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OPHTHALMIC DRUG DELIVERY



APRIL 10TH 2014 • ISSUE N° 48



ONdrugDelivery Issue N° 48, April 10th 2014

Ophthalmic Drug Delivery

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

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 July: Novel Oral Delivery Systems
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ONdrugDelivery Magazine is published by Frederick Furness Publishing Ltd. Registered Office: The Candlemakers, West Street, Lewes, East Sussex, BN7 2NZ, United Kingdom. Registered in England: No 8348388. VAT Registration No: GB 153 0432 49. ISSN 2049-145X print. ISSN 2049-1468 pdf

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OCULAR DRUG DELIVERY: REVIEW OF PRESENT TECHNOLOGIES & STEPS FORWARD

Here, Shikha Barman, PhD, Chief Executive Officer & Chief Technology Officer, Integral BioSystems, provides an overview of the current state of play in the ocular drug delivery market, sets ocular drug delivery systems, both for the anterior segment and the back of the eye, in the context of the wider ophthalmic therapeutics market, and highlights how important it is for both ophthalmic drug discovery and ophthalmic drug delivery developments to progress together in parallel.

OPHTHALMIC DRUG PRODUCTS MARKET: CLINICAL AND BUSINESS NEED-DRIVEN

Market research estimates performed in the last six months have shown that the market size for ophthalmic medications is expected to reach more than 16 billion, by the year 2018.¹ The ophthalmology drugs market classification is based on the type of drugs: treatment-based drugs, over-the-counter (OTC) drugs and ocular anaesthetics.

In the last decade, clinical need has driven the ophthalmic drug development industry to make extraordinary strides forward both in drug design and in ocular delivery. Following the high profile scientific breakthroughs of nucleic acid-based cell-targeted therapies (RNAi, aptamers), highly specific receptor-targeted small-molecule therapies, efficient cell-permeating small molecules and pro-drugs, retro-metabolic small molecules and drugs with better safety profiles, have been the introduction of intelligent drug delivery systems that claim to deliver to the targeted tissue for the required duration.

Combined with these clinical need-driven innovations are a plethora of technologies that are business-driven, aimed at product extensions for life-cycle management of existing products. Each of these extensions offers improvements and benefits over current technologies, such as offering preservative-free options, or “non-settling” formulations, amongst others. From a regulatory perspective, in the US, the number of 505(b)(2) applications claiming differenti-

ated technologies has risen dramatically, with fewer NDA (505(b)(1) applications for new chemical entities (NCEs) than there were in previous years.

The repurposing of previously approved molecules for other indications into products reformulated and optimised for ophthalmic delivery has the advantage of leveraging long-term relevant safety data in humans, offering a regulatory advantage with the US FDA approval process. If differentiated, IP protection is sought after, to gain maximum product lifecycle extension for these products. In lock-step with these products is the generic ophthalmic products industry, offering high quality, pharmaceutically compliant products at an affordable cost. Thus, the ophthalmic products industry continues to seek a fine balance between innovation to meet both business and clinical needs and a relatively short regulatory timeline.

ANTERIOR SEGMENT & CHALLENGES TO DELIVERY

Common disorders of the anterior segment of the eye include glaucoma, corneal keratitis, blepharitis, allergic conjunctivitis, cataracts, dry eye, and bacterial and fungal infections. Less common disorders are corneal dystrophies such as Fuchs’ endothelial dystrophy, and rarer infections (bacterial, viral and fungal) including herpes zoster and ocular herpes simplex. These infections can reduce visual clarity, produce corneal discharges and erode the cornea, sometimes leading to corneal scarring. Inflammatory



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disorders of the cornea include episcleritis, uveitis and keratitis.

Ophthalmic medications to treat the anterior segment of the eye are administered to the ocular surface, which includes the cornea, sclera and the highly intricate protein-rich mucosal-ocular membrane. Disorders of the biological-chemical-immunological balance of the ocular membrane can lead to the still-poorly understood dry-eye syndrome, which can then trigger a cascade of pro-inflammatory factors, which in turn can lead to other disorders.² In highly populated urban areas, a high propensity of contracting ocular surface diseases such as infections, allergies, symptoms of dry eye and corneal keratitis, has been reported. These diseases have been managed either by treatment of the symptoms (treatment-based drugs), or by addressing the root cause.

In the case of dry eye, treatment strategies have included use of drug-free artificial tear solutions to assuage the symptoms temporarily, or drug-containing formulations to address disorders caused as a result of the dry eye disorder (infections, inflammation, etc.). Other ocular diseases of the anterior segment of the eye include glaucoma, blepharitis, delayed corneal healing or conjunctival/corneal infections. The palette of therapies to treat these ocular surface disorders has been standard: anti-inflammatories, anti-microbials, NSAIDs and anti-glaucoma medications, for example.

In actual clinical practice, therapies to treat the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea) are in the form of solutions and suspensions, either as eye-drops, or as ointments or gels. For eye-drops (solutions and suspensions), high drainage rates of the drug to the naso-lacrimal duct make drug absorption sub-optimal, with an average bioavailability of less than 5%. This leads to requirements of multiple administrations per day, to reach effective drug levels in the target tissue. Multiple administrations in the eye are an issue in patient compliance, not only for the elderly and paediatric populations, but also for the timeline-driven average working adult. Some of these issues are assuaged by the utilisation of excipients to extend drug residence time.

Another critical obstacle to efficient drug absorption is the corneal and conjunctival barriers. Drugs with log P in the range 2-3 are ideal for absorption through the corneal and conjunctival membranes. Molecules

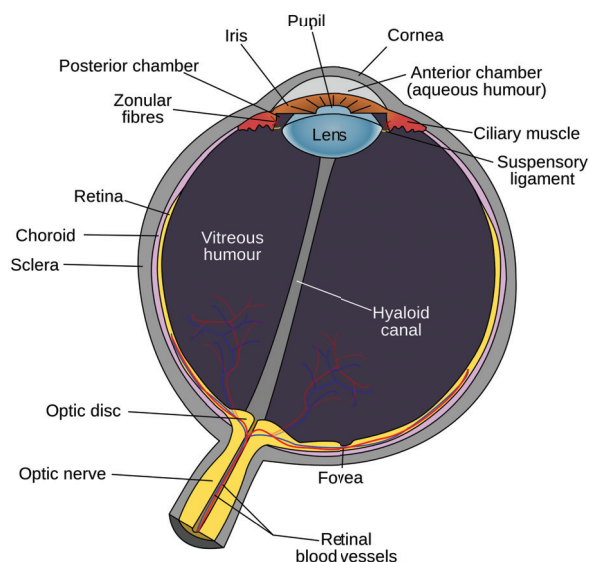


Figure 1: Simplified schematic of the human eye.

Image Source: Wikipedia. Reproduced with kind permission.

with a low partition coefficient do not penetrate the lipophilic epithelia of the cornea and the conjunctiva. Molecules with a log P value >3.5 do not permeate the hydrophilic stromal layer of the cornea.³

However, improvements have been made to render drugs efficient, effective and with fewer side-effects. In fact, the ophthalmic drug industry has witnessed a flood of improved medications with higher drug residence times, higher permeability and lower effective doses. To give just one example, Xibrom, the twice-daily formulation of bromfenac has now been discon-

“The ophthalmic drug industry has witnessed a flood of improved medications with higher drug residence times, higher permeability and lower effective doses”

tinued in favour of the improved version, Prolensa, which is only needed once-daily. Combination products of drugs that have been marketed as separate dosage forms are often now prescribed together to treat inflammation and infections, providing higher probability of patient compliance. For example, Zylet is a combination of loteprednol + tobramycin, which in one product does the job of Lotemax ointment (loteprednol alone) and Tobramycin

ointment). However, CMC issues in ensuring stability of co-existing drugs in the same dosage form and regulatory hurdles toward achieving FDA approval can slow down the drug development process.

Examples of other improvements are “non-settling” suspensions, which assure a uniform dose per administered eye-drop. An example is the market introduction of Lotemax, 0.5% gel. Compared with Lotemax 0.5% ointment (which causes blurred vision) the gel product incorporates formulation improvements such as physiologically-matched solution pH and addition of excipients that prevent settling.

As innovations in drug design, chemical structure modifications to enhance drug permeability, or reduce side effects are also improvements brought about by clinical need. For example, difluprednate (Durezol) is a structural design improvement on prednisolone, an anti-inflammatory drug indicated for the prevention of post-surgical inflammation.

Another elegant structural design improvement, loteprednol etabonate, is a novel carbon 20 (C-20) ester-based corticosteroid that has been developed as a topical treatment for ocular inflammation. Loteprednol etabonate was developed using retro-metabolic design, in which an inactive and nontoxic metabolite of a reference compound is used as the starting point for the synthesis of a therapeutically active, but metabolically unstable, compound that can be rapidly deactivated. In the case of loteprednol etabonate, the drug is rapidly deactivated to inactive metabolites by nonspecific tissue esterases in the ocular tissue, thereby limiting its potential to cause adverse effects such as ocular hypertension and glaucoma, side effects commonly known to occur with steroids.^{4,5}

POSTERIOR SEGMENT: CHALLENGES TO DELIVERY

Diseases of the posterior segment represent the leading cause of visual impairment and blindness in the US and most other industrialised nations. Increased vascularisation in retinal tissues due to diabetic retinopathy (DR) and age-related macular degeneration (AMD) has been the leading causative factor for irreversible blindness in the adult population.

Specifically, age-related macular degeneration (AMD) is a retinal degenerative

disease that causes a progressive loss of central vision. AMD is the most common cause of vision loss in individuals aged over 55. An estimated 10 million people in the US either have AMD or are at substantial risk of developing it. There are two types of AMD, wet AMD and dry AMD. Wet AMD accounts for about 10% of all cases of macular degeneration. Wet AMD is also

include: Unilife; iScience Interventional (acquired by Ellex Medical Lasers in January 2014); and Clearside BioMedical. Other innovative methods for delivery include: iontophoresis (e.g. EyeGate II from EyeGate Pharmaceuticals); free-floating intravitreal implants (e.g. Allergan's Ozurdex and pSivida's Iluvian); scleral-implanted intravitreal devices (e.g. Retisert also from pSivida);

delivery has taken giant steps forward in the last decade. Lastly, none of the delivery systems that have been marketed actually have been shown to improve the uptake of macromolecules and small molecules alike. Achievement of this goal will be a transformative step in drug delivery.

CONCLUSION

In conclusion, it can be stated that innovative drug delivery needs to proceed astride innovative drug design aimed at curing the disease, as well as managing the symptoms and slowing down disease progression. This requires intense interdisciplinary efforts to further disease understanding, identification of additional receptors and mechanisms of action, intelligent repurposing of drugs and precise, predictable and sustained drug administration at the target site for the requisite duration.

ABOUT INTEGRAL BIOSYSTEMS

Integral BioSystems is a contract research organisation specialising in biodegradable sustained-release dosage forms for proteins, peptides, nucleic acids and small molecules. Microspheres, liposomes, micro-nano suspensions are Integral's niche specialisation. Integral BioSystems invites collaborations that can be strictly on a CRO-basis to create drug products with compounds that already have IP protection, or as a co-developer with pharmaceutical companies to render repurposed drugs IP-protectable with Integral's proprietary drug delivery innovations.

PROPRIETARY OCULAR DELIVERY SYSTEMS

Integral scientists have developed a proprietary ocular delivery system (EySite™) that releases precise, predictable concentrations of drug over time. The composition of the EySite delivery system can be modulated for a drug regimen that lasts a week, to one that can be designed last 3-6 months. Both water-soluble and water-insoluble drugs, small molecule or macromolecular, can be designed into injectable dosage forms for both front-of-the-eye and back-of-the-eye indications. The company also announces OcuSurf™, a proprietary nanostructured delivery system designed to deliver drugs to the ocular surface, enhancing permeation into ocular tissues. The company invites collaborations with drug companies to co-

“Strategically, posterior segment drug delivery for inflammatory conditions, both non-infectious and infectious, should minimise collateral damage, and duration of treatment should be in accordance with the acute or chronic nature of the disease”

called choroidal neovascularisation (CNV), subretinal neovascularisation, or exudative or disciform degeneration. In wet AMD, abnormal blood vessels grow beneath the macula. These vessels leak blood and fluid into the macula that damage photoreceptor cells. Wet AMD often progresses rapidly and can cause substantial loss of central vision. Dry AMD is presented in 90% of the cases with AMD, affects vision less, is non-exudative and characterised by drusen, or fat cells or waste products from cells.

Topical medications do not reach the posterior segment of the eye. Thus, disorders of the posterior segment of the eye (retina, vitreous, choroid) have been traditionally addressed by high drug doses administered intravenously, by repeated intra-vitreous injections, or by surgical intervention. Surgical techniques include laser photocoagulation and vitrectomy. A combination of surgical and drug-based therapies have been adopted as a strategy to achieve improvement in vision acuity. Due to inaccessibility of the tissue, drug therapies are by repeated injections of drug suspensions, or solutions.

Strategically, posterior segment drug delivery for inflammatory conditions, both non-infectious and infectious, should minimise collateral damage, and duration of treatment should be in accordance with the acute or chronic nature of the disease. Drug therapies to treat wet AMD are available (Eylea, Macugen, Lucentis), all requiring multiple injections with a 27G needle.

Innovations with needle technology have provided options for delivering precise microlitre volumes into the vitreous or choroidal space. Companies in this space

and biodegradable formulations (e.g. Icon Bioscience's Verisome).

Iontophoretic drug transport across ocular tissues has been shown to be successful in animal models, although the pre-requisite for this method is that the drug would need to be charged.

Drug suspensions of glucocorticosteroids (such as Alcon's Triescence) injected into the vitreous are used to lower inflammation, but one serious adverse effect is increase in intraocular pressure (IOP), endophthalmitis and cataract formation, resulting from drug transport into the anterior chamber.

It is worth mentioning here that the rate of fluid turnover in the vitreous is very low, unlike other tissues. Thus, once drug saturation is reached in the vitreous, elimination of drug is by metabolism and absorption. Furthermore, drug suspensions post-injection agglomerate into a mass. Since drug release is a function of size and geometry, sustained-release delivery systems that form depots of various sizes and shapes in-vivo do not have predictable drug release. Additionally, it is to be noted that build-up of byproducts of biodegradable polymers (lactic acid, glycolic acid and combinations thereof) can induce biological incompatibilities and cause further inflammation.

Thus, game changing, transformative drug delivery therapies of the future can be envisioned as those that are targeted, non-invasive, biodegradable, does not itself elicit an immunological inflammatory response, biocompatible and achieves a predictable, precise sustained release of drug that allows less than three injections per year.

None of the delivery systems currently meet all criteria, although innovative drug

develop ophthalmic products utilising these delivery systems.

Generally, Integral BioSystems integrates interdisciplinary fields of physical chemistry, analytical chemistry, pharmacology/pharmacokinetics/biology and process engineering to design ophthalmic dosage forms. Led by drug delivery/analytical chemistry subject area experts, Integral BioSystems has developed numerous nano- and micro-engineered dosage forms for ophthalmic routes, specialising in providing solutions to long-held issues in drug products, especially in low drug absorption by target tissues due to cell impermeability, insolubility and instability.

As a CRO, Integral BioSystems offers pharmaceutical companies formulation development, process engineering, scale-up, technical transfer and CMC writing services for IND, NDA, ANDA and 505(b)2 submissions. Integral BioSystems is based in the Boston area, with offices and fully equipped laboratories at Bedford, MA, US.

ABOUT THE AUTHOR

Shikha Barman has more than 20 years' experience in the translation of concepts from the lab into clinical and commercial drug products. Her expertise is in the design of cell-targeted delivery systems, customised to permeate biological barriers such as the skin, ocular and intestinal barriers. Prior to founding Integral BioSystems as a hybrid CRO/innovation-based company with Boston-area patent attorney Dave Karasic, Dr Barman held senior research and pharmaceutical development roles at various companies including Inotek Pharmaceuticals, Inc, and Sontra Medical Corporation. She holds 17 issued US Patents and 56 US applications/PCTs, and has authored 65 publications and four book chapters. Dr Barman has a PhD in Polymer Science and in Plastics Engineering and an MS in Polymers from the University of Massachusetts at Lowell, and a BS/MS in Chemistry from Auburn University, AL, US.

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Integral BioSystems

Ocular Drug Delivery

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- Analytical Method Development
- Scale-Up/Process Engineering
- CMC Consulting
- IP Strategy/Patent Filing
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- Emulsions
- Liposomes
- Lyophilized Dosage Forms

Ask about our proprietary sustained release drug delivery systems for retinal disease.

COMPANY PROFILE: GRAYBUG



GRAYBUG OVERVIEW

GrayBug is advancing ophthalmic therapeutics through a continuum of polymer-based drug delivery platforms and innovative products offering sustained competitive advantage. Its technologies include proprietary biodegradable drug-loaded nanoparticles, microparticles and injectable implants providing extended release of small to large molecules for intraocular applications to treat ocular diseases.

The company's business objective is to build and implement two synergistic development strategies in major global ocular disease segments:

1) Proprietary Product Development Programs with lead compounds in neovascular diseases such as age-related macular degeneration (AMD) and diabetic retinopathy, and glaucoma. Worldwide markets for AMD and glaucoma currently exceed US\$9 billion with significant market need existing for product enhancements and innovation through extended release drug delivery.

2) Proprietary Polymer-Based Technologies that deliver a wide range of drugs, including small molecules, peptides, proteins, aptamers, and other biologics.

VALUE PROPOSITION

- Unique continuum of drug delivery platforms – small to large molecule spectrum including proteins – micro and nanoparticles, injectable implants
- Customised development for target drug
- Proven success rate with multiple molecules tested to date

- Elimination of inflammation associated with conventional particles, including PLGA microparticles
- Efficacy in multiple animal models for multiple drugs in the pipeline
- Published preclinical data – proof of concept for platform technology.

PROOF-OF-CONCEPT

Proof of concept has been demonstrated in animals for all products in the pipeline (see Figure 1) including GrayBug's AMD and glaucoma drug candidates. The company's proprietary controlled-release drug delivery systems can be tailored to meet performance requirements of duration and rate of drug release. GrayBug possesses the technical expertise, experience, and capacity to collaborate with select partners in areas of mutual interest.

Our world-class team and advisors have over 80 peer-reviewed publications on the long-term, controlled delivery of biologics.

Products	Pathway Identification	API Selection	Formulation Development	In Vivo Efficacy	PK/PD	Non-GLP Toxicology	Lead Optimisation	GLP Studies	IND
Wet AMD	GB-101								
	GB-102								
Glaucoma	GB-201								
	GB-202, GB-203 & GB-204								
Corneal Graft Rejection	GB-301								

Figure 1: Development pipeline showing milestone achievements.

"GrayBug's controlled-release technologies may reduce dosing frequencies to only 2-3 times per year, which is expected to improve patient compliance and drug efficacy"



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Former GM, VP Global Strategy
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Alza, Pfizer, and 3M



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Center for Nanomedicine at the Wilmer Eye
Institute, Johns Hopkins School of Medicine

GRAYBUG'S TECHNOLOGY

GrayBug's proprietary technologies allow customisable sustained release of all therapeutic classes, when delivered intraocularly (see Figure 2). GrayBug's controlled-release technologies may reduce dosing frequencies to only 2-3 times per year, which is expected to improve patient compliance and drug efficacy.

Pipeline products include GB-101 and GB-102, which are single drug agents that inhibit multiple pathogenic angiogenesis signals, and innovative glaucoma therapies, both for the controlled-release of intraocular pressure-lowering drugs and for long-term protection of the optic nerves to prevent blindness.

SUMMARY

- GrayBug offers major product development opportunities for the extended and controlled release of small and large molecules including proteins
- Strong intellectual property position. US and international patent application families protecting two drug delivery platform technologies through 2031
- Proprietary preclinical product development programs in AMD and glaucoma
- Strong and experienced management team in ocular drug delivery development and commercialisation, and world-class leaders in development of long-lasting protein delivery systems
- Awarded Small Business Innovation Research (SBIR) grants

"Our world-class team and advisors have over 80 peer-reviewed publications on the long-term, controlled delivery of biologics"

GrayBug welcomes invitations from interested parties to enter discussions about significant business development and partnership opportunities.

ABOUT GRAYBUG

GrayBug® is developing a continuum of proprietary controlled-release drug delivery technologies for strategic partnership and its own therapeutic products for major ocular diseases.

GrayBug's technologies were co-developed by GrayBug founder, Justin Hanes, PhD, who is the Lewis J Ort Professor of Ophthalmology at the Wilmer Eye Institute of the Johns Hopkins University, in collaboration with GrayBug co-founders, and leading clinician-scientists in ophthalmology from the Wilmer Eye Institute, Peter A Campochiaro, MD, and Peter J McDonnell, MD. The technologies were licensed from the Johns Hopkins University.

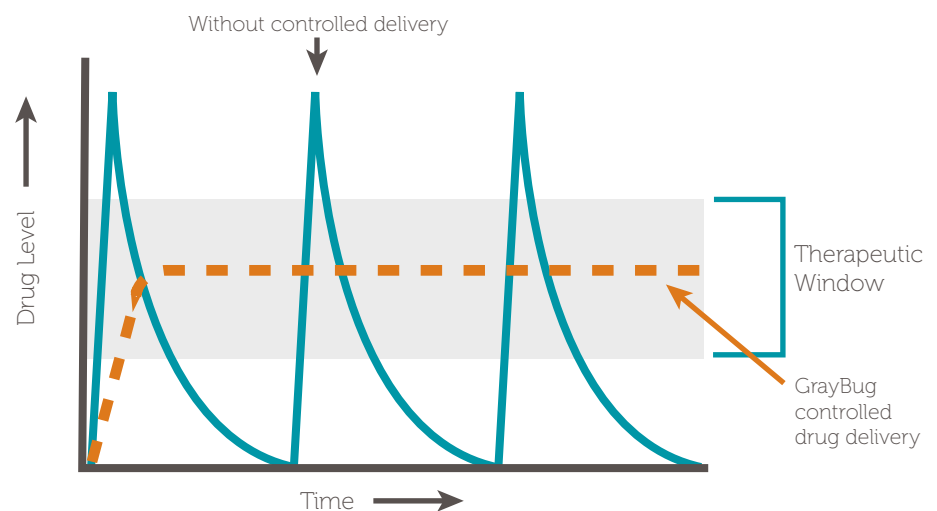


Figure 2: GrayBug controlled-release drug delivery.



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IMPROVING OUTCOMES IN OPHTHALMOLOGY VIA SUSTAINED DRUG DELIVERY

In this piece, Tomas Navratil, PhD, Vice-President, Development; Benjamin Maynor, PhD, Vice-President, Research; and Benjamin Yerxa, PhD, Chief Scientific Officer, all of Envisia Therapeutics, Inc, describe the company's particle engineering technology and its application in improving the delivery of prostaglandin analogues and anti-VEGF therapy.

Despite the abundance of efficacious small and large molecular entities targeting ophthalmic diseases, the effectiveness of ocular therapies remains limited by available drug delivery methods. For topical therapies, the compliance is generally low, the bioavailability is limited by short residence times

BIODEGRADABLE POLYMER SCIENCE MEETS PRINT PARTICLE ENGINEERING

To address the unmet medical need in ophthalmic drug delivery, Envisia has combined its PRINT particle engineering technology with biodegradable polymer science. The PRINT technology offers a unique ability to reproducibly fabricate particles of virtually any size, shape, chemistry, surface functionality, modulus and porosity. Additionally, PRINT has been shown previously to be broadly compatible with a wide range of biodegradable polymer chemistries and molecular entities including small molecules, nucleic acids, enzymes, and therapeutic monoclonal antibodies (see Figure 1).¹

"A high percentage of patients experience hyperaemia side effects and as many as 30-60% of patients discontinue topical therapies for glaucoma within the first year of treatment"

combined with low efficiency transport across the ocular surface and often there are undesirable local and systemic side effects. For intravitreal (IVT) therapies frequent, often monthly intraocular injections are required, thus exposing the patients to an excessive treatment burden and small but repeated risk of intraocular infections. By combining biodegradable polymer science with its unique PRINT® particle engineering technology, Envisia Therapeutics has developed new extended drug delivery approaches for ophthalmic drug delivery. Based on this technology, Envisia is developing novel, extended-release therapies for the treatment of glaucoma, age-related macular degeneration (AMD) and other ophthalmic diseases, with extended treatment effect ranging from weeks to months following a single dose.

BIODEGRADABLE NANO- AND MICRO-PARTICLE SUSPENSIONS & IMPLANTS

The unique flexibility of PRINT has been used to develop biodegradable nano- and microparticle suspensions and biodegradable implants for extended drug delivery into the eye. The resulting PRINT-based ocular formulations are capable of targeting all major ocular tissues: the ocular surface (subconjunctival implants and topical nano- and microsuspensions); the anterior chamber (intracameral implants and subconjunctival implants); and the vitreous/retina (IVT implants and IVT microsuspensions,

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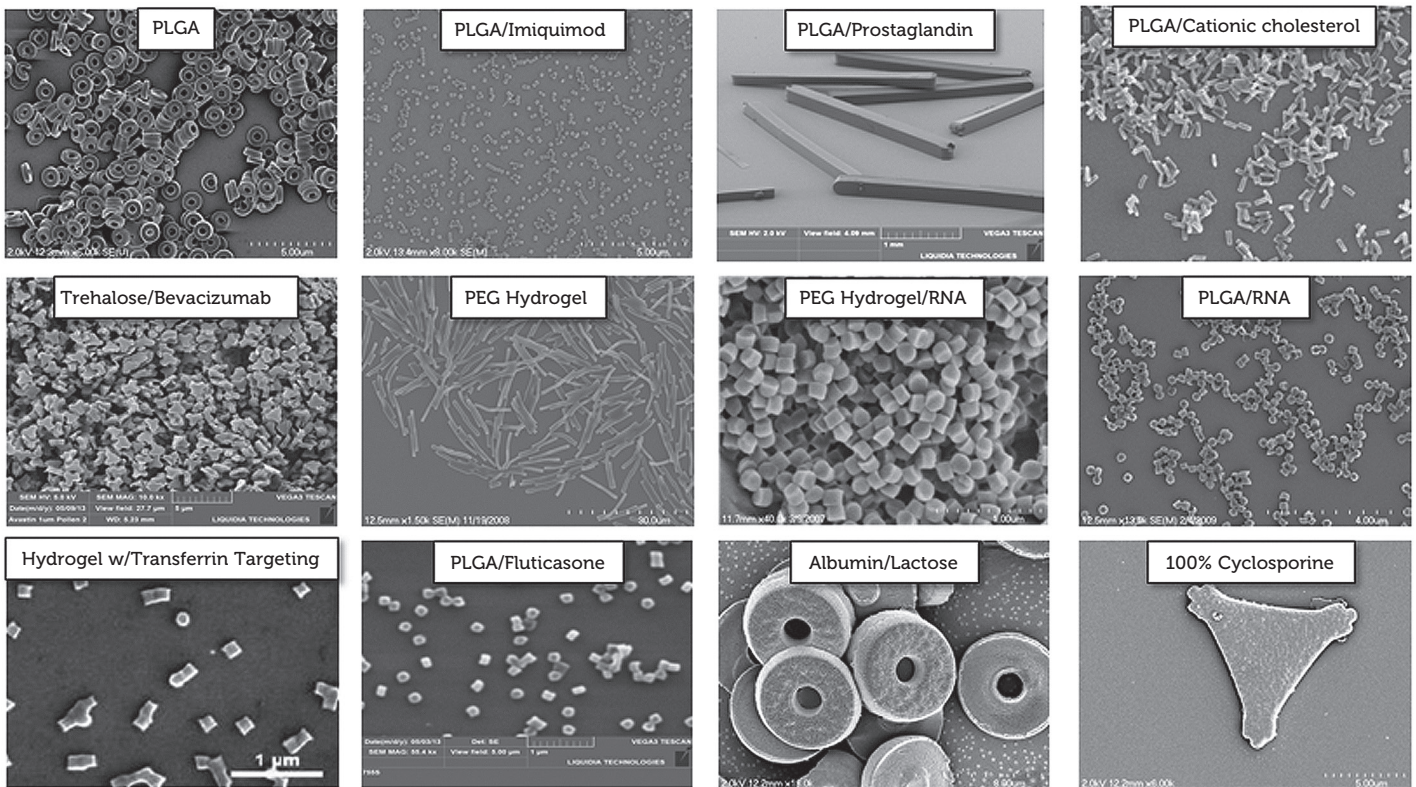


Figure 1: PRINT technology is compatible with small molecules and biologics and allows for precise control of size, shape and chemistry.

see Figure 2a). Lastly, the availability of numerous biodegradable polymer chemistries results in fully tuneable sustained rates of drug release (Figure 2b). In combination with targeted delivery into individual anatomical compartments in the eye, these tuneable features are essential to the development of future ophthalmic therapies with extended efficacy and fewer side effects.

OPPORTUNITIES FOR EXTENDED DELIVERY OF PGAS IN GLAUCOMA

Glaucoma is an optic neuropathy that results in progressive and irreversible visual field deterioration. It affects approximately 70 million patients and is the second leading cause of blindness worldwide. Prostaglandin analogues (PGAs) are the most prescribed class

of topical therapies for glaucoma in the US but possess several shortcomings: low adherence; hyperaemia side effects; and fluctuation in ocular drug levels and intraocular pressure (IOP).^{2,3} For example, a high percentage of patients experience hyperaemia side effects and as many as 30-60% of patients discontinue topical therapies for glaucoma within the first year of treatment.⁴ Additionally, the

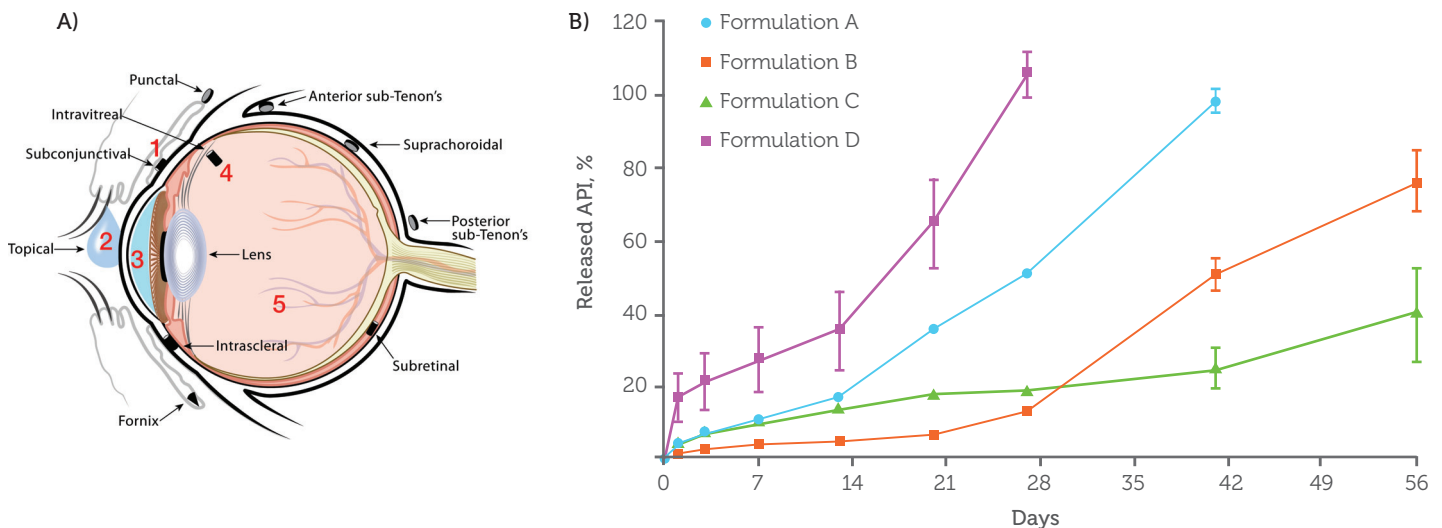


Figure 2: A) PRINT-based subconjunctival (1), intracameral (3) and intravitreal (4) implants, and topical (2) and IVT (5) Suspensions. B) Tuneable drug release from PRINT formulations.

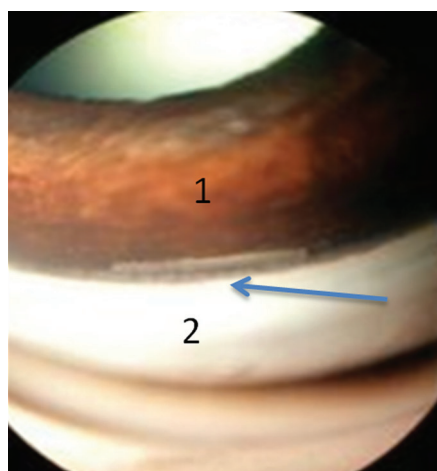


Figure 3: ENV intracameral insert in iridocorneal angle of beagle dog (1. iris; 2. cornea).

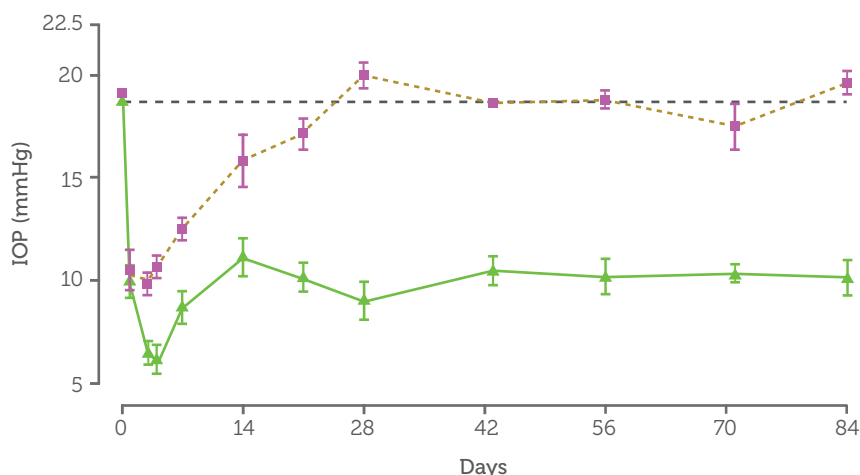


Figure 4: IOP-lowering effect of ENV55-8 – PGA extended-release formulation in normotensive beagle dogs (green: ENV55-8, purple: placebo).

“The simple in-office insertion procedure, the implied 100% compliance, and the sustained drug levels leading to lasting IOP-lowering effects address the top shortcomings of the existing topical PGA therapies”

topical PGA therapies. ENV515 is currently in preclinical development. Envisia plans to initiate clinical trials of ENV515 in glaucoma patients in the second half of 2014.

OPPORTUNITIES FOR EXTENDED DRUG DELIVERY OF ANTI-VEGF THERAPY FOR WET AMD

AMD is a retinopathy characterised by choroidal neovascularisation (CNV) and central retinal thickening due to vessel leakage resulting in macular oedema. These pathophysiologies occur due to increased secretion of vascular endothelial growth factor (VEGF) and lead to consequent rapid vision loss, with AMD becoming the leading cause of blindness in the elderly in the developed world.⁵

There are approximately 30 million AMD patients worldwide, with the overall financial cost of visual impairment due to AMD being assessed at US\$343 billion (2010 estimates based on approximately three million blind individuals due to AMD).⁶ The current standard of care is based on repeated, office-based intravitreal injection of anti-VEGF therapies comprising monoclonal antibodies (bevacizumab and ranibizumab) and VEGF receptor-trap (aflibercept). The first approved effective anti-VEGF therapy is indicated for monthly intravitreal injections.

However, to reduce the cost, patient treatment burden and risk of infection, other approaches with less frequent dosing – such as treat and extend or *pro re nata* – have been proposed and studied. The optimal schedule has currently not been determined and can differ from patient to patient. Targeted, extended-release formulations of anti-VEGF therapies would likely address the key short-

comings of topical PGAs. daily bolus administrations of topical therapies lead to drug level peaks and troughs, which in turn may lead to IOP fluctuations and potential faster disease progression. Targeted, extended-release formulations of PGAs are being developed by Envisia to address the key shortcomings of topical PGAs.

ENV515 INTRACAMERAL EXTENDED-RELEASE PGA FOR GLAUCOMA

Envisia is developing ENV515 PGA therapy, a PRINT-based biodegradable polymer drug delivery system using an extended-release formulation of the PGA. The PRINT technology was used to fabricate ENV515 as a rod-shaped implant to fit the anatomy of the iridocorneal angle in the anterior chamber (see Figure 3), and to allow its administration via acceptably-sized needle.

Multiple formulations were evaluated in preclinical models and demonstrated robust, sustained IOP-lowering effect for periods of 3-8 months following single insertion via intracameral injection (see Figure 4 for a representative formulation). The simple in-office insertion procedure, the implied 100% compliance, and the sustained drug levels leading to lasting IOP-lowering effects address the top shortcomings of the existing

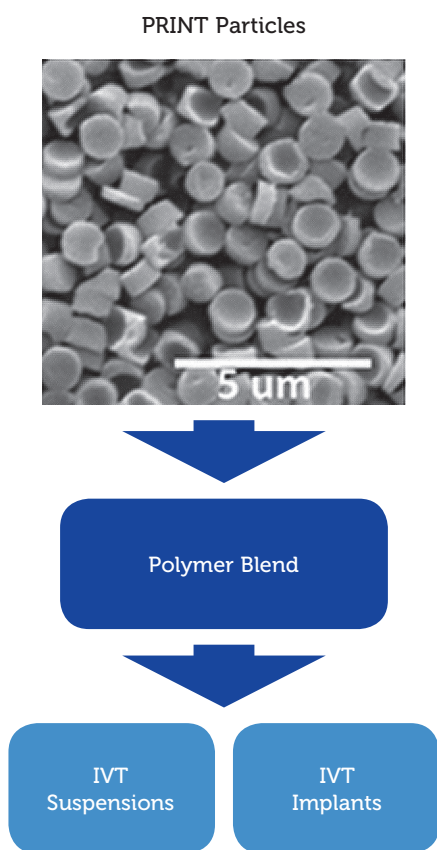


Figure 5: Envisia formulation process for extended-release IVT biologics.

comings of the current standard of care. However, none are approved today.⁵

ENV705 EXTENDED-RELEASE ANTI-VEGF THERAPY FOR AMD

Extended-release, biodegradable implants of anti-VEGF therapies may reduce burden on patients and physicians, and improve outcomes. However, development of such therapies is a challenge due to the fragile nature of anti-VEGF biologics. The PRINT technology provides the unique ability to control size, shape and biological activity of protein particles. Envisia has developed a formulation process in which monodisperse PRINT particles are composed of excipients and anti-VEGF agents. These microparticles are then uniformly dispersed throughout various polymer blends and moulded into IVT implants or microsuspensions (see Figure 5).

The resultant IVT formulations retain the anti-VEGF activity and are tuneable for rate of and duration of drug release (Figure 6). Retention of the biological activity and the tuneable properties are essential for the development of the future extended-release anti-VEGF agents for AMD.

CONCLUSIONS AND FORECAST

Envisia Therapeutics has developed a targeted extended drug delivery technology at an intersection of biodegradable polymer science and PRINT-based particle engineering. Similarly to the PGA intracameral formulations (Figures 3 and 7B), Envisia's subconjunctival formulations are fabricated as rod-shaped implants and enable extended drug delivery to the ocular surface and into the anterior chamber (Figure 7A). Hence Envisia's nanosuspension, microsuspension, and implant based, extended-release formulations are capable of targeting the ocular surface, anterior chamber and posterior segment with both small molecules and biologics (Figures 3-7).

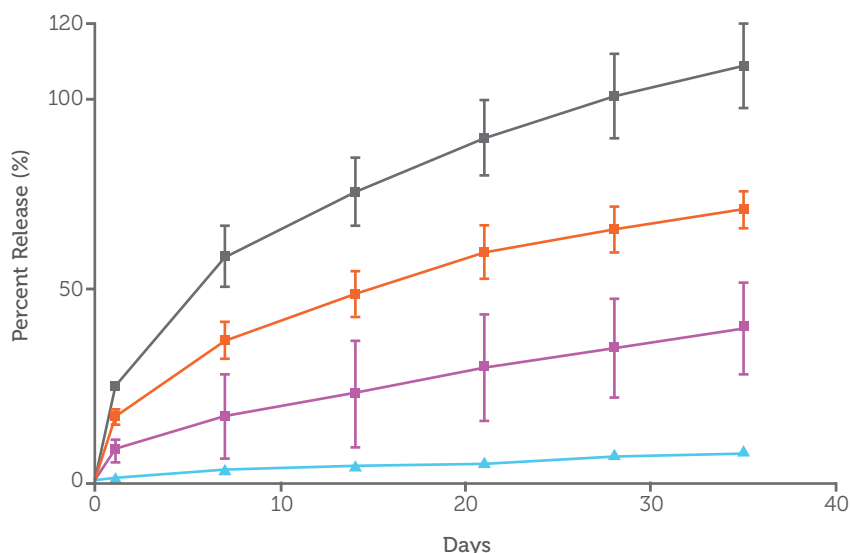


Figure 6: Tuneable rate of release for PRINT-based anti-VEGF formulations.

“Retention of the biological activity and the tuneable properties are essential for the development of the future extended-release anti-VEGF agents for AMD”

Envisia is currently developing multiple extended-release therapies for the treatment of ophthalmic diseases.

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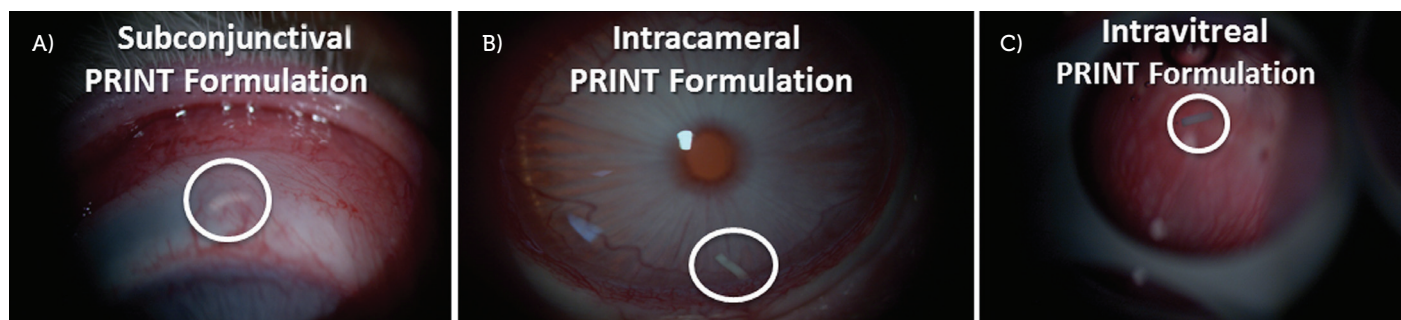


Figure 7: PRINT-based sustained-release formulations administered as subconjunctival (A), intracameral (B), and intravitreal (C) implants in New Zealand white rabbits.

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TRANSLATION of Delivery Technology: Innovation to Commercialization



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Chad Mirkin

Chad is the director of the International Institute for Nanotechnology and the George B. Rathmann Professor of Chemistry, Chemical and Biological Engineering, Biomedical Engineering, Materials Science and Engineering, and Medicine. He has authored over 550 manuscripts, is an inventor on over 900 patent applications worldwide (242 issued), and is one of only 12 scientists, engineers, and medical doctors to be elected to all three U.S. national academies.

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CUTTING EDGE TECHNOLOGY, TRANSFORMATIVE OCULAR THERAPEUTICS

The Challenge

As many as 285 million people suffer from disease-related visual impairments and blindness,¹ but an estimated 80 percent of these visual impairments are actually preventable.² Unfortunately, the safety and effectiveness of many medical therapies for ocular disorders are limited due to poor drug uptake, non-specificity to target tissues, systemic side effects, or poor adherence to therapy. With a rapidly aging population, the unmet medical needs of patients with ocular disease are becoming even more pronounced. As a result, patients and physicians are seeking improved ocular therapeutics that can significantly enhance patient outcomes and convenience.

The Company

In 2013, Liquidia Technologies spun out Envisia Therapeutics, a new company committed to engineering the future of ophthalmology. At Envisia, a talented team of scientists is harnessing the unique characteristics of a revolutionary product development technology to create novel therapeutics that can address critical unmet needs in ophthalmology and transform the treatment of ocular disease.

The Technology

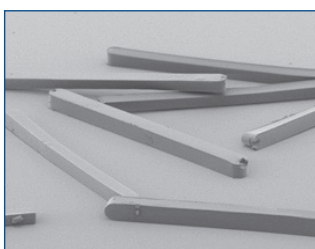
To address these critical unmet needs, Envisia is using the proprietary PRINT[®] technology to rationally design and manufacture micro- and nanoparticle systems. Unlike self-assembled particle systems or harsh micronization techniques, the PRINT technology offers the unique ability to rationally design precise particles of virtually any size, shape and chemistry,

including small-molecule active pharmaceutical ingredients (API), biologic APIs, nucleic acids, and polymeric drug delivery systems (e.g. extended release formulations). Also, because each particle is manufactured with precision, the PRINT particles and implants have been designed to have unparalleled lot-to-lot and dose-to-dose consistency. These particles are designed and manufactured with the goal of next-generation therapeutics that have improved delivery, safety and efficacy.

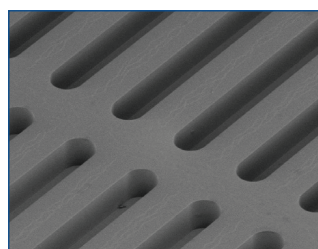
The Pipeline

Envisia's lead product, ENV515, is an undisclosed marketed prostaglandin analogue that uses a proprietary, fully biodegradable PRINT particle formulation to provide sustained intraocular pressure (IOP) reduction over many months, offering the potential to address the poor compliance that exists today and to limit glaucoma progression and vision loss. Envisia plans to initiate clinical development for ENV515 by the second half of 2014. Envisia is also developing ENV705 for wet age-related macular degeneration (AMD) and exploring how this unique technology can address other important ocular diseases.

PRODUCT	RESEARCH	LEAD OPTIMIZATION	PRE-CLINICAL	PHASE 1	PHASE 2
ENV515 (Glaucoma)	[Progress bar]				
ENV705 (AMD)	[Progress bar]				
Other Undisclosed Programs	[Progress bar]				



Biodegradable PRINT particles are implantable in various compartments of the eye.



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Contact

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¹ World Health Statistics. World Health Organization, 2011 ISBN 978 92 4 156419 9

² World Health Statistics. World Health Organization, 2010 ISBN 978 92 4 156398 7



BREAKTHROUGH NANOTECHNOLOGY ENHANCES DELIVERY TO THE FRONT AND BACK OF THE EYE

In this article, Hongming Chen, ScD, Executive Vice-President of Research at Kala Pharmaceuticals, and Robert Langer, ScD, Company Co-Founder and Board Member, discuss applications of the company's Mucus Penetrating Particle nanotechnology in ophthalmic drug delivery. Dr Langer believes the delivery technology has the potential to allow effective treatment of diseases of the back of the eye using topically administered formulations.

By Malaika I Hill, Medical Writer

Drug delivery in the eye has been a frustrating undertaking for eye-care professionals as current drug delivery methods are limited when considering convenience and bioavailability. The burgeoning field of nanotechnology could lead to better treatment for patients suffering from myriad ocular diseases.

NANOTECHNOLOGY

Nanotechnology, the science of engineering materials at the molecular and supramolecular scale, is on the cusp of forever changing the approach to current therapeutic challenges in eye care.¹ Nanotechnology is a major focus of one of history's most pro-

eye, more effectively. One element of Dr Langer's research involves the design of polymer, lipid, and polymer-lipid hybrid nanocarriers for improved drug delivery, as well as controlled delivery systems for genetically engineered therapeutic proteins, DNA, and RNA. His work also involves the creation of novel approaches for engineering of new tissues and organs.

NANOTECHNOLOGY IN OPHTHALMOLOGY

Innovative treatments for ocular diseases are needed to address the significant unmet needs in both the front and the back of the eye. Kala Pharmaceuticals is rising to meet this challenge by developing a mucus penetrating particle (MPP) platform nanotechnology. MPPs are based on decade-long work at Johns Hopkins University (Baltimore, MD, US) by one of Dr Langer's former students, Dr Justin Hanes, which focused on developing systems to improve the delivery of drugs to mucus-protected tissues. With its proprietary MPP platform technology, Kala is building a diversified pipeline of ophthalmic products to include topical therapies for post-surgical inflammation, ocular surface diseases, and wet age-related macular degeneration (AMD). By penetrating mucus layers in the eye, MPPs can dramatically transform treatments

"With its proprietary MPP platform, Kala is building a pipeline of ophthalmic products to include topical therapies for post-surgical inflammation, ocular surface diseases, and wet AMD"

lific inventors in medicine, Massachusetts Institute of Technology (MIT) Professor Robert Langer, ScD.

Dr Langer's research is focused on developing new nanoparticle delivery approaches to treat disease, including diseases of the



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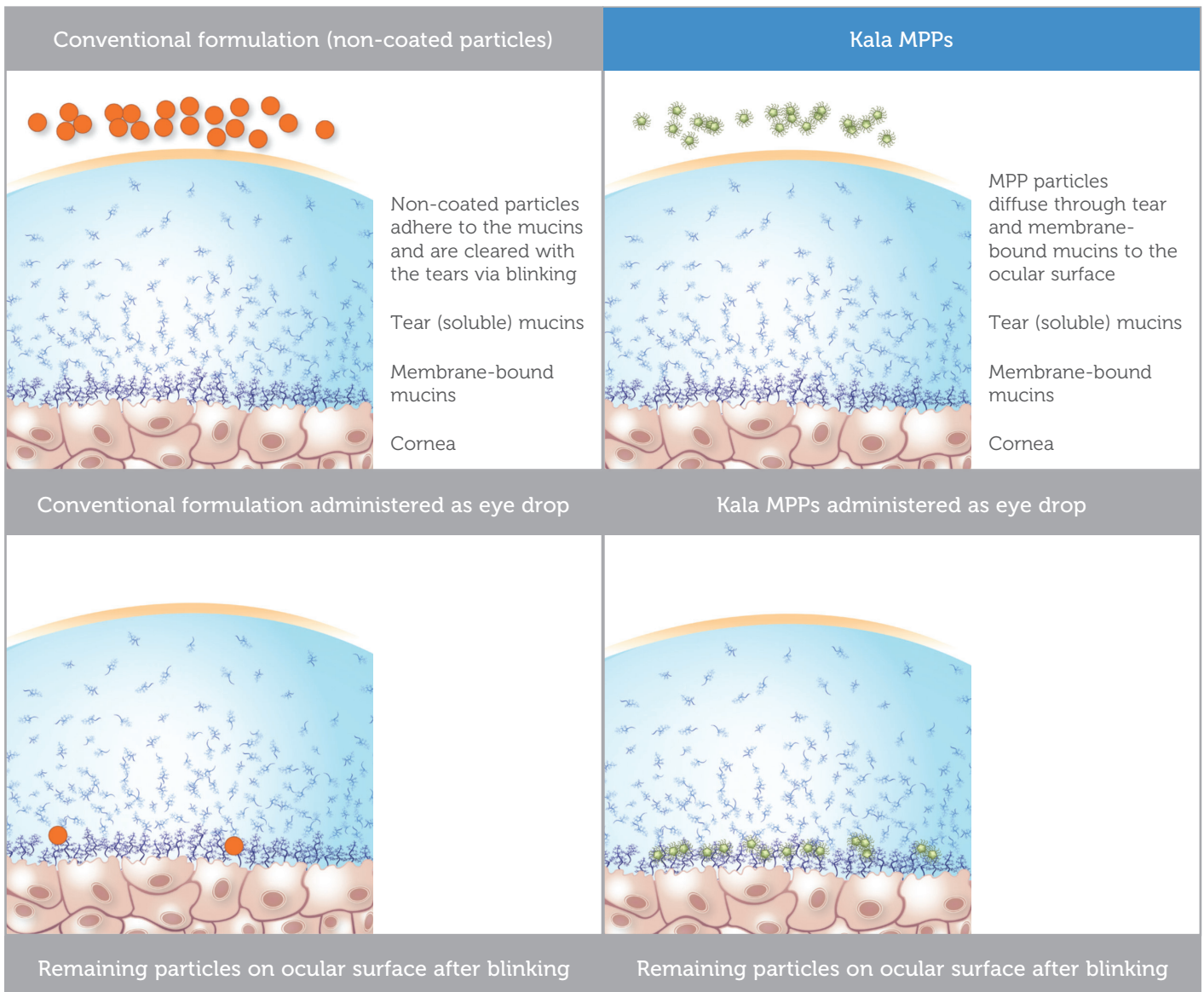


Figure 1: Mechanism of action of the mucus penetrating particle (MPP) platform nanotechnology (right), compared with conventional, non-coated particles (left).

for conditions affecting both the anterior and posterior segments of the eye. Mucus layers have been largely viewed as a limitation for drug efficacy for a variety of mucus protected tissues, including the lung, gastrointestinal tract, vaginal tract and the eye.

Mucus is a heterogeneous mesh of mucin fibers that defends against pathogens and other particles by sterically excluding particles larger than the pore size of the mucins and binding particles via the glycosylated macromolecules that are part of the meshwork. It serves as a primary defense mechanism in the body, protecting against pathogens and other foreign material and facilitating their clearance.

Particles trapped in the surface mucus layer of the tear film are cleared with blinking, which limits the delivery and

mucus layer by engineering the size and surface characteristics of the particles. For delivery to the eye, MPPs prevent

“MPPs prevent therapeutic agents from being caught by the tear film and then cleared via blinking. This enhances the penetration and prolongs the drug’s retention at the disease site”

efficacy of drug delivery with eye drops. The MPP platform technology enhances the penetration of drugs through the

therapeutic agents from being caught by the tear film and then cleared via blinking. This enhances the penetration and

prolongs the drug's retention at the disease site.

"Nanotechnology will revolutionise ophthalmology because it offers a much more effective delivery to the front of the

PRODUCTS IN THE PIPELINE

Loteprednol etabonate ophthalmic suspension (marketed as Lotemax® by Bausch + Lomb) is a popular medication for reducing

"A new kind of eye drop that will tremendously enhance duration of action and localisation of action for delivery to the front or the back of the eye"

eye with longer action, and we can now apply the drug precisely where we want it to be," commented Langer. "I envision a new kind of eye drop that will tremendously enhance duration of action and localisation of action for delivery to the front or the back of the eye."

MPPs were engineered combining nanometric particle size and proprietary surface engineering to achieve particles that can freely diffuse through the mucus layer. The process features the creation of a nanoparticle crystalline core consisting of the therapeutic agent, surrounded by surface-engineered polymers that allow the drug to be inert to the mucin fibers. MPP platform technology can deliver a wide variety of molecules and could also be amenable to the delivery of biologic agents and controlled delivery (see Figure 1).

"I believe we are about to see nanotechnology making a grand entry in ophthalmology and addressing the drug delivery challenge in the eye, one of the organs of the human body that is best protected," said Dr Hongming Chen, Kala's Executive Vice-President of Research, a 20-year industry veteran in drug delivery, and also one of Langer's former students.

post-ocular inflammation. Kala is applying the MPP platform to enhance the delivery of loteprednol for a number of ocular diseases. Preclinical data has demonstrated pharmacokinetic and efficacy results for Kala's 1% formulation of loteprednol etabonate (1% LE-MPP) that are superior to that of current loteprednol products.

"In head-to-head preclinical studies, LE-MPP delivered significantly greater levels of drug to the aqueous humour, as well as the cornea, conjunctiva, and retina than either Lotemax® Suspension or Lotemax® Gel with similar dosing regimens. The objective of the upcoming clinical trial will be to demonstrate if twice-daily administration of 1% LE-MPP is effective in the treatment of inflammation and pain following cataract surgery. If successful, this would represent a significant dosing advantage compared to other topical steroids, which are currently indicated for four times a day dosing," said Kala's Chief Medical Officer, Dr Kim Brazzell.

It is set to enter a pivotal Phase II/III clinical study this year for post-operative pain and inflammation following cataract surgery, followed by a second Phase III

trial to be completed in 2015. A 0.25% loteprednol etabonate-MPP formulation designed for treatment of dry eye and blepharitis is set to enter clinical trials this year as well.

Kala also plans to test MPPs ability to deliver drugs topically to the back of the eye, based on data demonstrating substantial levels of loteprednol and other drugs in the retina following topical administration. The trial could expand the possibilities for LE-MPP use for treating retinal diseases such as diabetic macular edema (DME) and cystoid macular edema (CME).

Kala is also currently advancing toward selecting clinical candidates for a research phase programme featuring a topical receptor tyrosine kinase 1 (RTK1-MPP) for the treatment of wet AMD and other retinal diseases.

Although Kala's MPP technology platform internally focuses on ocular diseases, the company is also pursuing collaborations with partners to transform the therapeutic properties of both marketed drugs and compounds in development for a broad range of disease indications, including the gastrointestinal tract, airway, and cervicovaginal tract. An even mucosal coating is achieved in various tissues using MPP. For these indications, Kala will partner its technology with other companies rather than develop the applications internally.

Leading investors, including Lux Capital, Polaris Venture partners, Third Rock Ventures, and Crown Venture Fund.

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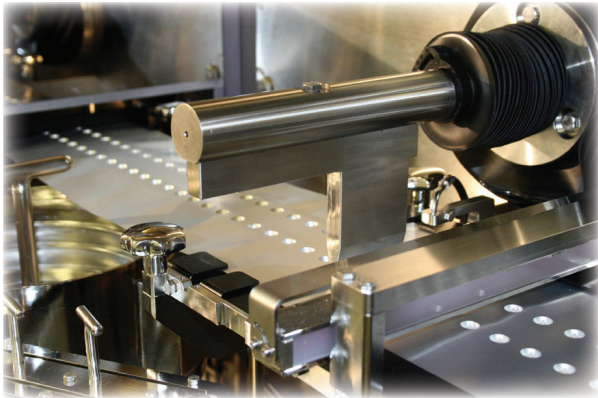
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ZERO-ORDER SUSTAINED DRUG DELIVERY TO THE RETINA FROM A NANOPOROUS FILM DEVICE

This article describes how a team of senior UCSF researchers, including Daniel Bernards, PhD, Robert Bhisitkul, MD, PhD, and Tejal Desai, PhD, are developing a nanoporous membrane-based implant which can significantly improve drug delivery to the back of the eye. Zordera, Inc, is the company set up to take the device through commercial development.

An increasing number of biologics and the emergence of biosimilars have focused attention on the development of advanced drug delivery technologies. This industry is expected to reach US\$51 billion (£30 billion) by the year 2015, primarily driven by the introduction of new biologics, uptake of delivery platforms, and utilisation of controlled release systems.

Despite recent successes in the treatment of ophthalmic diseases, delivery of such therapeutics remains a challenge. To this end, in the laboratory of Tejal Desai and in collaboration with retina specialist Robert Bhisitkul at UCSF, a proprietary nano-engineered polymer film technology platform has been developed for long-term delivery of small and large molecule therapeutics.

"To enable cost-effective and streamlined fabrication, sterilisation and packaging, its design is based on proven large-scale manufacturing processes."

To further the commercialisation of this technology, Zordera, Inc, has been founded. Zordera's bioerodible nanotechnology platform is designed to enhance the utility and bioavailability of hard-to-deliver compounds by allowing continuous, sustained zero-order release of therapeutics, which can improve patient compliance and contribute to superior clinical and economic outcomes.

Currently, treatments for macular degeneration are typically injected into the eye, often monthly. On average patients receive 7.7 injections per year. Since these frequent injections are often required for many years, there is an increased risk of infection, retinal detachment and cataracts. A portion of the injected dose is broken down or cleared through the circulation before it even reaches its target, the retinal tissue. This low bioavailability is compensated for by increasing the initial administered dose, increasing the risk of toxicity. A proportion does reach the retina but during the two or three weeks following injection, the drug is present at the target tissue in steadily declining amounts.

Zordera's core technology is a nano-engineered device that allows transport of drug molecules from a reservoir through a nanometre-sized porous biodegradable polymer thin-film.

The thin film is manufactured by first creating an oxide mould, which has millions of nanowires each approximately the size of the intended drug molecule. A polymer solution is applied to the mould and once solidified, the oxide mould is chemically dissolved leaving just the polymer, with nanopores where the nanowires had been. The drug in pellet form is sealed in between two membrane layers to give a resulting device that is around 40 µm thick (see Figure 1).

By matching a target drug's molecular diameter to the pore size, drug molecule



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release from the membrane can be constrained to single-file – i.e. only one drug molecule at a time can leave through any given pore. This, together with decoupling drug release from subsequent device degradation, means that a precisely controlled release profile can be achieved throughout the life of the device. The device itself degrades safely later on, after the drug payload has been completely delivered.

Unlike many sustained delivery technologies, these nano-engineered polymer films are functionally tuneable to achieve a zero-order release profile such that drug concentration falls within a narrow range over the course of several months. This technology was also designed to address several key development issues that have prevented commercialisation of competing technologies. For example, to mitigate potential safety risks, the device is made of materials that are widely used in approved medical products and can be removed from the eye using standard surgical procedures, if necessary.

To support provider and patient adoption, the device is designed to be deployed with a standard gauge needle. To enable cost-effective and streamlined fabrication, sterilisation and packaging, its design is based on proven large-scale manufacturing processes.

To date, much of the development has taken place at the University of California, San Francisco (UCSF) under the support of the US National Institutes of Health (NIH) as well as grants from the Rogers

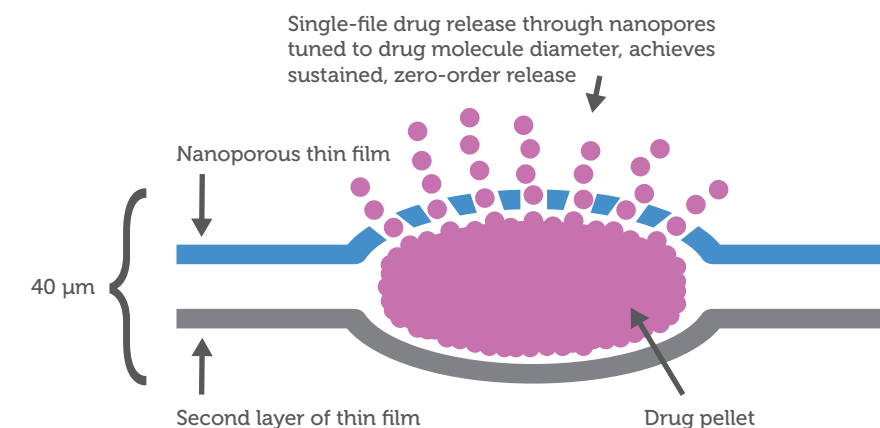


Figure 1: Schematic diagram showing the configuration of Zordera's nanoporous film device.

Foundation (CA, US) and the Wallace H. Coulter Foundation (FL, US). Numerous *in vitro* and *in vivo* studies using model and therapeutic compounds have demonstrated safety and performance of the technology.

Sustained, zero-order delivery has been shown in excess of seven months with model therapeutic albumin, through four months with AMD therapeutic Lucentis®, and two months with rapamycin. *In vitro*

ment/degeneration have been observed. Histology similarly showed a lack of long-term adverse effects.

A number of aspects differentiate these devices from competing technologies. Tuning the design and properties of the nanostructured thin film device, it is possible to deliver therapeutic at a constant rate that is optimised for the desired drug delivery profile. Because of their thin film nature,

“Because of their thin film nature, these biodegradable devices can be furled to fit inside and be deployed by syringe.”

stability of antibodies, such as Lucentis and IgG, has been demonstrated to be excellent, with no appreciable degradation over several months.

Safety in a rabbit model has been demonstrated over nine months with no inflammation, no increase in ocular pressure and no adverse effects. No device-related reports of iritis, cataract, endophthalmitis, vitreous haemorrhage or retinal detach-

these biodegradable devices can be furled to fit inside and be deployed by syringe. This provides more reliable drug levels in the eye, simplifies the administration of the product and minimises the potential for infections.

Although initially under development for AMD, the device is also being tested for the treatment of increased intra-ocular pressure and inflammation. It also has potential in the treatment of glaucoma and uveitis.



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July	Novel Oral Delivery Systems	June 9th
September	Prefilled Syringes	August 4th
October	Drug Formulation & Delivery, Services & Solutions	September 15th
November	Pulmonary & Nasal Drug Delivery (OINDP)	October 13th
December	Delivering Biotherapeutics	November 10th
January 2015	Ophthalmic Drug Delivery	December 15th
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COMPANY PROFILE: ENCOMPASS OPHTHALMIC DRUG DEVELOPMENT SERVICES



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Encompass Pharma was formed in 2004 by a highly experienced team of ophthalmic development and analytical scientists. Based in Norcross, GA, US, we are a global leader in ophthalmic drug development, formulation, and analytical services for the ophthalmic pharmaceutical market. We offer a full range of ophthalmic development and formulation services from pre-formulation through clinical supplies manufacturing and scale-up.

PRECLINICAL SUPPORT

We have a strong knowledge base of existing ophthalmic compounds, excipients, and drug delivery technology. Our dedicated staff and state-of-the-art, cGMP compliant laboratory is dedicated to supplying preclinical screening studies.

OPHTHALMIC FORMULATION

We have significant experience in the optimisation of ophthalmic drug forms and delivery technologies for your product and as such we understand the unique challenges presented in ophthalmic development and formulation. We have formulation experience with all ophthalmic dosage forms including solutions/suspensions; ointments/gels; emulsions; depot and sustained-release technologies; and lyophilized products.

Topical delivery of medications to the eye is challenged by the elimination of drug formulations from the pre-corneal area by tear flow. We utilise our proprietary *in vitro* formulation evaluation tool named the Differ (diffusion/erosion) model to evaluate topical ocular drug and drug delivery characteristics. The Differ model was developed to offer clients an *in vitro* model

to optimise the formulation prior to *in vivo* studies. It utilises a modified Franz diffusion cell to include simulated tear flow to assess the impact of formulation changes on the diffusion of active moieties better, across isolated rabbit corneas and sclera. The amount of drug that diffused across the cornea (or sclera), as well as the amount of drug eliminated in the pre-corneal or scleral (donor) area, are compared to evaluate the effects of various formulations on diffusion /delivery.

OPTIMISING OPHTHALMIC DRUG DELIVERY

We have an extensive working knowledge of currently available and new ophthalmic drug delivery systems and technologies which can be used to meet the unique delivery and therapeutic objective established by our clients. In past projects we have assisted our partners to enhance ophthalmic drug delivery by increasing ocular surface/tear residence; improving therapeutic efficacy; optimising active ingredient concentration; reducing systemic exposure/increasing safety; extending product lifecycles; and enhancing delivery to the posterior of the eye.

PROLOC BIOADHESIVE OCULAR DRUG DELIVERY SYSTEM

PROLOC bioadhesive minitablets are inserted into the cul-de-sac of the eye and rapidly adhere to the ocular mucosa and remain in place until fully eroded. Typically, the drug is released for a period of eight hours or more. PROLOC is easy to insert. Directly after insertion, the tablet hydrates rapidly (in approximately one minute) and creates a comfortable viscoelastic outer surface. It becomes completely hydrated within 2-3 hours after application, and is subsequently transformed into a highly concentrated gel (see Figure 1).

PROLOC offers intellectual property protection and provides the opportunity to expand a current drug franchise or to open new possibilities for new drug molecules and uniquely delivered therapies. Clinical trials have been conducted to support ocular delivery as well as vaginal, buccal and intranasal delivery.

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Encompass provides state-of-the-art analytical services to some of the leading pharmaceutical companies in the world. Our extensive experience provides for regulatory GMP compliance along with scientific excellence. We bring you results with the interpretation and direction to ensure your products successful completion. Our analytical services include method development and testing; stability services; packaging system characterisation; and cleaning validation.

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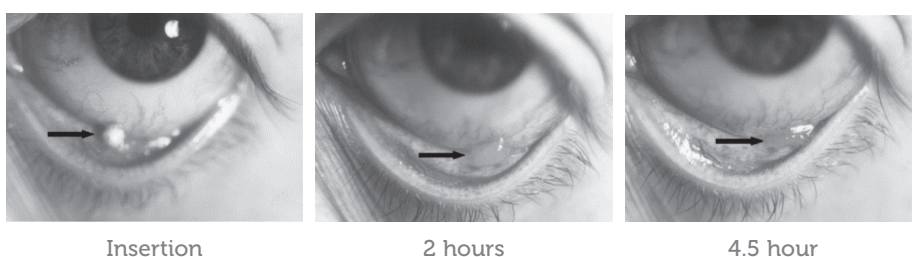


Figure 1: PROLOC bioadhesive minitab completely transforms into a highly concentrated gel at 4.5 hours.

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When microns matter...

MICRO OPHTHALMIC OCULAR IMPLANTS

More often than not, the smallest component in a medical or pharmaceutical implant or device is the enabling component. Micro manufacturing (micro injection molding, micro machining, and micro automation) has blazed the trail for many new developments, implants, micro surgery, and robotic surgeries today. This article, by Donna Bibber, Plastics Engineer & Chief Executive Officer of Micro-Engineering Solutions, explores one such market segment in which micro manufacturing has played and will continue to play a significant role in worldwide growth in the next five years ... ophthalmic devices.

Age-related eye diseases such as cataracts, diabetic retinopathy, glaucoma and macular degeneration (to name only a few) continue to cause loss of vision either significantly or completely. Driven by a baby boomer aging population, technology innovations and vast, rapidly emerging markets in China and India, the ophthalmic devices sector is expected to attain a double-digit growth. Ophthalmic and intraocular implants are largely made up of many micro sized and highly precise components and assemblies. This market sector continues to remain one of the largest and fastest growing micro medical and pharma micro device sectors, globally.

MARKET DATA

The global ophthalmic device market was valued at \$10 billion (£6 billion) in 2008 with the US market comprising \$5.5 billion of this. Driven by growth in the vision care and cataract surgery market categories, the market is forecast to grow by 8.5% annually during 2008-2015 to reach \$15 billion worldwide (\$9.8 billion in the US).

On the downside, due to reduced consumer discretionary spending in the US, the market continues to grapple with growth decline in refractive surgery. On the upside, the treatments for other conditions are the major factors for the vastly emerging growth markets worldwide.

Major players in the ophthalmic pharmaceutical space include:

- Alcon (now part of Novartis)
- Allergan Inc
- Bausch & Lomb Inc

- Daiichi Pharmaceutical Co Ltd
- Genentech Inc
- Inspire Pharmaceuticals Inc
- ISTA Pharmaceuticals Inc
- Johnson & Johnson (Vistakon Pharmaceuticals LLC)
- Merck & Co Inc
- Pfizer Inc
- Santen Pharmaceutical Co Ltd.

Major players in the surgical ophthalmic space include:

- Abbott Medical Optics
- Alcon
- Bausch + Lomb Inc.

CONDITIONS AND TREATMENT

The eye is a complex and sensitive organ. There are many structures and targets, located closely together and sometimes, in terms of targets for treatment, these structures are conflicting with one another in their proximity. Existing in the eye are significant defense mechanisms, such as the tear film and the cornea, which present challenges for medication to enter. Specifically, the vitreous fluid is difficult for injected medication to traverse to reach the posterior of the eye.

A number of conditions of varying seriousness and interest are:

1. Glaucoma
2. Cataracts
3. Diabetic retinopathy
4. Age-related macular degeneration
5. Dry eye syndrome
6. Uveitis
7. Retinal detachment



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8. Advanced age and lifestyle diseases; still an extremely high level of unmet need
9. Others of lesser importance can be treated / managed with eye glasses, OTC medication, antibiotics, and specific hygiene protocols and, in limited instances, with surgery.

Treatment often requires contributions from two or more parts of an inseparable therapeutic triad:

- Ophthalmic pharmacology
- Surgery of the visual tract
- Implantable ophthalmic medical devices.

Highly innovative specialist companies dominate pharmacological development. Innovative companies on the drug delivery side are equally important. Industry development occurs through a large number of highly-focused, research driven specialist companies, often very small and funded through innovation-support funding programs. Such companies can need to be able to easily find a large marketing partner as big pharma is often funding this development externally in lieu of doing it themselves in-house.

Highly innovative specialty companies define and epitomise the requirement for treatments for these conditions that comprise micro sized and ultra-precision components and assemblies. Anyone who has ever worn corrective contacts and/or been on the bad end of a windy day near an outdoor fire pit, you have probably noticed that the smallest speck in your eye can cause you severe pain.

The reasons for intraocular implants being micro sized then are to provide the eye an extreme level of comfort with the least invasive, yet compliant implants in the human body. The thin and delicate structures of the eye require paper thin and flexible components that are nonetheless strong enough to withstand extreme fluid pressures in and behind the eye. The successful creation of a device that is both paper thin and strong is an engineering challenge that requires the skill and expertise that only micro moulding and nano surface specialty companies can understand and implement. Let us explore this micro requirement specifically for some of the more common conditions/treatments.

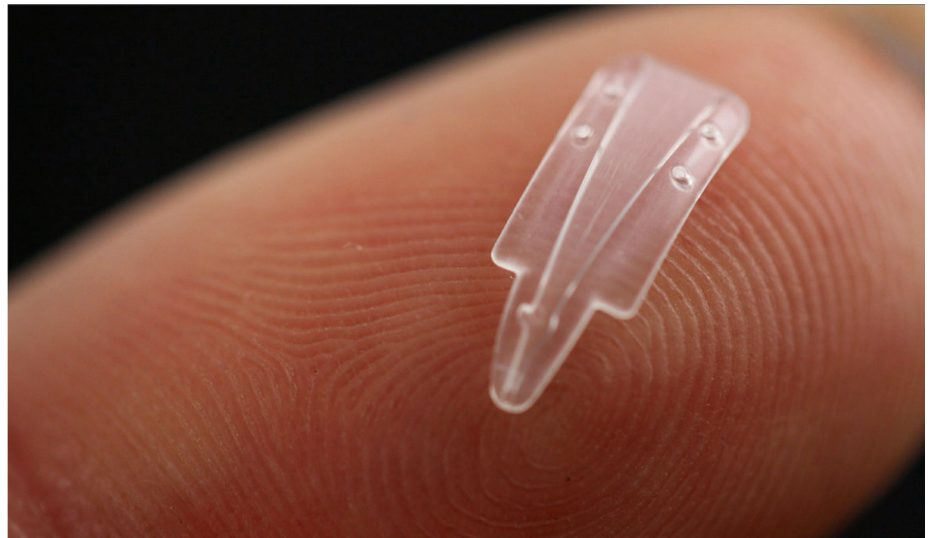


Figure 1: A micro-injection moulded glaucoma drain (shunt).

For example, glaucoma, the “sneak thief of sight”, affects many elderly, African Americans, and those with a family history. Considered the second leading cause of blindness (after cataracts), glaucoma is principally caused by elevated intraocular pressure within the eye. Micro surgical devices and intraocular implants are used if eye drops are not an effective treatment. Micro components and surgical treatments include:

- Trabeculectomy (laser surgery) is most common approach; creates a hole in sclera to allow fluid to drain into the outer cyst
- Conventional surgery can also be used to create a drainage hole in the white part of the eye if laser surgery is unsuccessful
- Implant surgery positions a device to aid

Shunts are mostly tubular, however this one is shaped and designed for placement in the sclera (side of the eye). It is designed to act like a venturi system which uses the pressure of the eye to push the discharge from glaucoma to behind the eye where it can drain. In addition to the 250 μm entry orifice, there are 4 suture holes of 250 μm diameter (2x a human hair) moulded into the top of the implant. These suture holes also must be free and clear of particulate or flash to prevent sutures from cutting during implantation or after surgery.

Age-related macular degeneration (AMD) is the leading cause of permanent impairment of reading ability and loss of fine detail for those over age 65 years. The macula is the

“Successful creation of a device that is both paper thin and strong is an engineering challenge that requires the skill and expertise that only micro moulding and nano surface specialty companies can understand and implement”

the drainage; estimated that several thousand are performed each year in the US

- Canaloplasty places a microcatheter into Canal of Schlemm to enlarge the natural drainage channel for healthy eyes.

Figure 1 shows a glaucoma drain, commonly known as a shunt. This shunt is injection moulded, spherically shaped with a wedge-shaped radial side action in the tool that creates the drain geometry. At the end of the side action travel is a 250 μm orifice whereby no moulding flash can be tolerated.

central portion of the retina used for seeing fine detail and can be destroyed in one of two ways beginning at age 60.

In 2004, 1.5% of adults over age 40 experienced advanced AMD and 6.1% had intermediate AMD (1.8 and 7.3 million adults, respectively). The dry form is most common form of AMD but it can become wet form which is more destructive. In dry AMD light sensitive cells in macula break down. Dry AMD is treated by oral ingestion of high dose of anti-oxidants and zinc.

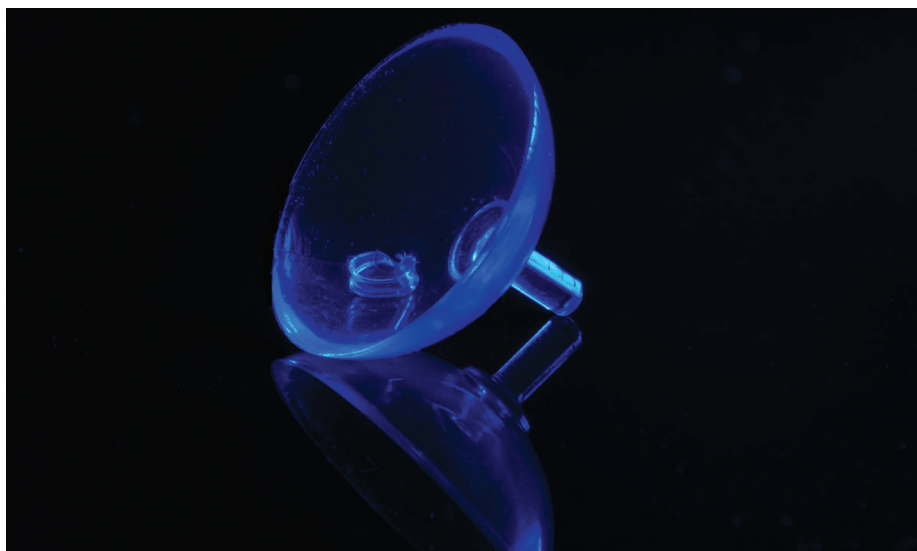


Figure 2: Macular degeneration laser guide.

Wet AMD is characterised by growth of abnormal blood vessels behind retina. Laser surgery is used in small proportion of patients to destroy these vessels but the treatment also damages the retina. Another treatment approach involved intravenous injection of a photo-activated drug (into the arm). When exposed to light in the eye the drug is activated and it destroys the unwanted new blood vessels. Injections into the eye to block growth of abnormal new blood vessels are also available.

Prior to 2007, medicine was not available to treat AMD; in 2007 the market was estimated to represent more than \$1.2 billion in sales.

Figure 2 shows an AMD guidance device used in laser surgery. The spherical radius sits on the cornea and the lens underside must be free of flash, mould parting lines, and surface imperfections. The 300 μm laser hole shuts off on the spherical radius and blending these geometries three-dimensionally in steel to produce the polymer micro injection moulded component is very challenging.

In this case, material selection was also a

necessary and also require OEM testing even if they are shown to be Class VI compliant.

Dry eye is one of the most common reasons for an appointment with an ophthalmologist. Dry eye condition is defined as an irritation of the eye due to an inability to produce or maintain/retain enough tears on the surface of the eye. It can result in damage to the front surface of the eye and impair vision. The causes vary from specific diseases (such as Sjögren's syndrome or lacrimal and meibomian gland dysfunction) to other causes including age, gender (women are more susceptible), medications, certain medical conditions, environmental conditions such as exposure to smoke, wind, or dry climates, and other factors such as prolonged use of contact lenses or refractive eye surgeries (LASIK).

Treatment, may require micro components (approximately a quarter of the size of a grain of rice) including punctal plugs (see Figure 3) whereby a plug is surgically placed in both the top and lower eyelid to prevent fluid in the eye from draining, thereby keeping the eye hydrated.

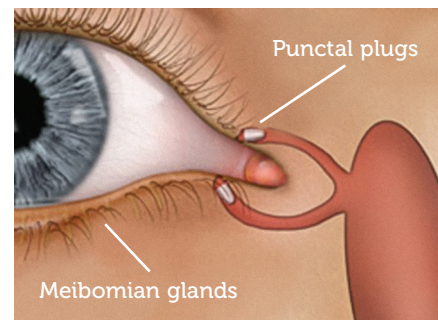


Figure 3: Punctal plugs placed in drainage channels of the upper and lower eyelids

(Source: allaboutvision.com).

properly (balancing the dropper over the eye and making sure it all gets into the eye) defeats the purpose and wastes consumer and healthcare costs. Much effort is put into micro pumping and micro administering of these fluids with aspirators, implantable pumps, and slow release polymers that release the drug in timed increments.

DESIGN CONSIDERATIONS

Many drug delivery devices are now manufactured in non-traditional ways such as silicon wafer technology, MEMS, and ground-up manufacturing methods. These methods are then matched to more traditional top-down methods to provide medical and pharmaceutical companies with differentiated and strategic value. These processing techniques are typically developed using "conventional" single micron level positional accuracy using current work holding devices. These methods are inadequate in preventing cross contamination of actives in capillaries and other microscopic microfluidic assemblies.

Nanometre-positional accuracy was not available to the mainstream even 2-3 years ago. Even today, traditional pallet-holders coupled with automatic X, Y, Z probing can barely guarantee a one micron positional accuracy. It is also strange to think this isn't good enough for the eye, but the surface finish is absolutely necessary, orders of magnitude tighter tolerances than seen in conventional or macro manufacturing.

So it is evident that developing ophthalmic and intraocular implants requires thinking at the scale on which the human body operates, and the human body operates at the scale of nanometres. White and Red blood cells on average range from 8-100 μm in diameter and

"New methods combine traditional top-down methods with futuristic bottom-up methods to provide medical and pharmaceutical device companies with enabling products to treat the likes of glaucoma, macular degeneration, cataracts, dry eye, and even diabetes around the world"

key factor in providing the rigidity required to hold the guide in place during laser deployment. USP Class VI materials (they have previously been used in medical products) are

Additional treatments use OTC eye drops or prescription lubricants and anti-inflammatories. These medications are extremely costly and if not administered

“Top Down” Methods	“Bottom Up” Methods
Laser Machining	Genetic Code
EDM-WEDM	Complexity Theory
Ultrasonic Machining	Self-assembly
Ion Machining	Biological Cell
Grinding	Proteins
CNC Machining	DNA and RNA
Chemical Milling	LIGA
Photochemical Milling	3D Printing
Electrochemical Machining	

Figure 4: Summary of Micro-Engineering Solutions’ micro and nano manufacturing methods used today and in the future.

DNA can be as small as 2-3 nm. In between these two range a great deal of discovery and science that we cannot begin to understand without simulation outside the body, for example mimicking strands of DNA and blood cells working together. It is for this reason that ophthalmic, intraocular, drug delivery and pharmaceutical device companies are looking for help from manufacturers to push the boundaries of what is possible to achieve features and tolerances in the nanometre range.

As shown in Figure 4, what we have discovered in the micron range has certainly helped us to learn some top down methods that didn’t work, and some bottom up methods that worked but needed some refinement using a combined top-down/bottom-up method.

Growing structures (i.e. bottom-up methods) to create geometry was also not mainstream until 2-3 years ago. A good rule of thumb is that material and process marrying will force a top down methodology until we can mill, grind, edm (electrical discharge machine), diamond turn, and etch no more. We have already used LIGA (German acronym meaning lithography, electroplating, and moulding) for many years as a bottom-up method. However, with the emergence of 3D printing, at some point in the near future, we will be looking that technology to create geometry, surfaces, and – when the materials are available and 3D printable – even human organs. This will push micro manufacturers and macro manufacturers beyond our current capabilities in top-down methods, or there might be a “marriage made in heaven” employing both methods.

For example, in the area of diabetes, Google is developing a smart contact lens for measuring glucose in tears (see Figure 5).

Google said the lens comprises “chips and sensors so small they look like bits of glitter, and an antenna thinner than a human hair”. The chip and sensor are embedded between two layers of soft contact lens material. A tiny pinhole in the lens allows tear fluid from the surface of the eye to seep into the glucose sensor. The prototypes currently being tested can take glucose level readings every second. The project was co-founded by Brian Otis and Babak Parviz who worked together at the University of Washington (Seattle, WA, US) before moving to Google.

One can’t help imagining that, beyond diagnostics, completely encased electronics placed onto the cornea may one day bring vision, gaming, web browsing, and social interaction to a completely new level.

Alternative methods are coupling neuroscience with ophthalmic science as seen in Figure 6, which shows a retinal implant embedded in the eye that restores vision to the vision impaired or the visionless.

Non-traditional methods for manufacturing such as nanometre positional accuracy and dust-specked sized injection moulded, machined, and assembled components are spawning technological advances in ophthalmic intraocular implants and intraocular drug delivery devices. These new methods combine traditional top-down methods with futuristic bottom-up methods to provide medical and pharmaceutical device companies with enabling products to treat the likes of glaucoma, macular degeneration, cataracts, dry eye, and even diabetes around the world.

Areas unknown can be explored with micro manufacturing – restoring lost vision, enhancing vision, hydrating eyes in harsh conditions, gaining less invasive, viable

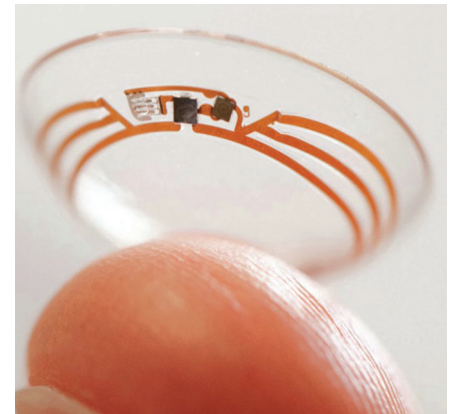


Figure 5: Google’s smart contact lens (Source: Google Inc).

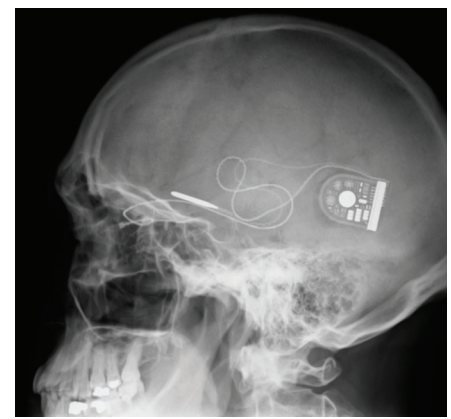
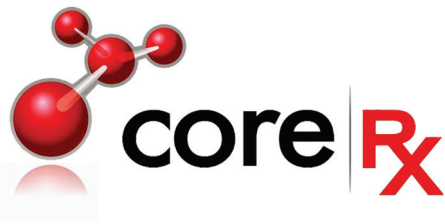


Figure 6: Retinal implant (Source: Institute for Ophthalmic Research at the University of Tübingen).

ways to cross the elusive blood-retinal barrier, micro-electronics and eyes controlling the brain to control prosthetics, and even controlling motion for paraplegics. Imagine a technology allowing people to see..... people they haven’t seen in years, objects in a room, light in a sky, food on a plate, and to recognise a smile. We are fortunate to be well positioned in micro and nano manufacturing to play a part in enabling these treatments and products that contribute to worldwide health.

ABOUT THE AUTHOR

Donna Bibber is a Plastics Engineer and CEO of Micro Engineering Solutions, a micro-focused design and manufacturing company providing micro moulding and micro automation/assembly services to start-up and Fortune 500 companies alike. Ms Bibber has published and lectured on hundreds of technical papers on micro moulding medical and pharmaceutical devices, and associated topics worldwide and was voted onto the MD+DI List of 100 Notable People in Medical Devices in 2008.



CURRENT AND FUTURE OPHTHALMIC FORMULATION AND PROCESS DEVELOPMENT TRENDS

In this short piece, Brian McMillan, Vice-President Product Development, CoreRx, provides some insights into his personal experiences in the development of ophthalmic products and the significant role of innovative delivery systems in improving efficacy and reducing side-effects. He also highlights how aseptic process development and manufacturing have become increasingly important in the development of ophthalmic therapeutics.

I had the opportunity in the late 1990s and early part of the 2000s to be one of the lead scientists for the development of Retisert by Bausch + Lomb. It was the first intravitreal implant for diseases affecting the rear of the eye. I played a role in the formulation development, process development and manufacture of early-stage clinical trial material. Retisert delivers the corticosteroid, fluocinolone acetonide, 0.59 mg, to the posterior segment of the eye, and was the world's first intravitreal drug implant for the treatment of chronic non-infectious uveitis.

Uveitis can ultimately lead to conditions and disease states such as cataracts, glaucoma and retinal edema. At the time of development, the Retisert platform offered a great technological advancement over con-

temporary therapies which included injectable technologies with extreme side effects.

temporary therapies which included injectable technologies with extreme side effects.

The dosage form included micro-tablet technology (tablets were 1.5 mm wide and a few mg in weight), encapsulated by a silicon layer covered with a water soluble polymer,

designed to deliver the corticosteroid for approximately 30 months to the posterior segment of the eye. It was a great opportunity for us at Bausch + Lomb to work on the technology at the time. We were shown stories of grandparents who were able to see their grandchildren for the first time after having the procedure which included surgery to implant the dosage form into the rear of the eye.

Working on this development platform with the group of scientists at Bausch + Lomb made me realise that as a whole the ophthalmic industry had not yet evolved. Early Retisert prototypes lacked sophistication as far as both the formulation matrix itself and the crude methods with which we had to manufacture the product at the time.

Analytical testing of prototypes also presented unique challenges such as in vitro release testing of the product using novel dissolution systems. Other challenges included uniform coating of the polymeric system onto the micro-tablets, and incorporation of the micro-tablets into the silicon tubing. The process was hardly automated and presented troublesome processing and validation issues from a manufacturing standpoint.

Now, approximately 14 years later, ophthalmic drug delivery continues to transcend with various trends in the pharmaceutical industry. Companies are targeting their drug delivery systems and molecules toward glaucoma, retinal disorders, dry-eye treatments

“We were shown stories of grandparents who were able to see their grandchildren for the first time after having the procedure which included surgery to implant the dosage form into the rear of the eye.”



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and as anti-allergens, anti-inflammatory and anti-infective agents. The human eye is obviously a unique organ with traditional routes of treatment primarily focusing on non-invasive treatment options such as topical dosage forms, which cannot reach diseases affecting the posterior segment of the eye. Topical ophthalmic drug delivery primarily has efficacy for the treatment of anterior ophthalmic diseases leaving the posterior segment of the eye as a critical ocular target for drug delivery.

Numerous factors leading to visual impairment in the industrial regions are correlated to disorders affecting the rear of the eye. New drugs for delivery to the posterior segment of the eye have emerged, however most of these drugs are delivered by repeated intravitreal injections with severe side effects.

Current delivery platforms of ophthalmics include numerous delivery systems and formulation matrices with the goal of therapeutic efficacy toward both segments of the eye. These include delivery of prodrugs, which are bio-activated into active form by metabolic processes. Prodrugs can enhance permeability of the drug into the cornea and are effective in the delivery of poorly soluble drugs.

Liposomes, micro-emulsions and nano-suspension are other options to deliver lipophilic drug molecules to the cornea. Iontophoresis is a technology where charged drug molecules are delivered into tissue at anodes and cathodes. This technology is known to increase efficacy of both anti-bacterial and anti-inflammatory agents. Cyclodextrins (cyclic oligosaccharides) which are often used in solid oral dosage formulations for taste masking, solubility and permeability enhancement are also currently being used in ophthalmic matrices. In the case of ophthalmic delivery, cyclodextrins are complexed with drug molecules to enhance permeability of the drug into the cornea of the eye. Additional delivery and enhancement technologies include use of simple penetration enhancers. Benzalkonium chloride (BAK) which is used as a preservative in ophthalmic solution formulations can aid in absorption of the drug. Muco-adhesive polymers (which are hydrophilic in nature) are also being used. These systems include hydrogels, carbopols, polyacrylic acids, chitosan and penetration enhancers incorporated into the dosage form. Advances in polymer technology has aided this field leading to such dosage forms as gel forming mini-tablets and inserts as treatment options. These are just a few of the techniques and options being used in the pharmaceutical industry today for ophthalmic development in an attempt to enhance delivery systems.

PROCESS DEVELOPMENT & MANUFACTURING

From the process development and manufacturing side of ophthalmic development, many companies which develop and manufacture sterile products are using disposable process technologies which incorporate single-use components. This is often useful for compounds with special handling considerations. In these cases, traditional manufacturing vessels and components utilising

“New delivery systems and technologies could negate these side effects when dosing the same drug molecule via a different platform.”

stainless steel are replaced by polymeric materials which must be sterilised using commonplace sterilisation techniques.

At CoreRx we have a LevTech mixing system from ATMI, Inc. which utilises a disposable bag system as a mixing vessel. The technology can be used for anything from potent compounds, irritants, or simply a process where neither cleaning verification nor validation of a traditional mixing system is desired. The system offers a versatile mixing unit which has a mixing wand with “fingers” which protrude down into the disposable bag. ATMI also offers larger, non-invasive units for batch sizes from 200-500L which incorporate a bottom mounted magnetic driven impeller. All of the product contact surfaces in these systems are 100% disposable.

There are many considerations when companies switch to disposable systems versus traditional stainless steel units. Process engineers and corporate management need to establish that the single-use unit has the same manufacturing cost effectiveness and capability of traditional units. As companies such as ATMI introduce these systems there may be numerous challenges from both the vendor and the pharma company utilising the technology.

The vendor will need to offer validation packages for the product and insight into the materials the systems are made from. Generally these types of disposable systems might be gamma irradiated for sterilisation purposes so the components of the systems would need to be immune to changes in their physical properties after irradiation.

When CoreRx purchased the LevTech mixer the company supplied a great amount of compatibility data, however, many of the drug molecules utilised in ophthalmic systems will need compatibility studies performed with the bag structure, bag neck and mixing wand of the bag system. Evaluation of these components will be critical to any successful study. The CoreRx scientific team recently performed detailed compatibility studies for one particular dosage form with the active ingredient, excipient technology

and bag components of the LevTech mixer. In this case the active ingredient and formulation matrix were fully compatible with the bag and mixer components.

Validation of these disposable systems offers unique challenges for the engineering team. After irradiation, endo-toxin levels need to be quantified to verify sterility validation, while performance validation verifies the system performs processes at an acceptable, repeatable level. This may include mixer speed, or in the case of the larger LevTech units, magnet speed, burst testing of the mixing vessel (in this case the polymeric bag system), extractables validation and stability testing of disposable components.

Aseptic filling validation of a system like the LevTech would require (like traditional process systems) media fills using microbial growth medium in place of the sterile product. During this part of validation filled containers are evaluated for fill accuracy, sterility integrity and repeatability of the systems. For a disposable system this part of validation might be challenging because of filling an empty bag versus working with traditional stainless tanks which have fixed volumes. These are some of the elements which must be taken into consideration when an ophthalmic company considers making the switch from traditional stainless pharmaceutical processing equipment to a disposable system using polymeric components.

Disposable systems may cost in excess of hundreds of dollars for one bag requiring scientific and corporate teams to perform internal market research regarding whether

the technologies are cost effective versus traditional systems requiring repeated cleaning and verification by analytical groups.

FORMULATIONS & DELIVERY

As with any industry, as ophthalmic drug developers move into the future it will be a necessity to incorporate innovative formu-

extreme increase in intra-ocular pressure and ultimately development of cataracts. We saw how new delivery systems and technologies could negate these side effects when dosing the same drug molecule via a different platform. Development of novel dosage forms for delivery to the posterior segment of the eye will be critical in coming years with the current escalation of type 2 diabetes in the US.

“We saw how new delivery systems and technologies could negate these side effects when dosing the same drug molecule via a different platform.”

lation and process techniques in an effort to develop efficacious products leading to profitable markets.



Formulation matrices using cutting-edge excipient technologies and delivery systems yielding fewer side effects should be future goals of drug development platforms. At Bausch + Lomb we saw the side effects of repeated injections of corticosteroids for delivery to the rear of the eye, including

Macular swelling, inducing blurred vision and ultimately loss of visual acuity may be attributed to diabetic retinopathy. Corticosteroids are often used as a treatment option for this condition leading to the previously mentioned side effects. Thus, it will be up to pharmaceutical scientists to challenge the norm to come up with novel delivery systems yielding fewer side effects.

Similarly novel manufacturing techniques like the disposable systems may become critical to manufacture products with high efficiency and market profitability.

ABOUT THE AUTHOR:

Brian McMillan, MS Pharm is a Principal and Co-Founder of CoreRx, Inc, located in Clearwater, FL, US. Brian also serves as Vice-President of Product Development, having 24 years of relevant experience in the pharmaceutical development arena. Brian is also an Assistant Professor of Pharmacy at The University of South Florida where he has taught classes in pre-formulation and dosage form development. Brian has worked for such companies as Roxane Laboratories, Bausch + Lomb and MDS Pharma Services prior to joining CoreRx in 2006. In his career Brian has worked on virtually every type of dosage form from solid oral, liquid oral, ophthalmic, parenteral, semi-solids and topicals (creams, gels, ointments, lotions). Brian holds a BA in Biochemistry from The Ohio State University and an MS in Pharmacy & Pharmaceutical Chemistry from The University of Florida.

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OPHTHALMIC PRODUCT DEVELOPMENT: REDUCE RISKS, MITIGATE FAILURE & DRIVE TIMELINES IN A COMPETITIVE MARKET

In this technical white paper, Badre Hammond, MBA, Associate Director, Business Development at Next Breath, LLC, together with Shailuja Somaraju, PhD, Vice-President, and Julie Suman, PhD, President, highlight key considerations and present strategies to reduce risk and ultimately accelerate the process for gaining approval of an ophthalmic product, with a focus on the US. The authors present a stepwise approach that Next Breath believes is critical in managing the complexities and the unknowns around the development of ophthalmic drug products. They also describe the efforts to support early-stage development through registration stability and batch release. The process described below will assist both NDA and ANDA applicants in developing robust regulatory packages to gain approval for ophthalmic products.

INTRODUCTION AND RATIONALE

The global market value for ophthalmic products was estimated around US\$16.9 billion (£10.2 billion) in 2012 and was expected to increase to more than \$20.2 billion in 2017.¹ An aging population worldwide coupled with higher occurrence of eye conditions and diseases such as diabetic retinopathy, dry eye, glaucoma, and age-related macular degeneration (AMD), have resulted in increased growth in the eye care market.² The emergence of novel formulations like Restasis®, a cyclosporine oil-in-water emulsion formulation, sophisticated dispensing systems such as the Ophthalmic Squeeze Device (OSD; see Figure 1), and ophthalmic injections such as Lucentis® will inevitably lead to higher expectations and scrutiny from the US FDA as their developers seek product approvals.

Currently there are no guidance documents from the FDA for *in*

vitro testing of ophthalmic products. From a CMC standpoint, generics drug developers do not have formal FDA guidelines to support their development of ophthalmic equivalents and the associated ANDAs. Yet, there seems to be an expectation from the FDA to request more information regarding the CMC attributes of ophthalmic drug products.

In the absence of CMC guidelines, it is difficult for the NDA and ANDA applicants to navigate the regulatory process in ophthalmic product development. In addition, there is also a growing expectation for extractables and leachables (E&L) testing on ophthalmic products. Product Quality Research Institute (PQRI; Arlington, VA, US) released guidelines for PODP (parenteral and ophthalmic drug products) last year, which increase the testing burden for all stakeholders.³

To address the changing regulatory landscape in the ophthalmic area in an effective way, Next Breath proactively developed a comprehensive list of *in vitro* analytical testing requirements. This



Figure 1: Aptar Pharma's Ophthalmic Squeeze Device (OSD).



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*Test	Development	Irritation	In Vitro Comparability	Stability	Batch Release
Drop Weight	X		X	X	X
Refractive index	X	X			
EpiOcular model	X	X			
pH	X	X	X	X	X
Osmolarity	X	X	X	X	X
Viscosity	X		X	X	X
Surface tension	X		X	X	X
Assay	X		X	X	X
Related substances/ impurities	X			X	X
Appearance	X			X	X
Turbidity	X			X	X
Drug content per drop	X		X		
Foreign particulate matter				X	X
Particle size by microscopy	X		X	X	X
Globule size	X		X		
Zeta potential	X		X		
Drug release by dissolution	X		X		
Partitioning by ultracentrifugation	X		X		
Gel-strength	X		X		
Leachables				X	

Figure 2: Table outlining analytical methods for ophthalmic drug products. *Preservative content and microbiological testing are not included, but recommended.

analytical package was developed based on Next Breath's regulatory expertise, close collaborations with leading ophthalmic device developers, and ongoing FDA interactions (workshops/conferences).

FORMULATION DEVELOPMENT

An ophthalmic formulation could be a solution, suspension, ointment or an emulsion. A typical eye-care product is sterile, nearly isotonic, has some buffering capacity, contains anti-microbial agents (unless the active itself is bacteriostatic) and is packaged into a suitable tamper-evident, multi-dose dispensing system. However, there is a growing trend to invest in multi-dose, preservative free formulations.

During formulation development, the choice of excipients and buffers must be based upon physiological comfort and product stability, and preferably with a proven track record with the FDA. The ideal pH for an ophthalmic formulation is 7.4, equivalent to tear fluid. However, most drugs are chemically unstable at this pH. Therefore a buffer, if included, must facilitate pH as close as possible to the physiological pH, while not causing chemical instability. Thickening agents such as methyl cellulose or hydroxypropyl-methylcellulose may be added to prolong the contact time of formulation with the eye surface. Colouring agents are not recommended for ophthalmic products in the US.

Once the formulation profile is identified, the first step in product development is estab-

lishing its physical and chemical attributes such as appearance, viscosity, surface tension, osmolarity and pH. Figure 2 provides a comprehensive list of tests that are understood to be expected from the drug developer.

DEVICE SELECTION AND EVALUATION

The current standard for ophthalmic medications is either preserved multi-dose configurations or the unpreserved blow fill seal (BFS) single-dose preparations, which are not easy to handle for elderly patients.

For chronic eye care treatment, multi-dose systems are most convenient and cost effective. Patient surveys suggest that they prefer easy, intuitive-to-use systems that

dispense medication in a drop format *versus* a spray.⁴

Since eye products are required to be sterile, they must be manufactured under strict aseptic conditions. In the US, preservatives such as benzalkonium chloride are added to ophthalmic products to minimise/eliminate microbial growth. However, many such preservatives are known to cause eye irritation and allergic response in many patients. Besides causing sensitivity in some patients, there is also increasing concern regarding the toxicity of preservatives and the damage they cause to the eyes with prolonged use.^{5,6} It has been demonstrated that preservative-free formulations offer a significant medical advantage by reducing ocular damage and discomfort and increasing compliance in glaucoma patients.⁷ Therefore, the current trend is towards unpreserved multi-dose systems to combine the advantages of both approaches.

To address this clinical need to eliminate preservatives, new devices and technologies have emerged which combine a mechanical tip seal technology with sterile air filtration. The Ophthalmic Squeeze Dispenser (OSD) is an example of a class of novel devices designed to eliminate the need for preservative in the formulation and which can be used with existing filling technologies.⁴ Key advantage of OSD (Figure 1) is the prevention of contamination entering through the tip of dispensing system. The single-dose BFS containers could be filled with preservative-free formulations such as the marketed product Restasis. Mystic Pharmaceuticals' VersiDoser[®] ophthalmic delivery system promotes a patient-focused design to facilitate self-administration, ease of use and compliance. Individual liquid doses are contained within blister packaging with each blister having a proprietary, single-use Vjet[™] dispensing nozzle.

Some researchers have demonstrated *in vitro* that preservatives in general, and benzalkonium chloride in particular, can significantly increase the corneal penetration of the drug, compared with control formulations. The formulator must take into consideration the impact of omitting the preservatives in the formulation on drug absorption and its surface spreading properties upon administration.^{8,9,10}

The NDA applicant will need to review the advantages and disadvantages of the available devices and identify an appropriate platform to dispense the medication. In addition, formulation composition (particularly the use of preservatives) should be established early in the development in order to make appropriate container

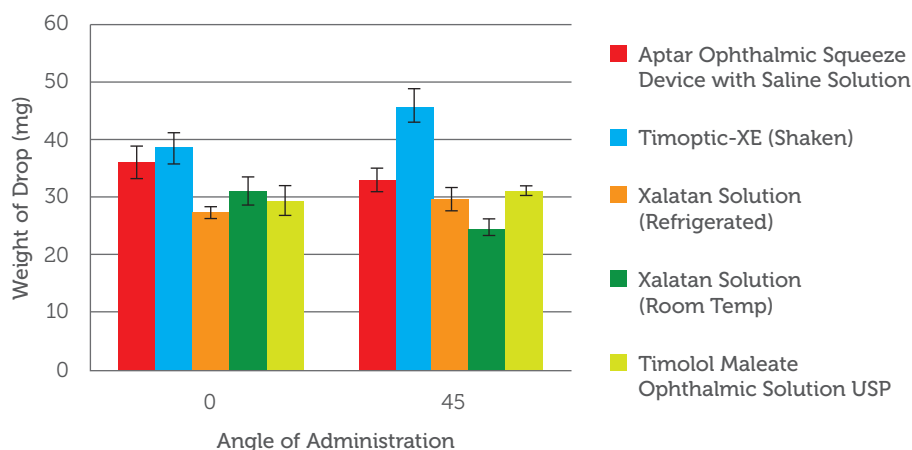


Figure 3: Graph showing Angle of Orientation versus Weight of Drop Dispensed (mg) for various ophthalmic products.

selection (glass *versus* plastic bottles). For example, glass containers are inert but expensive, whilst plastic containers are cost effective and more commonly used, but may interact with the preservatives. There are a limited number of CMOs that offer sterile manufacturing as a service offering, which makes the process further challenging for the drug developer.

Among the various analytical tests that are required of the ophthalmic drug product, an extractables and leachables (E&L) study demonstrates the absence of any adverse interactions between formulation and the packaging material. Both NDA and ANDA applicants are required to evaluate E&L profile for all container closure systems. Leachable studies are particularly relevant during stability studies (Figure 2).

As part of the device screening and selection process, simulated “patient factors” need to be considered and should be representative of human use conditions. For example, the force applied to the bottle as well as the angle of orientation during dosing may affect the size of the droplet formed, which ultimately may affect the dispensed dose. Figure 3 illustrates how the weight of a drop can be affected by the angle of administration for four different ophthalmic formulations. These studies can be used to support selection of appropriate device closure system.

Additional analytical techniques such as high-speed photography to capture droplet size during dispensing could be performed to assist in formulation development and device optimisation. For finished products containing multiple doses, emitted dose through container life (beginning, middle and end of life through label claim) will need to be performed. Shaking studies to establish consistent dosing profile for multi-dose suspension formulations may be necessary.

KEY ANALYTICAL CONSIDERATIONS

Particle Size and Dissolution

Particle size influences the rate and extent of dissolution, as well as eye irritation for suspension and emulsion formulations.¹¹ In general, particles <10 µm are recommended for ophthalmic suspension formulations to facilitate patient comfort and minimise damage to cornea. In order for the deposited drug particles to be useful, the dissolution rate is even more critical for a slowly soluble substance in relation to its residence time in the eye.^{11,12}

There are no approved guidelines or published methods that describe the dissolution/release of drug from an ophthalmic suspension or emulsion. Various studies have been published using conventional dissolution testing apparatus without definitive outcomes. Equipment such as the USP Apparatus 4 modified for ophthalmic application could be used to develop and validate methods to generate drug dissolution profiles.

Ocular Irritation Studies

Ocular Irritation studies will need to be performed to establish that the API and the excipients in the formulation will maintain adequate comfort levels for the patients.¹³ Ocular irritation testing can be conducted using the MTT ET-50 method (time of exposure needed for a formulation to reduce the viability to 50% of control tissues) or with human cell-derived *in vitro* corneal tissue model. Several of these are commercially available and claim to provide an *in vitro* alternative to the Draize rabbit eye test.¹⁴

In Vitro Comparability: Generics

In addition to the tests described above for the NDA applicant, there are further considerations for the ANDA applicant. During generic product development process, the

ANDA applicant must determine that the test product (generic formulation + dispensing system) is comparable to the marketed reference listed drug (RLD). It is important that the ANDA applicant understands the innovator's dispensing system in the generic context during method validation. The ANDA applicant will need to compare results from test and RLD products and demonstrate that the test product is qualitatively and quantitatively equivalent (Q&Q) to the RLD. A comparative approach may be taken for the final analysis based on population bioequivalence statistics.

We highlight the comparative *in vitro* tests for ophthalmic (ANDA) applicants in the table in Figure 2. In the absence of FDA guidance for *in vitro* bioequivalence requirements, these tests may be considered supportive of the *in vivo* studies that are required for solution and suspension formulations. The tests shown in Figure 2 may be relevant for solution, suspension, gels and emulsion formulations. In addition, long-term stability study is expected to be performed by the ANDA applicant.

Stability Program

A robust stability program will need to be performed to establish stability of the ophthalmic drug product. Long-term storage conditions of 25°C/40% relative humidity (RH), and accelerated conditions of 40°C /20 to NMT 25% RH, could be considered. Crystal growth and agglomeration will need to be monitored for suspension formulations and likewise any evidence of breakdown in emulsion formulations. In addition, CMC tests (see Figure 2) on stability, including preservative content, if used, and microbiological testing, may need to be performed. Critical parameters such as drug release or gel strength may need to be analysed during stability studies. Next Breath recommends the inclusion of leachables testing as part of the stability program (assuming the extractables were identified early in the product development). The proposed stability studies are applicable to both NDA and ANDA applicants.

Batch Release

The scope in Figure 2 is proposed to be considered for clinical and finished product batch release for ophthalmic drug products. ANDA applicants will need to perform some of the tests below to show comparability to the RLD.

CONCLUSION

The increased scrutiny by the regulatory agencies and the growing market share for ophthalmic products are expected to rise sharply in the coming years. The complexities in the formulation, device design,

“Formulation composition, particularly the use of preservatives, should be established early in the development in order to make appropriate container selection (i.e. glass versus plastic bottles)”

performance, and absence of FDA guidance present a number of unique challenges as well as opportunities for the NDA and ANDA applicants in the development and commercialisation of ophthalmic products.

Preservatives such as benzalkonium chloride are receiving closer scrutiny from regulators. Avoiding such agents brings new challenges and adds complexity. However, it also offers new opportunities in terms of drug tolerance.

This paper attempts to shed some light on the complexities surrounding ophthalmic product development. It is our judgment that if the drug developer follows a stepwise approach focusing on the key considerations discussed here, and moves to the next phase only if a “go/no-go” decision is achieved, the development process will become more manageable.

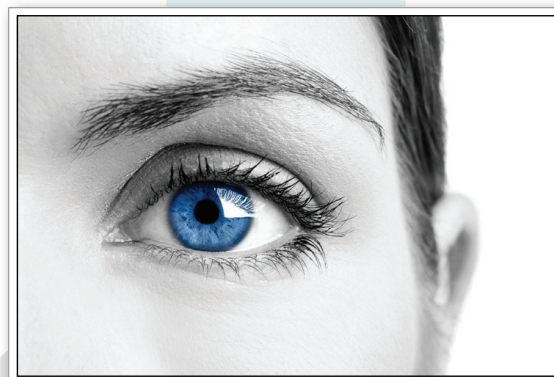
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