OPHTHALMIC DRUG DELIVERY

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OPHTHALMIC DRUG DELIVERY

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EDITORIAL CALENDAR

Feb 2018 Prefilled Syringes & Injection Devices
Mar Skin Drug Delivery: Dermal, Transdermal & Microneedles
Apr Pulmonary & Nasal Delivery
May Injectable Delivery: Devices Focus
Jun Connecting Drug Delivery
Jul Novel Oral Delivery Systems
Aug Industrialising Drug Delivery Systems
Sep Wearable Injectors
Oct Prefilled Syringes & Injection Devices
Nov Pulmonary & Nasal Delivery
Dec Connecting Drug Delivery
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SUSTAINED RELEASE OCULAR THERAPEUTICS

In this article, Michael O'Rourke, President and Founder of Scotia Vision Consultants, gives an overview of the current state of the ophthalmics market, going into greater detail on the opportunities offered in the area of sustained-release technologies and therapies.

INTRODUCTION

The ophthalmic pharmaceutical market is projected to grow from an estimated US$24.5 billion (£18.3 billion) to $28.9 billion by 2022, with retina being the most significant sector, growing to $13.9 billion (Figure 1).

In the majority of cases, retinal diseases, including wet age-related macular degeneration (w-AMD), continue to be treated by intravitreal injections (IVT), with an estimated 22.3 million procedures performed in 2017 (Figure 2). Despite the reliably successful treatment provided by this delivery route, the necessity of monthly to bi-monthly injections remains a challenge for patients. Additionally, complications potentially may occur, the most serious (but rarely occurring) of which include endophthalmitis,[1] cataract, retinal detachment and vitreous or choroidal haemorrhage.[2]

At present, within the glaucoma segment, an estimated $5.3 billion market by 2022, approved therapeutics are delivered almost exclusively by the topical route. Topical therapy also has delivery challenges, however, with patient compliance being the most common issue. In interviews with patients and their doctors, 95% of patients claim to take every drop; doctors think 80% of patients are compliant; but in reality, patients are only taking drops 70% of the time.[3]

Therefore, given the current state of affairs within these multi-billion dollar segments, there are clear opportunities for new delivery approaches through sustained release drug delivery technologies.

SUSTATINED RELEASE TECHNOLOGIES

> "Despite the challenges, there is an intense development effort underway across the industry to bring new technologies to the market."

IVT agents have to date demonstrated that sustained release implantable technology is not, in and of itself, a prerequisite for commercial success, but that the sustained clinical efficacy of the drug is critical.

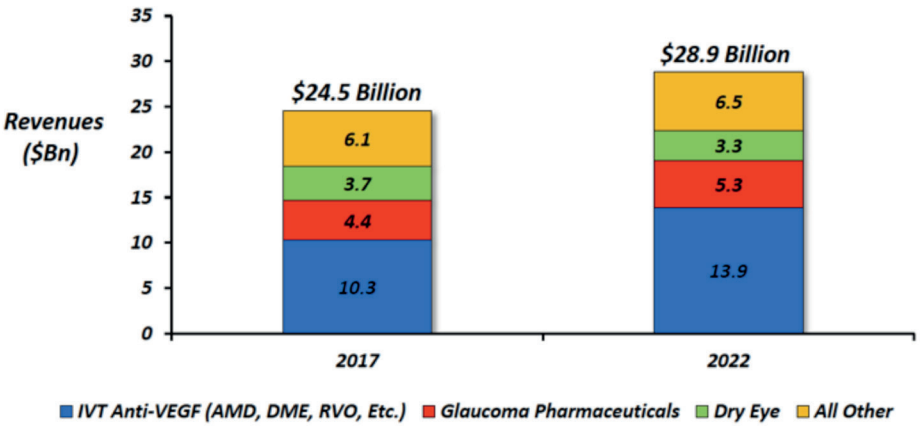

Figure 1: Global ophthalmic pharmaceutical market revenues by speciality. Courtesy of Dave Harmon, Market Scope estimates 2017.

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However, the market potential for sustained release versions of current anti vascular endothelial growth factor (anti-VEGF) products is significant, and this situation is changing with a significant effort being made to deliver large molecules – i.e. biologics (including proteins, peptides and aptamers).

Developing and achieving global regulatory approval for new sustained-release intraocular technologies is still relatively rare in ophthalmology. Only four have been approved to date:

- Vitrasert (ganciclovir), 1995, for CMV Retinitis, non-biodegradable, 4-6 months delivery.
- Retisert (fluocinolone acetonide), 2005, for posterior non-infectious uveitis (PNIU), non-bio degradable, 30 months delivery.
- Ozurdex (dexamethasone), 2007, for macular oedema after branch retinal vein occlusion or central retinal vein occlusion, PNIU, with several months estimated delivery.
- Iluvien (fluocinolone acetonide), 2012, for diabetic macular oedema in patients who have previously been treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

However, despite the challenges, there is an intense development effort underway across the industry to bring new technologies to the market. In a recent analysis (Table 1) there were at least 15 novel technologies in preclinical or later-stage development for w-AMD and diabetic eye disease, 19 for glaucoma and, if we consider anterior sustained release systems, at least nine technologies covering a range of target indications including the emerging segment of sustained delivery targeting dry eye. Of note, however, is the corresponding approximate number of therapeutics (preclinical to Phase III) in development in the absence of any drug release technology: 69 therapeutic development programmes

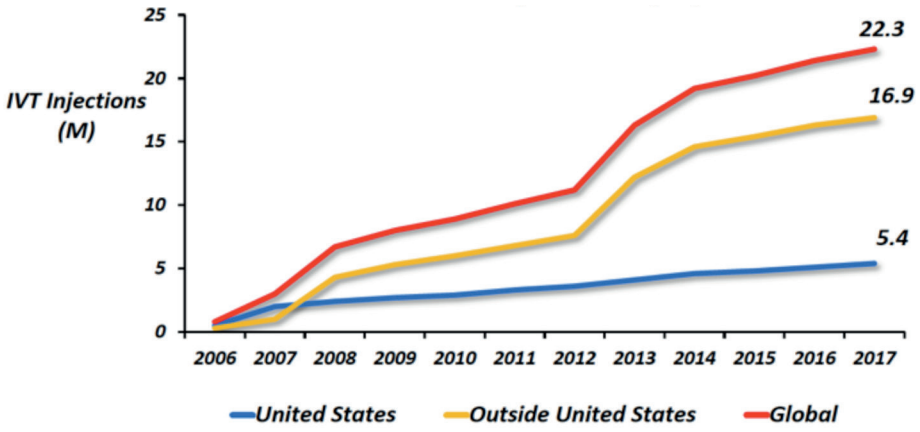

Figure 2: Global anti-VEGF injections. Courtesy of Dave Harmon, Market Scope estimates 2017.

Segment	Sustained Release Technology	New Product Development
Glaucoma	19	6
Retina	15	69
• wet AMD		• 30
• dry AMD		• 12
• DME		• 23
• ME		• 4
Posterior Uveitis	1	13
Anterior	9	50
• Dry Eye		• 17
• Anterior Uveitis		• 4
• Post Cataract Inflammation		• 4
• Infection		• 4
• Presbyopia		• 2
• Allergy		• 2
• Blepharitis		• 2
Orphan	–	15
Gene Therapy	–	12
Stem Cell	1	4

Table 1: Drug delivery and new product development in the ophthalmic sector.[4]

"There has been no sustained release, ocular delivery system approved to date that incorporates a new chemical entity, in part due to the elevated risk and expense of achieving success with the combination of both a new technology, with its physical characteristics, and a novel drug product, with its own chemical and pharmacokinetic properties."

just within the field of retina alone, at least six in glaucoma and at least 50 in the anterior segment.

From a development perspective these numbers appear reasonable. The four systems that have approved to date have incorporated generic drugs (i.e. steroids and an anti-viral). There has been no sustained release, ocular delivery system approved to date that incorporates a new chemical entity, in part due to the elevated risk and expense of achieving success with the combination of both a new technology, with its physical characteristics, and a novel drug product, with its own chemical and pharmacokinetic properties. The approach so far has been to increase the chances of success by working with a well-documented and approved drug. However, that is expected to change in the future and we are already witnessing this in some early-stage glaucoma programmes.

Of particular note is the wide range of technologies and methods being considered for drug release systems – to name but a few:

- Refillable drug reservoirs
- Photocrosslinking technology with UV light for both small and large molecules
- Microparticle and nanoparticle systems for w-AMD, glaucoma (including neuroprotection) and potentially the anterior segment for dry eye and corneal disease
- Prostaglandin analogue delivery systems for ocular hypertension and open-angle glaucoma
- Topical semifluorinated alkane delivery, enhancing drug solubility and ocular surface retention for anterior and posterior segment applications
- Proprietary hydrogel technology
- Suprachoroidal delivery or implants, including injectable suspensions
- Injectable polymer-based protein delivery systems
- Topical peptides for neovascular AMD and corneal injuries
- Contact lens delivery systems
- Iontophoresis.

CONCLUSION

In summary, the opportunity for future development in sustained release technology remains a multi-billion dollar prospect. Some of the greatest (and most challenging) possibilities include sustained release delivery (three months minimum, four to six months optimal) of large molecules (proteins, peptides, aptamers) for retinal diseases, thus avoiding frequent injections, and prolonged release of therapeutics for glaucoma. The future for sustained release ocular drug delivery lies in reducing the treatment burden, with innovations in delivery technology, biologics delivery, targeting gene therapy to the appropriate cell types and combining effective small-molecule therapeutics with the appropriate drug delivery system. Reimbursement, patient compliance and convenience will be the key driver for drug delivery. However, in addition to just compliance, a demonstration of enhanced efficacy and compelling pharma economics for a new product may be essential if the delivery technology is to achieve a competitive advantage and commercial success.

ABOUT THE AUTHOR

Michael O'Rourke is the President and Founder of Scotia Vision, a specialised ophthalmic consulting company with extensive expertise in global ocular drug delivery commercial and product development strategies. Mr O'Rourke has over 30 years drug delivery experience across ophthalmology, periodontal and pulmonary markets in sales, marketing, product launch, strategy development and global commercialisation. In addition to multiple Scotia Vision clients, his career experience includes several leading global organisations and start-ups, including 3M, Alza, Chiron Vision, Bausch + Lomb, GrayBug Vision, and Re-Vana Therapeutics.

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USING PHYSICAL FORCES TO ENHANCE OCULAR DRUG DELIVERY

Di Huang, PhD Candidate, Erica Chen, PhD, Postdoctoral Research Fellow, and Ilva Rupenthal, PhD, Senior Lecturer and Director, all of the Buchanan Ocular Therapeutics Unit of the University of Auckland, discuss the possibilities offered by physical force-based methods of enhancing the efficacy of ophthalmic drug delivery by providing a way past the eye's natural barriers.

This piece reviews a 2017 article the authors published in *Advanced Drug Delivery Reviews*.[1]

INTRODUCTION

Delivering therapeutics to specific sites in the eye whilst also achieving effective drug concentrations is a difficult task, due to a number of inherent anatomical and physiological ocular barriers, including the cornea, the sclera, Bruch's-choroid complex and the blood-retinal barrier. These barriers not only protect the eye from invasion by foreign substances, but also regulate the intraocular milieu, which is essential for the eye's physiological function. However, these barriers also pose a major obstacle to efficient drug delivery, overcoming which remains a major challenge to improve ocular drug bioavailability, with various strategies having been investigated over recent decades.

Formulation-based approaches include chemical penetration enhancers, prodrugs and drug delivery carriers such as liposomes and nano- or microparticles able to penetrate the ocular barriers. Physical force-based methods, initially utilised in transdermal drug delivery, generally require a power-driven physical device to deliver energy to the barriers, thereby enhancing transient drug transport. Compared with formulation-based approaches, physical force-based strategies may allow greater control over the drug dosage whilst also offering the possibility to record parameter information. Here follows a brief overview of physical methods (Figure 1), including iontophoresis, sonophoresis and microneedles, which can enhance drug penetration by transiently disrupting the ocular barriers in a minimally or non-invasive manner.[1]

> "Compared with formulation-based approaches, physical force-based strategies may allow greater control over the drug dosage whilst also offering the possibility to record parameter information."

IONTOPHORESIS

Iontophoresis, application of a low-intensity electrical current, enhances drug delivery across biological membranes by causing electrorepulsion and electro-osmosis of the drug molecule.[2,3] Electrorepulsion primarily applies to the movement of ionic drugs,[4] while electro-osmosis can enhance the transport of both neutral and charged molecules by convective solvent flow.[5] The relative contribution of electrorepulsion and electro-osmosis depends on both the physicochemical characteristics of the drug (e.g. size, charge and charge to molecular-weight ratio) and the electrical properties of the biological membrane. Iontophoretic permeability enhancement of small, charged molecules is mainly governed by electrorepulsion, along with a minor contribution by electro-osmosis, whereas for macromolecules the mechanism is highly dependent on the charge to molecular-weight ratio.

The basic design of ocular iontophoretic devices consists of a power source and two electrodes: the donor electrode (an ocular applicator or eye cup) and the

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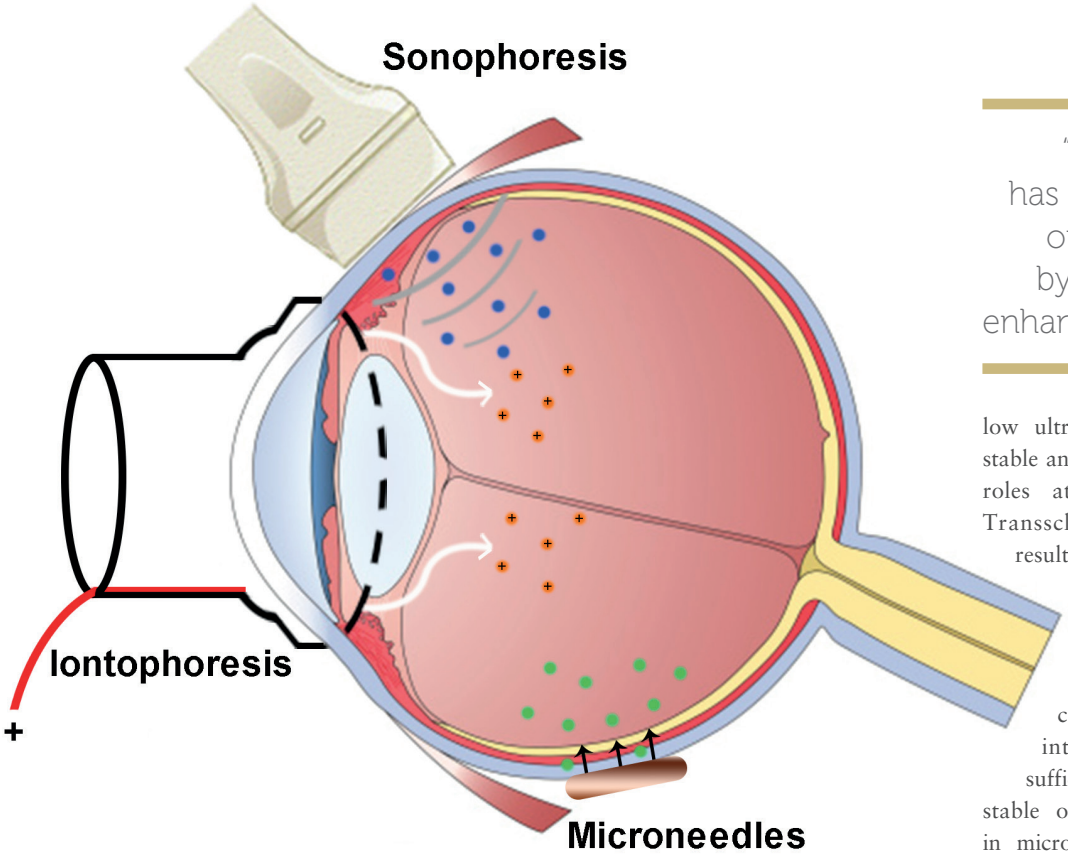

Figure 1: Overview of physical force-based methods for ocular drug delivery enhancement.

"The basic design of ocular iontophoretic devices consists of a power source and two electrodes: the donor electrode and the return electrode. The drug is filled into the applicator and the return electrode is placed on the forehead to form an electrical circuit."

return electrode. The drug is filled into the applicator and the return electrode is placed on the forehead to form an electrical circuit. The EyeGate® II Delivery System (EyeGate Pharma, MA, US), an annular shaped silicone probe with a 0.5 cm^2 contact area and a 13 mm inner diameter used for transscleral iontophoresis, for example, is currently being investigated in a number of clinical trials for delivery of a sustained release dexamethasone formulation (EGP-437) in the treatment of anterior uveitis, dry eye and macular oedema, as well as for prevention of ocular inflammation in patients who have undergone cataract surgery.

SONOPHORESIS

Sonophoresis, also called ultrasound, involves the application of a sound field at frequencies higher than 20 kHz to improve drug transport across biological membranes, including ocular barriers.[6] It has been utilised in the field of ophthalmology for decades but primarily as a diagnostic imaging tool.[7] However, therapeutic ultrasound has recently emerged as an option to treat glaucoma by cyclocoagulation[8] or to enhance ocular drug uptake. The mechanisms for ultrasound enhanced drug delivery take into account non-thermal (e.g. cavitation, acoustic streaming and mechanical stress) and thermal effects with ultrasound parameters, co-administration of microbubbles and drug characteristics, all having an effect on delivery efficacy. Cavitation is generally considered the predominant factor for enhanced drug delivery and is defined as the formation of microbubbles due to an acoustic pressure gradient within the coupling medium. Continuous pulsation of cavitation microbubbles over many pressure cycles without any collapse is considered stable cavitation, while the growth and collapse of microbubbles within a few pressure cycles is associated with inertial cavitation.

Corneal permeability enhancement is generally a result of stable cavitation at

"Therapeutic ultrasound has recently emerged as an option to treat glaucoma by cyclocoagulation or to enhance ocular drug uptake."

low ultrasound intensities, whereas both stable and inertial cavitation play important roles at higher ultrasound strengths.[6] Transsclerally applied ultrasound results in the formation of transport channels and the modification of the proteoglycan fibre morphology, without significantly disturbing the collagen network. Here, low intensity ultrasound produces sufficient acoustic pressure to generate stable oscillating microbubbles, resulting in microstreaming with higher intensities being required to achieve inertial cavitation.[9] Due to the sensitivity of the ocular tissues, it is incredibly important not to sacrifice patient safety, even if doing so could potentially achieve greater treatment efficacy. The eye's temperature increase due to absorption of sound waves is of particular concern; the thermal safety requirements for diagnostic ultrasound allow a maximum temperature increase of 1.5 °C.

The majority of studies published to date have investigated transcorneal ultrasound in combination with microbubbles; however, a limited number of studies also exist on the application of ultrasound for enhanced drug delivery to the posterior segment of the eye. Recently, transscleral ultrasound has also been combined with the use of nanocarriers, in order to enhance the vitreous diffusion and retinal permeability of peptide loaded nanoparticles following intravitreal injection, thus achieving higher retinal drug concentrations.[10] However, so far, there has been no evidence that ultrasound can enhance retinal permeability upon extraocular administration in large animal models or humans.

MICRONEEDLES

Microneedles (MNs) are micrometre sized needles, or arrays of such, fabricated by adapting microelectronics tools. Applying MNs to biological membranes can create tiny transport pathways, thereby allowing drugs to permeate across these barriers. To

date, numerous MN fabrication approaches have been utilised, resulting in a variety of shapes, sizes, materials and configurations.[11]

According to their delivery mechanism, ocular MNs can be categorised into four types:

1. Solid MNs, able to create micropores in the ocular surface through which therapeutics can diffuse after MN removal.
2. Drug-coated MNs, with the drug coating dissolving and diffusing into the eye after insertion.
3. Dissolving MNs, which disintegrate over time, thus releasing the matrix encapsulated drug into the ocular tissues.
4. Hollow MNs, able to infuse pressure-driven liquid drug formulations.

Enhanced drug delivery into the cornea and anterior segment of the eye can be achieved by insertion of MNs across the corneal epithelium, the main barrier to penetration encountered after topical eye drop administration, to deposit drugs directly into the corneal stroma. Solid stainless steel MNs, coated with different compounds ranging from small drugs to macromolecules, were inserted into rabbit corneas *in vivo* providing up to 60-fold higher bioavailability compared with the topically administered drugs.[12] However, *in vivo* application is still challenging due to the corneal curvature and lack of a supporting pressure during MN insertion.

Various polymeric MNs have found great use in intrascleral drug delivery. Unlike solid or hollow MNs, dissolving MNs minimise accidental retinal damage, whilst also remaining as a depot for sustained drug delivery. Thakur, *et al*,[13] developed a simple and cost-effective mouldcasting method for fabrication of rapidly dissolving MNs, using polyvinylpyrrolidone, which efficiently penetrated the outer scleral layers, thus enhancing intrascleral permeation of macromolecules.

Currently the most advanced ocular MN application includes drug delivery into the suprachoroidal space, a potential space between sclera and choroid. Drug solutions injected into this space can flow circumferentially around the eye, with suspensions of particles up to 1 µm having been successfully delivered into the suprachoroidal space of rabbit, pig and human eyes.[14] Clearside Biomedical (GA, US) initially evaluated the efficacy of suprachoroidal delivery using hollow MNs for the treatment of acute posterior segment uveitis by injecting triamcinolone acetonide into the suprachoroidal space of living pigs.[15] The company subsequently completed a Phase II clinical trial to determine the safety and efficacy of suprachoroidally administered, proprietary, non-preserved triamcinolone acetonide (Zuprata™) via 1000 µm long MNs in subjects with macular oedema associated with non-infectious uveitis. Currently participants are being recruited for a Phase III study for further efficacy evaluation. Clearside Biomedical also completed a Phase II clinical trial in subjects with macular oedema following retinal vein occlusion and is currently investigating suprachoroidal application of a small tyrosine kinase inhibitor (Axitinib™) in the treatment of wet age-related macular degeneration.

CONCLUSION

Safe and effective treatment of ocular diseases is a challenging task due to the presence of various protective ocular barriers and elimination mechanisms. A vast number of novel strategies have been utilised to overcome these barriers and improve drug delivery to the target site, thereby enhancing drug bioavailability and avoiding potential side effects. The enhancement of drug permeability, ease of application and minimally or non-invasive delivery characteristics render physical force-based methods an exciting option for the treatment of both anterior and posterior segment disorders.

Iontophoresis is the most extensively investigated approach among these physical techniques so far, with numerous therapeutic agents (such as low molecular weight drugs, macromolecules and nanocarriers) already having been successfully delivered to various ocular tissues. Although the number of studies on ultrasound and MN mediated ocular drug delivery is still limited, both have specific advantages, including site-specific drug delivery to the ocular tissues as well as the possibility to combine them with sustained release particles. Further *in vivo* studies are required to understand the contribution of dominant mechanisms, optimise device design and parameter settings, and evaluate the feasibility and safety of repeated and long-term application of such methods in the clinical setting.

ABOUT BOTU

The Buchanan Ocular Therapeutics Unit aims to translate ocular therapeutic related scientific research into the clinical setting, whether pharmaceutical, cell or technology based. Projects include the development of stimuli-activated systems investigating implants responsive to ultrasound, light or a small electrical current. Dr Rupenthal's team, including five PhD candidates

ABOUT THE AUTHORS

Di Huang obtained a BSc in Pharmacy from Central South University in Changsha, China (2011) and an MSc in Pharmaceutics from Sun Yat-sen University in Guangzhou, China (2014), which focused on transscleral ultrasound for protein loaded nanoparticle delivery. She has been a PhD student within the Buchanan Ocular Therapeutics Unit since 2015 and is currently investigating ultrasound-mediated delivery of peptide-loaded nanoparticles for efficient treatment of diabetic retinopathy.

Dr Erica Chen is a postdoctoral research fellow within the Buchanan Ocular Therapeutics Unit and the co-supervisor of Di Huang's PhD project. Dr Chen obtained a BPharm from Kaohsiung Medicine University, Taiwan (2004) as well as a Postgraduate Diploma in Pharmaceutical Sciences (2008) and a MHSc (2009) from the University of Auckland, New Zealand. In 2014, she completed her PhD investigating intravitreal peptide delivery for the treatment of optic neuropathies.

Dr Ilva Rupenthal is a Senior Lecturer in the Department of Ophthalmology, University of Auckland, and the inaugural Director of the Buchanan Ocular Therapeutics Unit established in 2013. She currently also holds a Sir Charles Hercus Health Research Fellowship and received the 25th Anniversary Emerging Researcher Excellence Award from the Health Research Council of New Zealand in 2016. Dr Rupenthal is an author on over 50 peer-reviewed journal articles and has attracted over NZ$5 million in research funding.

and two postdoctoral research fellows, is also investigating other ocular therapeutics in the area of dry eye, diabetic retinopathy and age-related macular degeneration management.

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NOVALIQ

Transforming Ocular Therapeutics

OVERCOMING THE CHALLENGES OF OPHTHALMIC DELIVERY USING AQUEOUS-FREE TECHNOLOGY: REDEFINING DRY EYE DISEASE

Traditional aqueous vehicles for topical ophthalmic medications suffer from a number of limitations. In this article, Christian Roesky, PhD, Chief Executive Officer and Managing Director, Novaliq, reviews the benefits of EyeSol®, a proprietary aqueous-free drug delivery technology, and findings from preclinical and clinical trials of marketed and investigational EyeSol®-based products.

Topical eye drops are the mainstay of therapy for many ocular diseases, but features of existing aqueous-based formulations create issues that can limit a product's efficacy and safety. The typical dispensed drop size of an aqueous-based ophthalmic preparation is 40-50 µL. This large volume exceeds the eye's external reservoir capacity, resulting in spill-over. The high surface tension of an aqueous-based drop further hinders its spreading on the ocular surface. In addition, the application of an aqueous-based eye drop can activate the defence mechanism of the eye, causing rapid blinking after instillation and tear secretion. Taken together, these factors reduce a drug's residence time and contribute to the low bioavailability of conventional topical ophthalmic medications, which is reported to be as low as 3-4%.[1]

> "As Novaliq advances its product development portfolio, it has the potential to redefine dry eye disease."

Another limitation of using aqueous-based formulations as a topical drug delivery platform relates to the fact that up to 60% of today's new chemical entities are lipophilic compounds or large molecules with poor water solubility.[1] The addition of oils and/or surfactants into aqueous-based formulations is a common strategy used to address this problem, but the presence of these agents can lead to visual disturbance and tolerability issues. Tolerability can also be affected by preservatives that must be included in aqueous-based ophthalmic products that are packaged in conventional multi-dose containers.

DISRUPTIVE DRUG DELIVERY TECHNOLOGY

Novaliq, a German speciality pharma company, has developed EyeSol®, a proprietary, aqueous-free platform that overcomes the aforementioned issues. Novaliq is leveraging this disruptive technology in an extensive development programme to create innovative products that address unmet needs in ophthalmology and, as the company advances its product development portfolio, it has the potential to redefine dry eye disease.

EyeSol® is the first and only aqueous-free technology for ocular drug delivery. Therefore, it is distinguished from aqueous based technologies by a host of physical characteristics that translate into enhanced stability, bioavailability, efficacy and tolerability (Figure 1).

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	Water-based Technologies	EyeSol®
Drop Size	Ca. 40-50 µL (Blink reflex activated)	<12 µL (Blink reflex not activated)
Bioavailability	Bioavailability topical formulations: 1-10%	Up to 4x higher
Drug residual time	Reduced to 3-5 min due to blink reflex	No rapid blink reflex at instillation
API Solubility	75% of NCEs are poorly soluble	Enables lipophilic drugs and biologicals
Spreading	High surface tension hinders spreading	Reduced vision impairment, less "spill-over"

Figure 1. Comparison of aqueous-based and aqueous-free EyeSol® drug delivery technologies.

EyeSol® is based on specific semi-fluorinated alkanes (SFAs). These compounds have the same refractive index as water and are transparent, inert, non-toxic, amphiphilic liquids that are able to formulate lipophilic and large molecules, such as biologic agents. Because they have very low surface tension and viscosity, SFAs dispense as a low volume drop (<12 µL) that does not stimulate blinking or reflex tearing. Having both low surface tension and low interface tension, EyeSol® products spread rapidly over the ocular surface and form a flat, transparent monolayer that enables clear vision without blurring. Because of their amphiphilic nature, EyeSol® products also interact with tear film lipids and have been shown to stabilise and restore the tear film (Figure 2).

Being aqueous-free, EyeSol® products avoid hydrolytic and oxidative reactions that can degrade active pharmaceutical ingredients, thus improving product stability. In addition, the aqueous-free EyeSol® technology platform does not support microbial growth, therefore allowing manufacturing of preservative-free formulations in multi-dose containers. It also avoids the tip clogging that can occur with suspensions.

> "Only about 2 million people with DED are being treated due to limited treatment options and a lack of robust non-contact diagnostics."

DRY EYE DISEASE

Dry eye disease (DED) is a very common disorder estimated to be diagnosed in more than 16 million adults in the US alone.[2] However, only about 2 million people with DED are being treated due to limited treatment options and a lack of robust non-contact diagnostics. Tear supplementation with ocular lubricants (artificial tears), with or without lipid-containing agents, remains the cornerstone of DED therapy. Such products primarily address aqueous deficiency in the tear film, and although they effectively improve comfort, they have not demonstrated a curative therapeutic effect.

A large majority of people with DED have evaporative disease, most often caused by Meibomian gland dysfunction (MGD).[3] These patients require both prevention of tear film hyperevaporation and improvement of Meibomian gland function.

TIERED FAMILY OF PRODUCTS

Novaliq's EyeSol®-based pipeline addresses this multifactorial disease across its clinical spectrum (Figure 3, next page). The core focus is DED, for which Novaliq has a tiered family of products that targets the spectrum of this condition's subtypes and severity.

NovaTears®, the first DED product from Novaliq, is a preservative free, surfactant free, non-aqueous, non-blurring formulation that particularly targets evaporative DED. Containing perfluorohexyloctane as its only ingredient, NovaTears® is the first eye lipid layer stabiliser. Marketed in Germany since October 2015, this innovative product has demonstrated clinical efficacy and safety in four clinical trials and has sold more than one million units. It is being launched in other European countries with reimbursement, as well as in Australia and New Zealand.

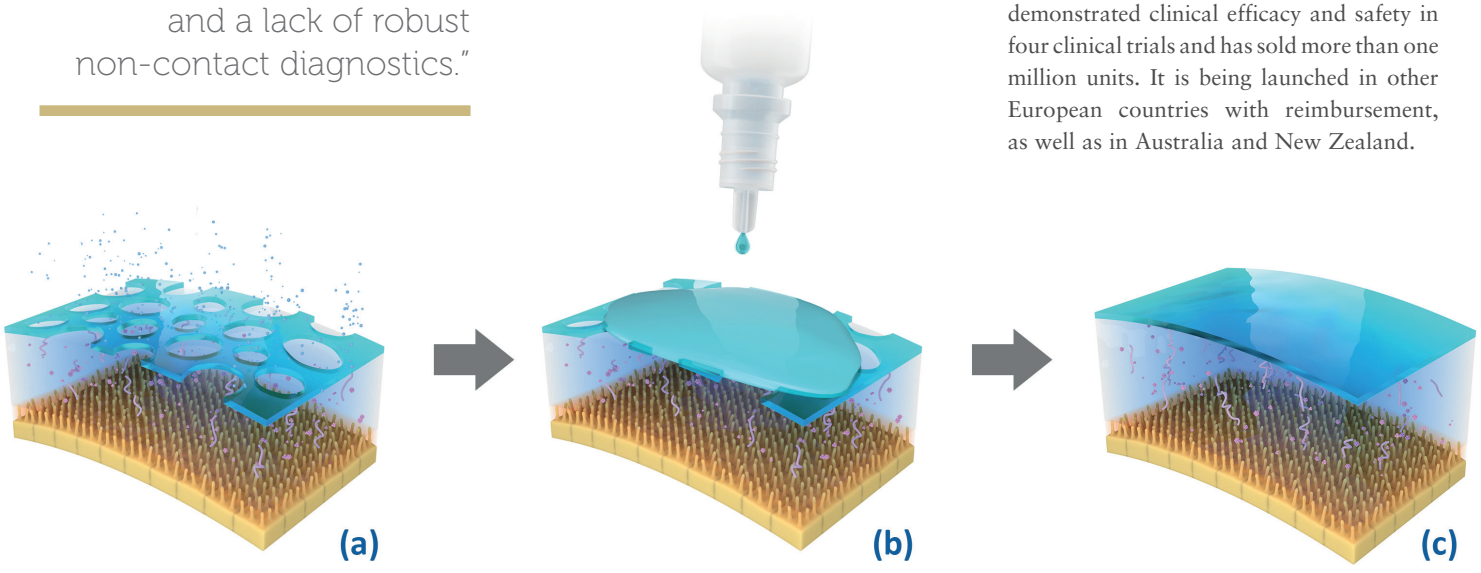

Figure 2: In dry eye, the tear film is unstable and breaks up rapidly (a). A single EyeSol® drop spreads rapidly across the cornea (b), restoring a smooth, uniform tear film layer (c). Image courtesy of Novaliq.

Dry Eye Disease Product Family

Product/ Program	Indication	Region	Disc.	Pre-clinic	Phase I	Phase II	Phase III	Reg.	Market
NovaTears® (NOV01)	Dry Eye, mild – moderate	EU/Med. Dev.							2015
NovaTears® +Omega-3	Dry Eye, mild – moderate	EU/Med. Dev.							2017
CyclASol® (NOV02)	Dry Eye, moderate – severe	US/EU						FPFV, Nov 2017	
NOV03	Dry Eye, evaporative, MGD*	US/CN/JP						IND granted, Nov 2017	
NOV07	Dry Eye, ocular pain, anti-inflamm.	US/EU					Successful pre-IND, Dec 2017		

Glaucoma & Retina Development Programs

Product/ Program	Indication	Region	Disc.	Pre-clinic	Phase I	Phase II	Phase III	Reg.	Market
NOV04	Glaucoma	Global							
NOV05	Retinal Diseases (Topical)	Global							
NOV06	Retinal Diseases (Back of the Eye)	Global							

Figure 3: Novaliq's pipeline has a major focus on dry eye disease, but it is also targeting other ocular diseases with unmet therapeutic needs.

In a six week, prospective, non-interventional clinical trial (NT-001), in patients with mild to moderate hyper-evaporative DED, NovaTears® four times daily was safe and effective for improving DED-related objective signs and subjective symptoms.[4] Statistically significant improvements from baseline were achieved in four of five outcome measures, including a clinically meaningful and dramatic decrease in the Ocular Surface Disease Index (OSDI) score from 55.0 at baseline to 34.3 at six weeks. Mean tear film breakup time (TFBUT) also improved significantly, reflecting increased tear film stability, as did mean scores for Schirmer 1 testing and corneal fluorescein staining (CFS).

A recent clinical trial (NT-004) showed statistically significant increases in total tear film and lipid layer thickness among patients with mild to moderate DED who used NovaTears® for four weeks.[5] These tear film improvements were documented with high-resolution optical coherence tomography (OCT) images acquired in the morning, before patients used their first daily dose.

A third clinical trial (NT-002) was designed to specifically investigate NovaTears® as treatment for DED related mild to moderate MGD.[6] Its results were consistent with those of the earlier study and showed benefits relating to Meibomian gland function. Specifically, patients using NovaTears® four times daily, as directed, for six to eight weeks achieved statistically significant improvements in OSDI, TFBUT and corneal and conjunctival fluorescein staining. In addition, improvements were seen in meibum quality and quantity (Figure 4), and there was a statistically significant increase in the number of expressible Meibomian glands reported.

> "It is known that NovaTears® is able to dissolve lipids and, in an animal model using radiolabelled product, it was shown to distribute into the Meibomian glands after instillation onto the ocular surface."

The improvements related to MGD are explained by the ability of NovaTears® to penetrate into and subsequently liquify the meibum within the Meibomian glands. It is known that NovaTears® is able to dissolve lipids and, in an animal model using radiolabelled product, it was shown to distribute into the Meibomian glands after instillation onto the ocular surface.[5]

Based on these new insights, Novaliq is pursuing regulatory approval of NovaTears® as a prescription medication in the US. SEECASE, a Phase II randomised, controlled, double-masked clinical trial, is now underway (NCT03333057). The study has a planned enrolment of 300 patients, and topline results are expected in the second half of 2018.

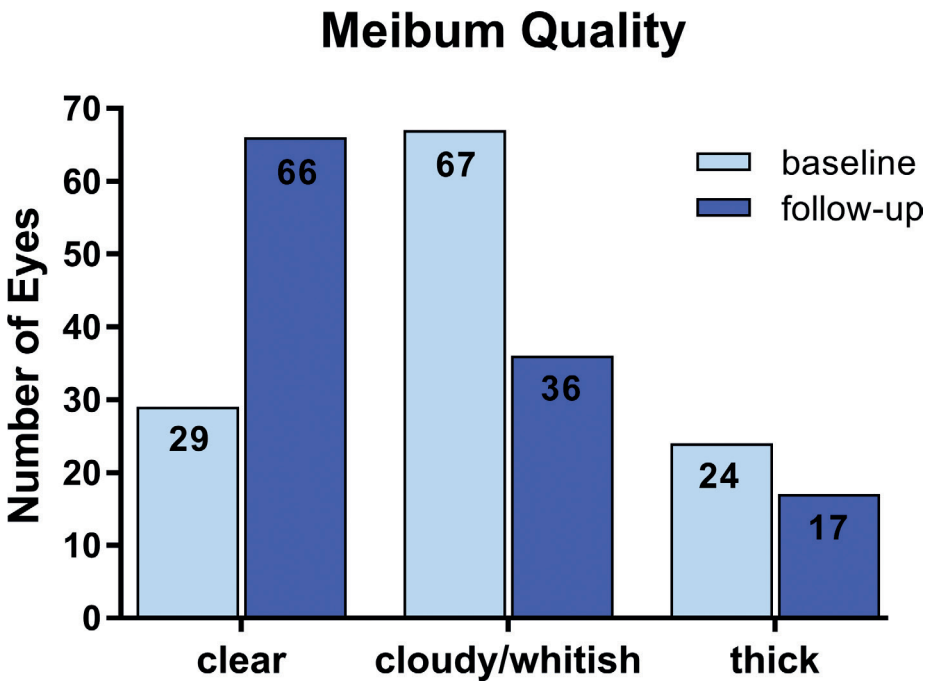

Figure 4: Findings from assessments of meibum quality at baseline and follow-up show improvement in patients with mild to moderate MGD who used NovaTears® for 6 to 8 weeks.

In addition, the NovaTears® line was recently extended when Novaliq received CE Mark for NovaTears®+Omega-3. Omega-3 fatty acids are considered to have a role in DED management because they have anti-inflammatory effects, and there is also evidence from *in vitro* studies that they affect the quality and quantity of intracellular lipids produced by Meibomian gland epithelial cells.[7,8]

For patients with moderate to severe DED with an inflammatory component, Novaliq is developing CyclASol® (0.1% cyclosporine A in perfluorobutylpentane) as a novel treatment for improving both signs and symptoms. Commercially available topical immunomodulatory treatments that target the etiological role of ocular surface inflammation in DED include two cyclosporine oil-based emulsions, Restasis® (cyclosporine A 0.05%) and Ikervis® (cyclosporine A 1 mg/mL), and an ophthalmic solution containing a novel integrin antagonist, Xiidra® (lifitegrast 5%). Based on available results from clinical trials, limitations of these products include delayed onset of benefit and unfavourable tolerability profiles that can affect patient compliance, or even lead to treatment discontinuation, and inconsistent efficacy for improving both signs and symptoms.

In a prospective, exploratory, unpowered, multicentre, vehicle-controlled, double-masked Phase II dose-ranging study, CyclASol® groups demonstrated earlier onset of efficacy compared with Restasis® for improving corneal and conjunctiva staining parameters (Figure 5).[9] With a model based approach, the CyclASol® effect was statistically significant over vehicle (total corneal staining $p<0.1$, central corneal staining $p<0.01$, conjunctival staining $p<0.01$).

In addition, CyclASol® further showed a greater benefit for improving visual function related symptoms (OSDI, OSDI Q6-9 and reading) compared with vehicle. In the model based analysis, the CyclASol® effect for OSDI as symptom parameter even reached statistical significance ($p<0.01$).

The treatment benefit of CyclASol® was seen particularly among patients with more significant ocular surface damage. CyclASol® also showed excellent safety, tolerability and comfort in this study where 98% of patients randomised to its use completed the four month treatment period.

The robust effects of CyclASol® on both the signs and symptoms of DED observed in the Phase II study are being validated in ESSENCE (NCT03292809), a pivotal Phase IIb/III trial. In ESSENCE, patients will be randomised to CyclASol® 0.1% or vehicle twice daily. Planned enrolment is 316 patients. Topline data is expected to be available in the second half of 2018.

Novaliq is also applying its unique EyeSol® drug delivery technology to develop a first-in-class therapeutic to simultaneously treat signs and symptoms in patients with DED associated with ocular pain. NOV07 contains an active pharmaceutical ingredient that targets the cannabinoid receptors in the cornea and has the potential to provide benefit through multiple mechanisms of action.

Cannabinoids are an attractive treatment for DED because they modulate pain and inflammation and have been shown to have neuroprotective activity. The formulation of a topical cannabinoid ophthalmic product, however, has been challenging because these compounds are extremely unstable in aqueous-based formulations.

Preclinical research, using a mouse model, conducted at the University of Cologne, Germany, found that NOV07 caused dose-dependent improvement in corneal staining and tear volume. The company is now working towards translating the evidence from the preclinical investigation to plan a clinical study.

PIPELINE BEYOND DED

Novaliq's pipeline is not limited to DED. NOV05 formulates tacrolimus, a highly potent anti-inflammatory agent and immunomodulator, in EyeSol®, and is being developed as a topical treatment for non-infectious uveitis of the anterior segment. Tacrolimus is poorly water soluble and a tacrolimus ophthalmic suspension is only commercially available in Japan, even then only indicated for the treatment of vernal keratoconjunctivitis. EyeSol® technology may enable delivery of therapeutic concentrations of tacrolimus into the anterior eye segment and fill an unmet therapeutic need for non-infectious uveitis.

Current local treatment for this inflammatory disorder involves corticosteroids that are associated with risks for intra-ocular pressure elevation, and cataract. NOV05 holds promise for providing a long-term effective topical therapy to avoid recurrences of the disease with a more favourable safety profile than existing options.

CONCLUSION

Available evidence supports the idea that aqueous-free EyeSol® technology has

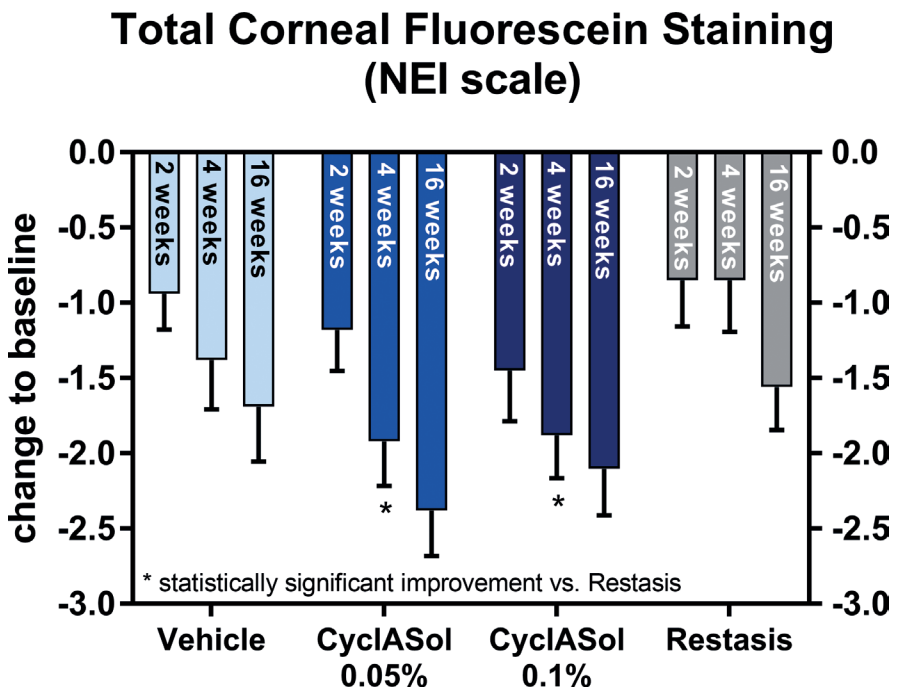

Figure 5: Improvement in total corneal fluorescein staining score was significantly greater after 4 weeks in eyes treated with CyclASol® 0.05% and 0.1% compared with active controls using Restasis®.

> "EyeSol® is distinguished from aqueous-based technologies by a host of physical characteristics that translate into enhanced stability, bioavailability, efficacy and tolerability."

great potential for overcoming the limitations of topical ophthalmic drug therapy and providing innovative products that are safer, better tolerated and more effective than existing gold standards. Backed by the leadership and guidance of a management team that brings tens of decades of experience in all areas of pharmaceutical development and a scientific advisory board comprised of renowned experts in both basic science and clinical ophthalmology, we are confident that Novaliq will be successful as it moves forward with its mission to transform topical therapeutics into highly effective products for both the front and back of the eye.

ABOUT THE COMPANY

Founded in 2007, Novaliq GmbH is a Heidelberg-based speciality pharmaceutical company focused on ophthalmology. Its mission is to transform poorly soluble drugs into effective ocular therapeutics for both the front and the back of the eye. Novaliq's proprietary EyeSol® technology enhances the topical bioavailability, stability and safety of traditionally insoluble or unstable drugs improving the delivery, efficacy and convenience of treatments for ocular surface diseases, including dry eye through preservative-free and multi-dose formulations. Novaliq has developed a tiered and long-term sustainable dry eye family of differentiated products that addresses the different needs of dry eye patients. The company's most advanced products are NovaTears® with CE-approval marketed under the brand name EvoTears® in Europe, and NovaTears®+Omega-3, which was just recently CE-approved in Europe. CyclASol® a second-generation prescription drug is currently in pivotal phase of clinical development.

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ABOUT THE AUTHOR

Christian Roesky is chief executive officer of Novaliq GmbH. Dr Roesky holds a PhD in Chemistry, has been involved in eye care for more than 15 years and has extensive operational experience at multiple international pharmaceutical companies. Previously, Dr Roesky has served as general manager of Bausch + Lomb GmbH / Dr Mann GmbH in Berlin; managing director of the Diagnostics Division and general manager and speaker of the Country Management Board of Abbott GmbH & Co KG in Wiesbaden; and general manager of Alcon Germany & Austria (Novartis).

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FANNY SELLIER, NEMERA
EYEDROPPERS DESIGNED FOR PATIENTS

Fanny Sellier is responsible for ophthalmic products at Nemera, including the preservative-free technology, Novelia®. She joined the company in 2011. A graduate from the ISEG business school in Strasbourg and the IUT de Chimie (chemical sciences) in Besançon, France, Ms Sellier worked for seven years for Rhodia (now Solvay) in the US in marketing, Lean enterprise and business development. She was then with BASF in a marketing position managing products for the home care industry.

Talking here with ONDrugDelivery Magazine, Ms Sellier discusses Nemera's multidose eyedropper system Novelia® for preservative-free formulations. She explains how this platform has been developed to improve patients' lives.

Q Thinking of all the stakeholders – patients, clinicians, pharma industry – what do you see as the most significant trends and most pressing demands driving ophthalmic drug delivery system development at present?

A I feel that one of the most significant factors driving the ophthalmic market today is adherence to treatment. There is a demand on pharma companies to provide products that are easy for patients to use with as few side effects as possible.

In particular the treatment should not irritate the patient's eyes. That's why preservative-free formulations are very useful for patients who take their treatments every day, for chronic diseases. In addition, patients need to have a product that is easy to use and that makes it simple for them to deliver the product into the eye. So a low squeeze-force is desirable, meaning that the patient does not have to squeeze the bottle too hard in order to make a drop. Also it should be easy for them to aim the drop so that it lands in the eye and does not miss. Our Novelia® platform (Figure 1) incorporates a "blue dot" which really improves the patient's ability to aim the drops accurately (Figure 2).

> "One of the most significant factors driving the ophthalmic market today is adherence to treatment."

Another aspect that I feel will be making ocular products easier to use in the very near future will be the addition of electronics into the systems. The emergence of delivery systems incorporating connectivity and electronics is very visible in the parenteral and pulmonary areas but very soon we will see electronics adopted for all types of delivery system, including ophthalmic. In fact we are working on an e-Novelia® system at Nemera – an electronic version of Novelia® which lets patients know when they need to take their drug, records whether a drop has been delivered, knows how much formulation remains in the dropper bottle and sends reminders when the patient needs to get a new bottle.

Q Please could you give a broad overview of Nemera's offering in the ocular delivery field?

A Novelia® is not just a product, it is a platform. It was one product when we first designed and developed it but we have now extended the range to provide one system that can be adapted to handle different ophthalmic formulations.

For example we have adapted the flow-control technology within Novelia® that avoids multiple drop delivery into the eye and ensures that only one drop is dispensed at a time (see Figure 3). We have three different

Figure 1: Novelia®, the only multi-dose eyedropper for preservative-free formulation registered in the UK for a Rx product.

Figure 2: Novelia® improves the patient's ability to aim the drops well.

PureFlow® versions available, each suited to formulations of different viscosities. One of the systems is for extremely liquid / non-viscous formulations (with the consistency of water), even if you squeeze really quite hard on the bottle you might get another drop but never a jet.

We also have different valves available, each one delivering a different drop size. In addition to the "standard" valve, which was the first one developed, we now have a wide range, including two smaller valves and two larger ones. The size of the drop can be customised depending on the needs of specific client products. This is particularly important for generics companies because when creating a generic version of an originator compound they are required to replicate the drop size as well as the composition of the originator product.

Additionally, we have a full range of bottles available in terms of size, material and sterilisation type. We have 5 mL, 7.5 mL, 11 mL and 15 mL bottles. For the material, all of these sizes are available in low density polyethylene (LDPE) and we're also working on polypropylene (PP). In terms of the sterilisation mode, the Novelia® bottle has been validated using both gamma and ethylene oxide (EtO) sterilisation. Offering two options for sterilisation allows us to better answer to our customers' compatibility needs.

We don't only focus on the nozzle, but also on the cap. Originally the Novelia® cap was white but we've just launched an olive green cap and we're working on other colours for specific demands. Additional cap options include a vented cap which is useful for sticky formulations, and a child-resistant cap.

> "A range of drop sizes is possible and this is particularly important for generics companies because when creating a generic version of an originator compound they are required to replicate the drop size as well as the composition of the originator product."

The objective is to enable Novelia® to be adapted to different sets of circumstances so it can be used for numerous products, not only from different clients but also different formulations within the same individual client's pipeline. That is a true platform.

Q Why did Nemera opt for preservative free with Novelia®? And why multi dose?

A Nemera chose to develop a multi-dose system for preservative free formulations because there was a real need from patients. It is about helping patients who have chronic disease avoid side effects. These patients really need preservative-free formulations.

Of course, preservative-free ophthalmic products have been available on the market for a long time. But, crucially, these were single-dose products. Unit-dose products are expensive. They're not eco-friendly either. Thinking about using unit doses over a month, that's about 30 dose units instead of one multi-dose system. There is a lot of waste when using single-dose products: waste in terms of the formulation itself; of plastic primary packaging; of secondary packaging; and in terms of storage and transportation.

Patients using unit doses could also face other issues: inconvenience of handling, difficulty of targeting the eye and risk of hurting it, caused by the long tip. The drop size is far from consistent and can vary widely depending on how the patient opens the packaging. We found that many patients around the world do not like using unit-dose products for chronic ophthalmic diseases and that's a major reason why we decided to develop a re-usable system.

Q Nemera is well known as a company with highly innovative, intelligent design capabilities applied in various areas within drug delivery. How was this expertise applied to Novelia®?

A At Nemera we always think about the patient while we're designing a product, and all throughout the development process until manufacturing. Patients are always first. We have conducted several user tests to make sure that patients understand the system and can use it easily. They always provide very useful feedback and, at the development stage, we are still able to adapt the system. So not only do we listen to their feedback but we act.

This is what happened with Novelia® at the beginning of the project. We learned from patients' feedback that is was difficult to see the drop as it emerged from the dropper. They were right. At this point the dropper valve was transparent and we realised it was important to have a

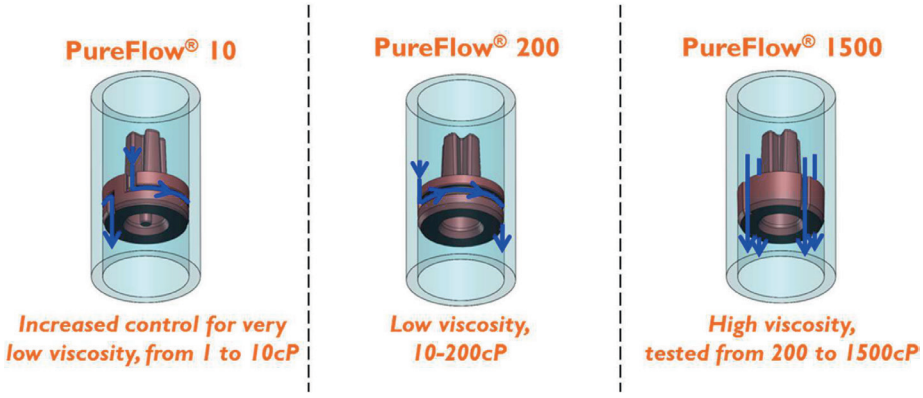

Figure 3: Three versions of PureFlow® flow-control technology adapted for different formulation viscosities.

"We received feedback from patients that is was difficult to see the drop as it emerged from the dropper. They were right. At this point the dropper valve was transparent and we realised it was important to have a contrast. So this is why we now have the blue valve – the blue tip."

contrast. This is why we now have the blue valve – the blue tip that totally contrasts with the white top part of the nozzle. This enhances the patient's view of the drop and makes it easier to aim the drop at their eye. During the development stage we're already thinking about how we'll manufacture the product. Our Innovation Center uses a quality-by-design development procedure to ensure we can manufacture the product at the highest level of quality, and to make sure we can control the quality of the product during the manufacturing.

Novelia® was initially developed with a filter technology (rather than the PureFlow® system we now use, which has a silicone membrane). However, we had to look at the evidence that it was impossible to perform full quality controls on the filter during the manufacturing process: inspecting a filter is a destructive test. As our objective was to have 100% automated control of every single product for patient safety, we decided to go for a silicone membrane instead of a filter.

Another important feature of Novelia® is its protective cap. With the Novelia® cap, patients can easily see that the bottle has never been used, thanks to its tamper-evident ring. In fact, when the patient unscrews the cap for the first time, the tamper-evident bridges break. This feature differentiates Novelia from most multi-dose eyedroppers for preservative-free formulations on the market. We see devices that allow the medication to be dispensed even when the tamper-evident ring is still in place, and others that do not even have a tamper-evident feature.

However, if microbial contamination on the tip does take place while the cap is removed, the system contains silver ions embedded in two components – the surface of the cap and on the top of the nozzle. Silver ions inhibit the growth of microbial contamination and are globally widely used in a variety of applications including pharmaceutical and medical applications such as lens cases, wound dressings and also in other eyedroppers.

The silver ions are not in permanent contact with the formulation contained in the bottle. Any leaching of silver in the delivered drop will be consequently minimal and well below any safety threshold.

Figure 4 shows the Novelia® function summarised in five steps including the function of the valve, the PureFlow® technology, which allows air to diffuse into the bottle to equalise the pressure inside and outside the bottle whilst preventing microbial ingress, and the silver ions embedded in the cap.

"As our objective was to have 100% automated control of every single product for patients' safety, we decided to go for a silicone membrane instead of a filter."

Q Another strength of Nemera is its industrialisation know-how including substantial in-house manufacturing facilities. Does Novelia® take advantage of these capabilities?

A Nemera is expert in high volume manufacturing of drug delivery devices. We manufacture hundreds of millions of parenteral and pulmonary devices, on fully automated lines and in GMP conditions. We design our products from scratch with the manufacturing process in mind. This experience we have at Nemera with other types of delivery system certainly helped us develop

[Continued on Page 20...]

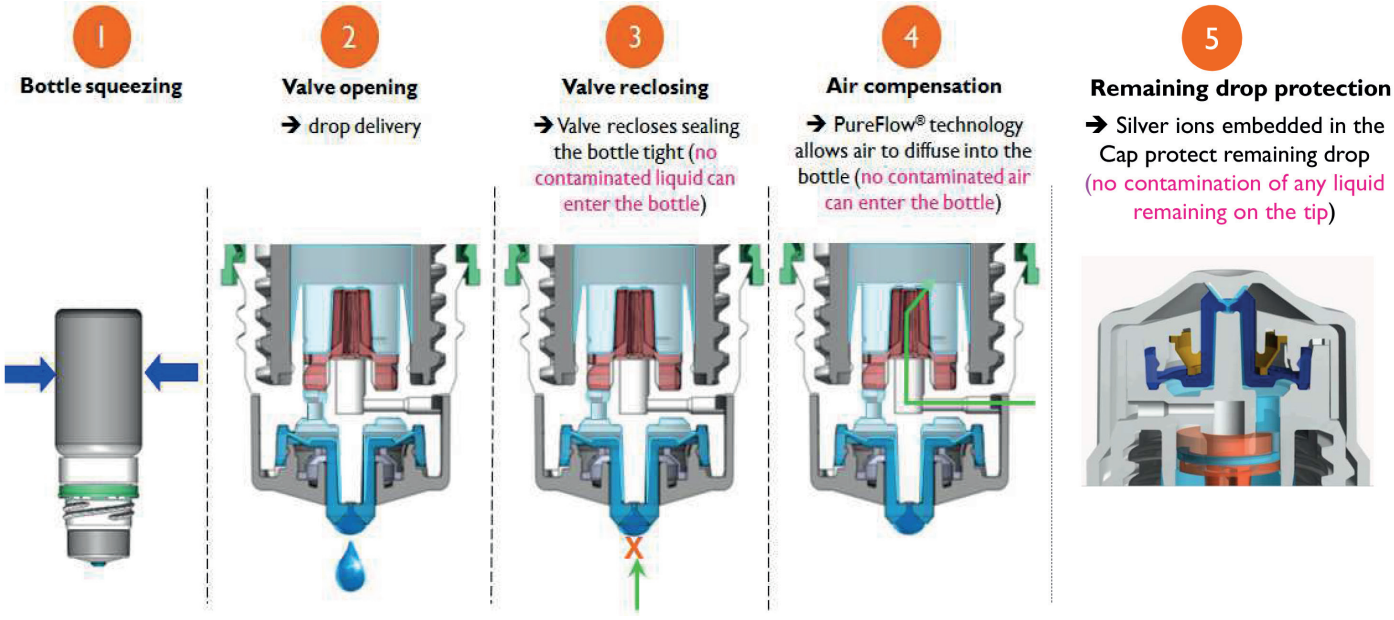

Figure 4: Novelia® functioning in five steps.

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[...Continued from Page 18]
the manufacturing process for the Novelia® platform.

Novelia is manufactured in a specific ISO7 clean room, with injection machines for plastic components and a fully automated assembly line. Half of the line is dedicated to inspecting every single product on all critical functions to ensure that Novelia® is perfectly safe for every patient.

Nemera industrial teams were involved right from the conception of the product and their input was incorporated into the design, so that Novelia® could be manufactured in high volumes while guaranteeing the required quality.

Regulatory requirements have been consolidated from the start of the development. Solid design history and regulatory files are available to help our customers register their formulation with our delivery system. We support them in their registration process to secure the product launch.

Q Could you talk about what unique benefits Novelia® brings to the patient?

A As we already discussed, we conceived Novelia® by putting ourselves in the patient's shoes. We designed the product with several patient-focused features, as the "blue tip", the low squeeze force and the PureFlow® technology.

There are some other important ways in which we considered the patient during the design of Novelia® in order to ensure that the system delivered the best possible patient experience. So, we knew we wanted a multi-dose system for preservative-free formulations. For this we could have chosen a pump system instead of a bottle. And we could have gone for a snap-on / snap-off cap rather than a screw cap. We decided on a bottle with a screw-cap because it is more convenient for patients to take their drops in this way. It is a system they are already used to. The patient unscrews the cap, turns the bottle upside down and squeezes the bottle to deliver the drop from the nozzle. We wanted to retain these simple and familiar steps.

Another key aspect was of course safety. We can't possibly have any contamination in the bottle. That's why we developed the one-way valve that prevents all backflow. No liquid can come back into the bottle. Another feature that keeps the drug free from contamination is the PureFlow® system. We conducted comprehensive microbiological challenge tests – to check the safety of the product. These have shown the system is safe even when exposed to severe contamination.

There were also safety advantages with the screw-cap. Whatever the conditions of use, the screw cap does not come off, whereas if you use a snap-on cap it can get loose after a while and it can come off in your pocket or bag.This is undesirable because of formulation leakage and contamination hazards.

As I mentioned, we conducted user tests with Novelia® several times during its development, building on patient feedback to improve the product. We also designed a study to assess patient preferences comparing multi-dose eyedroppers for preservative-free formulations. Novelia® stood out as the preferred device. This is rewarding because at Nemera our motto is always to put patients first and we can see that we have succeeded when patients put Novelia® first.

Q Thinking about Nemera more generally, how does ophthalmic drug delivery fit with the wider Nemera organisational structures and strategies?

A Ophthalmic is one of the four strategic franchises at Nemera. Multi-dose eyedroppers for preservative-free formulations is still a budding market, bound to boom in the next ten years. We are growing very aggressively in this area and we will help many more patients with their eye treatments in the future. Novelia® is manufactured near Lyon, France, at our La Verpillière facility, which is also where Nemera has its headquarters and Innovation Center.

Q Finally, please could you tell our readers a little about yourself? Describe your career and interests and experiences in and around ocular drug delivery, and tell us what is it about Nemera in particular that makes it attractive organisation to be a part of?

A I discovered the drug delivery business six years ago when I joined Nemera. For me it was a big change because I was coming from the chemical industry. It was very different – in the chemical industry it took several months to develop and manufacture a new product whereas in the drug delivery industry it takes several years! However, while it moves more slowly in that respect, it is so rewarding working to really improve patients' lives and put myself in the patient's shoes. Nemera is a wonderful company to work for. It's very dynamic and we have so many smart people. It's fun! I truly like working there.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture of drug delivery devices for the pharmaceutical, biotechnology and generics industries. Nemera's services and products cover several key delivery routes:

- Ophthalmic
- Nasal, buccal, auricular
- Inhalation
- Parenteral
- Dermal and transdermal.

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including innovative off-the-shelf systems, customised design development, and contract manufacturing.

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ESTABLISHING PHYSICOCHEMICAL **BIOEQUIVALENCE** IN OPHTHALMIC MICROEMULSIONS

Establishing bioequivalence is a necessary step for US FDA approval of new generic drug products. Here, Paul Kippax, PhD, Director, Product Management: Morphology, Malvern Panalytical, describes the methods by which bioequivalence can be established for ophthalmic microemulsions by *in vitro* testing, saving the need for costly clinical trials.

The use of microemulsions has increased significantly over recent decades as the knowledge base associated with their successful formulation has rapidly grown. Microemulsions are now used as drug delivery vehicles, as exemplified by topical products for eye complaints. Key benefits of these ophthalmic microemulsions include their excellent thermodynamic stability and fine droplet size, which can aid optical clarity, drug delivery, retention and absorption. However, formulating such products remains challenging, particularly with respect to ensuring product stability over a long shelf life.

> "The FDA has set out the requirements for assessing bioequivalence *in vitro* via the use of appropriate analytical techniques, with the goal of providing sponsors with a faster route to market for new generics by avoiding costly clinical endpoint studies."

Ophthalmic microemulsions are classified as complex generic products on the basis of their formulation structure and route of delivery. However, the challenge of proving bioequivalence with a reference drug product is significant for such products, as pharmacokinetic data obtained via clinical trials may not provide a realistic measure of bioavailability at the point of local action. As a result, the US FDA has set out the requirements for assessing bioequivalence *in vitro* via the use of appropriate analytical techniques, with the goal of providing sponsors with a faster route to market for new generics by avoiding costly clinical endpoint studies.

In this article, we discuss the value of particle size, rheology measurements and zeta potential in the characterisation of microemulsions and the *in vitro* demonstration of Q3 bioequivalence – physicochemical equivalence between a test and a reference product – for ophthalmic microemulsions. Relevant analytical techniques are introduced and their application is discussed with reference to case study data for cyclosporine, the active pharmaceutical ingredient in Restasis®, an ophthalmic emulsion for the treatment of dry eye disease.

INTRODUCTION TO MICROEMULSIONS AND OPHTHALMICS

Aqueous eye drops are the most common ophthalmic formulations. However, with conventional dosage forms like ophthalmic solutions and suspensions, demonstrating the bioavailability of such formulations can be tricky, especially given their low residence time in combination with the

> "The low surface tension and small droplet size of microemulsions may result in increased drug absorption and permeation, and hence, an improved possibility of drug delivery to the posterior segment of the eye."

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eye's natural defences (e.g. lachrymal fluid secretion, lachrymal fluid-eye barriers, and blood-ocular barriers).

Microemulsions normally consist of an aqueous phase, an oil phase, a surfactant and a co-surfactant (usually an alcohol). When the concentrations of these components are favourable they spontaneously emulsify to form a monodisperse, thermodynamically stable, transparent microemulsion. The low surface tension and small droplet size (5-200 nm) of microemulsions may result in increased drug absorption and permeation and, hence, an improved possibility of drug delivery to the posterior segment of the eye (vitreous humour, retina, choroid and optic nerve).[1] Microemulsions are appealing to ophthalmics formulators not only due to these benefits, but also because of their ability to solubilise and deliver otherwise immiscible liquids by, for example, loading a hydrophobic drug into the oil phase. They also allow for a phase transition to a high viscosity liquid-crystal state, which can increase residence time and thus bioavailability.

The potential of microemulsions to increase the effectiveness of ophthalmic drugs means that they are the subject of many current R&D efforts, by innovators and complex generics manufacturers alike. In the case of generics, identifying optimal analytical strategies for demonstrating bioequivalence is an important goal, with FDA guidance highlighting the benefits of applying orthogonal analytical methods.[2]

BIOEQUIVALENCE AND BIOAVAILABILITY

To gain FDA approval, a test generic drug must be shown to be bioequivalent to a reference innovator drug.[3] Bioequivalence includes bioavailability – the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action (21 CFR 320.1(a)). How efficiently a drug is released in the system differs between dosage forms. For example, if a drug is ingested orally, it may be only partially absorbed and metabolised, leaving less of the drug to act upon the target site. Drugs that are administered intravenously, however, are generally found to be much more bioavailable. In the case of conventional ophthalmics, such as solutions and suspensions administered topically to the eye, low residence time means bioavailability can be as little as just 5%.[4]

Abbreviation	Terminology	Definition
Q1	Qualitatively the same	The generic and innovator products contain the same active and inactive ingredients (i.e. they have the same components)
Q2	Quantitavely the same	The generic and innovator products contain the same amounts of active and inactive ingredients (i.e. they have the same amounts of the same components)
Q3	Physicochemical attributes of a specific dosage form	The generic and innovator products have the same physicochemical properties (i.e. they have the same amounts of the same components arranged in the same way)

Table 1: Bioequivalence categories.

"Particle size and polymorphism, along with viscosity and rheology, are important examples of the physicochemical attributes which enable us to understand how a drug will be released and behave in the system."

In bioequivalent products, there is no significant difference in the rate and extent to which the active ingredient or moiety becomes available at the site of drug action, when administered at the same molar dose under similar conditions in an appropriately designed study (21 CFR 320.1(e)). Showing the bioequivalence of a reference and test product satisfies one of the FDA's key requirements for generic drug approval.

To establish the bioequivalence of two drug products, they must be compared qualitatively (Q1), quantitatively (Q2) and also physicochemically (Q3) as shown in Table 1.

Particle size and polymorphism, along with viscosity and rheology, are important examples of the physicochemical attributes which enable us to understand how a drug will be released and behave in the system. This type of information can be especially useful when a drug is administered via a complex formulation, such as a microemulsion, applied topically to the eye. It is these types of characteristics which must be analysed in order to establish Q3 bioequivalence.

For ophthalmic cyclosporine emulsions, some of the Q3 bioequivalence attributes required for generic approval are as follows:[5]

- globule/particle size distribution
- viscosity profile as a function of applied shear
- zeta potential.

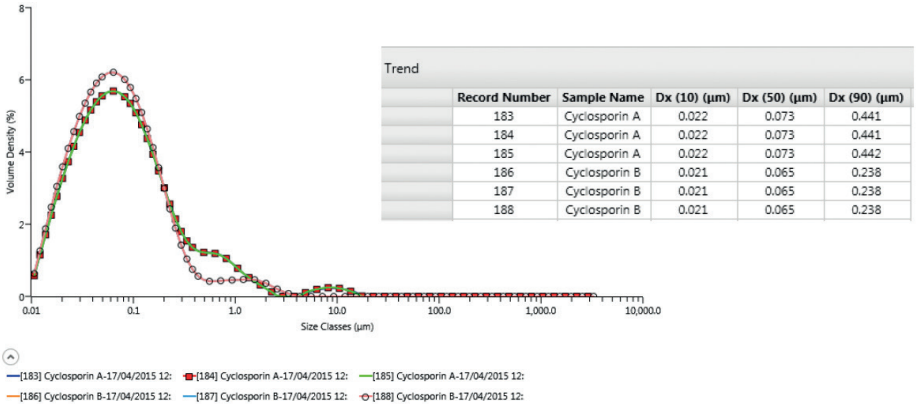
Effective methods for analysing such characteristics to demonstrate Q3 bioequivalence for ophthalmic microemulsions will be considered in the following sections.

Particle Size Characterisation

Determining the globule or particle size distribution of ophthalmic microemulsions and suspensions provides information on drug release, formulation clearance and product stability. Dynamic light scattering (DLS) and laser diffraction are particle size measurement techniques suggested by the FDA as useful for establishing bioequivalence of these product types *in vitro*.[5] The most appropriate technique for the particle size characterisation of microemulsions depends on the physical attributes of each sample, with DLS being more suitable for characterising particles in the submicron range and laser diffraction better suited to those in the micron range. It is typically preferable to avoid diluting microemulsion systems for analysis; for some techniques, such as laser diffraction, it is necessary however to disperse particles in a medium.

An example of the comparability data that can be obtained for test and reference ophthalmic formulations is provided in Figure 1 (next page), which shows measurement of globule size distribution

for cyclosporine using laser diffraction. These data confirm that the primary particle size for microemulsion globules within the reference and test formulations are similar. In addition, both formulations show the presence of large particles which may represent the onset of globule flocculation. The differences in the percentage of large globules is shown in the reported values for the Dv50 (median) and Dv90 (particle size below which 90% of the volume of material exists). This may have an impact on bioavailability, as it suggests that there may be stability differences between the formulations. However, to confirm this, the particle size data must be considered alongside the other Q3 physicochemical parameters advised by the FDA.



Record Number	Sample Name	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)
183	Cyclosporin A	0.022	0.073	0.441
184	Cyclosporin A	0.022	0.073	0.441
185	Cyclosporin A	0.022	0.073	0.442
186	Cyclosporin B	0.021	0.065	0.238
187	Cyclosporin B	0.021	0.065	0.238
188	Cyclosporin B	0.021	0.065	0.238

Figure 1: Globule size distribution for two cyclosporine products, labelled A and B.

Rheological Characterisation

In rotational rheometry, stress is applied to a sample that is sandwiched between two plates. By rotating, oscillating or applying a step function to the measuring system, and by controlling the force (stress-controlled rheometry) or the speed (strain-controlled rheometry) applied, various rheological characteristics of the sample can be determined. Under such conditions, the sample will experience some manner of shear deformation. Rheology testing therefore involves measuring some standard variables:

- shear stress (force per area)
- shear strain (displacement divided by height)
- shear rate (change in strain with time).

From this shear profile, the sample's typical material properties can be calculated. A common test mode is rotation, used to measure shear viscosity, calculated as:

$$\frac{\textit{Shear stress}}{\textit{Shear rate}}$$

Viscosity measurements can provide a wealth of information about the stability of the suspension/emulsion. The higher the viscosity, the stronger the suspended particle interactions, and therefore the more stable the formulation.

Another common test mode is oscillation, which is used to measure viscoelastic modulus, calculated as:

$$\frac{\textit{Shear stress}}{\textit{Shear strain}}$$

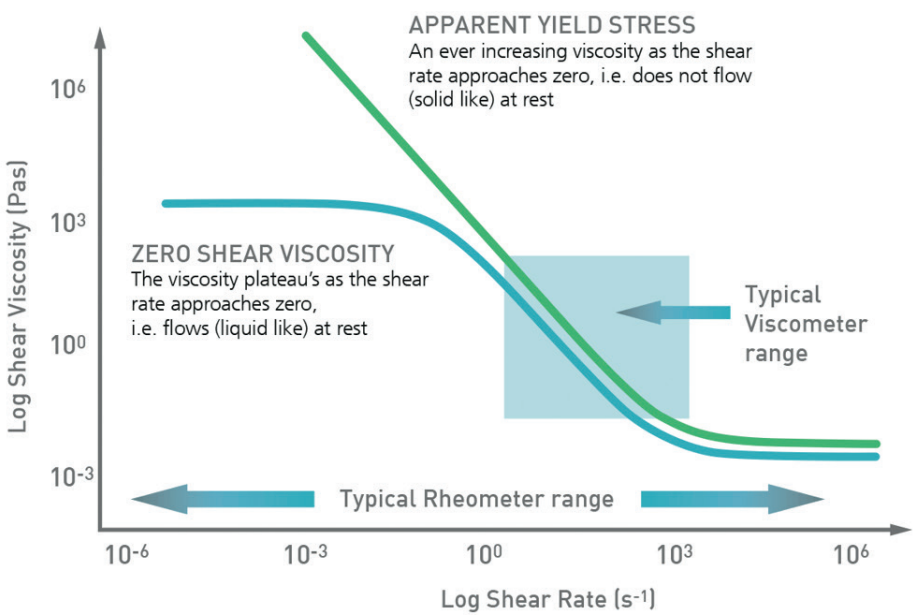


Figure 2: Rheological analysis showing how a material behaves at rest (whether it is solid- or liquid-like).

Other characteristics can also be determined through rheological analysis, such as:

- **yield stress**: the stress that must be applied for the material to break down and flow.
- **thixotropy**: the dependence of the viscosity on the timespan of the applied shear or how long it takes for the microstructure to rebuild after breakdown.
- **viscoelasticity**: how solid- or liquid-like the material is, and how this property changes with time, temperature, stress or strain.

Low shear rates show how a material behaves at rest. For example, a sample with an ever increasing viscosity as the shear rate approaches zero is solid-like, i.e. does not flow at rest, whereas if a sample's viscosity plateaus as the shear rate approaches zero it is liquid-like, i.e. flows at rest (Figure 2).

As well as helping explain the microstructural changes that occur in microemulsion systems as a result of dilution, rheological characterisation can also provide insights into the sample's responses to processes such as storage and delivery.

For example, when looking at the shear viscosity versus the shear rate of cyclosporine, the yield point, i.e. the point at which the material breaks down and flows (Figure 3), has an impact on ocular retention time and drug release. The more difficult it is to "break" the microemulsion, the higher the ocular retention. Moreover, if the "cohesive energy" (the energy required to break the suspension) is calculated, the stability of the microemulsion can be quantified. The data obtained for the reference and test formulations in this case are similar, suggesting that the formulations have a similar structure.

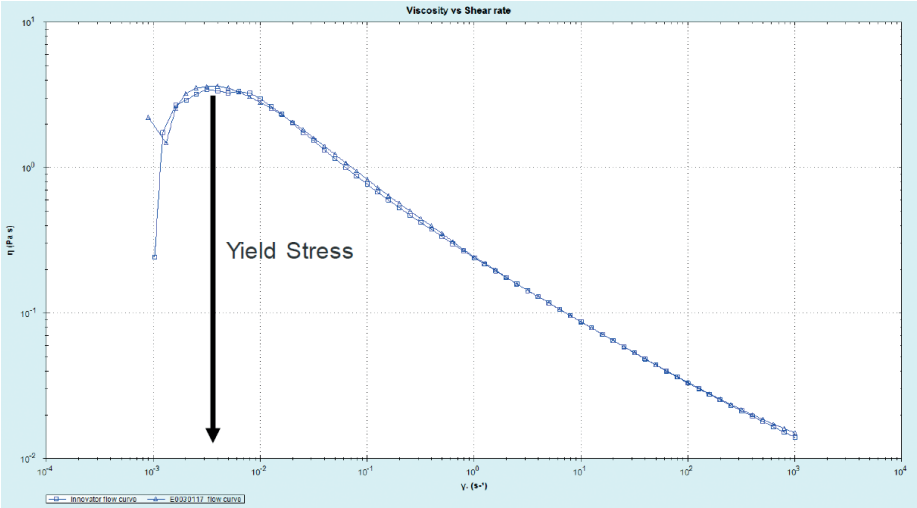


Figure 3: Yield point of cyclosporine – test and reference samples showing near-identical results.

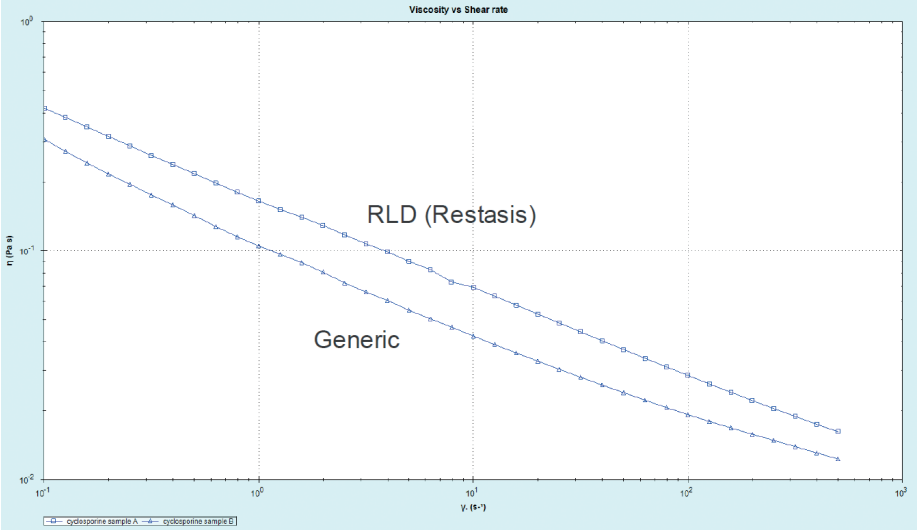


Figure 4: Cyclosporine reference and test products: viscosity versus shear rate.

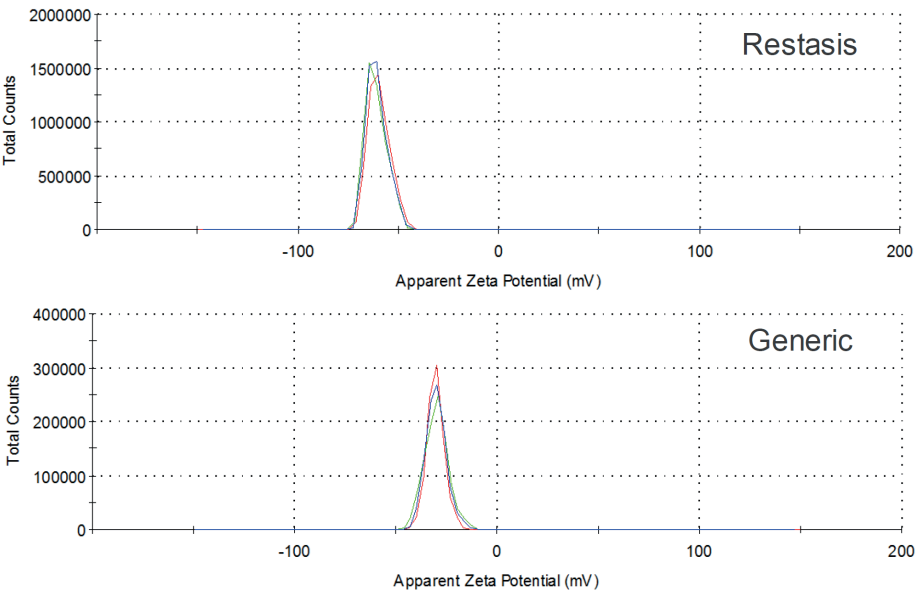


Figure 5: A comparison of zeta potential in cyclosporine reference and test products – the reference product has a more negative zeta potential, suggesting that it may be a more stable product.

It is also important to consider the flow behaviour of the formulations, as this can impact delivery of the formulation and also its dispersion following delivery. Viscosity versus shear rates for test and reference cyclosporine products can be seen in Figure 4, which shows that the reference listed drug (RLD) is more viscous than the generic. This may impact its ocular retention time and drug release characteristics.

Zeta Potential

Zeta potential is a parameter which relates to the charge a particle acquires in a particular medium. It can be related to formulation stability and dispersion, as well as to the adhesion of particles to cell membranes.

The results of the determination of the zeta potential of cyclosporine (in the RLD and test products) can be seen in Figure 5. This shows that the reference product has a more negative zeta potential compared to the test product, suggesting that the reference product may be more stable over time. This difference may also have an impact on the way in which the two formulations are absorbed following delivery.

CONCLUSION

FDA guidance recommends that an orthogonal approach is applied to pharmaceutical bioequivalence testing. For example, dynamic light scattering or laser diffraction techniques provide the particle size distribution of the sample which, in turn, gives an idea of drug release properties, formulation clearance and product stability. However, this needs to be considered alongside rheological characterisation, which can provide information relating to suspension/emulsion stability, as well as an understanding of the behaviour of the formulation during storage, delivery and drug release. And to further complement this analysis, measuring a product's zeta potential gives an additional prediction of its stability.

The establishment of particle size distribution, viscosity profile and zeta potential are some of the Q3 bioequivalence attributes required as part of the approval process for generic ophthalmic cyclosporine products. By applying complementary analytical methods such as these in combination – that is, by taking an orthogonal approach – a well-rounded picture can be created of the physicochemical comparability

of ophthalmic microemulsions. This can yield significant benefits to sponsors by enabling bioequivalence to be assessed *in vitro*, thus avoiding complex and time-consuming clinical endpoint studies.

ABOUT THE COMPANY

Malvern Panalytical technologies are used by scientists and engineers in a wide range of industries and organisations to solve the challenges associated with maximising productivity, developing better quality products and decreasing time to market. The company's focus is on creating innovative, customer-focused solutions and services to enhance efficiency and deliver tangible economic impact through chemical, physical and structural analysis of materials.

Malvern Panalytical was formed by the merger of Malvern Instruments Limited and PANalytical B.V. in January 2017, has headquarters in both Almelo (Netherlands) and Malvern (UK), and employs over 2,000 people worldwide. The combined entity is a strong player and innovator in the materials characterisation market and leverages the strengths of the individual companies in their end markets, having applications laboratories around the world, a global sales and service presence and a strong distributor network.

Malvern Panalytical is part of Spectris plc, the productivity-enhancing instruments and controls company.

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ABOUT THE AUTHOR

Paul Kippax is Director, Product Management; Morphology at Malvern Panalytical. A chemist and colloid scientist by background, holding a degree in Chemistry and a PhD in Physical Chemistry, he joined Malvern 20 years ago as a technical specialist. In 2002, Dr Kippax moved into product management where he used his experience gained working with the pharmaceutical industry to guide the development of the Spraytec and Mastersizer 3000 platforms.

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RE·VANA
VISION IN THE FUTURE

BIODEGRADABLE IMPLANTS FOR SUSTAINED INTRAOCULAR DELIVERY OF SMALL AND LARGE MOLECULES

Presently, there is an unmet need for more effective methods of treating diseases that manifest in both the front and back of the eye. In this article, Raj Thakur, PhD, Chief Scientific Officer, and Prof David Jones, PhD, Chief Scientific Adviser, both co-founders of Re-Vana Therapeutics, discuss this issue and introduce a possible solution: OcuLief™ and EyeLief™, Re-Vana's two proprietary sustained-release platforms.

BACKGROUND

Diseases that originate in the back of the eye can cause permanent loss of vision if left untreated. In practice, untreated conditions, such as age-related macular degeneration (AMD), diabetic retinopathy (DR) and uveitis, are a major cause of blindness. Worldwide estimates indicate that approximately 30-50 million people are affected by AMD.[1] Current therapies for the wet form of this disease require frequent intravitreal injections, which have been shown to prevent further vision loss and increase visual acuity. However, adverse events of frequent intravitreal injections include increased risk of infection, retinal detachment, haemorrhage, pain, discomfort and rise in intraocular pressure.

Chronic diseases manifesting in the front of the eye can also result in significant loss of vision. For example, glaucoma is the considered to be the second leading cause of blindness, affecting more than 60 million worldwide.[2] The application of topical eye drops daily and sometimes multiple times a day, in order to control raised intra-ocular pressure, is the standard method of treatment for this disease. However, this form of treatment has significant drawbacks, such as the potential for long-term side effects, reduced efficacy over time and a negative impact on patient compliance, which may lead to disease progression.

> "The largest problem plaguing the development of ocular therapeutics is maintaining an effective concentration of the drug at its target site of action, in order to achieve the expected pharmacological response."

These issues further escalate healthcare costs and create a significant burden on patients, carers and physicians. Therefore, the largest problem plaguing the development of ocular therapeutics is maintaining an effective concentration of the drug at its target site of action, in order to achieve the expected pharmacological response.

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SUSTAINED DRUG DELIVERY SYSTEMS

Biological barriers and faster drug clearance rates, coupled with conventional formulation approaches, have led to poor ocular bioavailability of both small- and large-molecule therapeutics. Therefore, frequent intravitreal injections of large molecules (e.g. ranibizumab) in treating back of the eye diseases or frequent eye drops of small molecules (e.g. latanoprost) in treating front of the eye diseases is necessary for the management of ocular conditions.

This has led to increased research in the area of sustained release systems. Sustained release drug delivery systems can achieve prolonged therapeutic drug concentrations in target ocular tissues, whilst both improving patient adherence to therapy and limiting adverse events caused by systemic exposure.

Formulation strategies that have been investigated to address this issue so far include:

- Surgically sutured implants
- Inserts (e.g. punctal plugs)
- Injectable implants
- Hydrogels
- Nano-/micro-particles
- Liposomes
- Iontophoresis
- Microneedles
- Ultrasound.

> "Sustained release drug delivery systems can achieve prolonged therapeutic drug concentrations in target ocular tissues, whilst both improving patient adherence to therapy and limiting systemic exposure and side effects."

Although significant research is ongoing in the development of novel sustained release systems, since 1995, only four implant-based sustained release systems have achieved both global regulatory approval and commercial success. These include:

- Sustained release non-biodegradable implants:
  - Vitrasert® (ganciclovir 4.5 mg) – approved in 1995 for AIDS-related cytomegalovirus retinitis with a six to eight month drug release profile.
  - Retisert® (fluocinolone 0.59 mg) – approved in 2005 for chronic non-infectious posterior uveitis with an approximately two-and-a-half year drug release profile.
  - Iluvien® (fluocinolone acetonide 0.19 mg) – approved in 2011 for DME with an approximately three year drug release profile.
- Sustained release biodegradable implants:
  - Ozurdex® (dexamethasone 0.7 mg) – approved in 2009 for macular oedema with an up to six month drug release profile.

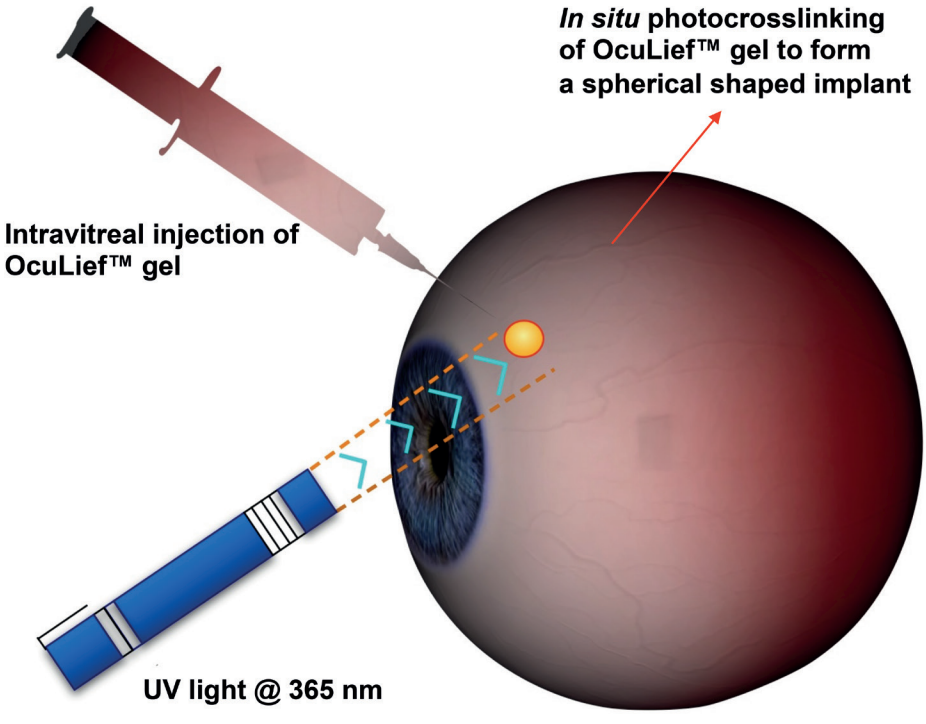

Figure 1: Schematic representation of *in situ* implant formation of OcuLief™.

Irrespective of ongoing developments, to date, there is no viable alternative to frequent intravitreal injection for the delivery of therapeutic proteins in treating back of the eye diseases or frequent eye drops in treating front of the eye diseases.

RE-VANA'S TECHNOLOGY

Re-Vana's proprietary sustained drug release technologies, OcuLief™ and EyeLief™, offer delivery of both small and large molecules with a wide range of physicochemical properties. The technologies are comprised of photosensitive polymeric materials that are selectively photocrosslinked to provide tailored release profiles for a wide range of therapeutics in the treatment of various ocular diseases. The platforms are both biodegradable and biocompatible in nature.

The first of the two technologies, OcuLief™, is a photosensitive, injectable gel-based platform. OcuLief™, is injected through the intravitreal route – using conventional hypodermic needles – followed by a short-term application of UV light to induce *in situ* photocrosslinking resulting in a photocrosslinked implant formation (Figure 1).

The second technology, EyeLief™, is a preformed photocrosslinked implant. EyeLief™ is engineered to allow intraocular administration to achieve sustained delivery of selected therapeutics.

Proof of Concept

Proof of concept data of Re-Vana's proprietary photocrosslinked sustained drug release systems have shown the ability to provide the release of small and large molecules for markedly extended periods. Using the OcuLief™ and EyeLief™ technologies, Re-Vana has demonstrated sustained release of candidate therapeutic molecules, including molecules that are employed in the treatment of both front and back of the eye diseases such as AMD, DR and glaucoma.

OcuLief™ is a polymeric gel-based formulation which, upon injection in the eye followed by UV light application,

forms a spherical photocrosslinked implant, *in situ*. Injections in the eye can be achieved using conventional narrow-bore hypodermic needles, such as those that are presently used in intraocular injections. Localised delivery of this platform technology achieves high drug levels at target tissues, prolonged delivery times, reduction in adverse events linked with systemic delivery and improved patient compliance.

EyeLief™ is a preformed implant (Figure 2) that can be administered intraocularly to achieve sustained delivery of a wide range of drug molecules. Being photosensitive, the implant can be selectively crosslinked so as to achieve the desired release rates over an extended period. EyeLief™ can be engineered into different shapes and sizes to accommodate desired routes of intraocular delivery.

Re-Vana does not employ extreme pH conditions or elevated temperatures in the engineering of its implants, which otherwise can cause issues when working with temperature or pH labile drugs, such as proteins. Furthermore, rapid crosslinking at physiological temperatures can swiftly entrap drug molecules, thereby reducing high burst release and thus sustaining drug delivery over a longer term. The degree of crosslinking of the implants influences their pore structure, which in turn controls the rate and extent of drug release. This technology has achieved sustained release, from two to twelve months, of therapeutic molecules such as triamcinolone acetonide (435 Da), dexamethasone (392 Da) and bevacizumab (Avastin®; 149 kDa). A sample *in vitro* release profile of bevacizumab is shown in Figure 3.

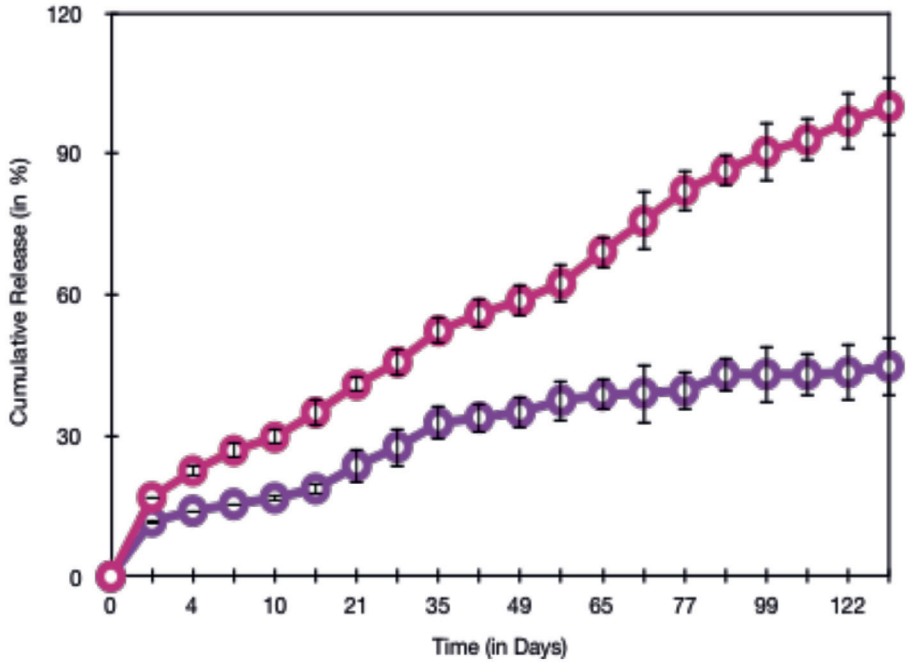

Figure 3: Tailored *in vitro* release profile of bevacizumab from OcuLief™ implants.

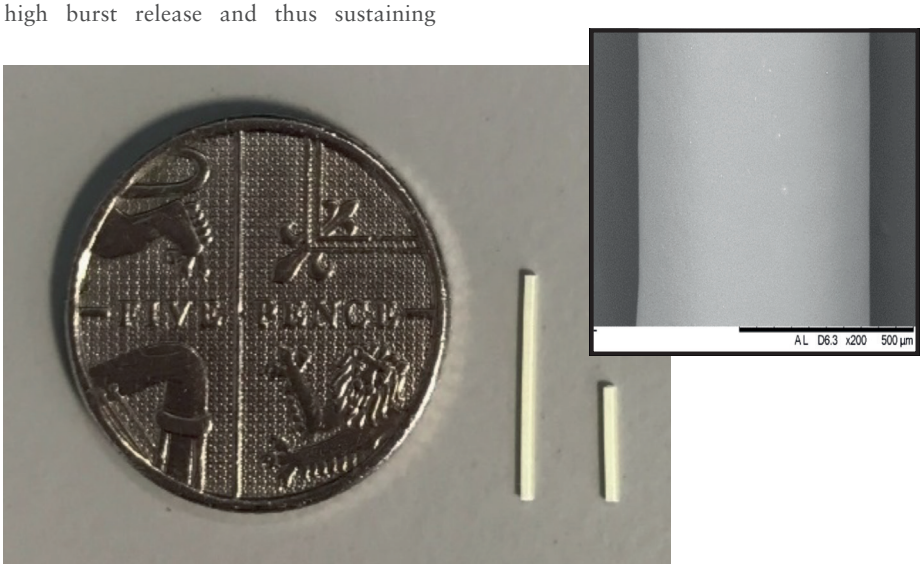

Figure 2: Preformed rod-shaped EyeLief™ implants adjacent to a UK five pence piece and imaged by an electron microscope.

VALUE PROPOSITION

- Proprietary photocrosslinked drug delivery platforms providing sustained, long-term drug delivery.
- Proven delivery of a range of small and large therapeutic molecules.
- Biocompatible and biodegradable drug delivery platforms.
- Ability to achieve tailored release profiles – with controlled burst release.
- Able to address both front and back of the eye diseases by delivery using different routes.

SUMMARY

Re-Vana Therapeutics has developed two proprietary photocrosslinked drug

delivery platforms that can sustain release of both small and large molecules.

The company has:

- Ongoing preclinical development programmes addressing both front and back of the eye diseases.
- Scientific and management team situated in both the UK and the US, experienced within the areas of ocular drug delivery systems, polymer science, regulation and commercialisation.
- Intellectual property rights protecting both platforms and routes for ocular applications.

ABOUT THE COMPANY

Re-Vana Therapeutics is an ocular pharmaceuticals and drug delivery company focused on the development and commercialisation of revolutionary long-acting biodegradable drug delivery platforms to treat chronic eye diseases such as AMD, DR, glaucoma and ocular infections. It is a spinout company from the School of Pharmacy, Queens University Belfast (UK).

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ABOUT THE AUTHORS

Dr Raj Thakur is a Senior Lecturer in Pharmaceutics at Queen's University Belfast's School of Pharmacy (UK). He holds a PhD in Drug Delivery (UK), MSc in Pharmaceutical Sciences (Malaysia) and Bachelors in Pharmacy (India). Dr Thakur's research interests lie in the design and physicochemical characterisation of advanced polymeric drug delivery systems for ocular applications. He has authored over 140 scientific publications and four books.

Professor David Jones is a Pro-Vice-Chancellor and holds the Chair in Biomaterial Science at Queen's University Belfast's School of Pharmacy (UK). He has a DSc in Biomaterial Science, PhD in Pharmaceutics, BSc in Pharmacy and a BA in Mathematics and Statistics. His research concerns the characterisation, formulation and engineering of pharmaceutical materials/dosage forms and biomedical devices. He is the author of three textbooks, 10 patents and over 400 research papers. He is a Chartered Engineer, a Chartered Statistician and a Chartered Chemist and is a former Royal Society Industry Fellow.

CREATING SUSTAINABLE BIOTHERAPEUTICS FACTORIES IN THE EYE TO TREAT MAJOR OPHTHALMIC DISEASES

In this article, Patricia Zilliox, PhD, Chief Executive Officer, Eyevensys, discusses the inherent difficulties in drug delivery to the back of the eye and how this creates an unmet need in ophthalmology. Dr Zilliox goes on to describe Eyevensys' novel solution to this problem, and the company's first lead product, EYS606.

CURRENT DRUG DELIVERY METHODS IN OPHTHALMOLOGY

Traditionally, the eye has been an extremely difficult target for drug delivery due to its unique anatomy and physiology (Figure 1). It has a range of protective barriers, both static and dynamic (different layers of cornea, sclera and the blood-retina barrier), that unfortunately limit the therapeutic effectiveness of systemic drug delivery and make local drug delivery challenging.

Disorders that manifest at the back of the eye are particularly difficult to treat, as it is still not possible to administer the drugs needed to manage these conditions using methods typical to the front of the eye, such as eye drops, ointments or gels. Traditionally such indications have been addressed using high doses administered by repeated intravitreal injections or by surgical intervention. Neither of these are ideal options for patients; intravitreal injections can have serious adverse consequences, such as intraocular infection (endophtalmitis), increased intraocular pressure and cataract formation. Even then, it remains difficult to sustain the appropriate concentration of the drug in the eye using these suboptimal methods.

Despite the success of current blockbuster drugs, such as Lucentis (ranibizumab) or Eylea (aflibercept), the ophthalmology industry is still facing a need to overcome the barriers to ocular drug delivery and improve ocular bioavailability for the treatment of back of the eye diseases, a need which remains unmet. A number of innovative alternative approaches have recently been developed, such as free-floating intravitreal implants, scleral implant devices and biodegradable formulations. These innovative solutions have come to market,

> "Despite various promising new options for back of the eye diseases, such as gene therapy, their clear limitations, especially in the drug delivery aspect, mean there is an urgency to improve the effectiveness of ocular therapies."

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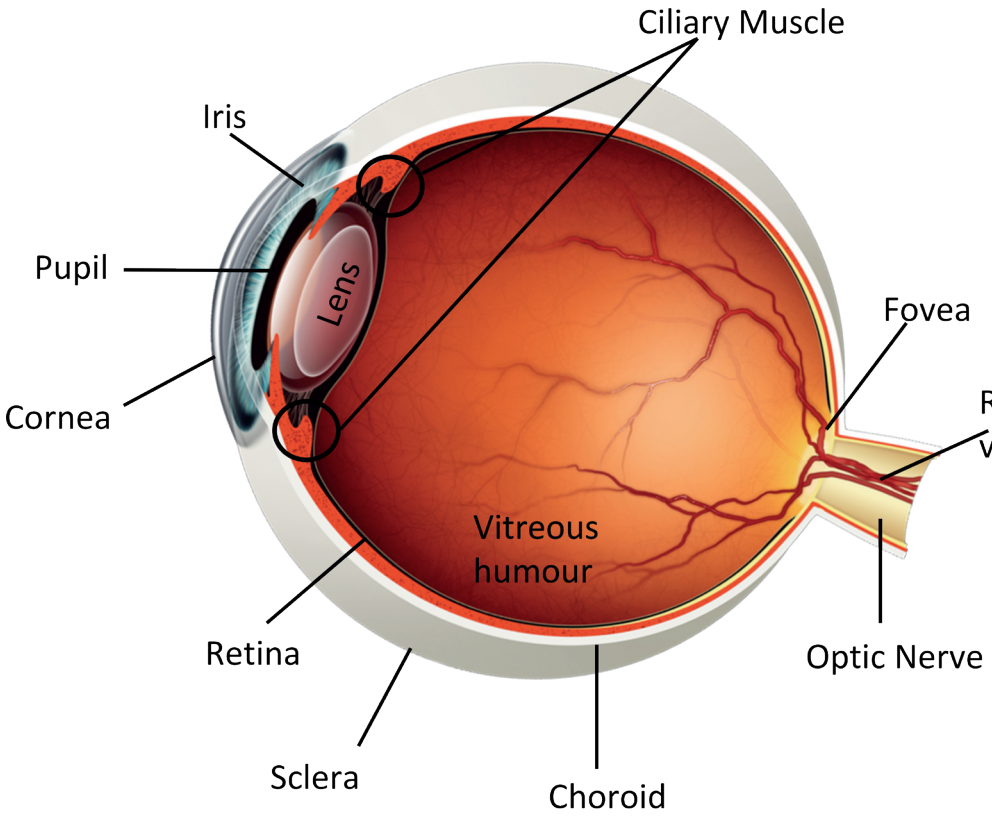

Figure 1: Simplified schematic of the human eye.

providing options for delivering precise microlitre volumes into the vitreous or choroidal chamber of the eye. However, all of these new treatments come with drawbacks, the primary culprit being that they require particularly invasive procedures. Additionally, predictable drug release from an implant is extremely difficult to achieve, given that it is a function of size and geometry and biological incompatibility can cause further inflammation for biodegradable formulations.

Despite various promising new options for back of the eye diseases, such as gene therapy, their clear limitations, especially in the drug delivery aspect, mean there is an urgency to improve the effectiveness of ocular therapies. To address this unmet medical need, Eyevensys has developed a truly innovative approach.

"A therapeutic "bio-factory" is created in the eye itself, a feat achieved by reprogramming the cells in the ciliary muscle of the eye to safely and locally produce therapeutic proteins."

EYEVENSYS' NOVEL APPROACH

Eyevensys has developed a method to treat back of the eye diseases whereby a therapeutic "bio-factory" is created in the eye itself, a feat achieved by reprogramming the cells in the ciliary muscle of the eye to safely and locally produce therapeutic proteins. Electroporation, a technique in which an electrical field is applied to cells in order to increase the permeability of the cell membrane (allowing chemicals, drugs, or DNA to be introduced into the cell), is utilised to deliver protein coding plasmids into the ciliary muscle of the eye. This enables local sustained production of therapeutic proteins. This approach is built upon Eyevensys' EyeCET platform, which uses the company's proprietary electro-transfection injection system (ETIS) to deliver the plasmids (Figure 2).

The treatment procedure, which takes less than five minutes, is designed to provide the patient with a safe and local treatment with long lasting effects between three to twelve months. The ETIS device is gently fixed to the eye and applies the electroporation technique to the ciliary muscle cells allowing the plasmids to penetrate the cells. The plasmids then encode the production of therapeutic proteins in the ciliary muscle. The ETIS device means that the process is easily controlled and reproduced.

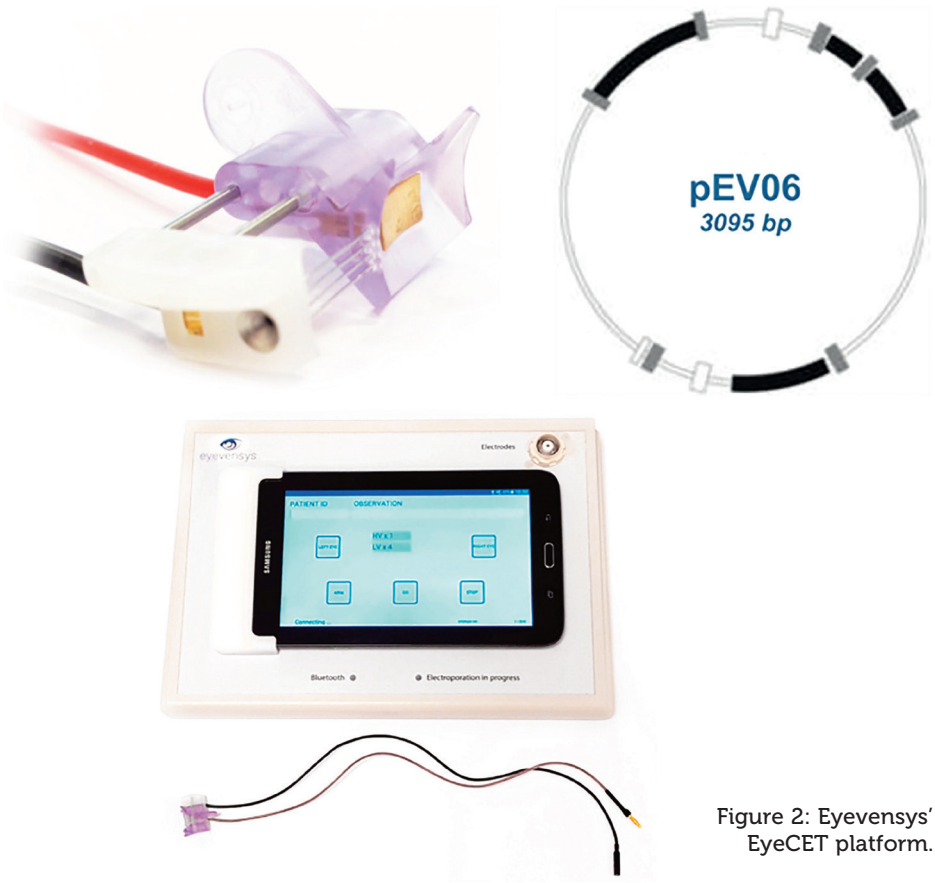

Figure 2: Eyevensys' EyeCET platform.

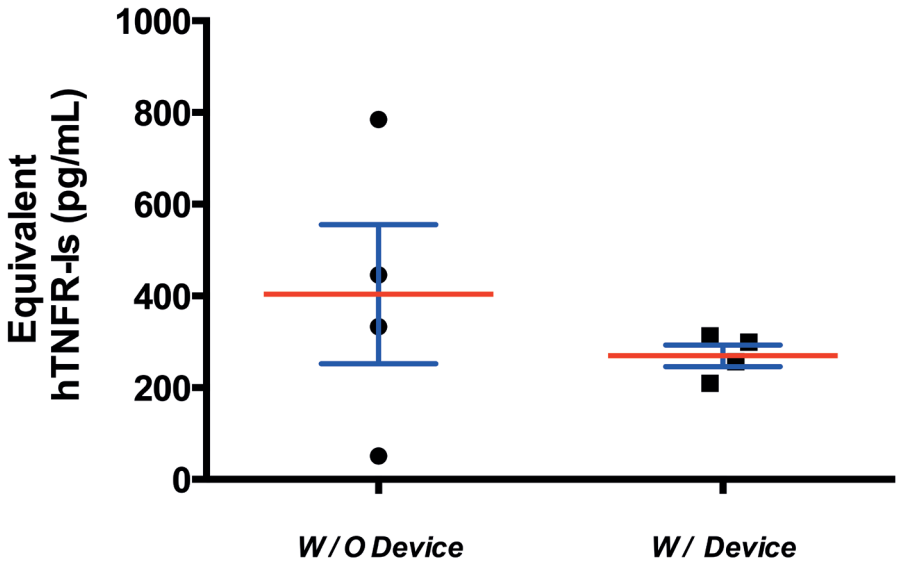

Figure 3: Comparison of the transfection reproducibility without and with an ocular device.

This translates into accurate and consistent expression of the therapeutic proteins (see Figure 3).

Eyevensys founder Dr Francine Behar-Cohen explained the thinking behind the technology thusly, "The idea was to use the only muscle inside the eye as a therapeutic producing cell, given that it was an ideal candidate for transduction, offered no visual risk and was easy to reach with minimally invasive procedure." Dr Behar-Cohen also elaborated on the delivery method: "Electroporation is a well-known method that has been used in different parts of the human body, but which represents a revolution in the field of ophthalmology. Eyevensys' technology is an innovation that applies electroporation in the ciliary muscle of the eye for the first time."

A POTENTIAL NEW TREATMENT FOR NON-INFECTIOUS UVEITIS

Eyevensys' first lead product, EYS606, is a potential new treatment for non-infectious uveitis (NIU). EYS606 has been granted an orphan designation by the EMA for the treatment of NIU and is currently being evaluated in a first-in-human Phase I/II clinical trial. EYS606 is the first non-viral product that has the potential to treat NIU patients for three to twelve months following an electro-transfection procedure.

EYS606 uses plasmid encoding for the production of inhibitors to suppress TNF-α, a pro-inflammatory cytokine that has been shown to play an important role enhancing intraocular cytotoxic events in immune diseases, including uveitis. Animal models of uveitis (EIU and EAU) have consistently shown that the treatment efficiently reduces inflammation, significantly lowers inflammatory marker levels such as TNF-α and NOS2 (Nitrate Oxide Synthase 2), and protects the outer nuclear level (ONL) from degeneration.

EYEVENSYS' AMBITIONS TO TREAT A RANGE OF MAJOR OPHTHALMIC DISEASES

Eyevensys aims to build a high value product pipeline by enabling sustained production of a number of therapeutic proteins in the eye, thus improving clinical outcomes and reducing the burden of frequent intravitreal or systemic injections in a range of important ophthalmic diseases.

Eyevensys is presently developing a preclinical pipeline where the expression of fully functional proteins has consistently been achieved in animal models.

This preclinical pipeline could lead to drug candidates to treat diseases including:

- Retinitis pigmentosa
- Dry age-related macular degeneration (AMD) & geographic atrophy
- Glaucoma
- Diabetic macular oedema
- Retinal vein occlusion (RVO/BRVO).

ABOUT THE COMPANY

Eyevensys is a private clinical-stage biotechnology company developing its EyeCET gene therapy electroporation technology to enable the sustained intraocular production of a range of therapeutic proteins. Eyevensys' vision is to use the EyeCET technology to develop a pipeline of products that address major unfulfilled needs in the treatment of sight threatening ophthalmic diseases. Eyevensys was founded in 2008 and is headquartered in Paris, France. It is funded by Boehringer Ingelheim Venture Fund, Bpifrance, CapDecisif, Inserm Transfert, and Pontifax.

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ABOUT THE AUTHOR

Patricia Zilliox, who joined the Eyevensys board in May 2016 and became CEO in December 2017, has over 25 years' experience of global clinical development in ophthalmology. Prior to this position, Dr Zilliox served as Chief Drug Development Officer of the Clinical Research Institute, a division of the Foundation Fighting Blindness, Columbia, MD, US, where she led the financing of several start-ups in the field of gene therapy. She also spearheaded validation of a new clinical endpoint in the field of retinitis pigmentosa, opening the path for drug developers to focus on treatment of this rare condition of the retina. Previously, Dr Zilliox held several positions at Alcon/Novartis, including head of clinical development for ophthalmology.

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2018/19 EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
February 2018	Prefilled Syringes & Injection Devices	DEADLINE PASSED
March 2018	Skin Drug Delivery: Dermal, Transdermal Microneedles	Feb 8th 2018
April 2018	Pulmonary & Nasal Drug Delivery	Mar 8th 2018
May 2018	Injectable Drug Delivery: Devices Focus	Apr 5th 2018
June 2018	Connecting Drug Delivery	May 3rd 2018
July 2018	Novel Oral Delivery Systems	Jun 7th 2018
August 2018	Industrialising Drug Delivery Systems	Jul 5th 2018
September 2018	Wearable Injectors	Aug 2nd 2018
October 2018	Prefilled Syringes & Injection Devices	Sep 6th 2018
November 2018	Pulmonary & Nasal Drug Delivery	Oct 4th 2018
December 2018	Connecting Drug Delivery	Nov 1st 2018
January 2019	Ophthalmic Drug Delivery	Dec 6th 2018

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