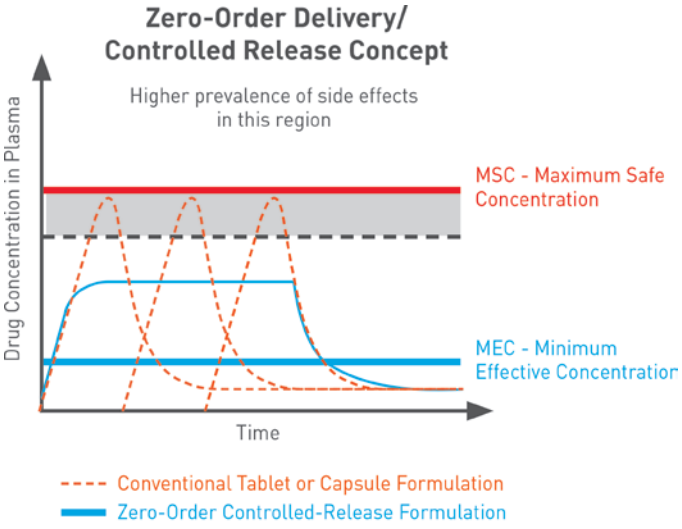

Figure 1: EVA is a biostable polymer offering better control of drug dosing, and eliminating undesirable bursts, with a zero-order controlled-release profile.

improves bioavailability and may mitigate issues associated with repeated injections. Sustained drug release is achieved by the adjustable diffusion of the drug from such a system, which improves the half-life of the molecule, delays degradation and reduces elimination.

Polymeric approaches are being considered to leverage the versatility of biocompatible thermoplastics to:

1. Provide tunable drug release of molecules ranging from small molecules to large biologics
2. Provide innovative shapes and designs for customised implant delivery options
3. Incorporate drug elution to existing medical devices to provide dual functionality.

BIODURABLE IMPLANT ADVANTAGES

Polymer-based, biodurable ocular implants offer distinct advantages in ocular delivery and have demonstrated versatility in the delivery of small molecules to large biologics. Biodurable ocular implants can be designed with high drug loading without compromising mechanical integrity or long-term release kinetics. High drug loading is critical in achieving drug-release profiles of 6+ months that are relevant to the treatment of chronic eye diseases that use a combination of drugs or a high molecular weight API.

> "Biodurable ocular implants can be designed with high drug loading without compromising mechanical integrity or long-term release kinetics."

Additionally, a reliable drug-release profile can be achieved with a biodurable implant as this approach does not rely on a bulk degradation mechanism with less predictable drug release. Biodurable implants also reduce the risk of drug molecule instability that may be caused by polymer degradants from erodible materials. As a result, release and accumulation of these degradants does not occur, thus mitigating inflammatory risk.

> "An EVA implant in the suprachoroidal space serves as a unique approach to deliver therapeutic agents with various molecular weights."

TUNABILITY FOR PRECISE DELIVERY

Biodurable implants using polymers such as ethylene-vinyl acetate (EVA) can achieve tailored release profiles over a wide range of molecules. Tunability can be further achieved through the pairing of drug-filled cores and customisable porous membranes. This approach adds another layer of adjustability as both the core and membrane properties can be modified to achieve a range of release profiles for small molecule, biologic and RNA delivery. Additionally, these two tunable components of an EVA implant – the core and membrane – also allow for dual release of more than one molecule through separate mechanisms, resulting in a fixed-dose combination implant.

TARGETED DELIVERY

Nearness of an implant to a targeted region can increase the therapeutic bioavailability of a molecule. As a result of localised biodurable implant delivery, lower drug concentrations are needed to elicit the desired therapeutic effect within the eye.

Due to the high compartmentalisation within the eye, unique locations for biodurable implant placement exist. As an example, suprachoroidal administration appears to be a promising and less-invasive technique for treatment of ocular posterior segment diseases. A polymeric implant must provide flexibility to mould into various shapes and sizes that may fit spaces such as the suprachoroidal space while maintaining mechanical integrity. As a result, an EVA implant in the suprachoroidal space serves as a unique approach to deliver therapeutic agents with various molecular weights.

Sustained delivery of molecules to treat chronic eye diseases can be achieved through polymeric implants, and biodurable implants offer an innovative approach to achieve desired therapeutic release profiles. As prevalence and patient needs continue to increase, ocular therapeutics need to adopt newer dosage forms to overcome challenges associated with traditional routes of administration. Biodurable implants address this growing unmet need and are ideal for the treatment of chronic eye disorders.

CELANESE SUSTAINED-RELEASE DRUG DELIVERY SOLUTIONS

Celanese has extensive expertise as a solutions provider for the pharmaceutical and medical device industry. Through collaboration with its customers, the company solves challenging drug delivery problems with innovative solutions that improve patient care. VitalDose® EVA, a pharmaceutical-grade polymer, is in pipeline and commercialised products and can be manufactured and designed to address a wide range of therapeutic areas and molecule types. VitalDose is a registered trademark of Celanese. Additionally, the Celanese Pharmaceutical Laboratory offers formulation support for early-stage pharmaceutical research and development.

ABOUT THE COMPANY

Celanese Corporation is a global chemical leader in the production of differentiated chemistry solutions and speciality materials used in most major industries and consumer applications. The company's businesses use the full breadth of Celanese's global chemistry, technology and commercial expertise to create value for its customers, employees, shareholders and the corporation. Celanese partners with its customers to address their most critical business needs, and strives to make a positive impact on communities and the world through The Celanese Foundation. Based in Dallas (TX, US), Celanese employs approximately 8,500 employees worldwide and had 2021 net sales of US$8.5 billion (£6.3 billion).

Celanese offers the VitalDose® EVA drug delivery platform, providing controlled drug release through implants and inserts. Compared with traditional dose forms, the VitalDose® platform reduces treatment burden, addresses patient adherence issues and improves bioavailability. The company partners with clients to enable innovative drug delivery of small molecules, biologics and RNA within the desired release profile. With decades of experience in medical and pharmaceutical applications, Celanese seeks to improve product development and elevate patient care.

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Brian Wilson earned his PhD in Biochemistry from the University of Notre Dame (IN, US). He has 11 years of API experience in the areas of formulation development, drug delivery and new product development. At Celanese, Dr Wilson serves as a New Business Development partner for the pharma and medical businesses. He holds patents and has numerous published articles in peer-reviewed journals.

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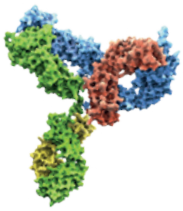

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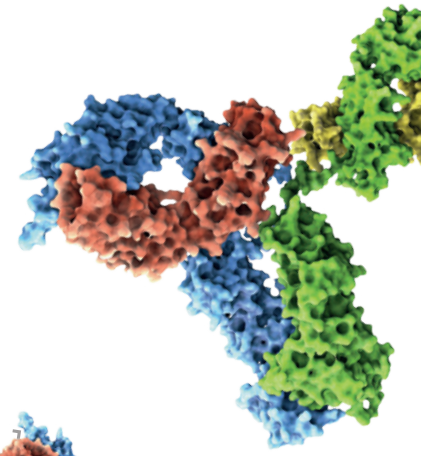

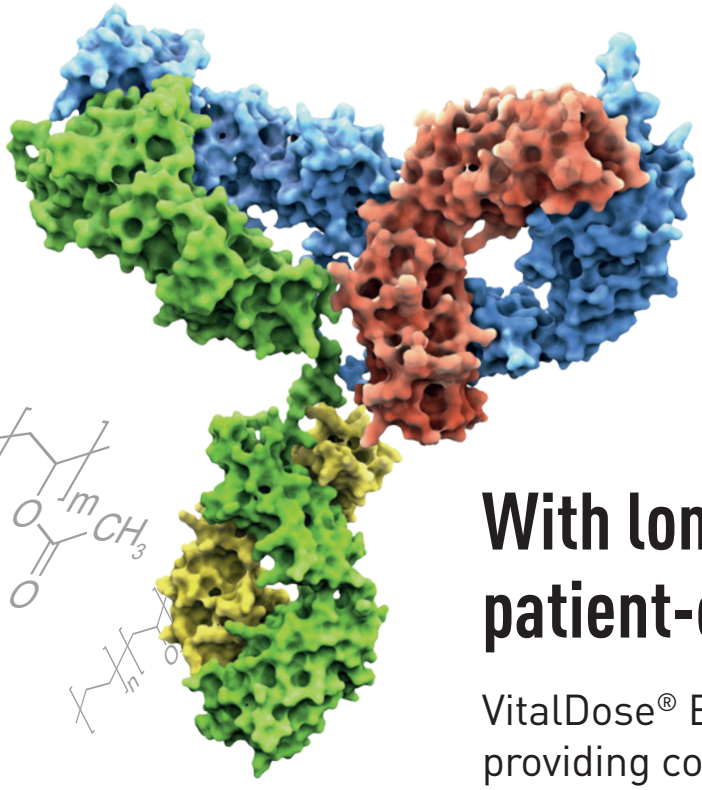

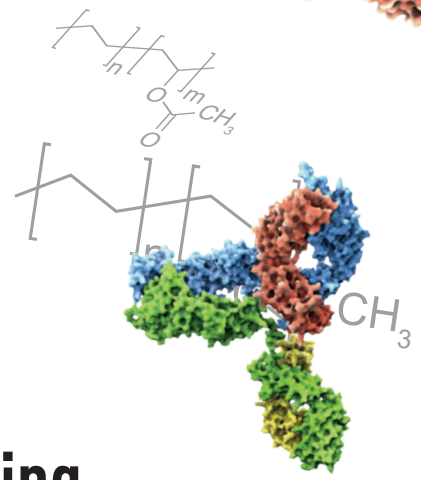

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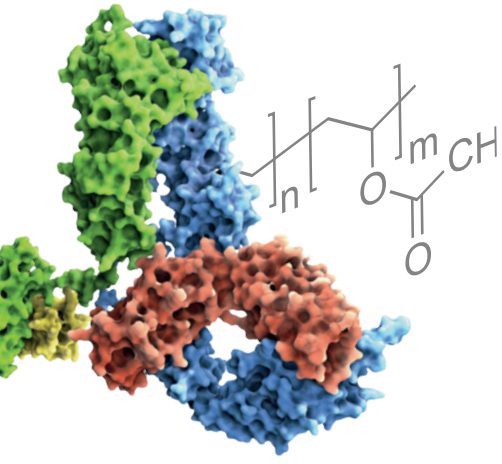

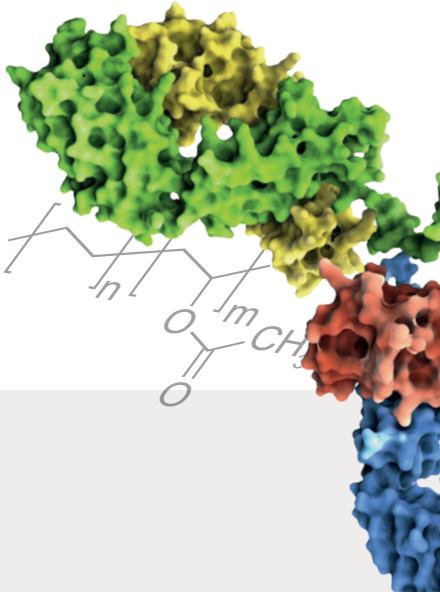

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Agenda at a Glance

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Improving Drug Product Development & Formulation

Biologics & New Modalities Drug Delivery

Stability, Bioanalysis & Characterisation

Inhalation & Drug Delivery

Development & Formulation of Inhaled Therapies

RNA Therapeutics & Delivery

RNA Formulation & Development

DAY TWO - 06 May 2022

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WHY GENE THERAPY IS PERFECT FOR TREATING OCULAR DISEASES

In this article, Yongdong Zhou, MD, PhD, Head of Ophthalmology Team, Senior Director, at WuXi AppTec, discusses the applications, advantages and challenges of gene therapy in the ophthalmic sector.

Gene therapy is not a new treatment, having been used to alter abnormal or mutated genes and produce valuable proteins since the 1970s. However, apart from a brief resurgence in the 1990s, gene therapy has largely lain dormant for decades. Today, it is once again a subject of investigation, as there has been a renaissance in gene therapy in the 21st century, in large part an international team of researchers having sequenced and mapped every gene as part of the Human Genome Project.

The Human Genome Project has essentially created a genetic blueprint for human beings. For the first time, researchers can identify diseases based on a specific gene's presence or absence within a patient's genetic make-up. As such knowledge grew, so too did researchers' understanding of the mechanisms of genetic diseases and the technology needed to combat conditions once thought to be untreatable.

Gene therapy began to gain steam in 2008 and, by the first half of 2021, the number of active cell and gene therapy developers worldwide had reached 1,195. The number of clinical trials sponsored by private companies, governments and academic institutions passed 2,600 over the same period. Of those trials, 243 have reached Phase III.[1]

The treatment of ocular diseases has benefited tremendously from the resurgence of gene therapy. Two ocular characteristics make gene therapy advantageous and, in some cases, the only option for some genetic diseases, cancers and viral infections. That said, drug developers and laboratory partners must understand the challenges that have already been encountered – and those that lay ahead – for novel genetic therapies.

WHAT MAKES THE EYE A GOOD CANDIDATE FOR GENE THERAPY?

Two characteristics of the human eye make it well suited for successful gene therapy. Whether a condition calls for gene replacement, editing, suppression or growth, researchers must engineer vectors to deliver the suitable genetic material to the right place in the ocular microenvironment. Vectors can be DNA molecules, bacteria or viruses and are engineered to integrate into chromosomes (i.e. retroviruses) or cell nuclei (i.e. plasmid DNA). Ocular disease patients can receive vectors through topical eye drops, oral medication or injections. Regardless of which method researchers use, the end goal is to deliver a new gene that can help create a functioning protein and improve vision.

"The number of clinical trials sponsored by private companies, governments and academic institutions passed 2,600 over the same period. Of those trials, 243 have reached Phase III."

Immunologic Privilege

Alongside the central nervous system, the placenta and foetus, and the testicles, the human eye enjoys immunologic privilege. Tissue grafts or foreign antigens placed into sites with immunologic privilege can survive and thrive without the immune system attacking them or shutting down the host organ. This immunity occurs because those sites are insulated from direct contact with systemic circulation and thus are protected from strong immune reactions to foreign antigens like disease or viral vectors. Researchers believe immunologic privilege is an evolutionary protective measure developed to protect specific sites from inflammation and potential organ failure. In the case of the eye, inflammation could cause vision impairment, and rejection of the vector could lead to complete vision loss.

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Researchers first viewed ocular immunologic privilege as an experimental phenomenon explained by the eye's unique anatomical features. Experts do not fully understand the complexities of immunologic privilege but they do know that the ocular microenvironment regulates antigens within the eye via anti-inflammatory proteins and neuropeptides.[2] The anterior chamber, subretinal space and vitreous cavity all enjoy immunologic privilege and are thus good candidates for ocular gene therapy. It is also important to note that immunologic privilege helps to avoid severe inflammatory reactions to foreign antigens but it does not prevent such reactions altogether. Researchers and drug developers should be prepared for some level of immunologic response when conducting gene therapy but the duration and severity should be less than is experienced in other sites.

A Multitude of Options

The Human Genome Project sequenced and mapped around 30,000 genes in the human DNA. 55 of those genes have been isolated in the human eye, and 118 retinal disease loci have been mapped.[3] Many of the mutations in the isolated genes are responsible for damaging the structure and function of the retinal pigment epithelium (RPE) and photoreceptors. RPE cell and photoreceptor damage cause a host of degenerative diseases, including age-related macular degeneration (blurred or lost vision in older patients), retinitis pigmentosa (loss of night vision, side vision and finally central vision) and Stargardt's disease (an inherited disease that causes vision loss in children and young adults). The accessibility of ocular tissue and the number of associated diseases, combined with the various emerging delivery methods, provide researchers with many therapeutic strategies.

> "The mechanism of the disease (i.e. the defects in molecular or cellular processes) determines the approach that will be most successful in treating the condition."

OCULAR GENE THERAPY APPROACHES

The most common ocular gene therapies include gene replacement, suppression or enhancement. The mechanism of the disease (i.e. the defects in molecular or cellular processes) determines the approach that will be most successful in treating the condition.

If a single mutation causes a disease, gene replacement is often the best treatment. Not only is gene replacement the most common form of gene therapy but scientists Jean Bennett and Katherine A High used the procedure with patients possessing a mutation in the RPE65 gene to reverse Leber congenital amaurosis, an inherited form of vision loss that can lead to blindness. The therapy delivers an undamaged copy of the RPE65 gene to retinal cells and then provides instructions for producing the protein needed to restore vision. Bennett and High's research led to the US FDA's first ever gene therapy approval.[4]

But if a disease-causing mutation has a dominant molecular function or triggers an over-expression, researchers can use small interfering RNAs to suppress it. Finally, genes with multiple mutations and other risk factors (i.e. neurodegenerative diseases like glaucoma or age-related macular degeneration) can be enhanced by using adeno-associated virus (AAV) vectors to introduce various protective factors. AAV vectors are attractive candidates because they do not contribute to known diseases and the immune responses they provoke are insignificant.

Whether a target disease is acquired or inherited in nature, the procedures to treat it using gene therapy, whilst varying in complexity, are similar in their fundamentals. Of the more than 350 inherited ocular diseases, those with single mutations – e.g. choroideremia (progressive vision loss in males) and the subtypes achromatopsia (colour blindness), retinitis pigmentosa and Leber's congenital amaurosis – are the best candidates for success. Replacing the deficient gene with a fully functioning copy often results in a cure once thought unachievable.

Acquired ocular diseases have entirely different mechanisms and often require more complex treatments. The molecular and cellular processes that trigger these diseases can vary from genetic to environmental. Gene enhancement or suppression allows researchers to modify or manipulate gene function using a series of viral and non-viral vectors in multiple loci. For acquired ocular diseases, the treatment strategy is similar to that for inherited diseases with multiple mutations and other risk factors, such as age-related macular degeneration. The treatment may not target a specific disease-causing gene but it can indirectly target a gene introducing a protective factor or an antagonist to a problem-causing factor. Gene therapy could be an alternative to the conventional pharmaceutical approaches, especially those requiring long-term medication or supplemental trophic factors.

CHALLENGES & MISCONCEPTIONS WITH OCULAR GENE THERAPY

Gene therapy is a therapeutic reality that has the potential for groundbreaking results; however, it is far from an exact science. This is especially true when treating a site as delicate as the ocular microenvironment. Researchers must consider three factors when deciding the viability of gene therapy for their ocular patients.

Which are the Best Candidates?

There are two primary considerations when answering this question. First, researchers have a greater likelihood of success if they catch the disease early, which might mean treating young children using invasive and potentially risky procedures for inherited ocular diseases. Second, for clinical trial considerations, it is advantageous to treat the patient group with the most severe symptoms, such as patients whose vision is 20/200 or less and who are therefore legally blind. Slight vision improvements are easier to recognise in this patient group and ineffective treatments will not further decrease their vision.

What is the Best Delivery Method?

Choosing a suitable vector and administration route is critical to maximising safety and efficacy in ocular gene therapy. Researchers have largely abandoned adenoviruses and lentiviruses due to their strong immunogenicity and propensity to cause tumours, despite their effectiveness and ability to carry large genes. Very low immunogenicity and pathogenicity make AAVs the most common viral vectors used but they can only carry smaller genes.[5] Researchers can engineer non-viral vectors to carry larger genes safely but they lack the effectiveness and durability of their viral counterparts.

"A bevy of new drug developers and billions in financial investment have demonstrated massive industry confidence in gene therapy to treat ocular diseases, cancers and viral infections, and innovative approaches have the potential to unlock even more exciting new treatments."

The administration route is another challenge. Eye drops, intravitreal injections (i.e. an injection of medicine into the vitreous humour near the retina) and other pharmaceutical solutions can treat some conditions successfully. However, for genetic diseases, subretinal injections are the most effective method for delivering AAVs to the target cells and ultimately achieving success. It is a complex procedure that requires surgical intervention, which adds risk – the more invasive the procedure, the greater the immunogenicity and potential for adverse effects, such as retinal detachment and vitreous haemorrhage. Risk mitigation strategies exist for subretinal injections but their effectiveness depends on several factors, including proper patient selection and the clinician's experience with the procedure.

Can Researchers Control Toxicity?

It is worth restating that viral vectors introduce toxic viruses into the ocular microenvironment. The eye's immunologic privilege mitigates some of that toxicity but not all of it. Researchers must continue refining their formulations and dosages to ensure acceptable toxicity levels. Failure to do so can result in severe inflammation, high toxicity and, in some cases, increased vision loss. The patient's condition, age, the severity of vision loss and riskiness of the procedure should all contribute to the decision to move forward with viral or non-viral vector strategies.

THE BOTTOM LINE

A bevy of new drug developers and billions in financial investment have demonstrated massive industry confidence in gene therapy to treat ocular diseases, cancers and viral infections, and innovative approaches have the potential to unlock even more exciting new treatments. For example, administering injections into the suprachoroidal space is a novel targeted approach that promises to deliver drug concentrations 10 times greater than currently available while avoiding specific adverse effects.[6] Its viability as a therapeutic approach will, of course, depend on the disease target and the patient. Likewise, further research into more robust, more effective non-viral vectors has the potential to add new therapies and alleviate concerns about toxicity and other side effects.

While gene therapy may offer game-changing new solutions, it is not without risk. Choosing the right treatment path and delivery method for each patient is essential to controlling immunologic response, reducing toxicity and improving vision. Drug developers and their laboratory partners cannot afford to overlook or underestimate the challenges inherent in each step.

ABOUT THE COMPANY

As a global company with operations across Asia, Europe and North America, WuXi AppTec provides a broad portfolio of R&D and manufacturing services that enable the global pharmaceutical and healthcare industry to advance discoveries and deliver groundbreaking treatments to patients. Through its unique business model, WuXi AppTec's integrated, end-to-end services include chemistry drug contract research, development and manufacturing organisation services; biology discovery; preclinical testing and clinical research services; and cell and gene therapy contract testing, development and manufacturing organisation services, helping customers improve their productivity in advancing healthcare products through cost-effective and efficient solutions. WuXi AppTec received an AA ESG rating from MSCI in 2021 and its open-access platform is enabling more than 5,600 collaborators from over 30 countries to improve the health of patients – and to realise the vision that "every drug can be made and every disease can be treated".

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A NEW PLATFORM FOR SUPRACHOROIDAL DRUG DELIVERY USING STANDARD COMMERCIALLY AVAILABLE NEEDLES

In this article, Timo Kangastupa, Managing Director of Visionisti Oy and inventor of Visionisti's suprachoroidal injection platform, discusses the potential of the suprachoroidal space for highly effective, specifically targeted drug delivery to the choroid and retina, and how Visionisti's technology simplifies and standardises the procedure, enabling the use of standard commercially available needles for suprachoroidal delivery.

The ophthalmic sector is a rapidly growing part of the drug delivery industry. This is due to a number of factors, including ageing populations, greater awareness of ophthalmic conditions and increased pharmaceutical investment into ophthalmic research and development. With this growth comes new impetus to innovate on how we deliver drugs to the eye and to improve on our ability to target desired segments and increase the bioavailability of therapeutics.

SUPRACHOROIDAL DRUG DELIVERY

One exciting area of innovation has been delivery to the suprachoroidal space, a potential space between the choroid (the vascular layer of the eye) and the sclera (the white layer of the eye). The suprachoroidal space is an appealing route of delivery as it allows for a drug injected at the front of the eye to traverse the eye's circumference and be delivered directly to the choroid and retina, which would otherwise require a more invasive intravitreal injection, implant or even surgery. This has the dual advantage of increasing efficacy, with delivered drug concentrations at the choroid and retina being potentially 10 times greater than those achieved by intravitreal injection,[1] and enhancing safety, as the delivered therapy is largely compartmentalised away from non-target tissues.[2]

There are numerous potential applications for suprachoroidal delivery, including target indications such as neovascular age-related macular degeneration, diabetic retinopathy, diabetic macular oedema, uveitis and choroidal melanoma.[3] Suprachoroidal delivery has also been put forward as an ideal candidate for the administration of novel gene therapies targeting retinal cells and the retinal pigment epithelium, which could otherwise require a surgical subretinal injection.[1]

However, successfully delivering therapeutics to the suprachoroidal space is no mean feat. Initial approaches to access the suprachoroidal space were surgical in nature. More recently, research has been conducted on delivery into the space via injection. Using a standard hypodermic needle is exceedingly challenging, as under most circumstances the suprachoroidal space is collapsed (due to intraocular pressure), meaning that the injecting physician must rely on tactile cues to know when the sclera has been penetrated. In response to this issue, it has been suggested that use of a microneedle of a length precisely matched to the sclera and conjunctiva would be the ideal solution to avoid an accidental intravitreal injection taking place instead of a suprachoroidal one.[4]

Whilst presenting clear advantages compared with other methods of drug delivery to the retina, injection into the suprachoroidal space comes with its own set of challenges. For example, performing suprachoroidal injections using microneedles requires additional training and time

> "There are numerous potential applications for suprachoroidal delivery, including target indications such as neovascular age-related macular degeneration, diabetic retinopathy, diabetic macular oedema, uveitis and choroidal melanoma."

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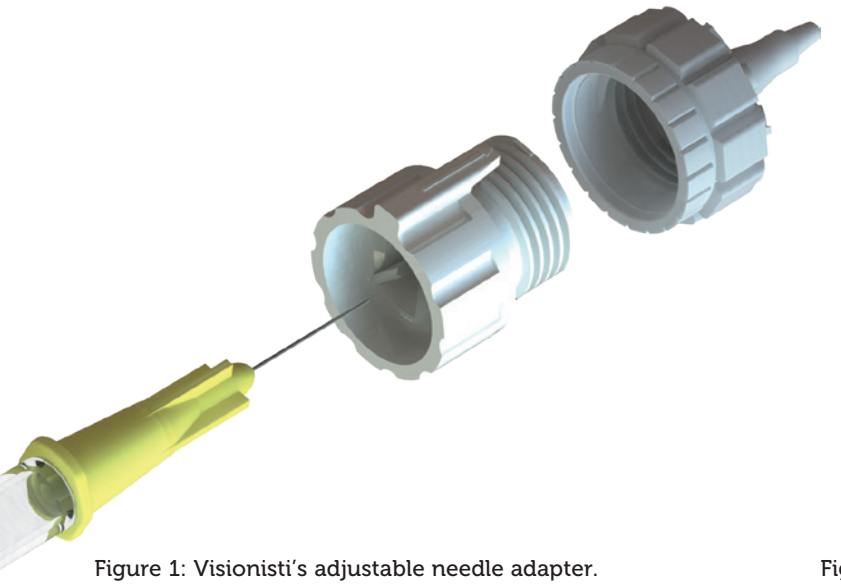

Figure 1: Visionisti's adjustable needle adapter.

Figure 2: Visionisti's needle guide.

compared with traditional intravitreal injection methods.[5] To tackle these challenges and unlock the potential of suprachoroidal injection, Visionisti has developed a novel drug delivery platform that enables the use of conventional, commercially available hypodermic needles and standardisation of the procedure to maximise convenience and minimise difficulty for all parties.

VISIONISTI'S PLATFORM

Visionisti's delivery platform consists of two parts: an adjustable adapter (Figure 1) and a needle guide (Figure 2). The adapter is a simple add-on device that transforms a conventional hypodermic needle into a suprachoroidal injection device by precisely controlling the exposed length of needle, while the needle guide stabilises the eye, keeps the eyelids open and standardises the injection procedure, ensuring that injections are always carried out with a predefined angle and distance from the limbus.

Adjustable Adapter

Visionisti's adjustable adapter is designed to fit on the end of commercially available hypodermic needles and provide easy and fast adjustment of their effective length. This is done by simply twisting the adapter, and it can be configured to allow for continuous, stepped or predefined levels of adjustment. In this way, Visionisti's platform prevents accidental injection past the choroid and into the vitreous humour in much the same way that a specialised microneedle would, but with the advantage of using commercially available injection devices with standard hypodermic needles (Figure 3).

The adapter is customisable and can be tailored to suit the needs of a specific ophthalmic injection device, including prefilled syringes, drug-coated solid needles and devices for injecting ophthalmic implants. As the adapter is an add-on to the injection device, it doesn't come into contact with any drug product and has a minimal regulatory burden associated with it.

Needle Guide

The needle guide part of Visionisti's platform is designed to standardise the suprachoroidal injection procedure. The guide is a cheap and disposable all-in-one tool to keep the eyelids open, stabilise the eye, control the injection angle and reduce injection pain. It also helps the needle track to close automatically, minimising the risk of endophthalmitis. Furthermore, the needle guide functions as a pressure plate after the injection, minimising the potential backflow. The guide is convenient to use, consisting of a single piece that is easy to put in place and keeps the eye focused forward, while an opening on the side controls the angle and approach of the needle (Figure 4).

Figure 3: The adjustable adapter can make virtually any commercially available injection device suitable for suprachoroidal delivery by precisely controlling the length of the exposed needle, preventing accidental intravitreal injection (image credit to Elias Jokiranta Photography).

Figure 4: The needle guide maximises the convenience of the injection and standardises the procedure (image credit to Elias Jokiranta Photography).

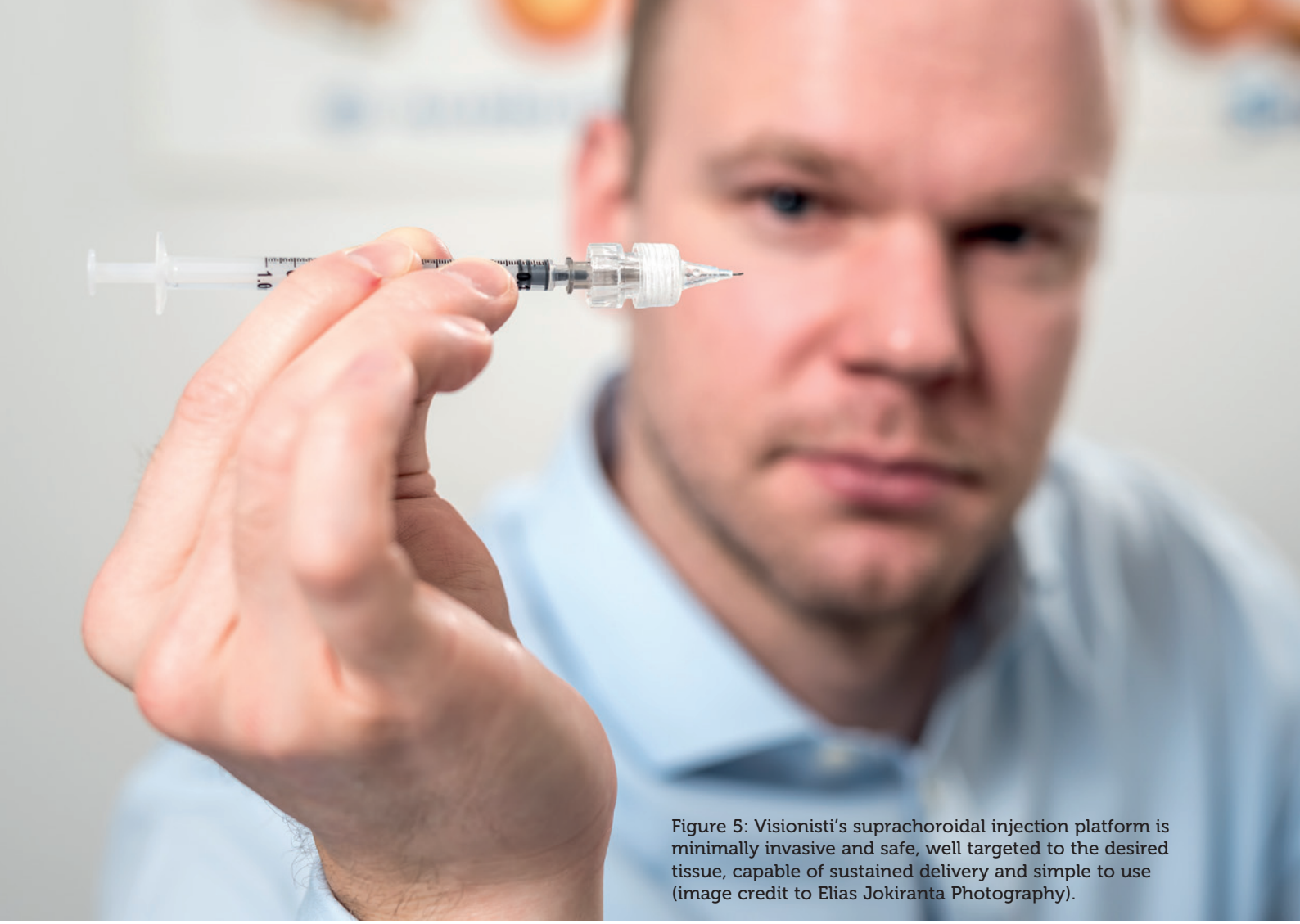

Figure 5: Visionisti's suprachoroidal injection platform is minimally invasive and safe, well targeted to the desired tissue, capable of sustained delivery and simple to use (image credit to Elias Jokiranta Photography).

An additional potential benefit being investigated is the possibility that some patients may experience reduced pain when the injection is administered with the needle guide. When the needle guide is applied to the eye, the pressure it exerts may have a paralysing effect on the ciliary nerves, resulting in a sensation of local anaesthesia.

Combined Platform

Together, Visionisti's adjustable adapter and needle guide provide a complete platform for transforming commercially available needles into convenient, ready-to-use suprachoroidal injection devices. Visionisti's platform is ideal to be incorporated into a sterile, pre-assembled, pre-adjusted package as part of a drug-device combination product.

A MODERN OPHTHALMIC DELIVERY SYSTEM

An effective system for drug delivery to the back of the eye should embody four general characteristics.[6] A successful suprachoroidal delivery system has the ability to meet all of these criteria, and Visionisti's platform achieves just that (Figure 5).

Minimally Invasive and Safe

Suprachoroidal injection using Visionisti's platform takes place as a standardised procedure within the administering clinician's office, consisting of a perpendicular transscleral injection without the need for a surgical operation or invasive cannulation of the eye. In particular, the needle guide enhances the consistency safety of the procedure by increasing the stability of the eye and making the process simpler and readily reproducible, reducing the necessary skill level required to administer the injection.

> "The platform standardises the injection procedure, making it repeatable, faster and easier for the administering clinician."

Well Targeted to the Desired Tissues

Suprachoroidal injection provides direct access to the site of therapeutic action (choroid and retina) and avoids the inner limiting membrane barrier. Additionally, the delivery route has been shown to maintain higher drug concentrations and increased bioavailability of therapeutics at the target site for longer periods of time, while also compartmentalising the administered drug to the desired target sites. Reduced drug exposure in undesired regions of the eye leads to fewer side effects and complications and means that the therapy does not affect the eye's optical axis.

Capable of Sustained Delivery

In order to reduce how frequently patients must receive injections to treat their ophthalmic conditions, it is desirable for drug product to remain available to the target site after the injection takes place. While still a subject of investigation, studies have shown that some drugs, such as triamcinolone acetonide, may reside in the eye for a significantly longer period when delivered into the suprachoroidal space compared with when delivered by intravitreal injection.[7] This, coupled with the higher bioavailability to the choroid and retina, means that suprachoroidal delivery has the potential to demand a less frequent dosing regimen, which may in turn reduce the burdens on both patients and treatment providers, improving quality of life for all parties.

Simple

Visionisti's platform is a convenient, easy-to-use all-in-one tool. It stabilises the eye and keeps the eyelid open, making the injection process simpler to perform and more comfortable for the patient. The platform standardises the injection procedure, making it repeatable, faster and easier for the administering clinician. In a similar way, the needle guide reduces potential user error by ensuring that injections are performed in a predefined way.

PRECLINICAL STUDIES

Visionisti's platform has successfully undergone both *ex vivo* and *in vivo* preclinical trials. A recent trial conducted by Absorption Systems California (CA, US) tested the feasibility of the system for suprachoroidal injection into rabbits. Prior to any injection, the eyes were imaged using fluorescein angiography (FA), infrared (IR) and optical coherence tomography (OCT). These baseline images showed a fully collapsed suprachoroidal space (Figure 6). After the baseline was taken, a 100 µL injection was delivered to the suprachoroidal space using a 30G needle with Visionisti's platform adapting it for suprachoroidal use. A second set of images was then taken, with the cross-sections taken by OCT clearly showing an opening of the suprachoroidal space (Figure 7).

FUTURE OUTLOOK

Further to its suprachoroidal application, research suggests that this technology has the potential to deliver to the supraciliary space,[8] subretinal space[9] and cornea.[10] One area of interest is in delivering an *in-situ*-forming hydrogel to the suprachoroidal space, which may reduce intraocular pressure in glaucoma patients.[11] An expansion of the potential applications of microneedles means a similarly expanded potential for Visionisti's platform to enable standard hypodermic and solid needles to be used for delivering injectable therapies to these sites. Furthermore, one added benefit of Visionisti's platform over specialised microneedles is that the same adjustable adapter can be used to tailor the exposed needle length to each of the potential delivery targets, rather than requiring different microneedles specifically suited to each. The intellectual property rights of Visionisti's platform are widely protected; Visionisti has technology patents in Europe, Japan and the US, as well as design patents in Europe and the US.

In summary, suprachoroidal delivery has the potential to be a major step up in drug delivery to the choroid and retina, which represents a rapidly growing sector of the market. Visionisti's platform fulfils all the requirements of a modern system with a simple, all-in-one tool that provides a safer, more effective and more convenient way to deliver drugs to the back of the eye for all stakeholders. This technology represents a rare opportunity to advance the field of drug delivery and may provide a better quality of life to patients and physicians.

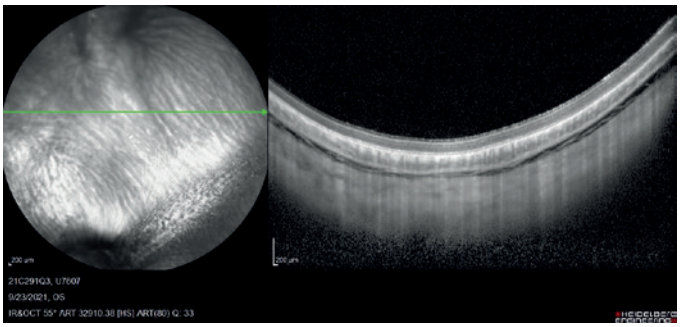

Figure 6: An IR image (left) and OCT cross-section (right) of a rabbit eye prior to injection into the suprachoroidal space.

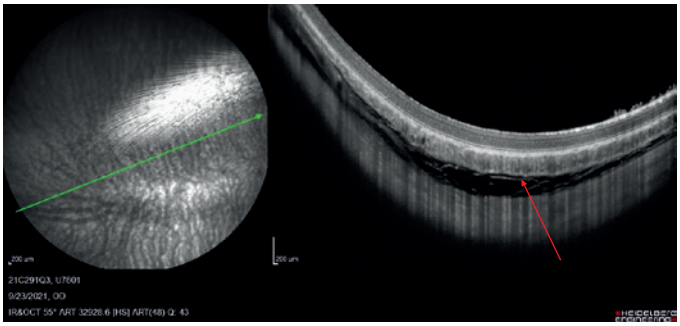

Figure 7: An IR image (left) and OCT cross-section (right) of a rabbit eye after a 100 µL injection into the suprachoroidal space using a 30G needle adapted using Visionisti's platform. The red arrow indicates the post-injection opening of the suprachoroidal space.

ABOUT THE COMPANY

Visionisti Oy is a private research and development company commercialising a patented platform for precise and simple delivery of drugs to the suprachoroidal space of the eye using standard commercially available needles. Visionisti was established in 2014 and is currently seeking partners for the commercialisation of its technology.

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ABOUT THE AUTHOR

Timo Kangastupa is Co-founder, Chairman and Managing Director of Visionisti Oy, holds an MSc in Biomedical Engineering and an MBA degree, and is the inventor of Visionisti's suprachoroidal injection platform. Mr Kangastupa has extensive experience in the field of ophthalmic devices and surgical consumables.

HOW TEN23 HEALTH IS MEETING DEVELOPMENTAL CHALLENGES FOR INTRAVITREAL PRODUCTS

Here Andrea Allmendinger, PhD, Chief Scientific Officer, and Hanns-Christian Mahler, PhD, Chief Enablement Officer, both at ten23 health, highlight new regulatory and quality requirements for intravitreal applications and discuss technical challenges during drug product technical development and manufacturing.

In an article published in *ONdrugDelivery*, April, 2021 – "State-of-the-art solutions for ophthalmic sterile drug product manufacturing" – swissfillon explained why ophthalmic products require a high level of process knowledge and state-of-the-art manufacturing technologies and expertise to maximise safety, meet stringent regulatory requirements and minimise costs. The article explained how swissfillon's aseptic manufacturing services, now part of ten23 health, and its innovative highly flexible automated filling line at its facility in Visp, Switzerland, meet the requirements and complexities associated with intravitreal (IVT) and other parenteral preparations. In this article, new regulatory and quality requirements for IVT applications will be discussed, along with technical challenges during drug product technical development and manufacturing.

> "The successful administration of IVT injection of typical injection volumes between 25 and 100 µL requires the development of highly concentrated formulations of the desired biologic, which presents major challenges during technical development and manufacturing."

Retinal disorders include diabetic retinopathy and age-related macular degeneration. They can be treated with anti-VEGF (vascular endothelial growth factor) drugs, which are usually administered by IVT injection into the back of the eye using prefilled syringes (PFSs). This allows direct delivery into the vitreous humour to achieve sustained levels of drug solutions and evade the blood-retinal barrier. IVT preparation requires very high-quality primary packaging and drug product manufacturing technologies to ensure patient safety, regulatory compliance and adequate product design for usability.

The successful administration of IVT injection of typical injection volumes between 25 and 100 µL requires the development

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"Silicone droplets may be detected as subvisible particulates or even visible particulates in the product, depending whether the formulation is stored in the silicone-coated syringe and/or in contact with the syringe during administration."

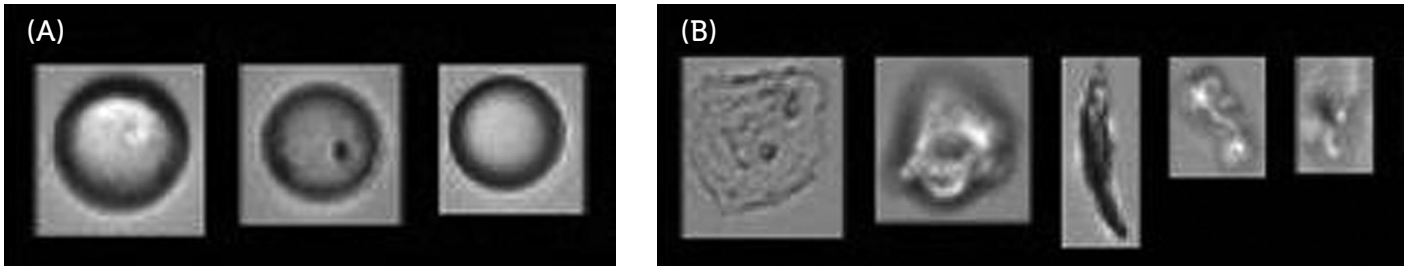

Figure 1: Illustrative examples of particles analysed by micro flow imaging extracted from Agra et al.[4] High particle variability across siliconised and oil-free syringes and needles from the same lots. A) Silicon oil droplets. B) Other contaminants.

of highly concentrated formulations of the desired biologic, which presents major challenges during technical development and manufacturing. Ideally, the drug product is designed to reduce injection frequency and prolong therapeutic levels.

In addition, ready-to-use injections using drug-combination devices, such as PFSs, are preferred, which adds another level of complexity and major challenges to drug product development.

NEW REGULATORY REQUIREMENTS

The European Pharmacopeia (Ph Eur) has recently updated its dosage form monograph "Parenteral Preparations", adding the sub-category of "Intravitreal Preparations". IVT preparations are defined as "sterile parenteral preparations intended for administration or implantation into the vitreous humour. They are solutions, colloidal dispersions, emulsions, suspensions or implants and comply with the requirements for injections or implants, as appropriate. Unless otherwise justified and authorised, they are supplied in single dose containers and do not contain any preservatives".

PARTICULATES FOR IVT PREPARATIONS REVISITED

The requirements for IVT preparations in the Ph Eur related to visible particulates (Ph Eur 2.9.20) as well as sub-visible particulates (Ph Eur 2.9.19) aligned with the requirements of other parenteral dosage forms (0520). These are "practically free of particles" for visible particle inspection and a maximum of 6.000 particles/container for particle sizes ≥10 µm and a maximum of 600 particles/container for particles ≥25 µm.

This is different from the US Pharmacopeia (USP), chapter <789>, where, for example, significantly tighter limits are defined for IVT preparations, e.g. not more than (NMT) 50 particles/mL for particle sizes ≥10 µm and NMT 5 particles/mL for particles ≥25 µm. Interestingly, there are no controlled clinical studies that relate to the clinical relevance of particulates after IVT injection, although particulates may – or may not – have clinical relevance in the eye, depending on a few parameters, such as their ability to dissolve in the vitreous humour or their density (e.g. if floating).[1] Whether any such particulates impact patients' vision is probably a significant consideration.

In general, particles may originate from the formulation in the final primary packaging as a result of protein or excipient degradation, or they may be extrinsically introduced during the manufacturing process.

Syringes are used either as final primary packaging for IVT preparations or for withdrawal and administration when using a vial-based product. Most syringes are siliconised to ensure lubrication and functionality (break loose and gliding forces) for the user. Hence, unsurprisingly, silicone droplets may be detected as subvisible particulates or even visible particulates in the product, depending whether the formulation is stored in the silicone-coated syringe and/or in contact with the syringe during administration.

Subvisible particle measurements, which are traditionally performed with classical light obscuration techniques, would count the droplets as part of the overall particulate product load, and products may fail the tight USP <789> criterion. This is where morphological characterisation tools for particulates, such as flow imaging, add value. These allow particulates to be differentiated qualitatively and provide insights into whether the particulates measured by light obscuration are indeed "contaminants" or "degradants", or just silicone oil droplets (Figure 1).

Polymer syringes and other silicone-free syringes may be an alternative to siliconised syringes but must be carefully selected based on drug-product device compatibility and device functionality and syringe quality.

Interestingly, silicone is also used for optical surgery, where approximately 2–3 mL silicone is used in the eye.[2] Minute amounts of silicone droplets are therefore typically considered not to be of significant medical concern.[3]

ENDOTOXIN REQUIREMENTS FOR IVT ADMINISTRATION

Endotoxins are a key consideration for parenteral preparations that relate to patient safety. IVT injections, in particular, require careful consideration for endotoxin limits, as they may relate to possible reversible and dose-dependent inflammation in the eye of different severity and reversibility. Inflammation of the eye may result from acute influx of protein and leukocytes into the anterior and may possibly also manifest clinically as haze persisting in the vitreous and lead to other safety concerns including immune response.

The no-observed-adverse-effect level (NOAEL) in both rabbits[5] and non-human primates[6] was reported as "not more than (NMT) 0.01 EU/eye." Endotoxin levels at 0.02 EU/eye and >0.04 EU/eye were found to induce dose-related inflammation.

This NOAEL is especially important considering that host cell lines used for the production of the API may be microbial. In addition, endotoxins may relate to different sources throughout the overall drug substance and drug product production process. The FDA Guidance for Industry (2015) on endotoxin testing recommendations for single-use intraocular ophthalmic devices discusses the limits of NMT 0.2 EU/mL, which, for IVT injection volumes of 10–100 µL, translates to 0.002–0.02 EU/eye, respectively, and, therefore, slightly higher acceptance criteria than the NOAEL derived from preclinical data.

TECHNICAL CHALLENGES OF LOW INJECTION VOLUMES

IVT injections have a defined volume range. The upper volume of IVT injections is typically around 100 µL, governed by medical concerns over clinically relevant symptoms, including an increase in intraocular pressure. The lower limit of IVT injections, typically around 25 µL, is governed by the precision of lowest administration volume and dose, which is influenced by syringe/needle configuration. In some cases, where only parts of the filled product volume are injected, such as 10 µL of drug product, the dose precision may be affected by the user and product usability, with influencing factors, such as graduation marks or the impact of air bubble in the syringe/needle.

It is important to note that product usability and the variability of dosing volume must be established in appropriate studies, including human factors studies. There is anecdotal evidence that (manual) down-dosing for an intended 10 µl injection actually yields doses corresponding to injection of zero µL (air bubble) to 30 µL (3 times the intended dose).

HIGHLY CONCENTRATED FORMULATIONS: VISCOSITY AND INJECTION FORCES

Compatibility with the primary packaging container is typically tested in long-term stability studies as well as in stress studies to test specific liabilities, for example, stability and sensitivity in final primary packaging. When considering plastic (polymer) primary containers, additional parameters are recommended for testing due to the higher permeability of such containers in comparison with glass, including testing for oxygen sensitivity and extractables/leachables.

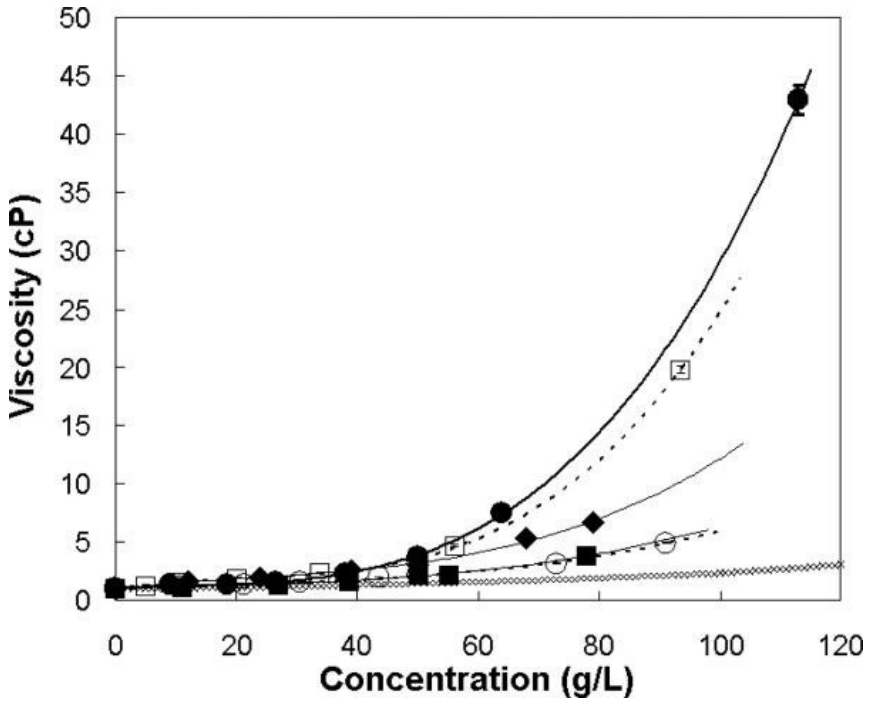

Figure 2: Concentration-dependent viscosity of different antibody solutions at pH 6 and two ionic strengths. (●) 10 mM histidine, (□) 2.2 mM sodium phosphate, (○) 10 mM histidine, 150 mM NaCl, (■) 2.2 mM sodium phosphate, 150 mM NaCl, (◆) 10 mM histidine, 2 mM NaCl, (◇) Viscosity of an equivalent hard-sphere using the Mooney approximation. Lines represent a polynomial fit. Modified according to Salinas et al.[7]

Given the limited injection volume for IVT administration, the need for high concentration formulations of protein APIs is typically warranted – depending on the target dose. However, protein concentrations correlate exponentially to product viscosity (Figure 2). This means that protein formulations for IVT use are often characterised by high viscosity, which directly implies increased injection forces, as described below.

As some protein formulations can show shear-thinning behaviour facilitating administration, it is imperative to characterise the shear-dependent flow behaviour of such formulations adequately during product development (see Table 1). Besides API concentration, viscosity is also dependent on temperature. Products stored at 2–8°C intended for administration at room temperature typically require equilibration. In the absence of such

Product characteristic: viscosity	Device characteristic: needle inner diameter
Characterisation of viscosity-protein concentration dependence	Choice of injection needle depending on product viscosity, user requirements and clinical considerations
Characterisation of viscosity-shear-rate dependence assessing (non-) Newtonian behaviour	Characterisation of variability in needle inner diameter
Characterisation of viscosity-temperature profile	Target setting and failure mode assessment (edge of failure assessments) of injectability (e.g. forces, time) in relation – to intended specification ranges – to user capabilities
Choice of formulation (excipients)	
Specification setting (content)	

Table 1: Product and device characteristics studied and controlled in development studies to mitigate delivery challenges.

"In the case of IVT formulations particularly, the choice of excipients is extremely limited, and only a few excipients in sufficiently high concentration have demonstrated clinical safety and regulatory acceptance."

an equilibration phase, the viscosity at 2–8°C product temperature is likely to be significantly increased and administration potentially compromised.

EXCIPIENTS

To mitigate high viscosity from a formulation perspective, the choice of an adequate formulation is crucial. A common consideration in managing formulation viscosity is the choice of appropriate pH and the use of one or several excipients. Amino acids or salts have been described as potentially managing product viscosity. However, a key parameter for the choice of an appropriate formulation is not only product viscosity but also ensuring that the API is sufficiently stable during manufacturing, transport, (long-term) storage and administration. In the case of IVT formulations particularly, the choice of excipients is extremely limited, and only a few excipients in sufficiently high concentration have demonstrated clinical safety and regulatory acceptance.

DEVICE DESIGN

Ready-to use injections are typically preferred for IVT applications using drug-combination devices, such as PFSs. As most early-stage clinical studies use vials, the ability to switch between product configurations from a vial to a PFS is extremely helpful, allowing the manufacture of both configurations at the same manufacturing facility.

Syringes for ocular administration are typically provided with a flexible Luer-lock system allowing the user (ophthalmologists) to choose the appropriate and preferred needle. The needle needs to be carefully chosen and selected in the context of the product parameters. According to Hagen-Poiseuille's law, injection forces depend on the inner radius of the needle to the power of 4 – this means that very subtle variations in the inner diameter of the needle lead to significant differences in required injection forces, and hence product usability and performance. Typically, 30G needles are used for IVT injections to minimise corneal damage, which may be caused by larger diameter needles. This provides specific limitations and challenges related to the maximum viscosity of a formulation in the context of a maximum injection force, as defined in user studies.

THE FILL-FINISH PROCESS

Filling of low volumes in primary packaging material is technically challenging, and sterile manufacturing capabilities, parameters and process set-up dramatically influence the lower fill volume and its related fill precision. As an example, gravimetric fill control, as implemented at swissfillon, guarantees a filling accuracy of ±5% and accuracy within 2%, which is suitable for IVT preparations at these very low fill volumes. In addition, swissfillon's filling line ensures the rejection of single syringes rather than large numbers of syringes, which can result in substantial savings.

"Filling of low volumes in primary packaging material is technically challenging, and sterile manufacturing capabilities, parameters and process set-up dramatically influence the lower fill volume and its related fill precision."

Fill volumes must be defined to achieve adequate extractable volumes, and overfills are ideally minimised to save costs. It is therefore recommended that filling parameters are defined in related process studies. In addition, stoppering of low volume dosage forms can provide specific technical challenges, which can be mitigated by the appropriate expertise of a contract development and manufacturing company (CDMO).

Headspace in syringes used for IVT administration is generally undesirable from a clinical perspective. Hence, manufacturing syringes for IVT administration that ensure zero headspace (bubble-free) are desirable. Especially in the case of ophthalmologic products, external sterilisation by ethylene oxide or hydrogen peroxide may be required by specific markets and countries. Residual contaminants need to be specified and their impact needs to be assessed regarding compatibility with the drug product compromising drug substance stability.

THE CONTAINER CLOSURE SYSTEM

A container closure system (CCS) refers to the sum of packaging components that together contain and protect the dosage form. This includes both primary and secondary packaging components, if the latter are intended to provide additional protection to the drug product. The suitability of the CCS for its intended use needs to be demonstrated, including protection of the drug product from, for example, moisture, oxygen or light; compatibility of the packaging

components with the drug substance; safety including extractable studies and their toxicological evaluation; and performance, such as functionality and delivery of the intended dose.

An integral part of CCS testing is the evaluation of container closure integrity (CCI), which is an obligatory critical quality attribute for sterile dosage forms. CCI testing evaluates whether there is a leak in the CCS that may allow contaminants (such as microorganisms) from the outside environment to potentially compromise sterility.

USP chapter <1207> (2016) and the revision of the EU Annex 1 for sterile product manufacturing (2020) currently represent the most thorough guidance documents on CCI concepts for sterile injectable products. USP chapter <1207> provides an overview of common CCI tests and categorises them into deterministic (e.g. electrical conductivity and capacitance test, headspace gas analysis, vacuum or pressure decay, and tracer gas vacuum mode, such as helium leak detection by mass spectrometry) and probabilistic tests (such as the conventional blue dye test). Deterministic tests are usually preferred for CCI evaluation.

Additionally, the use of positive and negative controls, including artificial leaks, is key. Importantly, the evaluation of the CCS should not be viewed as limited to end-product quality control testing rather than ensuring that the choice of components is qualified for integrity (CCI) based on quality-by-design, considering variations in primary packaging components but also considering processing. CCI testing strategies remain challenging, dependent on packaging material and configuration and there is no one-size-fits-all CCI testing set-up. Ideally, CDMO partners have established deep expertise and access to a toolbox that may be further optimised for a specific product configuration using science-based and quality-by-design-based approaches for CCS selection, method development and validation.

SUMMARY

In this article, the discussion about IVT products was continued with a key focus on challenges related to product design and development, and updates on any requirements or quality considerations.

Specifically, the following specific requirements and aspects were discussed, which must be considered to manage the complexity related to sterile product manufacturing of IVT injection drug products:

- Most early-stage clinical studies use vials but syringes are a preferred product configuration to facilitate usability. Switching between product configurations to manufacture both vials and PFSs at the same manufacturing facility will be facilitated by a partner with significant expertise to accompany such a switch.
- IVT preparations have specific regulatory requirements related to subvisible particles in the US, and the choice of appropriate methods and characterisation tools is a key consideration.
- IVT injection volumes are low, and individual containers should preferably be filled with only the patient-specific volume (dose) to avoid any down-dosing or product-handling issues. Hence, manufacturing facilities and processes that show highest fill precision accuracy at these very low volumes are key. Minimising over-fill, other than what is required to ensure extractable volume and accurate dosing, can achieve significant cost savings.
- Formulation viscosity and choice and design of formulation are of crucial importance. Identifying the right balance between optimal stability and viscosity, in relation to the choice and characterisation of the devices and needles used for administration is a key success factor.
- The selection of an appropriate CCS is not only a critical priority from a product use and administration perspective but must ensure integrity over its whole shelf life.

A CDMO such as ten23 health is appropriately positioned to support such challenges of IVT injections. In addition to

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manufacturing complex and high-precision containers in its swissfillon facility, ten23 can assist with formulation services, analytical development and characterisation and process design.

ABOUT THE COMPANY

ten23 health, located in Basel, Switzerland, is the human-centric and sustainable strategic partner of choice for the pharmaceutical industry and biotech start-ups: the company develops, manufactures and tests tomorrow's medicines. ten23 health supports its clients in developing differentiated, stable, usable and safe injectable treatment options for patients. swissfillon, a leader in the sterile filling of complex pharmaceuticals into innovative containers and devices, is a wholly owned subsidiary. ten23 health combines the latest scientific findings with its proven and tested world-class industry and regulatory expertise to forge new paths for supporting clients. The company provides its services in a fair and sustainable manner, respecting people's health and the future of the planet.

Regarding the company's name: the numeric value for the number of molecules in a sample of 1 mol is called Avogradro's constant and equals 6.022 x 10^{23}. Gram quantities of material contain the incredible number of 10^{23} atoms, which was an important discovery in the understanding of the composition of matter: the world is built from small units and not a homogeneous mass.

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Phillips Medisize
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A CULTURE OF COLLABORATION INSPIRES INNOVATION AND LIFE-CHANGING THERAPIES

In this article, Justin Westendorf, Product Development Manager at Phillips-Medisize Corporation, describes the company's collaborative approach with a leader in ocular disease treatments to overcome technical and stakeholder challenges.

Pharmaceutical innovation has been in overdrive for decades, aiming to keep pace with demand for safe and effective novel products and therapies that will improve patient outcomes and wellbeing. With that innovation comes increased complexity – particularly in the ocular drug delivery arena – as well as a host of unique and intricate challenges that span ideation and manufacturing to regulation and risk, and everything in between.

Medical solutions are being miniaturised and connected and can provide real-time data on patient health. Meanwhile, technological advances in manufacturing, increased access to data and the need to adhere to ever-more-stringent regulatory standards have made the road longer and increasingly more dynamic for patients and healthcare providers alike. The journey for innovative technologies is filled with potentially intractable challenges that could derail a project, cost time and resources and, most importantly, leave otherwise great ideas with no path forward.

Just as the products have evolved, so have the product development strategies. A collaborative culture, coupled with focused and facilitated ideation sessions with a specialised team throughout the entire product development and manufacturing process, has proven to be an effective way to work through the challenges of next-generation solutions.

Phillips-Medisize's collaborative culture, systematic approach to ideation, discovery and execution allows it to bring ideas to life, no matter how preliminary, from the moment of inspiration to a fully realised product built at the scale you need.

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Contributors are encouraged to identify challenges, risks and opportunities during ideation sessions with Phillips-Medisize.

IDENTIFY THE PROBLEM STATEMENT

The ageing population is driving tremendous demand for pharmaceutical innovation. The number of people aged 65 and older is expected to double by 2030, reaching nearly one billion.[1] In this growing population, an important area of focus is wet age-related macular degeneration (AMD) – which is the leading cause of blindness among people aged 60 and older. Currently, nearly 20 million people worldwide suffer from wet AMD and many must undergo monthly eye injections to arrest the growth of abnormal blood vessels in the back of the eye. The hope is that this will preserve their vision – but this process can negatively impact quality of life. The injections into the eye can be uncomfortable and monthly appointments, especially for seniors, can be burdensome and create adherence risks.

This prompted a leader in the field of wet AMD therapies to engage with Phillips-Medisize to develop a better solution; one that is aimed at delivering therapeutic benefit, reducing the frequency of visits and improving quality of life for patients. With a solution in mind, the customer worked with two other service providers before approaching Phillips-Medisize. The customer recognised that they needed to engage with an organisation capable of working collaboratively to solve complex problems, along with having the design and manufacturing capabilities to bring their idea to execution at scale. Therein lies the problem statement – how does Phillips-Medisize manufacture this novel solution?

EXECUTE A SUCCESSFUL AND COLLABORATIVE IDEATION SESSION

The first step in solving the problem statement is the execution of an ideation session. For an ideation session to have a successful outcome, the definition of success needs to be clearly understood by the participants and the facilitator planning the session. "Success" could be described as: "Create a wide range of potential solutions that address the problem statement and select one of the ideas for implementation." More often than not, "success" is not about making a selection, it is about using a collaborative process to:

- Identify potential ideas
- Document the risks and challenges of implementing each idea
- Evaluate ideas according to prioritised metrics and identify the most promising concepts
- Create an investigation or experimentation plan for the selected direction(s).

Execution of these tactics encourages collaboration, knowledge sharing and creative thinking – all beneficial outcomes of an ideation session. The team must also align on where the session should end, and chart the course and tools needed to bring the team members from the problem statement to the definition of success.

TEAMWORK AND POSITIVE FRAMING ENCOURAGES CREATIVITY AND IDEATION

To work through a problem statement, the right team must be assembled for the ideation session to delve into a variety of "what if" questions. Exploring "what if" scenarios in a team setting positively forces idea expansion and the identification and documentation of cross-disciplinary risks for later consideration. These sessions require representation of a broad range of expertise including manufacturing technologies, design and materials, human factors and the customer's pharmaceutical and clinical experts.

"To work through a problem statement, the right team must be assembled for the ideation session to delve into a variety of 'what if' questions."

In addition to the right mix of technical knowledge, team members must be willing to adopt a "find a way" mindset that encourages contributions from each representative's area of expertise. It is important that the contributors do not see obstacles but are encouraged to identify challenges, risks and opportunities. Positive framing acknowledges the importance of challenges without stifling creativity so that ideation can flourish.

TEST FOR FEASIBILITY FIRST, THEN VIABILITY

As with many pharmaceutical products pushing the boundaries of innovation, this groundbreaking solution required the assembly of micro, multi-material components at a scale so small that most high-volume commercial manufacturing methods did not have the precision to produce them. The ideation session exposed that structured experiments in manufacturing methods were needed to gain confidence and determine if the solution was feasible. Due to the manufacturing complexity of the solution, rapid prototyping methods would have been a waste of time and resources. These experiments required a significant early investment in advanced manufacturing technology for very specific operations; specially constructed proof-of-principle stations that allowed team

"Not all challenges are of a design or manufacturing nature. Some challenges involve the variety of stakeholders whose needs must be satisfied for a product to be brought to market."

members to slow down and understand what was going on in an operation and make incremental adjustments to understand changes in the behaviour of the parts they were producing. With an eye towards the longer-term goal of viability, manufacturing methods that could be scaled were chosen and the experiments focused on what would need to be controlled and how to control them.

Once the team determined microassembly was feasible, it began considering if it was viable. Viability looks at the reproducibility and scalability of a given technical solution. In addition to assessing each step of the process to determine whether it could be done in a manufacturing environment, the team had to determine whether it could be done at scale. Manufacturing advanced medical devices requires specialised manufacturing capabilities, including increased precision and controls. There were numerous challenges to evaluate, from dispensing adhesive in nanolitres in a band no more than a few hundred microns wide, to using features so small they could not be measured using available measurement equipment. In determining the viability of this solution, not only did there need to be precise and reproducible manufacturing methods – but equally precise and reproducible measurement and inspection methods.

CONSIDER ALL STAKEHOLDERS

Not all challenges are of a design or manufacturing nature. Some challenges involve the variety of stakeholders whose needs must be satisfied for a product to be brought to market.

As with many new treatments for ocular diseases, this solution was part of a larger system with many stakeholders, including the customer, the clinician who opens the product package, the surgeon performing the procedure, regulatory bodies and payers.

Understanding who all the stakeholders are, as well as their motivation to change, is central to designing a holistic product and preventing wasted effort on creating a solution in which a key stakeholder is not interested. This is especially important when bringing a novel product to market. To ensure adoption by all stakeholders, the product or procedure must account for their risks so those stakeholders are comfortable adopting the solution.

Healthcare is nuanced and complex. Improving the patient experience alone may not be enough to convince stakeholders to make a change. Phillips-Medisize believes that, for a product to be successful in the marketplace, it must be useful, usable, desirable and manufacturable – criteria that must be applied to all the stakeholders who touch the product.

Physicians need to be confident in the device; that they can hold the instrument securely in all orientations; that they can properly target the right location of the eye; and that there are mitigations for procedural anomalies. Solving this stakeholder challenge required deploying additional product solutions, each of which needed to be designed and developed as a complementary piece of the holistic solution.

A holistic solution also means extending the stakeholder landscape into the manufacturing supply base. Due to the sensitivity of the eye to contamination, suppliers and sub-suppliers involved in the entire manufacturing process – from materials and components of the product all the way through to the gloves operators wear during manufacturing – needed to be taken into consideration in the design and manufacturing development process. Doing this effectively required a clear translation between quality, manufacturing, operations and supply chain to make sure cleanliness requirements were well understood and executed at every level.

"Improving the patient experience alone may not be enough to convince stakeholders to make a change."

Identifying who the various stakeholders are and what they need from the solution is as important as identifying and collaboratively solving technical and manufacturing challenges. Phillips-Medisize's collaborative culture and systematic approach to ideation, discovery and execution allows it to work through the ambiguity that often comes with the development of novel pharmaceutical products. It's a tried-and-true approach that its customers trust to "Bring Possibilities to Life".

ABOUT THE COMPANY

Phillips-Medisize, a Molex company, brings decades of innovation to leading healthcare and life science companies to develop groundbreaking solutions that help people live healthier, more productive lives. On average, the company commercialises 50 new products a year for customers, including the first-to-market US FDA-registered drug-delivery device using a connected health system. Molex brings decades of experience in advanced electronics, connectivity and sensor technologies to help transform medical and pharmaceutical solutions.

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ABOUT THE AUTHOR

Justin Westendorf is a Product Development Manager, playing a lead role in Phillips-Medisize's product design and development efforts to solve complex problems serving millions of people worldwide with medical devices and combination products. With over 20 years of experience, he has a strong project management background and leads a multidisciplinary design and engineering team that values the user experience and the role of manufacturing development in bringing products to market in a highly automated and regulated environment. Mr Westendorf has a BSc degree in Engineering from Winona State University (MN, US).

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OPHTHALMIC INJECTION OF VISCOUS FORMULATIONS – WHY UNIQUE NEEDS REQUIRE A NOVEL DELIVERY APPROACH

In this article, Guatam Shetty, PhD, Chief Executive Officer and Founder, and Richard Whelton, Vice-President, Marketing & Business Strategy, both of Congruence Medical Solutions, outline the key considerations related to ophthalmic injection of viscous formulations and propose an innovative, user-validated and fully mechanical device-based solution.

THE TREND TOWARDS VISCOSITY

The trend towards more viscous formulations is widely acknowledged in parenteral drug delivery. The same trend is now also occurring in ophthalmic drug delivery, which includes formulations for intravitreal, subretinal and intracameral injections. However, given some of the unique attributes of the eye, the solutions to drug delivery challenges presented by high-viscosity ophthalmic formulations will be different from those for parenteral formulations.

The introduction of anti-vascular endothelial growth factor (anti-VEGF) agents administered via intravitreal injections transformed the treatment of retinal disorders such as age-related macular degeneration (AMD), diabetic macula oedema (DMO), diabetic retinopathy (DR), retinopathy or prematurity (ROP) and branch and central retinal vein occlusions (BRVO and CRVO). However, many challenges in ophthalmology remain to be solved and the occurrence of retinal disorders continues to increase, driven by factors such as an ageing population and the rising prevalence of diabetes.

Pharmaceutical investment in the ophthalmology sector is growing, with many injectable formulations in the pipeline. Within the injectable pipeline, an increasing number of viscous formulations (>20 cP at room temperature) are anticipated. The main drivers behind this trend are similar to those observed in parenteral delivery, including more long-acting drugs, high-strength formulations and bi-specific antibody drugs, as well as the need to store injectables at a low temperature.

"The main drivers behind this trend are similar to those observed in parenteral delivery, including more long-acting drugs, high-strength formulations and bi-specific antibody drugs, as well as the need to store injectables at a low temperature."

Long-acting drugs are a significant driving factor – one to which the story of anti-VEGF agents provides good context. Historically, anti-VEGF agents have typically been administered every

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4–6 weeks, and there is a strong desire to reduce this frequent injection schedule. The high frequency of injections has become a burden on the healthcare system as the patient population continues to grow; furthermore, non-compliance by patients is a concern, as it can cause sub-optimal clinical outcomes. Long-acting drugs can address these challenges.

Genentech (CA, US) recently received approval for the Susvimo™ implant, a port delivery system for slow, controlled release of ranibizumab for the treatment of wet AMD. A related approach is high-strength dosing, with an in-pipeline example being a high-strength dose of Eylea® (aflibercept – Regeneron, NY, US). High-strength formulations tend to be more viscous, with some drugs in the pipeline being extremely so. Bi-specific antibodies are another class of therapeutics known for high viscosity. Several of them are in the pipeline for ocular delivery, such as the recently approved Vabysmo™ (faricimab-svoa – Genentech).

The requirement for these and other molecules to be stored at low temperatures is also an important factor to consider. Viscosity increases with lower temperature, and clinicians often do not wait until a drug reaches room temperature before injecting. This occurs for several reasons but always results in an amplification of the drug's viscosity, for already highly viscous formulations.

VISCOSITY-RELATED CONSIDERATIONS FOR OPHTHALMOLOGY

The need to generate an increased injection force is a known challenge when injecting high-viscosity drugs. The Hagen-Poiseuille equation can help estimate the injection force required during drug delivery. It shows how greater viscosity requires a higher injection force, as well as how other parameters impact injection force. By analysing each variable, it is possible to explore options for reducing injection force when injecting viscous drugs into the eye.

$$F = \frac{128Q\mu LA}{\pi D^4}$$

F – injection force
Q – volumetric flow rate
μ – dynamic viscosity
L – needle length
D – needle internal diameter
A – syringe internal cross section

Viscosity

In parenteral drug delivery, one of the key approaches for handling viscous drugs is to reduce the viscosity by diluting the formulation. However, this increases the injection volume, which could cause a harmful increase in intraocular pressure if injected into the relatively small, fixed volume of the eye. Therefore, this approach is simply not a practical option for ophthalmic delivery.

The dependence of viscosity on temperature is an important, related factor. As mentioned previously, retina specialists often administer ophthalmic drugs without waiting for them to reach room temperature first, thereby increasing the likelihood that the drug is injected at an effectively higher viscosity.

Needle Internal Diameter

The Hagen-Poiseuille equation also shows us that a needle with a larger internal diameter reduces the injection force required, and using a larger needle is often a possibility for parenteral drug delivery. However, for injections into the eye, a thin needle is necessary to avoid complications; for example, larger needles can cause an intraocular pressure spike due to their higher penetration force. As such, ophthalmic injections are already predisposed to have higher injection forces, with viscous formulations further compounding the situation.

Volumetric Flow Rate

Reducing flow rate can help reduce the injection force. However, lower flow rate would mean longer injection time and therefore a longer residence time of the needle in the eye. This, combined with higher injection force for viscous formulations, could lead to instability and potential injury to the patient. Also, in the case of intravitreal injections, the patient is awake and aware of the fact that a needle is in their eye. Longer injection times could be a significant source of distress for patients and therefore deter compliance with their treatment. Injection times longer than 2–3 seconds would be considered a deviation from current clinical practice for intravitreal injections.

Syringe Internal Cross Section

The Hagen-Poiseuille equation indicates that using a syringe with a smaller cross section can help reduce injection force. For example, a 0.5 mL standard prefilled syringe (PFS) will have a lower injection force than a 1 mL long PFS. This is not a common strategy in parenteral delivery, as injection volumes tend to be 1 mL or greater, but is a potential option for ophthalmic drug delivery. The 0.5 mL PFS represents a possible reduction of syringe internal diameter in a standard size.

Needle Length

Decreasing the needle length can reduce the injection force. For intravitreal injections, standard practice is to use a 13 mm needle, which enables the needle tip to be placed in the vitreous cavity. Use of a shorter needle to reduce injection force must also ensure that the needle tip is able to reach the intended injection site.

NON-VISCOSITY CONSIDERATIONS FOR OPHTHALMIC DELIVERY

Manual User Control

In parenteral drug delivery, especially for self-injection, one approach to produce high injection forces is the use of a stored energy source, such as a spring or compressed gas. However, in ophthalmology this would run counter to retina specialists' preference to have complete control of the injection procedure, including injection of the drug itself. Therefore, stored energy is not a viable option.

Ensuring Sterility

In ophthalmic injections there is a risk of infection – endophthalmitis – that can lead to major complications, including blindness and possibly even death. As such, statutory requirements mandate that ophthalmic drug delivery devices, including PFSs, must be terminally sterilised. This requirement can be particularly challenging for electromechanical drug delivery systems, which are likely to be reusable for cost purposes. Liability and the burden of sterilising reusable delivery devices would be unacceptable for healthcare facilities, so single-use delivery solutions are preferable. Also, some ophthalmic injections are conducted in an operating room, so electromechanical systems would also need to demonstrate that they would not interfere with other operating room equipment.

Small, Low-weight Profile

Stability during the ophthalmic injection procedure is very important. The pars plana route for intravitreal injections ensures that the injection needle avoids impacting the eye lens or perforating/detaching the retina;

injection devices would be considered too bulky if they move the centre of gravity for the device too far away from the needle insertion site, thereby causing potential instability during the drug injection step. Again, this could be a disadvantage for electromechanical devices.

INJECTING A VISCOUS FORMULATION INTO THE EYE

Congruence Medical Solutions has conducted numerous studies in the ophthalmic space. Based on user feedback, the target injection force for manual intraocular injections should ideally be below 20 N, which is comparable to an acceptable injection force in parenteral drug delivery. Congruence's data indicates that there are three ways to potentially reduce the injection force to this level with conventional injection devices, although due to the various factors outlined previously, this may well not be sufficient or appropriate.

1 – Select the Right Injection Needle

A larger needle leads to a lower injection force and vice versa. Figure 1 shows injection forces when injecting a 100 cP formulation from a 1 mL long Gerresheimer (Düsseldorf, Germany) tamper evident Luer lock (TELC®) syringe with baked-on silicone using different needle gauge sizes (all 13 mm long). The experience of using a 27G needle in a PFS for Macugen (pegaptanib – Bausch+Lomb, NJ, US) was not well received by retina specialists; the most common intravitreal injection needle size is 30G. Assuming that the extra-thin-wall 30G needle has sufficient column strength, it can be a good choice for reducing injection force. Reducing needle length could also assist in reducing injection force as long as the drug is still injected into the target site.

2 – Increase Injection Time

For a 50 µL dose, Figure 2 shows injection force corresponding to various injection times for a 100 cP formulation injected using a 1 mL long Gerresheimer TELC syringe with baked-on silicone using 30G 13 mm needle. Even with a six-second injection time, the injection force would still be considered unacceptably high; patients are alert during an intravitreal injection, so retina specialists prefer for the needle to be in and out of the eye as quickly as possible. Longer injection times could, however, be considered for subretinal injections.

3 – Use a Syringe with a Smaller Internal Diameter

Congruence's studies show that a 0.5 mL PFS has lower injection force than a 1 mL long syringe, as shown in Figure 3. However, there is no standard PFS size that has a smaller internal diameter than a 0.5 mL PFS.

AN ALTERNATIVE APPROACH

It is very possible that all three injection force reduction strategies, even when used in combination, are inadequate for administering a

> "The most logical option to consider is a drug delivery device with a mechanical advantage, such as the Congruence Microlitre Dosing Syringe."

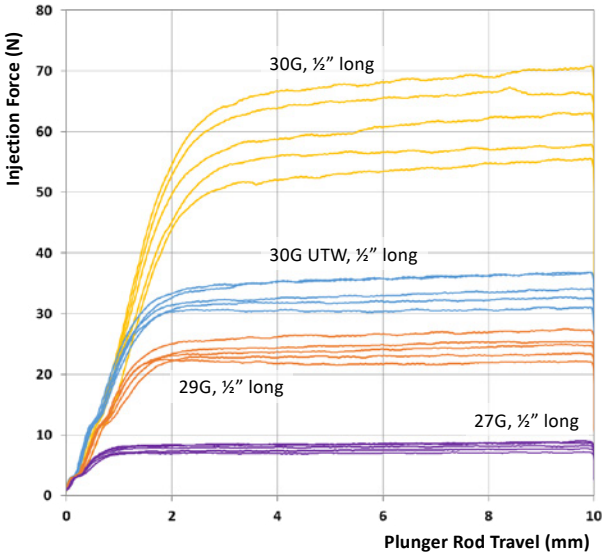

Figure 1: Comparison of injection force for various needles.

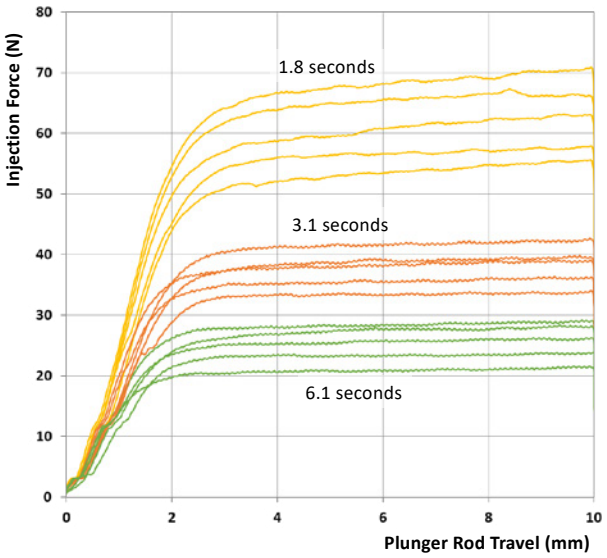

Figure 2: Comparison of injection force for various injection times.

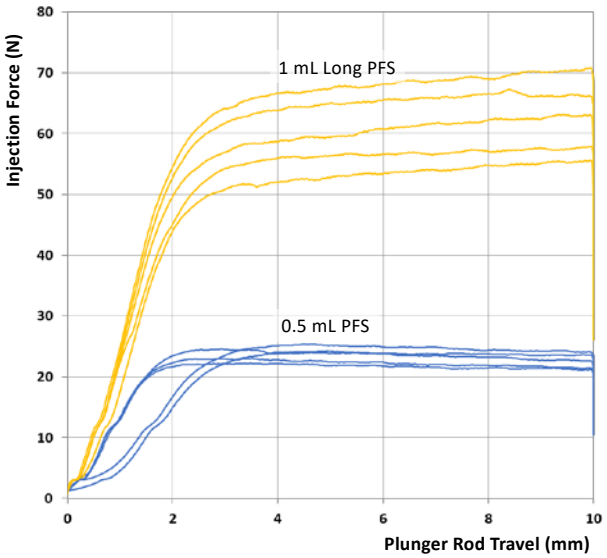

Figure 3: Comparison of injection force for 0.5 mL PFS and 1 mL long PFS.

viscous formulation to the eye. In this case, the most logical option to consider is a drug delivery device with a mechanical advantage, such as the Congruence Microlitre Dosing Syringe (MDS). The mechanical advantage designed into the device enables it to deliver a drug formulation at a high injection force but with the user experiencing a much lower force. The device works with standard PFSs, is manually operated, provides accurate microlitre dose delivery and is disposable and compact, thus meeting the criteria previously outlined.

The performance of this device strategy, combined with the aforementioned injection force reduction strategies, is illustrated in Figure 4. This graph shows the results from a benchtop study that measured injection forces for a 100 cP formulation when using a 1 mL long Gerresheimer TELC syringe with baked-on silicone using a 30G 13 mm needle. Figure 4 shows a comparison of injection forces with and without the Congruence MDS.

The results are clear – for the same plunger rod speed, there is a distinct reduction of the injection force felt by the user when using the Congruence MDS. In other words, the device generates a high injection force on the drug but the user should feel forces more akin to a regular injection, meaning that it remains easy to use and control.

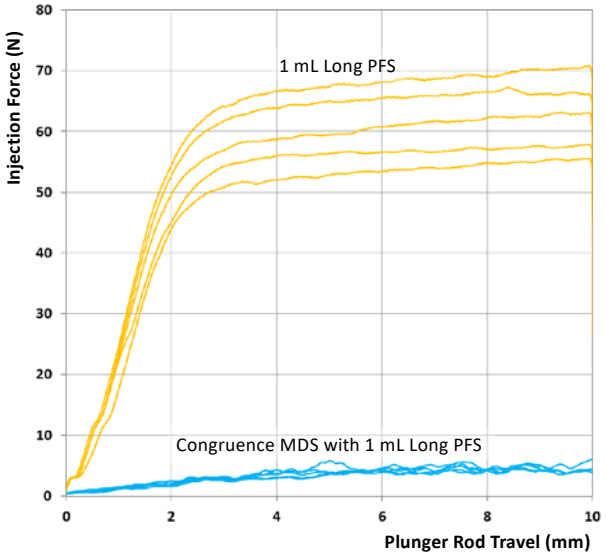

Figure 4: Comparison of injection force without and with Congruence MDS.

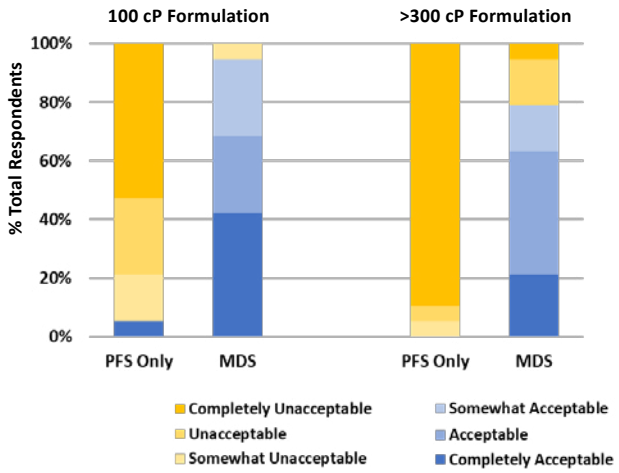

Figure 5: Comparison of injection force of PFSs without and with Congruence MDS.

USER STUDY TO CONFIRM CONGRUENCE MDS BENEFIT

In order to validate this benefit of the Congruence MDS, a user study was conducted with retina specialists. 20 retina specialists provided informed consent to participate in the study. The users were asked to inject two different formulations – one of 100 cP and one of greater than 300 cP. The injections were performed using a 1 mL long Gerresheimer TELC PFS with baked-on silicone using a 29G 13 mm needle – comparison was made between the same PFS and needle with and without the Congruence MDS. In each instance, the users were asked to quantify their acceptance of the force they had to apply in order to inject on a six-point scale – Completely Acceptable, Acceptable, Somewhat Acceptable, Somewhat Unacceptable, Unacceptable and Completely Unacceptable.

The results are summarised in Figure 5 and clearly show a near-universal acceptance of the Congruence MDS for both the formulations tested. In comparison, the PFS-only configuration was only acceptable to one of the users for the 100 cP injection and to none of the users for the 300 cP injection. Therefore, it is also no surprise that the Congruence device was highly preferred by participants.

Other key highlights from this user study on concerns with the PFS-only configuration were:

- One user indicated that they might only be willing to inject one 100 cP formulation per day with the PFS-only configuration due to the effort required.
- Several users raised patient safety concerns from the lack of stability experienced when injecting with the PFS-only configuration – for example, potential of the needle impacting the lens.
- Users who did manage to inject the 100 cP with the PFS-only configuration expressed concern about the length of time required to perform the injection.
- Most users could not even complete the 100 cP injection when injecting with the PFS-only configuration and none could with the >300 cP formulation.
- Injection force with the PFS-only configuration was so high that 26.3% of the users could not distinguish between the 100 cP and >300 cP formulations during the test.

SUMMARY

The approaches (with supporting data published) for injecting viscous formulations parenterally are varied and, thus far, there is no consensus solution to the challenges of high viscosity. Even then, the unique attributes of the eye mean that many of the potential solutions are not suitable for intravitreal delivery. However, a compact, mechanical, sterilisable device, such as the Congruence MDS, may enable comfortable injection of a viscous formulation into the eye using a fine-gauge needle. This requirement would be in addition to being able to deliver an accurate, precise microlitre volume dose.

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ABOUT THE COMPANY

Congruence Medical Solutions is an innovative drug delivery device solutions provider focused on development and supply of novel

drug delivery devices, including ophthalmic drug delivery devices. Congruence Medical Solutions has offices in Baltimore (MD, US) and Washington DC (US).

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PHARMACOKINETIC MODELS: INDISPENSABLE TOOLS FOR OPHTHALMIC DRUG DEVELOPMENT

In this article, Eva del Amo, PhD, Docent and Senior Researcher, DrugTech Research Community at the University of Eastern Finland, presents an overview of pharmacokinetic models for ophthalmic drugs, and discusses the value of these models for future drug development in the sector.

Financing in the global ophthalmic pharmaceutical sector has increased eightfold over the last 20 years, with an estimated value of US$42.1 billion (£31.4 billion) in investment by 2024.[1] Ophthalmic diseases can affect either the anterior segment of the eye, such as dry eye, allergy, infection, glaucoma and inflammation (e.g. conjunctivitis); or the posterior segment, such as age-related macular degeneration, diabetic retinopathy, retinal vein occlusion and neural changes induced by glaucoma. The prevalence of the posterior-affecting diseases is increasing in line with ageing populations, making retinal treatments a subject of particular interest. Such treatments are now being actively investigated in the pharmaceutical industry and academia, with a focus on new strategies to prolong and improve drug delivery to the retina.

Understanding the physiology of the eye and the relevant barriers to each route of administration and each type of drug (low molecular weight drugs (small drugs), biologics or controlled-delivery systems) is essential. The topical and intravitreal administration routes currently represent the gold standard for treatment of the anterior and posterior segments respectively (Figure 1).

Topical administration is the most common and least invasive route of ophthalmic administration, and patients can usually administer the drops themselves. However, eye drops require frequent administration during the day, and are only effective for treating illnesses of the anterior segment of the eye. Additionally, patient compliance is often low, especially for chronic indications such as glaucoma.[2]

Intravitreal injections are used to treat illnesses of the posterior segment of the eye. This is an invasive route but it is the only one that provides effective drug concentrations to the target tissue. In practice, neither topical nor systemic routes of administrations have proven to

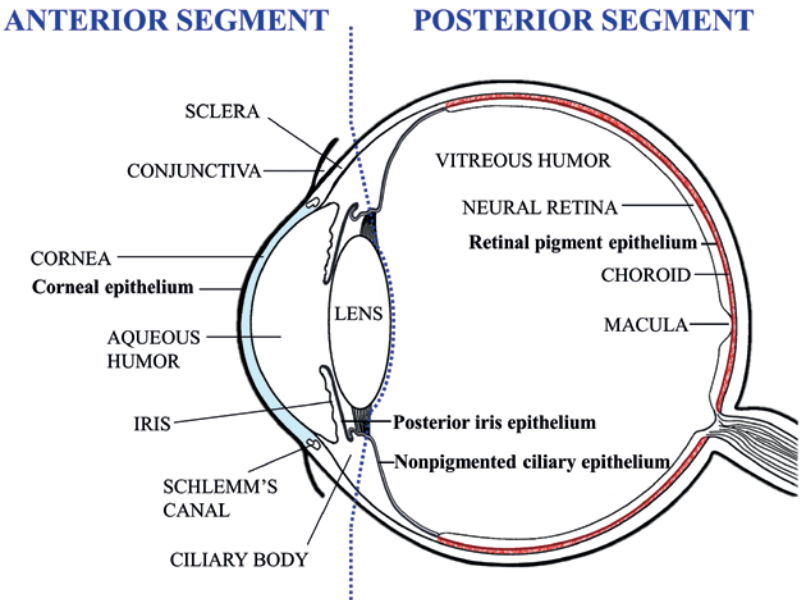

Figure 1: Graphical representation of the anatomy of the eye, with the tissues that contain tight junctions depicted in bold (excepting those in the ocular blood vessels).

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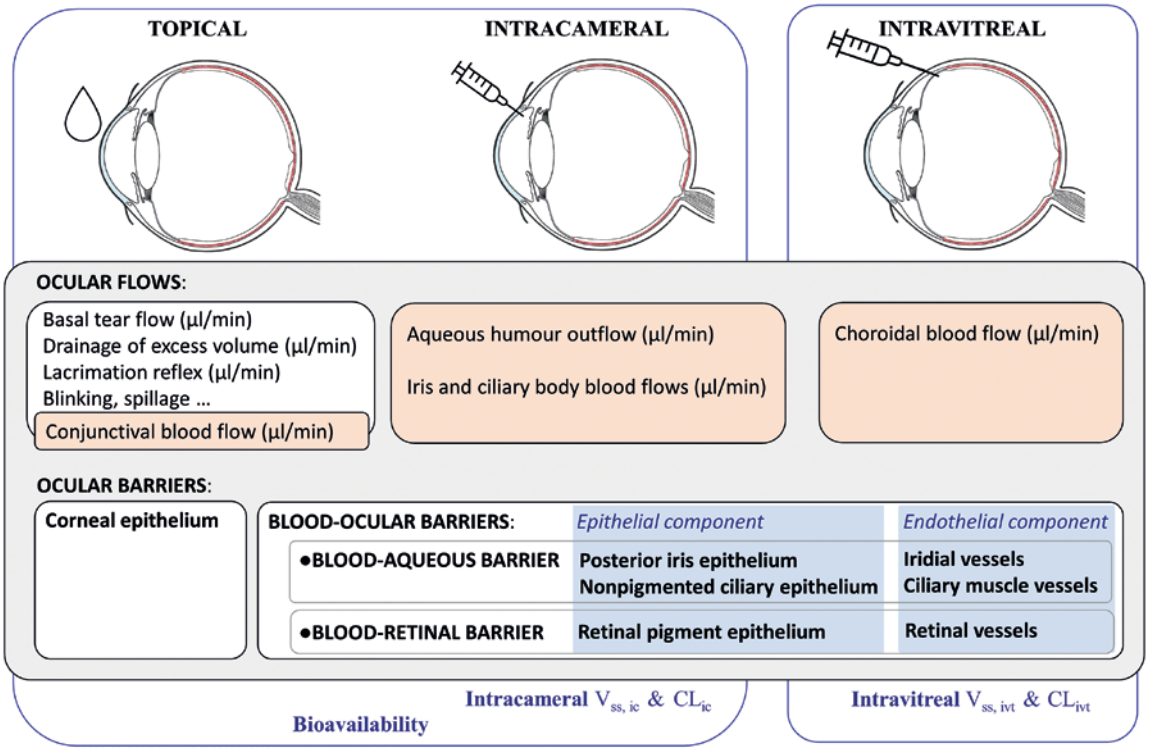

Figure 2: Topical, intracameral and intravitreal routes of administration, the ocular flows and barriers affecting the pharmacokinetics of small drugs, and the corresponding relevant pharmacokinetic parameters: intracameral (ic); intravitreal (ivt); volume of distribution (V_{ss}); clearance (CL).

be feasible alternatives. Topical administration does not ensure high enough drug concentrations at the back of the eye due to the anterior ocular barriers and flows, whereas systemic administration would require excessively high body-wide drug exposure in order to achieve a meaningful concentration of drug in the retina or choroid, because of the blood-ocular barriers (Figure 2).

> "New technologies aimed at prolonging the residence time of small drugs after intravitreal administration are currently being intensively investigated."

Typically, small drugs are applied topically, while biologics, such as ranibizumab (fragment antigen binding), aflibercept (soluble receptor) and the recent US FDA-approved faricimab (bispecific antibody), are intravitreally injected. Nevertheless, new technologies aimed at prolonging the residence time of small drugs after intravitreal administration are currently being intensively investigated (other areas of research include topical, intracameral and subconjunctival – between the conjunctiva and sclera – administration). Going forward, this article will focus on small drugs.

PHARMACOKINETICS

The importance of pharmacokinetics during drug design and development has been established for a long time. The primary cause of attrition of drug candidates in development in the 1990s was inadequate pharmacokinetics,[3] and today this still remains a challenge when moving into Phase I and II clinical trials.[4]

In simple terms, pharmacokinetics can be defined as what the body does to a drug: absorption, distribution, metabolism and excretion. The primary pharmacokinetic (PK) parameters are volume of distribution (V_{ss}, mL) and clearance (CL, mL/h). The V_{ss} is not a physiological volume but a theoretical volume that informs on the ability of the drug to permeate into the surrounding tissues and accumulate in them. The CL is the parameter that describes the efficiency of elimination of the drug from the body. These two parameters, in turn, determine the half-life ($t_{½}$, h) of the drug according to Equation 1:

$$t_{½} = \frac{Ln\ (2) \cdot V_{ss}}{CL}$$

For systemic drugs, the primary PK parameters are obtained after intravenous injection and their value range is well established.[5] For ocular drugs there are two possibilities, intravitreal or intracameral administration, both of which have limited data available.[6–10] The primary PK parameters can be related and explained by the physiological processes of the eye and are used to design dosage regimens, as well as to define PK models to simulate new data, such as for drugs incorporated in a delivery system.

For intravitreal administration, the blood-ocular barriers and the choroidal blood flow are the key physiological factors controlling the kinetics of these small drugs (Figure 2).

A few years ago, the most extensive and curated collection of primary intravitreal PK parameters of small drugs (40) and biologics (11) to date was published.[7] Based on this small drug set, a quantitative structure-property relationships (QSPR) model of intravitreal CL (CL_{ivt}) with good statistical values (R^2X and R^2Y over 0.5) was built, as shown by Equation 2:

$$LogCL_{ivt}\ (mL/h) = -0.25269 - 0.53747LogHD + 0.05189LogD_{7.4}$$

HD – Hydrogen bond donor capacity
$LogD_{7.4}$ – Logarithm of the octanol-water distribution coefficient at pH 7.4

This model enables the prediction of the CL_{ivt} of new drug candidates based on their HD and $LogD_{7.4}$, if the compound belongs to the same chemical space as the modelled drug set. Indeed, these properties correlate with drug permeability in biomembranes supporting the role of the blood-ocular barriers on CL_{ivt}.

"With knowledge of the primary PK values of a compound, PK simulations of intravitreal, intracameral, subconjunctival and topical drug delivery systems can be carried out."

Another process that may influence a drug's CL is metabolism. Metabolism in ocular tissues has only been sparsely studied. Recently, UEF DrugTech has published one of the most comprehensive ocular PK studies including the metabolism of four drugs (acetaminophen, brimonidine, cefuroxime axetil and sunitinib) and two administration routes (intracameral and intravitreal), wherein the concentrations of both parent drug and the main metabolite were analysed in six different ocular tissues.[8] It was observed that the impact of ocular metabolism on CL_{ivt} and intracameral CL (CL_{ic}) seems to be small, except in the case of drugs that are substrates of esterases. Therefore, it was concluded that CL_{ivt} and CL_{ic} are controlled by the ocular flows and barriers (i.e. by excretion rather than by metabolic processes), CL being permeability limited rather than perfusion limited.

Regarding $V_{ss,\ ivt}$, only a very narrow range of values was observed, those being typically one to two times the anatomical volume of the vitreous humour.[7] In UEF DrugTech's recent publication, the lipophilic sunitinib drug showed high partitioning to the surrounding ocular tissues after injection, with the highest $V_{ss,\ ivt}$ (3.73 mL) ever published, but still only 2.5 times higher than the volume of the vitreous humour.[8] The $V_{ss,\ ic}$ estimated for a narrow set of seven drugs showed a wider range – between two to five times the anatomical volume of the anterior chamber.[6,8–10]

DESIGN OF OCULAR DELIVERY SYSTEMS WITH PK TOOLS

With knowledge of the primary PK values of a compound, PK simulations of intravitreal, intracameral, subconjunctival and topical drug delivery systems can be carried out. Alternatively, QSPR-derived CL_{ivt}, and typical $V_{ss,\ ivt}$ values can be used when new intravitreal molecules are investigated, even before they are synthesised, as only the chemical structure is required to calculate the CL_{ivt}.[7]

The structure of these models is based on compartments or "building blocks" (where the drug is assumed to be well mixed and kinetically homogeneous) that are connected with drug flows (drug amount/unit of time). For example, the input flow into the "vitreal compartment" will be defined by the drug amount loaded in the delivery system and the release rate constant from the "formulation compartment", while the output flow will be specified by the amount of drug within the vitreal compartment, the volume of distribution and the clearance. Numerous simulations can be carried out to establish the relationships between drug dose, release rate, duration of action and target concentration. Depending on the drug potency (drug concentration required to ensure the desired therapeutic action in the target tissue), it is possible to estimate the required loading dose and make initial decisions, such as the practicability of the ocular formulation (e.g. ensuring the required dose is suitable for a 100 µL intravitreal injection).[7,11,12]

"The bioavailability of topical ophthalmic drugs is a key PK parameter that enables direct and quantitative comparison of the ocular exposure of topical drugs or formulations. However, this parameter is reported only for a few drugs."

For instance, the recently reported intravitreal and intracameral PK parameters of brimonidine[8] can be integrated into these models to guide the design of an intravitreal insert for a double action treatment for glaucoma:

1. Decreasing the intraocular pressure in the anterior segment (via the agonist effect on α2 adrenergic receptors), reducing the production of aqueous humour and increasing its outflow via the uveoscleral pathway.
2. Providing neuroprotective action to the posterior segment (optic nerve and retina).

These simulations provide brimonidine concentrations in vitreous and aqueous humour. By considering the dose, release rate constant and therapeutic levels, the reliable duration of a new therapeutic formulation can be estimated. These mathematical tools can advance the development of new ophthalmic formulations, not only for intravitreal administration but also for the intracameral, subconjunctival and topical routes.

Even though UEF DrugTech's recent study has shown that the role of ocular metabolism in drug CL seems to be of low impact (omitting esterase drug substrates),[8] one should observe the low levels of metabolites for all the investigated drugs. For this reason, ocular metabolite toxicity needs to be thoroughly investigated, especially when developing long-acting drug formulations.

BIOAVAILABILITY OF TOPICAL OPHTHALMICS

The bioavailability of topical ophthalmic drugs is a key PK parameter that enables direct and quantitative comparison of the ocular exposure of topical drugs or formulations. However, this parameter is reported only for a few drugs.[9,10,13] Bioavailability is calculated as the ratio of drug exposure in aqueous humour after the topical and intracameral administrations of the same drug, exposure (area under the concentration-time curve, $AUC_{0-\infty}$) being dose normalised, as shown in Equation 3:

$$Bioavailability = \frac{AUC_{0-\infty,\ topical} * Dose_{IC}}{AUC_{0-\infty,IC} * Dose_{topical}} * 100$$

Notice that, even though the aqueous humour is not the target tissue, it is the tissue that can be sampled and is therefore the one used for bioavailability calculations (similar to the plasma for systemic drugs). Bioavailability informs on the drug fraction absorbed and can be reliably compared across drugs to evaluate which one is the most penetrating. Nevertheless, more PK studies are required to calculate this parameter for more molecules. In particular, the number of published intracameral PK studies is limited, much more so than intravitreal ones, with only a few CL_{ic}, $V_{ss,\ ic}$ and $AUC_{0-\infty,\ ic}$ values reported in the literature[6,9,10] – in particular, the author recommends the literature review presented in Reference 6, excluding the ketorolac and flurbiprofen PK data (the aqueous

humour was sampled from the same animal). These PK studies are likely rare due to the difficulty of performing intracameral injections; however, they definitely yield relevant PK parameters for modelling, simulations and quantitating topical absorption data.

TRANSLATION FROM RABBIT TO HUMAN

Most of the ocular PK information available has been obtained from PK studies in rabbits, which is certainly the case for the data reported in this article. While one can easily argue the validity of the generated PK parameters due to the anatomical differences between the rabbit and the human eye, it is important to notice that models are defined by their purpose and are simplifications rather than exact replications of the system to model. A rabbit eye is not an exact replicate of a human eye but rabbit eyes can be used to predict ocular PK parameters in patients accounting for the key ocular physiological differences for the chosen administration route.

Namely, an extensive investigation on the available intravitreal PK data in humans was undertaken that compared the primary PK parameters between rabbits and humans for small drugs.[14] This is the recommended way of analysing the data, as primary PK parameters can be related to the physiology of the eye. Rabbit-to-human CL_{ivt} showed a positive correlation.[14] The appropriate scaling factor from rabbit-to-human CL_{ivt} for hydrophilic small drugs is expected to be approximately 1.4. On the other hand, for the rabbit-to-human $V_{ss,\ ivt}$, the scaling factor is closer to three due to the proportional difference between the vitreous anatomical volumes.[15,16]

More investigation is needed in this area, taking into account the different psychochemical properties of small drugs, other types of drug (i.e. biologics), administration routes and disease states. Nevertheless, these promising preliminary results are encouraging for using rabbits as a relevant ophthalmic PK animal model.

CONCLUSION

PK models and simulations can guide and inform us when navigating the significant uncertainties encountered during ocular drug development, guaranteeing a reliable drug- and route-specific framework for the design of drug delivery systems. The new data generated, PK parameters estimated and the translation factors established offer a solid foundation for future mechanistic models, such as physiologically-based pharmacokinetic (PBPK) models. In PBPK models, the compartments represent real anatomical spaces (tissue volumes) and the drug transfer is based on tissue blood flow, drug partition coefficients and clearances. PBPK models are much more demanding, requiring considerable *in vitro* and *in vivo* data for their construction. However, the payoff is greater too, with a greater capability for translating information from preclinical and clinical scenarios and enabling a deeper understanding of the physiological factors and disease effects on drug disposition. In conclusion, all these PK tools significantly benefit the development of ophthalmic drugs and formulations to treat ocular illnesses in both the front and back of the eye.

"PK models and simulations can guide and inform us when navigating the significant uncertainties encountered during ocular drug development, guaranteeing a reliable drug- and route-specific framework for the design of drug delivery systems."

ABOUT THE COMPANY

Based at the University of Eastern Finland, multidisciplinary research community Drug Discovery and Delivery (DrugTech) brings together experts from many pharmaceutical disciplines, medicine, chemistry and physics. DrugTech groups investigate basic science and technologies that are relevant in drug discovery and delivery. These investigations facilitate the development of new candidate drugs and delivery systems.

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