OPHTHALMIC DRUG DELIVERY

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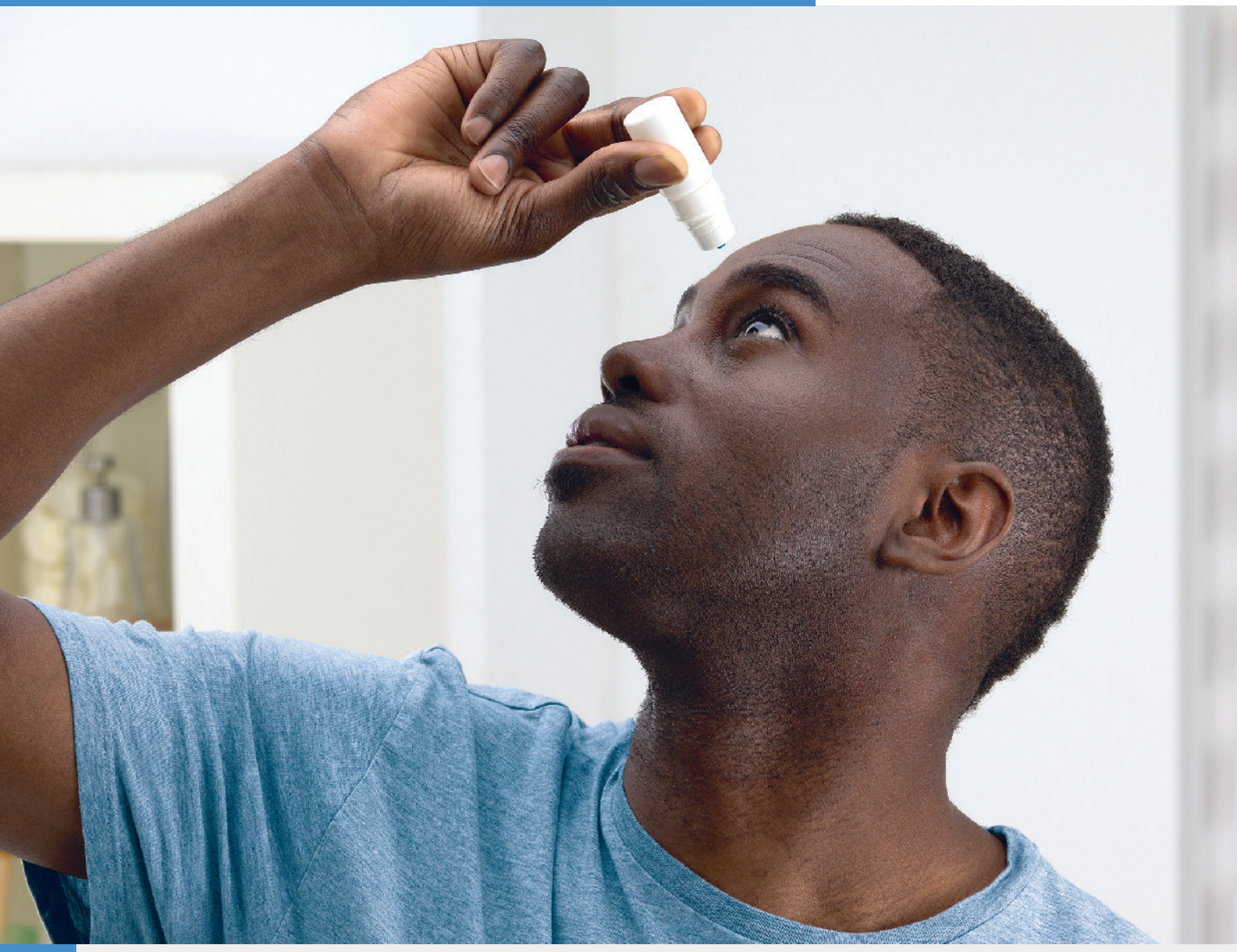

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ONdrugDelivery Issue N° 63, January 27th, 2016

OPHTHALMIC DRUG DELIVERY

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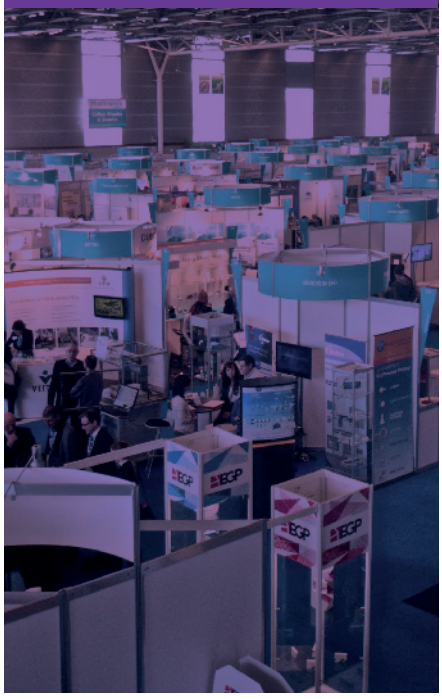

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EXPERT OVERVIEW: DEVELOPMENT OF SUSTAINED-RELEASE OCULAR DELIVERY TECHNOLOGIES

The global cost of vision loss is nearly US$3 billion (£2.1 billion) for the 733 million people living with low vision and blindness worldwide in 2010.[1] The global pharmaceutical market was estimated at $18.1 billion at year-end 2013, estimated to grow to approximately $23 billion by year-end 2018. Within this time period, retinal indications are demonstrating the greatest growth from $6.9 to $9.9 billion or 7.5% compounded annual growth rate (CAGR). Glaucoma is the second largest segment, forecast at $5 billion by the end of 2018, which is 3.1% CAGR followed by dry-eye at $3.1 billion, or 4.3% CAGR.[2]

There have been major advances in recent years in developing and launching new sustained-release ocular drug delivery systems to treat vision loss better. However, only a small number have achieved both global regulatory approval and commercial success. Only four posterior segment products to date have overcome the challenges of development and achieved broad regulatory approval with a degree of commercial success since 1995. These include:

- Vitrasert® (ganciclovir 4.5mg) – approved 1995
- Retisert® (fluocinolone 0.59 mg) – approved 2005
- Ozurdex® (dexamethasone 0.7 mg) – approved 2009
- Iluvien® (fluocinolone acetonide 0.19mg) – approved 2011.

Yet despite the challenges there remains a significant market opportunity to enhance current delivery technologies or develop new technologies offering improved treatment options for patients suffering from the major blinding eye diseases.

THERAPEUTIC FOCUS

The major blinding diseases, wet age-related macular degeneration (w-AMD), diabetic retinopathy (DR), diabetic macular edema (DME) and glaucoma, due to their whole or partial impact on the posterior and anterior segments of the eye, and their growing market sizes, may offer the most promising opportunities for future ocular drug delivery technologies. They affect large numbers of people and pose significant risk of vision loss and blindness for those affected.

> "Only four posterior segment products to date have overcome the challenges of development and achieved broad regulatory approval with a degree of commercial success since 1995."

Current therapeutic options for these diseases may at best manage the condition, slowing or halting further deterioration or disease progression. New breakthrough treatments would benefit from robust sustained delivery of the drug to the target tissues in the posterior segment and, importantly, enhance compliance of patients with long-term treatment regimens for these chronic diseases, for example avoiding or reducing the need for frequent injections.

In addition, from a product "market need" perspective, there are arguably at least five "Holy Grails" that would offer not only significant clinical and medical progress but would also offer multi billion dollar market opportunities and provide major competitive advantages over today's therapeutics; some or all could include sustained-release therapy:

1. Sustained release glaucoma therapy
2. Sustained-release large molecules including proteins, peptides, and aptamers

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3. Sustained anterior delivery to posterior segment
4. Dry AMD Rx therapy
5. Neuroprotection.

Drug-delivery developments to the posterior and anterior segments of the eye, for both small and large molecules may therefore provide a pathway to new market advances for the launch of new therapies based on enhanced current technologies or through innovation with new innovative approaches.

MEETING THE CHALLENGES OF SUSTAINED DRUG DELIVERY

Several factors contribute to the challenge of developing new sustained-release drug delivery systems including:

1. The primary need to match the drug with the delivery technology. This requires the demonstration of sustained delivery pharmacokinetics and using the appropriate animal models for testing the drug's safety and efficacy.
2. Tolerability of drug with the technology.
3. The right clinical trial design and understanding that platform compatibility differs with compound solubility and molecule size.
4. The identification and ultimate granting of intellectual property rights.
5. In addition, sourcing the appropriate funding or partnerships to move the technology through its IND and clinical stages is a critical success factor.

Despite these barriers, multiple technologies and approaches, both posterior and anterior, are in either pre - or clinical development. Based on recent analysis conducted by Scotia Vision for new or enhanced technologies in development, there are at least 11 in retina, 20 in glaucoma and six anterior delivery technologies.[3]

The current gold-standard to treat posterior segment conditions, such as w-AMD and diabetic related retinal disease, remains intravitreal injection (IVT) with anti VEGf agents. In 2005, approximately 22 million IVTs were administered globally.[4] However, this multi-billion dollar IVT injection market has demonstrated that a proven sustained-release implantable technology itself is not a prerequisite for commercial success, but that a sustained clinical and targeted effect of the drug may be critical. The onerous need for monthly or bi-monthly injections may not be ideal from a patient adherence or comfort perspective and, potentially, for safety reasons.

The future for sustained-release ocular drug delivery will include reducing the treatment burden of IVTs through innovations in delivery technology for both small and large molecules and in all cases combining effective therapeutics with the appropriate drug delivery system. Established big pharma companies will need to consider product lifecycle extension strategies to include new drug delivery technologies, although it is most likely that the innovation for the technology will come from the start-up environment.

All technologies approved today incorporate existing generic drugs, so the choice of drug comes first, then is matched with a delivery technology, although the process itself is not an exact science. It may be ideal to have a broad drug delivery platform technology, customised to new drugs, or a class of drugs, remembering each drug compound will require a different release profile and formulation.

Due to the large numbers of products in the pipeline, the selected product development strategy must offer a disruptive technology; that is, disrupting the market compared with what already exists or is in the development pipeline. It should offer true innovation both to patients and doctors, meet a significant market need, and offer both clinical feasibility and potential reimbursement.

> "New breakthrough treatments would benefit from robust sustained delivery of the drug to the target tissues in the posterior segment and, importantly, enhance compliance of patients with long-term treatment regimens for these chronic diseases, for example avoiding or reducing the need for frequent injections."

Some examples of such technologies in development include:

Posterior Segment Delivery

- Refillable drug reservoirs
- Encapsulated cell technology
- Cell-based programs, including stem cells for neovascular AMD
- Iontophoresis
- Novel adeno-associated viral (AAV) variant technology for long-term protein delivery to the eye in DME, neovascular AMD, glaucoma and other conditions
- Prostaglandin analogue delivery systems
- Hydrogel technology
- Supra choroidal implants or injectable suspensions
- Injectable protein delivery systems
- Microparticle and nanoparticle systems.

Anterior Segment delivery

- Topical systems for example semi-fluorinated alkane delivery, enhancing drug solubility
- Contact lens delivery systems
- Mucosal delivery
- Topical peptides for neovascular AMD and corneal injuries.

CONCLUSION

Novel technologies required to deliver agents specifically and effectively to the eye are rapidly evolving. These will have the potential to radically alter the way many ocular conditions are treated, especially retinal blinding diseases and glaucoma. The next decade promises great strides in therapy achieved through sustained-release drug delivery for many currently poorly-treated or untreatable ocular diseases.

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Nemera

USING INTELLIGENT DESIGN TO **DELIVER** SAFE PRESERVATIVE-FREE MULTI-DOSE EYE DROPS

A significant patient population requires the long-term use of eye drops multiple times a day. Maintaining the sterility of eye drops is important for patient health. Single-use doses are expensive and preservatives can cause allergies and irritation but, as Ms Fanny Sellier, Global Category Manager, Ophthalmic, Nemera, explains here, the intelligent design of multi-dose bottles provides a viable means of delivering safe, preservative-free eye drops.

PATIENTS NEED STERILE EYE DROPS

A large number of patients have conditions that require the long-term daily use of eye drops. For example, dry-eye syndrome is associated with aging, contact lens use and environmental factors such as windy and sunny weather. It affects an estimated 5% of over 50s in the US [1] and is usually managed using an artificial tear solution which needs to be applied up to four to six times a day, often for the rest of the patient's life. Conditions such as hay fever and glaucoma also require the long-term use of self-administered eye drops.

It is important that all eye drops are kept free from bacteria. The microbial contamination of eye drops is a significant risk factor in the development of bacterial keratitis.[2] Post-operative patients are at particular risk of infection, as are patients who have used topical steroids, since these lower the ocular defences.[3]

PRESERVATIVE-FREE BETTER FOR PATIENT HEALTH

One way of keeping multi-dose eye droppers safe for patients is to add preservatives to the formulation.

However, the use of preservatives can cause allergies or ocular irritation, and some can even cause a toxic response, damaging patients' eyes.[4] Any such reactions is a particular issue for patients who rely on the long-term use of eye-drops for chronic conditions.

In 2009, the European Medical Agency stated that the "inclusion of antimicrobial preservatives or antioxidants in a finished product needs special justification". Even when preservatives are tolerated in an adult population there are still questions over tolerance for the paediatric population. The EMA has stopped short of a general recommendation not to use preservatives in eye drops, but they recommend that "preservative free formulations whenever possible should be considered" and that "ophthalmic preparations without preservatives are strongly recommended for use in paediatric patients, especially neonates".

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PRESERVATIVE-FREE UNIDOSES: EFFECTIVE BUT EXPENSIVE

Unidose eye droppers are a commonly used delivery method for preservative-free eye drops. By virtue of being single use, there is no opportunity for bacterial contamination at the point of use.

Unidoses are ideal for clinical settings, especially during surgery. However, they are too costly and inconveniently bulky to be suitable for home use in chronic conditions. Single-unit, preservative-free drops have been calculated to be 1169% more expensive to produce than the equivalent preserved eye drops in a multi-dose bottle.[5]

INTELLIGENT DESIGN FOR PRESERVATIVE-FREE MULTIDOSES

The alternative way to keep eye droppers clean is by the intelligent use of technology. Rather than relying on the anti-microbial properties of preservatives to kill any bacteria that enter the bottle, the ideal approach is to prevent any entry of bacteria into the bottle in the first place.

Multi-dose bottles dispense drops using either a non-return valve or a filtering system. Most commercially available bottles designed for multi-dose preservative free eye drops rely on a filtering system to stop the entry of bacteria. When a drop is dispensed, the volume of the dose is compensated by air. Eye drops can become contaminated in two main ways: by contaminated air entering the device or by contaminated liquid re-entering through the filter.

FILTERING OUT THE BACTERIA?

Anti-microbial filters are typically made from a nylon fibre membrane that consists of tightly packed layers of strands of nylon fibres (see Figure 1). Filters work on the mechanical principle that bacteria are large molecules that do not fit through the very small holes, while air and non-viscous solutions are able to pass through without hindrance.

Sterile 0.22 µm filters are industry standards, but their effectiveness as bacterial filters has been challenged in the literature. Unfortunately it has been found that bacteria are capable of routinely penetrating 0.22 µm filters, even when the molecules seem to be too big to fit through the holes.

In a 2002 paper, "Big bacteria pass through very small holes," Wainwright *et al* found that: "Common, potentially pathogenic, bacteria (which are nominally larger than 0.2 µm) can cross a 0.2 µm nylon membrane.[6] All of the bacteria crossed from the upper membrane surface to the solid medium below the membrane; this ability was highly repeatable and did not depend on the make of membrane used. Bacteria growing below the membrane exhibited normal size and morphology."

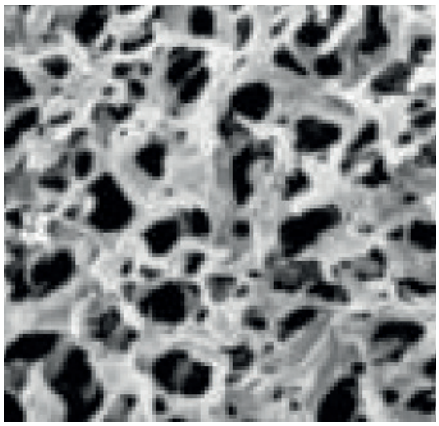

Figure 1: Scanning electron micrograph of nylon membrane filter (pore size 0.22 µm).

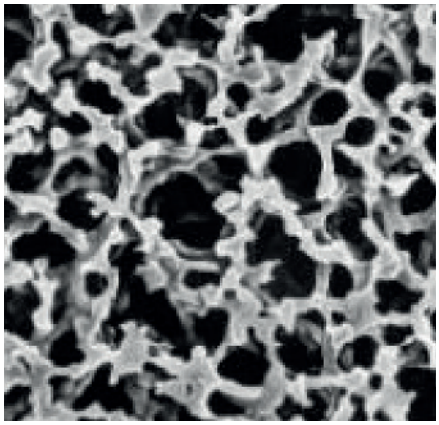

Figure 2: Scanning electron micrograph of a Millipore membrane filter (pore size 0.22 µm) showing a distribution of pore sizes.[10] (Bar in bottom right hand corner of image is 1 µm long.)

Even where filters are shown to be effective, the filtered bacteria clearly remain on the filter. A 2006 study on the efficacy of single-use bacterial filters showed "a significantly greater bacterial growth on the proximal side of the filter compared with the distal side".[7] Eye-drop filters act in two directions: pressure on the sides of the plastic bottle dispenses a dose through the filter to the patient's eye. When the pressure is released, air and a small amount of liquid passes back through the filter and into the bottle. Therefore, bacterial growth on the filter represents a contamination risk for the delivered dose.

WHAT MAKES FILTERS UNRELIABLE?

The evidence that bacteria can pass through 0.2 µm filters is clear, but the reasons are not obvious. One possibility for the observed passage of bacteria through filters could be due to the nature of the material of the filters. The sponge-like structure includes holes of varying sizes (Figure 2), some of which are statistically likely to be larger than 0.2 µm. In fact, one study found that 0.2 µm filters have a distribution of pore sizes that includes some as big as 0.5 µm.[8]

Individual testing would eliminate doubt over the viability of each filter, but the process used to test filters is destructive.[9] The testing method introduces bacteria and liquid onto the surface of the filter. This starts bacterial growth on the filter and therefore decreases the subsequent shelf life of the dispenser. Therefore, in-line testing of multi-dose dispensers that rely on filter technology is not possible. Instead, testing is carried out statistically on only a proportion of the dispensers.

However, it is likely that the presence of larger holes in the filters is not the sole mechanism of bacterial penetration. Hasegawa et al found that "*Pseudomonas aeruginosa* passed through a 0.22 µm pore size filter. The membranes which allowed passing-through of bacteria showed normal bubble point values in the integrity test". This demonstrates that bacteria are still capable of passing through a reliable 0.22 µm pore size filter.

BACTERIAL MOTILITY IS A CAUSE OF FILTER PENETRATION

Bacteria come in a variety of shapes and sizes, but many of them share the ability to self-propel by twitching, rotating or gliding. Twitching is the most common form of motility and is achieved through movement of the flagella in a way that makes the bacteria appear to swim. Studies have shown that this motility enables bacteria to move through very small channels relative to their size.

Hasegawa *et al* also experimented with a strain of *P aeruginosa* that was defective in twitching motility and found that it was unable to pass through the 0.22 µm filter. They concluded that it is the flagellum-dependent motility of *P aeruginosa* that enables it to penetrate fine filters.

BACTERIA ALSO PENETRATE BY GROWTH & DIVISION

Männik *et al* went on to find that *Escherichia coli* lose their ability to swim in channels narrower than their diameter.[13] Surprisingly, they found that despite this they are still able to penetrate narrow channels. They observed that over time, through the mechanism of growth and division, *E coli* were able to penetrate filter channels "with a width that is smaller than their diameter by a factor of approximately two. Within these channels, bacteria are considerably squeezed but they still grow and divide".

This has clear implications for the effectiveness of filters for multi-dose, preservative-free eye droppers. Filtering liquid several times a day means that the filter remains wet throughout the usable lifetime of the device, presenting ideal conditions for bacterial growth.

AN ALTERNATIVE TO FILTERS BASED ON SILICONE: NOVELIA®

A viable alternative to the use of sterile filters for multi-dose, preservative-free eye droppers is a non-return valve system used in conjunction with a silicone membrane to filter the returning air (Figure 3). The one-way valve ensures that no contaminated liquid can be re-introduced to the container after the drop has been dispensed, completely removing the need to filter the liquid. The intake of air into the dispenser takes place via a separate venting system with a silicone membrane called the PureFlow™ technology (Figure 4). The venting system filters the intake of air using a very fine membrane manufactured from silicone polymer.

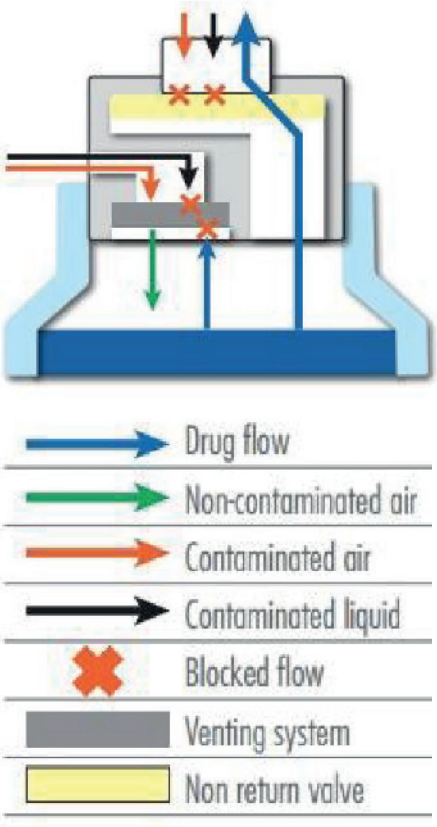

Figure 3: The Novelia® system uses a non-return valve that removes the need to filter the liquid. This makes it possible to use a silicone membrane to filter the air.

The silicone membrane is a solid, non-porous material. It is homogenous and does not contain any holes therefore its characteristics can be precisely engineered. The membrane's intermolecular distance is of the order of nanometres, allowing the passage of air through the membrane, but completely preventing the passage of any liquid or solid, including bacteria.

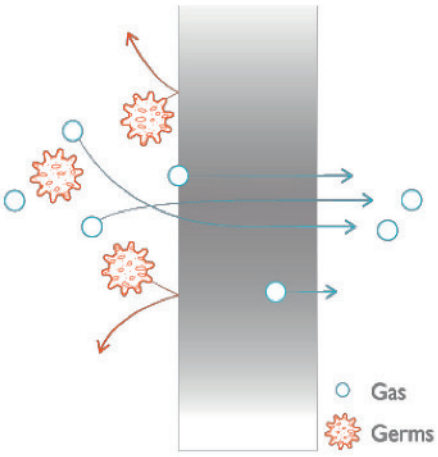

Figure 4: The PureFlow™ technology consists of using the air permeation property of the silicone to allow the air flow and avoid any bacterial penetration.

The function of the silicone membrane can be compared with an inflated balloon. The balloon is a continuous, waterproof material, yet gas slowly passes through the wall of the balloon until the pressures inside and outside reach equilibrium.

> "Devices that use this PureFlow™ technology can be tested individually in-line as a consistent part of the manufacturing process."

The separation of the dose delivery from the venting system means that the membrane is kept dry. This minimises the risk of bacterial growth on the surface of the membrane, and also means that the testing process is non-destructive. In fact, devices that use this PureFlow™ technology can be tested individually in-line as a consistent part of the manufacturing process to ensure robust quality standards. This provides an even greater assurance of safety for the patients.

SUMMARY

A non-return valve combined with a silicone membrane venting system demonstrates how intelligent design can be used to prevent the entry of bacteria into a bottle, making it possible to deliver safe, multi-dose preservative free eye drops.

NOVELIA® KEY ADVANTAGES

For the pharmaceutical company:

- 100% controlled and safe thanks to itspatented PureFlow™ technology
- Functional with suspensions and solutions up to high viscosities
- Large range of bottles
- Compatible with most existing filling lines (screw cap)
- Simplified manufacturing process thanks to preassembled cap and nozzle.

And of course for the patient:

- Preservative-free to protect the ocular surface
- User-friendly and intuitive, as easy to use as any standard eyedropper
- Blue tip for a better precision when targeting the eye
- One drop at a time in the patient's eye, calibrated drops
- Low squeeze force
- More sustainable and affordable compared to unit-dose, easier to carry.

With Novelia®, preserve patient's eyes, not drugs!

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ONdrugDelivery 2016 EDITORIAL CALENDAR

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April 2016	Pulmonary & Nasal Drug Delivery	March 7th
May 2016	Injectable Drug Delivery: Devices Focus	April 11th
June 2016	Connected Drug Delivery Systems	May 2nd
July 2016	Novel Oral Delivery Systems	June 6th
Sepetember 2016	Wearable / High Volume Injectors	August 8th
October 2016	Prefilled Syringes	September 12th
November 2016	Pulmonary & Nasal Delivery	October 10th
December 2016	Delivering Biotherapeutics	November 14th
January 2017	Ophthalmic Drug Delivery	December 12th

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Integral BioSystems

INTRODUCING OCUSURF™ NANOSTRUCTURED EMULSION AS A 505(B)(2) STRATEGY

Here, Dr Shikha P Barman, Chief Executive Officer and Chief Technology Officer, Integral BioSystems, describes how the company is developing a series of ophthalmic products with its OcuSurf platform, an aqueous nano-dispersion of dissolved hydrophobic drug in nanostructured "cores" that rapidly absorb into the lipid bilayers of target ocular tissues. The platform is suitable for application as an enabling technology for new products but here the focus is on employing a 505(b)(2) strategy on the reformulation of existing products.

GLOBAL OPHTHALMIC MARKET

Globally, the ophthalmic drugs market is witnessing significant growth due to increasing prevalence of ophthalmic disorders, both for the anterior and posterior segments of the eye. As a result, this market is expected to grow at a compound annual growth rate (CAGR) of about 5.2% during 2013-2018.[1] Accordingly, the ophthalmic drug industry has witnessed a plethora of technologies that are business driven and aimed at product extensions for lifecycle 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 differentiated technologies has risen dramatically, with fewer NDA 505(b)(1) applications for new chemical entities (NCEs) than there were in previous years.

> "The composition of the OcuSurf nano-dispersion allows interaction and bioadhesion with the ocular surface mucosa, "melting" of the nanocores, release of drug and rapid absorption."

THE 505(B)(2) STRATEGY

The 505(b)(2) NDA [2] is one of three US FDA drug approval pathways and represents an appealing regulatory strategy for many clients.

The pathway was created by the Hatch-Waxman Amendments of 1984, with 505(b)(2) referring to a section of the Federal Food, Drug, and Cosmetic Act. The provisions of 505(b)(2) were created, in part, to help avoid unnecessary duplication of studies already performed on a previously approved ("reference" or "listed") drug. The section gives the FDA express permission to rely on data not developed by the NDA applicant.

A 505(b)(2) NDA contains full safety and effectiveness reports but allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant. This can result in a much less expensive and much faster route to approval, compared with a traditional development path [such as 505(b)(1)], while creating new, differentiated products with tremendous commercial value.

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KEY STRATEGY FOR GENERICS

Generics company CEOs report that they are considering a spectrum of solutions to bridge the revenue gap, but perhaps none are more valid than the FDA's 505(b)(2) approval pathway, which can offer accelerated approval, reduced development costs, lower risk and, in certain cases, market exclusivity. Given the benefits, many generics developers are leveraging 505(b)(2) to carve out niche markets because there are opportunities for specialisation; 505(b)(2) development is more than a regulatory pathway, it is a competitive business strategy.

In the next section, we introduce OcuSurf™, a novel, patent-pending, differentiated and improved formulation approach for medications to treat disorders of the ocular surface and the anterior chamber.

NANOSTRUCTURED EYE-DROP WITH HIGH OCULAR PERMEABILITY

A substantial number of ophthalmic drug products for disorders of the ocular surface are hydrophobic, or sparingly soluble in water. Thus, in order to administer the drugs as eye-drops, they are formulated as multi-dose drug suspensions in a biocompatible, pH-adjusted aqueous vehicle. The process of drug absorption by ocular tissue is comprised of dissolution of the drug in the tear fluid, followed by diffusion of the dissolved drug into the tissue, a process that is counteracted by the high rate of fluid turnover and consequent drainage via the nasolacrimal duct. This results in less than 5% of each eye-drop actually being absorbed by the target tissue. Consequently, drug suspensions are typically formulated with a high concentration of drug to achieve a therapeutic effect. Thus, a clinical and market need exists for highly bioavailable, high tissue absorbing formulation compositions.

In one example, anti-inflammatories and anti-infectives are administered post operatively after cataract surgery to counter inflammation and infection. Multiple drugs are often administered simultaneously, with a regimen often 4-6 times daily, over three weeks. This regimen, combined with inefficient drug absorption, results in a less than ideal scenario for wound healing and disease management. To solve this problem, most eye-drops are now formulated with viscosity-enhancing polymers that enhance the residence time of the drug and hinder rapid clearance of fluid from the ocular surface. These viscosity-enhancing polymers range from cellulose derivatives (like hydroxypropyl cellulose and carboxymethyl cellulose) to polyvinyl alcohol, xanthan gum, guar gum, hyaluronic acid and polyvinyl pyrrolidone.[3]

To counter the need for multiple drugs administered simultaneously, fixed drug combinations have been developed and commercialised (e.g. Tobradex™ and Zylet™).[4,5] These approaches have had synergistic advantages in ophthalmic therapy. However, there is still a need for rapidly absorbing ophthalmic formulations that enable a lower drug concentration and achieve equivalent, or more effective, therapies.

Integral BioSystems has developed a proprietary platform, OcuSurf™, that can be formulated easily with multiple drugs and fixed drug combinations as product improvements of existing drug products, new applications of existing drug products or high performing products of new drug actives.

OcuSurf™ is an aqueous nano-dispersion of dissolved hydrophobic drug in nanostructured "cores" that rapidly absorb into the lipid bilayers of target ocular tissues. The composition of the OcuSurf nano-dispersion allows interaction and bioadhesion with the ocular surface mucosa, "melting" of the nanocores, release of drug and rapid absorption.

Products that have been enabled in this delivery system are loteprednol etabonate, 0.1% (OcuSurf-LP), moxifloxacin, 0.5% (OcuSurf-MOX), dexamethasone, 0.1% (OcuSurf-DX), fluticasone propionate, 0.1% (OcuSurf-FP).

Integral BioSystems is developing a series of ophthalmic products with the OcuSurf platform, employing a 505(b)(2) strategy on the reformulation of existing products.

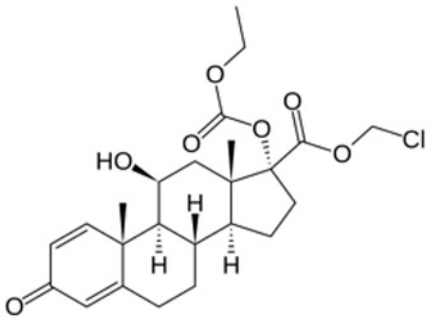

Figure 1: Chemical structure of loteprednol etabonate (OcuSurf-LP).

In particular, a loteprednol etabonate topical product (OcuSurf-LP) (Figure 1) for the prevention of inflammation post cataract surgery is underway. An elegant structural design improvement, loteprednol etabonate is a novel carbon 20 (C-20) ester-based corticosteroid [6] 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

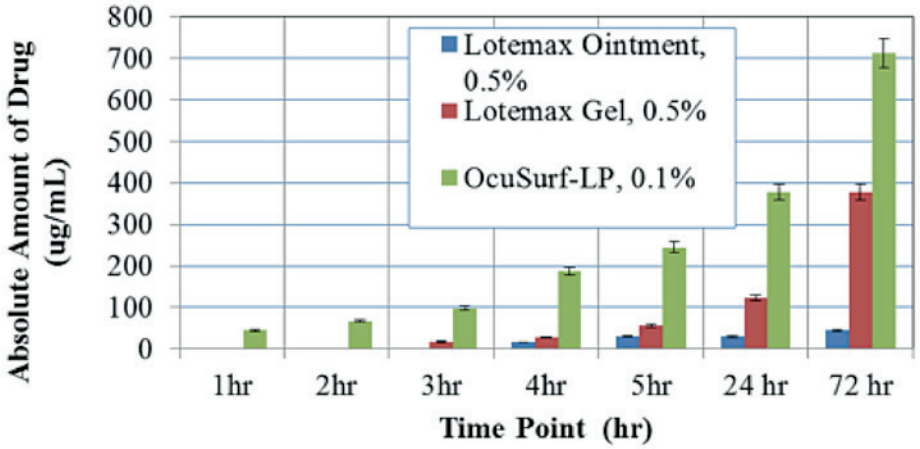

Figure 2: High permeability of loteprednol etabonate formulated in OcuSurf nanodispersion.

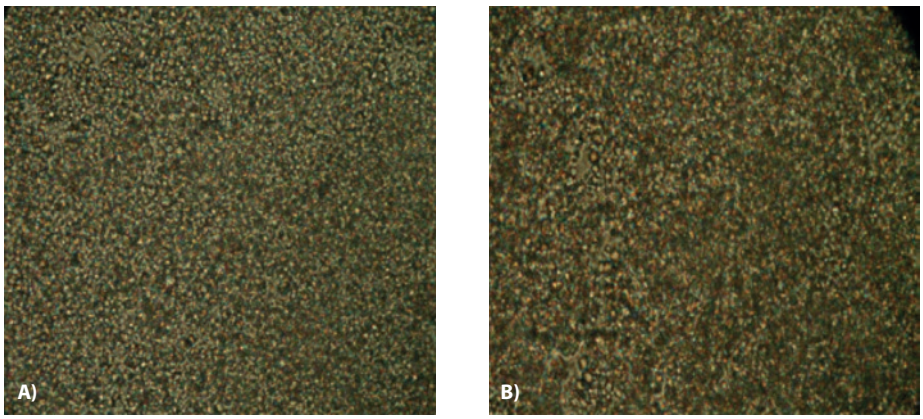

Figure 3: Optical microscopy of OcuSurf formulations using an Olympus BX51P, using an oil immersion objective at 1100X; A= OcuSurf-LP (LP=loteprednol etabonate); B=OcuSurf-DX (DX=dexamethasone).

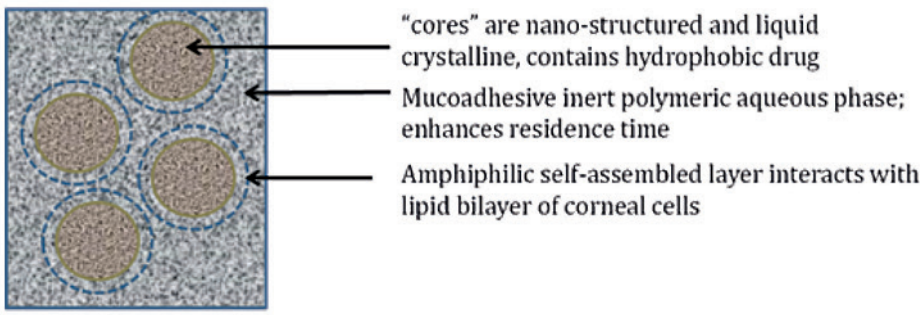

Figure 4: OcuSurf™ nanostructured dispersion.

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. Products containing loteprednol etabonate (LoteMax™ Ointment, 0.5%, LoteMax™ Gel, 0.5%) have been FDA approved, with high patient acceptance. Both product formulations contain micronised drug. OcuSurf™-LP is non-settling, membrane-adherent, stable for room temperature storage and demonstrates high bioavailability.

In a comparative *ex vivo* corneal permeability study using a Franz-cell set-up with a donor and receptor chamber, the diffusive characteristics of loteprednol etabonate was compared with commercial LoteMax Gel and LoteMax Ointment. 500 µg of each product was loaded in the donor chamber of the Franz cells with a freshly excised bovine cornea as the membrane. 0.1% HPCD in phosphate buffered saline, pH 7.4, was used as the receptor fluid. As shown in Figure 2, loteprednol etabonate formulated in OcuSurf demonstrated high corneal permeability. In addition, corneal drug concentrations were many-fold higher for the OcuSurf group (2176 µg/g) versus the LoteMax groups (1109 µg/g: LoteMax gel; 987 µg/g LoteMax Ointment).

Characterised by optical microscopy, the OcuSurf Platform is a uniform nano-dispersion with drug-containing "cores" (Figure 3 & 4). The cores contain dissolved drug, released at 37°C in the eye. The drug-containing cores are dispersed in an aqueous, bio-adhesive, polymeric phase (the continuous phase), with a viscosity of 350 centipoise (measured at 25°C, by Brookfield (Middleboro, MA, US) viscometer).

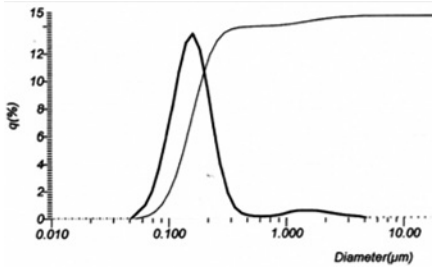

Figure 5: OcuSurf-LP particle size distribution measured by laser light diffraction.

Particle size distribution of OcuSurf-LP was measured by laser light diffraction (Figure 5), using a Horiba LA-950 particle size analyser. The statistical mode (most frequent occurrence) and mean (average particle size, d50) of the nanodispersion was <200 nm. Over three months at room temperature, there was no significant change in the particle size distribution. OcuSurf-LP was placed on stability (see Figure 6); no significant change in assay was observed at any temperature over three months.

As seen in Figures 7A and B, OcuSurf platform is a non-settling delivery system. *In vivo* pharmacokinetic assessment with OcuSurf-LP is underway.

The OcuSurf platform can being developed as part of a 505(b)(2) strategy to treat disorders of the eye, which include glaucoma, corneal keratitis, blepharitis, allergic conjunctivitis, cataracts, dry eye, bacterial and fungal infections. To that effect, Integral BioSystems is working on products for dry eye and ocular methicillin-resistant Staphylococcus aureus (MRSA).

In addition to the applications in ocular delivery described here, OcuSurf platform is applicable as a topical delivery system for dermatological, urological and otic medications.

Conditions	LOT#	% Loteprednol Etabonate: 0.1%			
	Initial	10 days	1 month	2 months	3 months
RT	102.05 ± 0.66	99.93 ± 0.32	97.60 ± 0.73	99.31 ± 0.84	97.20 ± 0.91
30°C/60%RH	–	99.04 ± 0.41	98.70 ± 0.33	99.37 ± 0.96	100.88 ± 1.34
40°C/75%RH	–	103.74 ± 0.29	101.34 ± 0.51	98.32 ± 0.88	102.86 ± 0.73

Figure 6: Stability data for OcuSurf-LP, 0.1%.

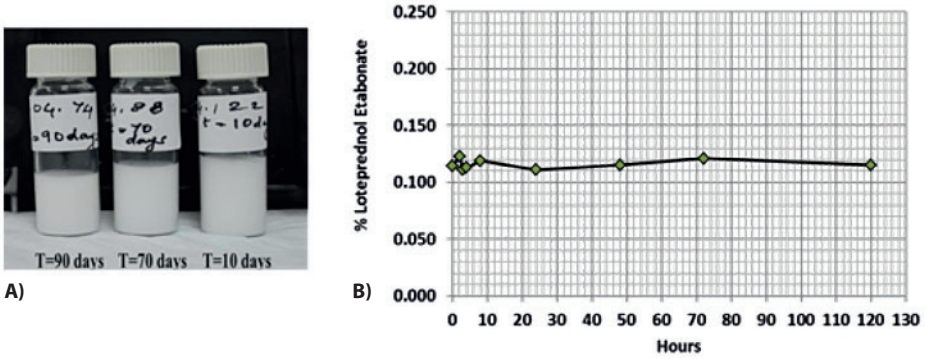

Figure 7: (A) Vials were stored at room temperature and visually assessed periodically. (B) Settling kinetics was assessed by measurement of drug concentrations over 120 hours at room temperature.

ABOUT THE AUTHOR

Named as one of "20 Women to Watch in Massachusetts High Technology in 2014", Shikha Barman, PhD, has more than 20 years of experience in the translation of concepts from the lab into clinical and commercial drug products. She is CEO, CTO and a founding member of Integral BioSystems, LLC.

Dr Barman's 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, she was Vice-President of Pharmaceutical Development and Preclinical Sciences at Follica, Inc (Boston, MA, US) responsible for multiple departments in CMC, preclinical DMPK and toxicology, developing dermal products in antimicrobials, onychomycosis, hair growth and acne. Prior to Follica, she was Senior Director of CMC/Pharmaceutical Development at Inotek Pharmaceuticals, Inc (Lexington, MA, US) developing products utilising novel small-molecule PARP inhibitors and A-1 agonists into ocular treatments for glaucoma and diabetic retinopathy and an injectable for a fast-acting treatment for atrial fibrillation. She was also Head of Vaccine and Transdermal Development at Sontra Medical Corporation (now Echo Therapeutics, Iselin, NJ, US), developing products delivered using an innovative transcutaneous ultrasound device (SonoPrep™) developed at the Robert Langer Laboratory at MIT. One of these products is marketed as a continuous glucose monitoring device. At Zycos, Inc, Dr Barman was Head of Gene Delivery, targeting PLG microsphere-based DNA-based therapies for the treatment of HPV and cancer. Lastly, at Focal, Inc, she helped develop one of first lines of biodegradable tissue sealants, now marketed as FocalSeal, by Genzyme BioSurgery.

Dr Barman has 17 issued US Patents and 56 US applications/PCTs, 65 publications and four book chapters.

Dr Barman's PhD is in Polymer Science and Plastics Engineering from University of Massachusetts at Lowell, an MS in Polymers from University of Massachusetts at Lowell, and a BS / MS in Chemistry from Auburn University, AL, US.

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ABOUT INTEGRAL BIOSYSTEMS

Integral BioSystems specialises in biodegradable sustained-release dosage forms for proteins, peptides, nucleic acids and small molecules. Microspheres, liposomes, and 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.

Integral scientists have developed a proprietary, bioengineered ocular surface mesh (NanoM™) that releases precise, predictable concentrations of drug over time. The composition of the NanoM delivery system can be modulated for a drug regimen that lasts a week, to one that can be designed last 3-6 months.

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-develop ophthalmic products utilising these delivery modalities.

As a CRO, Integral BioSystems offers pharma companies formulation development services, process engineering, scale-up, technical transfer and CMC writing services for FDA submissions. Integral BioSystems is based in the Boston, MA, US, area with offices and fully equipped laboratories at Bedford, MA, US.

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Keynote Speakers

Katherine High
President & Chief Scientific Officer
Spark Therapeutics

Distinguished Speakers

Vicken Karageozian
Allegro Ophthalmics

Megan McLaughlin
GlaxoSmithKline

Konrad Kauper
Neurotech Pharmaceuticals

Anand Swaroop
National Eye Institute, NIH

AGENDA HIGHLIGHTS

Session topics include:
I. Novel Targets Impacting Ocular Diseases
II. Regenerative Medicine and Cell & Gene Therapy
III. New Therapeutics in Dry Eyes Disease & Glaucoma
IV. Clinical Development Advances & Updates

Panel topics include:
I. Leveraging CROs to Externalize Research
II. Funding Avenues
III. Business Development and Partnering
IV. Regulatory Affairs

EmulTech
ADD CONTROL TO YOUR EMULSION

IMPROVING OPHTHALMIC DRUG DELIVERY WITH NOVEL EMULSION TECHNOLOGIES FOR STERILE SUSTAINED-RELEASE INJECTABLES

In this article, Robin de Bruijn, MSc, Chief Technology Officer, and Frank de Jong, MSc, Chief Executive Officer, both of EmulTech, describe the company's ET4ME micro-encapsulation process, and its suitability as a particle formation technology for enhancing and enabling injectable ophthalmic pharmaceutical products.

In the ophthalmic pharmaceutical world, there is a large need for and challenge to develop effective long-term delivery systems to solve problems with the retina. Typically, only systemic doses by administration directly into the eye are the only way to deliver sufficient concentrations of drugs. These are done by injections which can be very problematic. An increasing number of drugs designed to prevent or treat these diseases require repeated and high-dose injections due to the high ocular clearance rate, leading to clinical challenges in the form of side effects (infections, haemorrhages and cataract formation). One successful approach has been the surgical implantation of drug-releasing devices, such as Vitrasert® (ganciclovir), Retisert® (fluocinolone acetonide), Ozurdex® (dexamethasone), and Iluvien® (fluocinolone acetonide). Unfortunately, the aforementioned complications as a result of these (often non-absorbable) implantations are still not fully resolved.

> "Encapsulation in biodegradable matrices is used for controlling the release of all kinds of compounds. Demand for the process has led to the creation of advanced emulsion solvent evaporation/extraction based micro-encapsulation technologies. It is advanced process knowledge that can translate the formulation complexity into to a successful drug product"

Micro-encapsulation of small- and large-molecule APIs is a very advanced solution to injectable delivery problems. Micro-encapsulation is one of the most interesting areas in modern pharmaceutical technology. It is a complex, interdisciplinary field requiring specialist knowledge of polymer science and familiarity with emulsion technology. It includes the process in which the active pharmaceutical ingredient is trapped in small microparticles. Due to its complexity, micro-encapsulation is extensively studied inside major pharmaceutical companies, universities and research institutes. Encapsulation in biodegradable matrices is used for controlling the release of all kinds of compounds. Demand for the process has led to the creation of advanced emulsion solvent evaporation/extraction based microencapsulation technologies. It is advanced process knowledge that can translate the formulation complexity into to a successful drug product.

The process of micro-encapsulation can address complex modern drug delivery issues. EmulTech has developed, and put to use in

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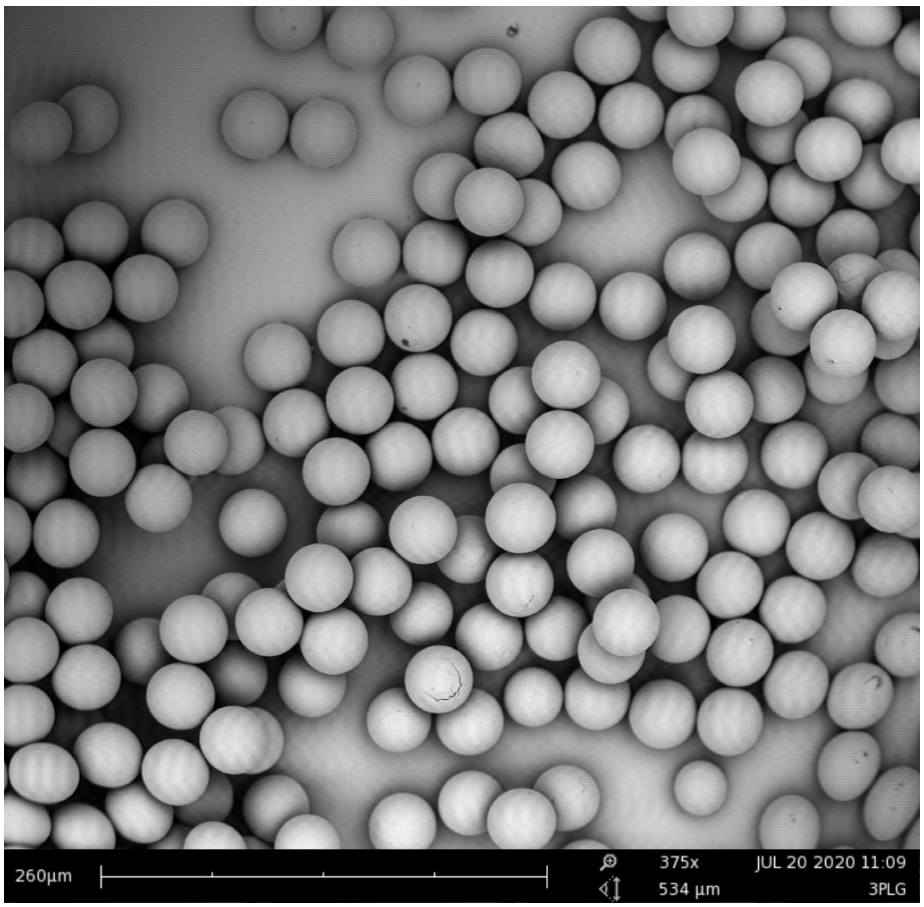

Figure 1: SEM image of 40 µm PLGA particles created with ET4ME.

the formulation of drugs for clinical trials, a microfluidic process that creates a measurable microparticulate suspension where particle size is uniform and reproducible.

This novel emulsion technology for micro-encapsulation, ET4ME, is usable in the formulation of multiple APIs, from small molecules right through to complex biomolecules, with high levels of batch consistency and reproducibility upon scale-up.

By utilising a closed system, sterile formulations can be achieved, coupled with resistance to oxidative degradation. After validation for several biodegradable microparticulate systems and successful aseptic process simulation trials using the ET4ME process, the technology's potential for pharmaceutically acceptable, sterile injectable product formulation has been demonstrated.

BUSINESS MODEL BRINGING EMULSION TECH TO LIFE

EmulTech has adopted a flexible and professional model to pool collective experiences and co-operate in a multi-disciplinary network to advance the use of innovative technologies in product formulation. For example, EmulTech has the capability to test formulations together with world experts in partnered academic institutions that require small volumes. The company offers a parallel strategy for swift and reproducible scale-up whilst providing product and process support throughout a product's development cycle. CMOs in the network provide a varied palette of formulation development expertise, analytics and GMP services and expert guidance through the processes of new medicine and material development for Phase I and Phase II clinical trials.

By collaborating, such companies are able to maximise budget effectiveness and minimise experimentation without sacrificing quality levels, and enhance productivity, thereby providing increased value to customers and achieving significantly shorter development times.

Following the preclinical formulation and lab-scale process development, EmulTech is in the process of installing the capability to validate the equipment further and to formulate products according to cGMP requirements.

EMULSION TECHNOLOGY BENEFITS

Droplet formation in microfluidic devices has always been an interesting approach. EmulTech has made a breakthrough by modelling droplet formation on the cross-intersection of a microfluidic channel structure. Process parameters can be identified by feeding measurable material specific parameters (e.g. viscosity, interfacial tension) and particle characteristics (e.g. particle size) into the model. When the process parameters are set correctly, each droplet is formed to the same characteristics, ensuring the uniformity of the batch and thus its quality. This way ET4ME translates the trial-and-error approach of many processes into a quality-by-design approach.

Scale-up is done through process intensifications (more channels per device) and numbering out (cartridges containing multiple devices). Process parameters identified in a single-channel setup can easily be translated to a multi-channel setup to create larger volumes (up to Phase II clinical depending on the application).

In principle, the technology is a highly controlled emulsification technology having various applications in different markets, such as the food industry (taste masking, protection of additives against its surrounding, delivery to the gastro-intestinal system), cosmetics (stability enhancement of uniform micro-emulsions), chemicals (increased control over reactions), pharmaceutical industry (drug delivery, markers, radiotherapeutics, etc). EmulTech's prime markets are the inhaled and injectable drug delivery markets, because of the significant added value ET4ME provides in these markets.

"This novel emulsion technology for micro-encapsulation, ET4ME, is usable in the formulation of multiple APIs, from small molecules right through to complex biomolecules, with high levels of batch consistency and reproducibility upon scale-up"

Parameter	Benefit
Quantifiable	Based on measurable parameters, particle formation is now "measure-and-make."
Compatible	APIs ranging from small molecules to complex biomolecules can be used.
Uniform	Particles are individually formed in the same way, leading to uniform size, loading and morphology.
Consistent	Droplet formation is based on a physical process: fixed process parameters give fixed product characteristics.
Scalable	Highly reproducible using mass parallelization.
Closed system	Degradation by air/oxygen can be eliminated.
Aseptic	Inline filtration in a closed system ensures sterility.
Static system	No moving parts, no high temperatures or high shear. Very reliable and stable.

Figure 2: Benefits of ET4ME as a particle formation process.

The inhaled market requires particles in the range 1-5 µm, preferable 2-3 µm for optimal lung deposition. ET4ME, because of its uniformity, is well suited to meet these requirements.

The ophthalmic injectable market requires sterile suspensions with high syringability, preferably with very small gauge needles (>28G). The closed system, combined with the 0.22 µm inlet filters, ensures the creation of sterile suspensions. Also the uniform particle size reduces the suspension's viscosity, making it more syringable and thus less painful for the patient. Also the uniform particle-size distribution of ET4ME ensures that large particles that may block the needle are not present. Very small particles that may result in immune response dose dumping are also absent. In short, the optimal particle size both to ensure release and deliver by small-gauge needles is now possible to achieve (see Figure 1).

Main advantages of the technology are:

- Quality-by-design approach
- Reproducibility between batches and during scale up
- No end sterilisation as a result of closed system with inlet filters
- Benign process; no shear, no heat increase.

Product benefits include:

- Microparticles with a very narrow particle size distribution
- Improved injectability
- Broad variety of APIs and carrier materials possible
- New products are feasible

The technology is a highly versatile particle formation technology based on a microfluidic process (see Figure 2). The process enables the particle size, loading and carrier material to be changed so as to create an optimal drug delivery system by offering a high level of control over droplet formation. Size ranges of 1–1000 µm (with a distribution of <1%) are possible, with up to 100% encapsulation in perfect spheres with no porosity.

The process is applicable to small molecules and biomolecules, is highly reproducible during scale-up and offers reliable batch-to-batch consistency.

Parameter optimisation is of critical importance with such emulsion technologies, particularly for criteria such as size, API load and morphology. ET4ME, for example, facilitates the combination of two fluids that cannot be mixed using standard droplet formation techniques. Particles in this purely physical process are produced in separate microchannels, which protect APIs during particle formation.

The particles in this versatile process are formed under very low shear conditions and the absence of temperature modifications. With the ability to process any two liquids in a drug delivery system, the optimal excipient and active blend can be achieved, resulting in the optimised product.

BIOMOLECULES

Highly potent biologically active ingredients are often easily deactivated and are a challenge to deliver in a pharmaceutical formulation. Technologies like ET4ME preserve the fragile three-dimensional structure of these actives; and the ability to define the optimal composition and release properties, via superior particle formation control, meaning that the challenges that accompany these highly potent active drug substances can be overcome.

FASTER DEVELOPMENT, BETTER PRODUCTS

This type of technology enables products to be developed with better therapeutic effects and improved patient compliance in a cost-efficient and timely manner. By eliminating poor batch-to-batch consistency, variable particle formation and numerous rounds of inaccurate, costly and time-consuming screening, ET4ME allows for more rapid, reliable and efficient prototyping. Such versatile enabling technologies are used for the non-destructive testing of fragile compounds, inhalables, injectables (including for ocular injection) and solid dosage forms.

Many different formulations and multiple parameters can be scanned and tested, facilitating more efficient R&D and accelerating the development, scale-up and commercialisation of highly potent APIs in the product pipeline.

CONCLUSION

The important development steps made by EmulTech resulting in the ability to produce sterile suspensions and reducing the need for end-sterilisation provide the pharmaceutical world with a new tool in their development programs.

INJECTABLE PLGA DELIVERY SYSTEMS

Current APIs often exhibit poor solubility and/or a short half-life, requiring novel approaches such as sustained release to achieve acceptable bioavailability. Injectable biodegradable and biocompatible polymer systems that utilise copolymers of lactic and glycolic acid (PLGA) are a promising advanced delivery system for week- to month-long controlled release and have been around for decades.

ET4ME type technologies address head-on the challenges of large-scale manufacturing/scale-up needs and convoluted production schemes. Polymer microspheres can be formulated with a highly defined size, encapsulating the API in a polymer matrix. The correct matrix sets the release duration (from weeks to months) and perfecting the monodispersed particle size establishes the zero order kinetics of the release.

The system operates under aseptic, closed conditions and eliminates the need for complex work-up steps. Scale-up is achieved by massive parallelisation, ensuring product consistency throughout the pharmaceutical development pipeline.

FORSIGHT VISION 5

A TOPICAL OCULAR RING DESIGNED TO REPLACE GLAUCOMA EYE DROPS

Here, Anne Brody Rubin, Vice-President, Marketing, ForSight VISION5, introduces the company's ring-shaped ocular insert containing prostaglandin for the lowering of intra-ocular pressure in glaucoma. The product, which has been successful in Phase II trials, is due to enter Phase III this year.

Eye drops that lower intra-ocular pressure (IOP) are very effective at slowing the loss of visual field progression in glaucoma patients – when patients take their drops regularly. However, fewer than 50% of patients who are initially prescribed prostaglandin eye drops continue to refill their prescriptions reliably one year later.[1]

Reasons patients cite for nonadherence include forgetfulness, physical challenges (such as tremor and arthritis) making self-administering drops difficult, and discomfort from the eye drops. The Bimatoprost ring from ForSight VISION5 is designed to provide a solution for these nonadherent patients.

Elevated IOP is associated with a loss of vision and reducing IOP is the only proven way to prevent vision loss. So, there remains an unmet need to provide clinically relevant IOP reduction with a simple, non-invasive product for patients who do not or cannot take their medications. Such a product can delay and prevent visual field loss in patients who are otherwise not receiving adequate treatment.

The Bimatoprost ring is a topical solution for sustained IOP control. This sustained release ring delivers a prostaglandin for six months. The ring has a durable effect, is non-invasive, well-retained and is dispensed by the physician in a simple, in-office procedure. The ring is designed with the goal of providing IOP control for non-adherent patients.

A single administration of the ring is designed to provide six months of clinically significant IOP control. The six-month durability profile of the product is important since it aligns well with established practice patterns for lower-risk glaucoma and ocular hypertension patients, and will therefore not require additional visits.

The Bimatoprost ring has been studied in Phase I and II trials involving more than 300 subjects. It is a soft, bimatoprost-infused ring that rests under the eye lids and is applied at the regular eye-care visit by the eye-care provider. In clinical trials, patients have found it to be comfortable and well-retained.[2] The company intends to start Phase III testing in 2016.

The ring (see Figure 1a) comes in multiple sizes to ensure it will be comfortable for the patient. Once the eye is measured, the ring can be placed under the upper eye lid and then under the lower lid (Figure 1b) and then rests comfortably under the lids (Figure 1c). In Phase I studies, approximately 90% of patients were comfortable wearing a non-medicated ring and retention of the rings in both eyes for up to six months of continual use has been excellent.

An extensive clinical program has been conducted on the Bimatoprost ring to date: a total of nine clinical studies, including two fully-masked, randomised, controlled, Phase II efficacy studies with safety extensions.

The ring delivers clinically significant IOP reduction for six months. Open-label Phase I studies in 27 subjects demonstrated that at screening subjects had a diurnal mean IOP of 16.3 mmHg and had been historically titrated to a single medication that had given them excellent IOP control. After a four-week washout, IOPs rose to approximately 24 mmHg. After a single placement of the ring in each eye, diurnal IOP control was

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maintained at about 18-19 mmHg with approximately a 5 mmHg reduction from baseline at six months. Overall, diurnal IOP reduction in the range of 4.7-6.5 mmHg was observed. IOP reduction in this range should provide clinically significant benefit to patients who do not adhere to their eye drops.

Results from the first of the Phase II studies were presented by the principal investigator, Dr James Brandt, at American Academy of Ophthalmology 2016, and the data have been submitted for publication. In that study, sustained IOP-lowering from a single Bimatoprost ring for six months was observed. A dose-ranging trial has also recently been completed and longer-term safety data on the product will be presented in March 2016.

Patients had a positive experience wearing the Bimatoprost ring. After participating in the dose-ranging study, patients were asked to submit an anonymous survey by mail describing their interest in the product. These data show that 85% of patients who have worn the ring-shaped ocular inserts either strongly agreed or agreed with the statement, "I would willingly recommend ocular inserts to a friend or family member with glaucoma with adherence challenges."

Physicians have also demonstrated a strong preference for the ring. More than 80% of ophthalmologists questioned prefer the prostaglandin ring concept with a profile of close to 100% adherence and clinically significant IOP reduction to a prostaglandin eye drop that has slightly more efficacy but uncertain adherence.[3] Furthermore, physicians have indicated that they would expect to prescribe the ring to more than half of the patients to whom they currently prescribe eye drops.

In the future, patients may have an alternative to daily eye drops not only for glaucoma but for other indications. Because the ring has a relatively large volume for a sustained release system, it has the capability of delivering two drugs for significant duration, for example bimatoprost and timolol. The company plans to start this fixed combination clinical study this year. The ring technology can be used to address additional clinical needs. Formulations for products for allergy and dry eye are currently in development. One can envision a future in which there is a full line of products that can replace eye drops and address a variety of clinical needs.

In summary, the ocular ring is designed as a "best in class" non-invasive sustained therapy for major eye diseases. The first product is the bimatoprost ring to treat glaucoma and ocular hypertension; this product is designed to enter and expand a market that is currently more than US$6 billion worldwide. Furthermore, the excellent comfort, durability, retention and safety data have validated the ring as a delivery system for pipeline products in fixed combination glaucoma, dry eye, allergy, as well as for use in several active research collaborations.

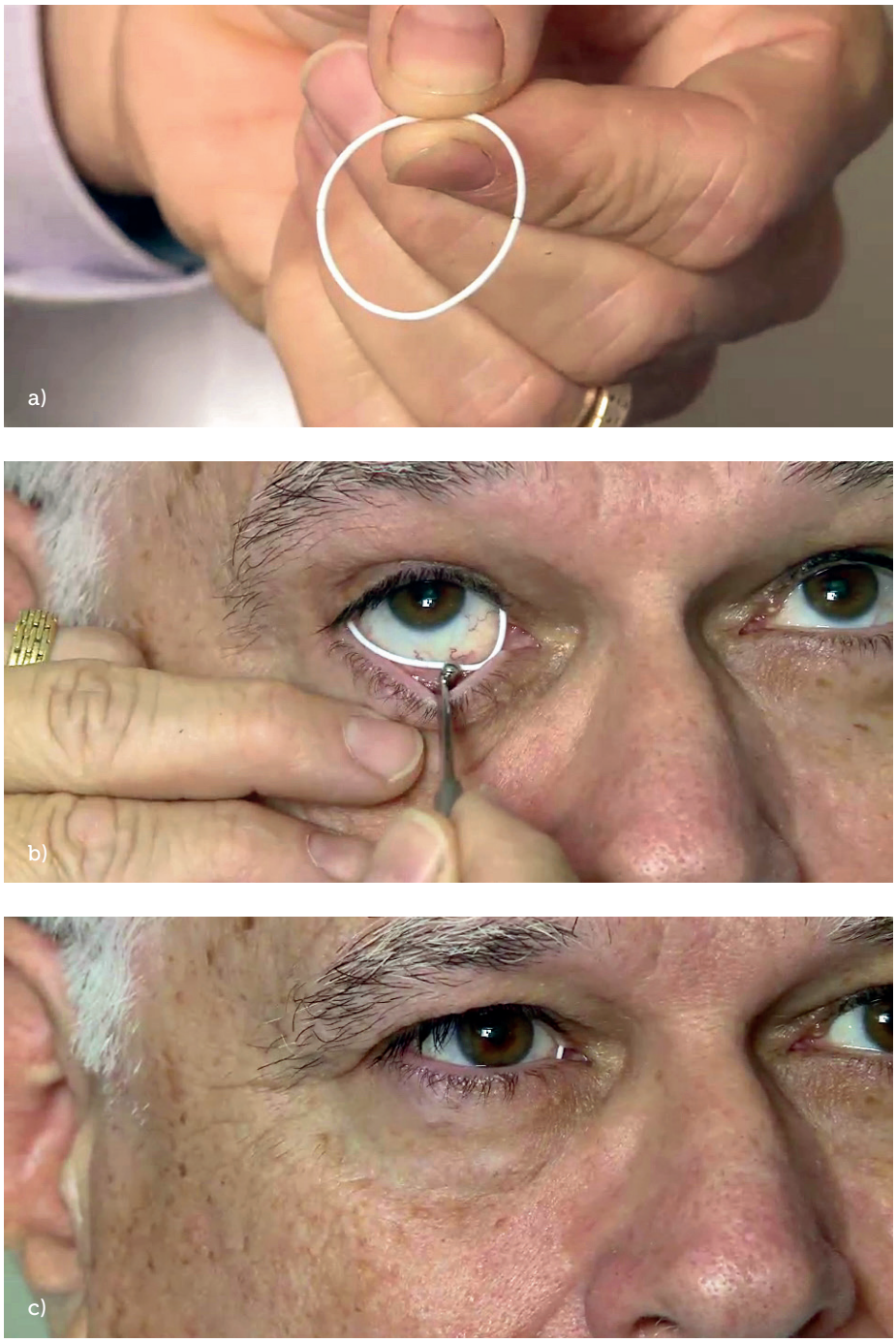

Figure 1: The Bimatoprost ring (a) comes in multiple sizes to ensure it will be comfortable for the patient. Once the eye is measured, the ring can be placed under the upper eye lid (b) and then under the lower lid to complete the application (c).

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SCALABILITY OF MICRO INTRAOCULAR IMPLANTS AND DEVICES

Scaling devices from tens to hundreds of thousands or millions sometimes requires a tightrope balancing act of economies of scale and product and process robustness. Micro molding is a proven, scalable, and economical process for thermoplastic micro-intraocular implants and devices. In this article, Donna Bibber, Plastics Engineer & Chief Executive Officer of Micro-Engineering Solutions, discusses some of these devices and the scalability challenges associated with each, from the perspective of a plastics engineer.

Recent developments and new-to-market intra-ocular devices and implants have led to the successful treatment of a number of ophthalmological conditions of varying seriousness and complexity such as:

- Glaucoma
- Cataracts
- Retinal detachment
- Diabetic retinopathy
- Age-related macular degeneration
- Uveitis
- Dry-eye syndrome.

> "In micro-moulded ophthalmologic implants and devices, parting lines where the mould's halves come together, and surface finish of the moulds that create the moulded parts, must meet stringent comfort standards required for them to be worn or implanted. The implications for compliance are clear."

Treatment of these conditions often requires collaboration between ophthalmological surgeons, pharmacologists, and micro-specific contract manufacturers. Development of these devices and implants occurs through a large number of highly focused, research-driven specialists, including and micro fabrication specialists, such as:

- Small, innovation-support funding programs
- Development companies that easily find a large marketing partner
- Big pharma funding the outsources of the development instead of doing it in-house.

To design and build scalable intra-ocular implants and devices, the design and fabrication plan must include highly precise, micro sized component made from ultra-thin yet strong materials. These materials must be selected and characterised carefully to be robust enough to last for many years in a moist and warm environment.

In order to scale-up a polymer device that may have been born in an academic or laboratory setting, one must first understand the physical characteristics of the eye (Figure 1) and how the surgeon will be installing the implant or device. The eye is a complex and sensitive organ with many structures and targets located closely together. These some-

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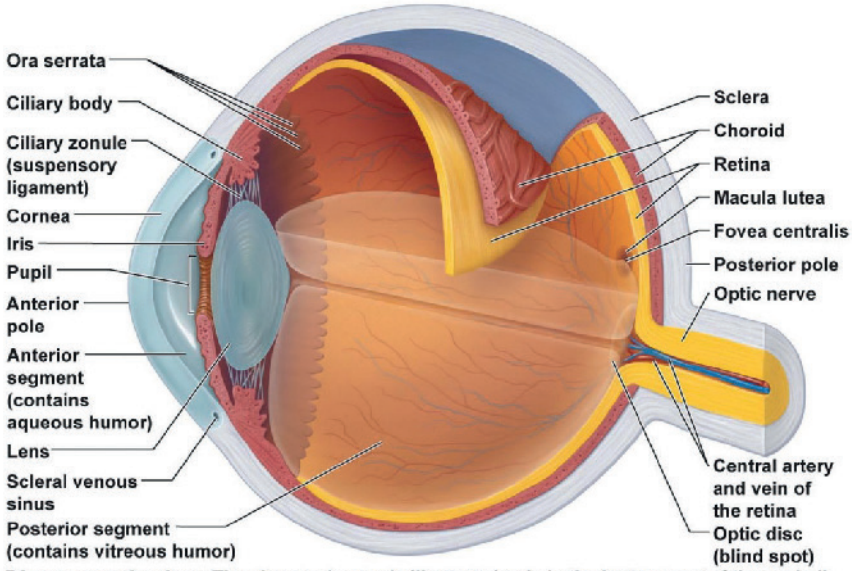

Figure 1: Sectional anatomy of the eye (photo credit: Visionbesteyecare.com).

times conflicting structures have significant defence mechanisms (tear film, cornea) that make it difficult for medication to enter. Vitreous fluid is difficult for injected medication to traverse to the posterior of eye.

When designing and fabricating micro-moulded devices and implants for the human eye, the physical characteristics and material consistency of the components of the eye are critical to understand. Figure 2 summarises the physical characteristics and function of each section of the anatomy of the eye.

The anatomy and physiology of the eye is one of the most complex and unique systems in the human body. Many of these components of the eye are gelatinous, flimsy, easily punctured, and sensitive. As a result, the implants and devices that are installed must be free of sharp edges, excess material or flash, and have absolutely pristine surface finishes to help ensure both surgeon and patient compliance. The instruments, however, which cut or slice into the various components of the eye to install the implants and devices must be very sharp and precisely made to create correctly sized and shaped incisions. Conversely, the instrument to hold or expand the eye open during surgery must be free from parting lines, flash, or sharp edges.

Eye Component	Physical Characteristics	Function
Lens	Dense, transparent, high-protein structure	Focused light to form and image
Iris	Pigmented muscle tissue (brown, blue, green, gray)	Controls diameter of the pupil and the amount of light entering
Pupil	Dark, round hole	Allows light to enter (aperature)
Retina	Vitreous gel layer of light-sensitive cells	Converts what we see into electrical impulses, sent to optic nerve which then get sent to the brain
Eyelid	Moistened skin flap	Controls the time taken for light to enter
Ciliary Body	Contractive musclular ring	Releases tension and changes the shape of the lens, produces aqueous humor
Cornea	Thin, transparent, no blood cells, received nutrients by diffusion	Major focus of the eye
Anterior Chamber	Protein-free, watery liquid	Supplies nutrients to cornea and lens
Macula	Central area of the retina	Responsible for the sharpest central vision
Vitreous Chamber	Thick, clear jelly	Transparent, colorless gelatinous filling
Optic Nerv	Sensory rubbery nerve	Carries impulses for sight from retina to brain
Sclera	White, fibrous outer layer of eye	Protective barrier along with the cornea
Choroid	Vascular layer with blood vessels	Provides oxygen and nutrients to the eye
Aqueous humor	Clear fluid	Helps cornea keep its rounded shape

Figure 2: Physical characteristics and functional elements of the eye.

Ophthalmologists are meticulously detailed surgeons with extremely good dexterity and their instruments must match their character traits, as their instruments and implants are considered an extension of meticulously planned and executed procedures. The many layers of the eye require the surgeons to switch quickly and accurately from one instrument to another because of the different surfaces they encounter in the eye.

US baseball star Yogi Berra once stated: "I'd give my right arm to be ambidextrous." But having the ability to switch hands and instruments and use both hands during eye surgery enables quick and precise positioning of instruments and safety and efficacy is maintained with instruments designed for the comfort and use in either hand. This requires a look at not only human factors, but also design-for-manufacturability, as the features and tolerances of the device and wall thickness and aspect ratios approach "design challenges" for a particular material selection.

MATERIAL & DESIGN CHARACTERISTICS

Understanding the body's reaction to polymeric implants is complex. Not only is the natural response affected by the chemical properties of the polymer but also by the physical properties of the implant. Development of an ophthalmologic drug delivery device requires design criteria compatible with the delicate nature of the eye, including proper materials, size, shape, and porosity.

Material Selection

Some materials, although tested for biocompatibility, may still cause inflammation and immuno-responses leading to long term effects on the eye. It is advantageous for safety, regulatory robustness, and speed to market reasons to select not only select a predicate material (PMMA, silicone), but also the predicate grade used in an intraocular application. Families of materials vary greatly from grade to grade in terms of both physical and chemical properties. For example, leachables and extractables over time can vary greatly with different grades of silicone and PMMA and these factors are critical to long term implant and device safety and efficacy. Additional material selection considerations include materials that are slippery , flexible, and non-hydroscopic for compliance adherence.

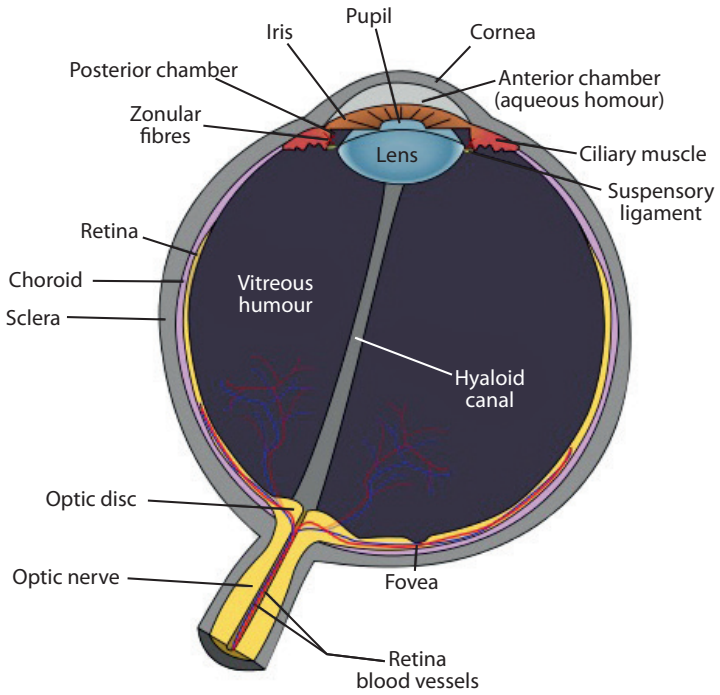

Figure 3: Sclera Image courtesy of Wikipedia.

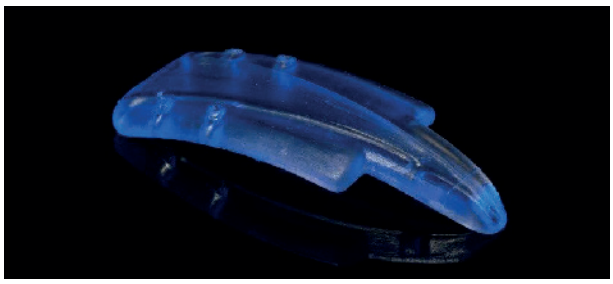

Figure 4: A polypropylene glaucoma drain.

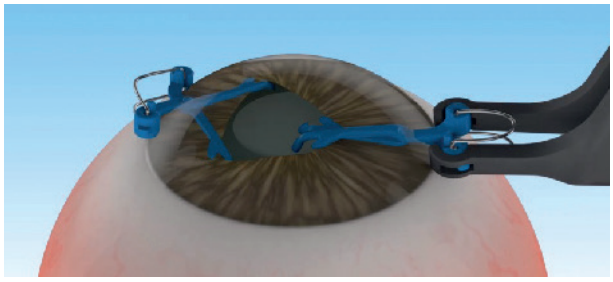

Figure 5: Pupil-expanding devices (photo credit: APX Ophthalmology).

Figure 6: Silicone corneal drug delivery device.

Size

Ophthalmologic implants or devices must be very small and pliable to fit into the sections of the eye. For example, a glaucoma drain must fit into the sclera which is from 0.3-1.0mm thick (see Figure 3). A part's thickness and size is dependent on the ocular area and location of the implant, but also chosen on the melt flow of the materials.

Shape

Implants within the wall of the sclera are radial in nature to rest within the semi-circular outer wall of the eye. Figure 4 shows a polypropylene glaucoma drain with a centre wedge bore which acts with a Venturi effect to allow the pressure of the eye to drain behind the eye. Glaucoma is a result of the increased fluid pressure in the eye due to the reduction or blockage of fluid from the anterior to posterior chambers. Devices such as these are possible using micro-injection moulding and micro-automation.

Figure 5 shows a pupil expander device with micro features and surface finishes necessary to fit comfortably in the eye and provide tensile strength with fine alignment and mechanical strength to hold them in place.

Figure 6 shows a delivery device that sits on the cornea – it's a thin membrane-like, silicone structure with radial design, and a 50 µm wall thickness to fit inside the upper eyelid. The cornea has 5-6 layers varying from 2-20 µm in thickness, made up of highly sensitive pain receptors. Cornea pain receptor density is up to 600 times that of skin, which is why even a slight injury to the eye is extremely painful.

Surface Finish/Porosity

In micro-moulded ocular implants and devices, parting lines where the mould's halves come together, and surface finish of the moulds that create the moulded parts, must meet stringent comfort standards required for them to be worn or implanted. The implications for compliance are clear. Surface finish, blending parting lines, spherical radii, and matching cores and cavities to ultra-precision tolerances (A2 or A1 finishes) are the keys to creating implants that can stand the test of time in an intra-ocular environment.

In the context of an ocular implant, smooth materials can have very different tissue and nerve responses compared with micro-structured materials. Tissue encapsulation of a foreign body (such as the implant) is higher with rougher surfaces because there is more surface area for the implant to attach to tissue. Nerve response to surface finish needs to be considered in implant design. Wear or degradation of a rough surface is more prevalent as well because the smaller porous particles in the surface can be toxic to tissue, can spread throughout the eye, and also trigger an allergic response.

CONCLUSION

The anatomy and physiology of the eye is one of the most complex and unique systems in the human body. Micro-moulding is a scalable process with particular design criteria met, including proper size, three-dimensional shape, wall thickness, material selection, and surface finish.

Micro-injection moulding is a viable and scalable process for fabricating ultra-precise, micro-sized, ultra-thin, yet robust implants and devices located in a highly complex environment such as the eye.

Scalability is an important consider stionat the initial product and process design phase in order to achieve the economies of scale – tens, to hundreds of thousands of parts, to millions annually – that micro-moulding offers.

Careful consideration of surface finish, feature size and material selection is paramount to the successful integration of marrying micro-moulding technology with the internal chambers and inter-connective functions of the eye.

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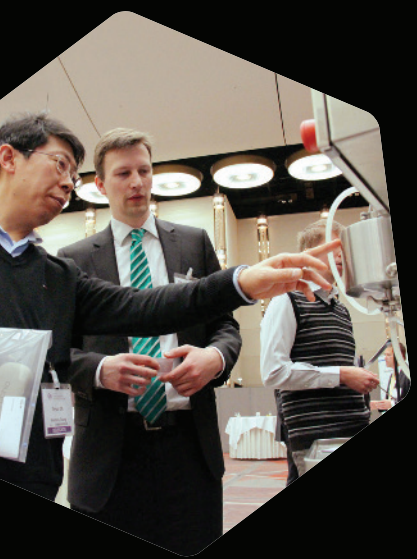

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THERAPY WITHOUT DROPS: A REALITY

Here, Chris Muller, Chief Commercial Officer, and Deepank Utkhede, Chief Scientific Officer, both of Mati Therapeutics Inc, introduce the company's Evolute® ocular delivery system, a non-invasive, sustained-release platform that combines a novel punctal plug with a sustained release drug eluting core.

Ophthalmologists are in agreement that a better option to administer ocular therapies rather than eye drops is needed for their patients since the lack of compliance is a serious and leading cause for concern.

When we consider the associated disorders that these medications treat such as glaucoma, inflammation, allergy or dry eye, each of these can be very problematic if not sight threatening if the treatment regimen is not followed. The therapeutic agents available for each of these conditions are very effective when prescribed and used appropriately. However, the problem is that they are rarely used appropriately or in accordance to the dosing regimen that is required and for diseases such as glaucoma, which is initially asymptomatic, this can lead to irreversible vision loss.

The ophthalmic community relies on the patient to adhere to the treatment regimen. However, due to a number of factors such as age of the patient population, the complexity of the dosing regimen or discomfort caused by drops, it is not realistic to expect that the majority of these patients will comply with the required treatment regimen. There have been many attempts to solve this issue but the sustained-release innovation by Mati Therapeutics may be the perfect answer for a majority of patients.

There are multiple approaches to the administration of sustained-release systems. One is invasive, where a physician either through incision or injection enters the anterior chamber of the eye to deliver the drug depot or creates an incisional pocket in the sclera or conjunctiva to house the depot. The problem with both of these methodologies is that because they are invasive in nature they expose the patient to potential sight-threatening infection and decreasing the overall health of the eye by undergoing multiple surgical procedures per year. The repeated tissue trauma increases scaring over time and could complicate future surgical procedures needed to control the disease.

"The ophthalmic community relies on the patient to adhere to the treatment regimen. However, due to a number of factors such as age of the patient population, the complexity of the dosing regimen or discomfort caused by drops, it is not realistic to expect that the majority of the these patients will comply with the required treatment regimen."

Mati has developed a completely non-invasive sustained-release platform by combining a novel punctal plug with a sustained release drug eluting core (see Figures 1 and 2). This platform is known as the Punctal Plug Delivery System (PPDS) or Evolute®, as it will be known commercially. The Evolute® is inserted into the patient's punctal duct by a simple in-office, non-invasive proce-

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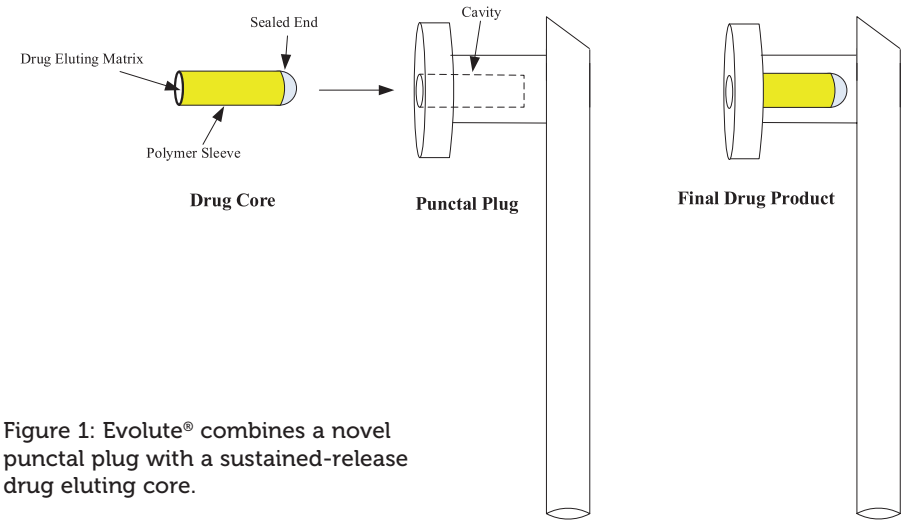

Figure 1: Evolute® combines a novel punctal plug with a sustained-release drug eluting core.

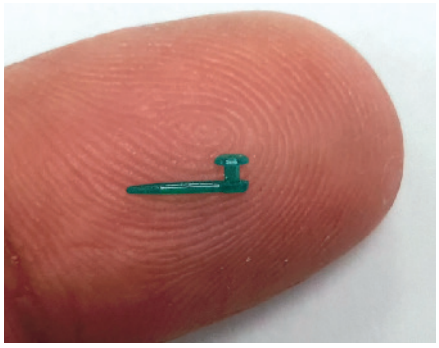

Figure 2: An Evolute® device, shown on a finger-tip for scale.

dure. After placement, the Evolute® delivers therapy to the ocular surface or tear film over a predetermined period of time. At the end of the treatment period for acute conditions, Evolute® is removed from the puncta without any further follow-up. At the end of the Evolute® elution period for chronic conditions, the patient returns to the clinic

"Mati has developed a completely non-invasive sustained-release platform by combining a novel punctal plug with a sustained release drug eluting core."

to have the depleted Evolute® removed and a new Evolute® placed to continue treatment. The Evolute® has the advantage of being easily removed unlike the more invasive techniques previously described, which require a surgical procedure for removal.

The Evolute's® unique configuration creates a unidirectional system that delivers therapy primarily to the tear film and ocular surface. This is a distinct advantage for any sustained release system because virtually all the formulated medication in the system can be directed to the targeted site rather than being absorbed by non-targeted tissue or lost down the canaliculus into the nasal cavity and/or systemically absorbed. Another advantage to the Evolute® is that both the punctal plug portion and the drug eluting core are non-bio-erodible and non-biodegradable. This leads to the ability to predict accurately when and how much of the formulated drug is delivered over the course of therapy. Also the punctal plug retention features will be unchanged over the treatment period which has resulted in very high retention rates for the Evolute®.

Clinical studies have demonstrated a reproducible and predictable retention rate in range of 92% to 96% over a 90-day targeted treatment period. Another advantage of a non-biodegradable and non-bio-erodible system is that if removal is required for any reason, the Evolute® is easily observable and removable with a pair of forceps. A bio-erodible platform will become smaller and/or weaker, during the implantation period potentially making removal more complicated.

The Evolute® is a platform technology that can be tailored to treat multiple front-of-the-eye conditions. Depending on the ocular condition, the elution rate and period of delivery can be adjusted for short-term, high levels (for example, in post-cataract surgery treatment), to long-term, low levels (for example, in glaucoma therapy) of drug delivery. Multiple products have been developed for the Evolute® including anti-inflammatories for post-cataract surgery, allergy medications, and glaucoma therapies.

Through extensive formulation development, Mati has developed the capability to adjust the elution profile for any of these therapies to potentially meet the needs of the ophthalmic community. For example, the Evolute® can be designed to deliver a high initial amount of medication followed by a consistent lower concentration over time or a much more limited initial delivery and increased delivery of medication over the treatment period.

There are several additional benefits to the Evolute® system, such as that it allows for the formulation of hydrophilic or hydrophobic compounds and it is a preservative free therapy so there is no need to worry about long-term exposure to preservatives such as benzalkonium chloride, which has been shown to cause ocular surface issues such as conjunctival inflammation, tear film instability, corneal toxicity, anterior chamber inflammation, and cataract development among other issues. In addition, since the Evolute® prevents loss of drug into the canaliculus, it will likely lead to less systemic absorption of the therapy in question, which may greatly reduce undesired systemic side effects associated with some ocular medications.

"In clinical studies, the vast majority of patients preferred the Evolute® system to their usual eye drops. This isn't surprising because of the passive nature of the system. The patient doesn't have to do anything once the device is inserted."

In clinical studies, the majority of patients preferred the Evolute® system to their usual eye drops. This isn't surprising because of the passive nature of the system. The patient doesn't have to do anything once the device is inserted. This may prove to be substantial benefit for ophthalmologists and their patients insuring better adherence and more consistent administration of the therapeutic agent leading to superior outcomes.

DelSiTech

NEW SOLUTIONS FOR OPHTHALMIC DRUG DELIVERY USING BIODEGRADABLE SILICA MATRIX

DelSiTech, a Finnish drug delivery company, has developed a proprietary non-mesoporous, biodegradable silica matrix technology where release of the active pharmaceutical ingredient (API) is based on the dissolution of silica in tissue. Here, Mika Jokinen, DSc, Research Director, Cora Griffin, PhD, Business Development Director, and Lasse Leino, PhD, President and Chief Executive Officer, all of DelSiTech, describe the novel opportunities that biodegradable silica matrix technology offers to ophthalmic drug delivery, and the different silica dosage forms for various types of APIs, ranging from large biological agents, such as proteins and viruses, to small molecules, covering injectable silica hydrogels, silica microsphere-silica hydrogel composites and silica implants.

Due to the aging population, chronic ocular diseases are becoming more common, and the number of patients suffering from conditions such as age-related macular degeneration (AMD), glaucoma, dry eye and diabetic retinopathies is increasing steadily. Drug treatment for ocular diseases is challenging due to the complex and protected structure of the eye, which prevents the penetration of active compounds at the site of action, e.g. the retina, after systemic administration. Although topical administration of eye drops is an easy and non-invasive method of ocular drug therapy, it suffers from low and easily saturated dose, poor bioavailability (less than 5% even in the front part of the eye) due to rapid drainage, and low patient compliance, especially in elderly patients.

> "The injectable silica hydrogel composites can be used both in IVT and subconjunctival delivery where at least one month's sustained release of the API is needed. It is also possible to develop much longer acting composite formulations with 3-6 months' controlled release of API ... With a very potent molecule, it would be possible to design products with more than 12 months release profile."

Invasive systems such as intravitreal (IVT) injections are used to treat the back of the eye. However, IVT injections cannot be given repeatedly in a short period of time because they are associated with potential severe side effects, such as increased pressure in the eye or infection, and they would generate a significant burden in ophthalmology clinics. For small molecules, which are typically rapidly eliminated within hours in the vitreous, immediate-release IVT formulations are not a realistic option because of the need for frequent injections. It is clear that there are unmet medical needs in ophthalmic drug treatment and these needs are not well served by current drug delivery systems. New concepts, tools and approaches should be generated and tested for the development of novel ocular therapies.

Amorphous silica matrix prepared by the sol-gel method is a well-known biomaterial for controlled drug delivery. Silica can be processed into several dosage forms, addressing a number of challenges in

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the development of sustained release parenteral products.

DelSiTech, a Finnish drug delivery company, has developed a proprietary non-mesoporous, biodegradable silica matrix technology where release of the active pharmaceutical ingredient (API) is based on the dissolution of silica in tissue, i.e. it is controlled by bulk matrix erosion rather than API diffusion. The properties of the sol-gel derived silica can be adjusted to ensure proper encapsulation of APIs and the desired degradation rate (dissolution of silica *in vivo*) from days to months, even up to years.1-3 In addition, silica is an inert material that is compatible with different types of APIs, including biologics and advanced-therapy medicinal products. Even compounds with either very low or very high water-solubility can be successfully encapsulated inside the silica matrix.

INJECTABLE SILICA DOSAGE FORMS IN PREFILLED SYRINGES

DelSiTech has developed several types of injectable, silica matrix-based formulation platforms that can be used in ophthalmic drug delivery. In all cases, the flowing (liquid) form of silica, a silica sol, is used to mix different components and API with silica before the system turns into a hydrogel. The silica sol-gel processing is a flexible, low-temperature method allowing the adjustment of the silica sol properties, such as pH to ensure the optimum pH environment on different types of APIs.

The first dosage form is a silica-silica composite material consisting of silica microspheres embedded in a silica hydrogel. The API, either a small molecule or a biologic, is encapsulated in the silica microspheres, which act as the API eluting reservoir and control the drug release by matrix dissolution. By controlling the silica microsphere (bio)degradation rate, it is possible to obtain an accurate control of API release.

Silica matrix itself is water-soluble and when placed in the body it dissolves in aqueous tissue fluids. Water-solubility of silica microspheres is a tuneable property that mainly depends on the number and density of OH-groups on the surface of silica matrix. By simply adjusting and varying the silica sol-gel composition and reaction parameters, such as concentrations of the main precursors (water and tetraethyl orthosilicate (TEOS), the source of silica), it is possible to produce silica microspheres that have different surface characteristics.

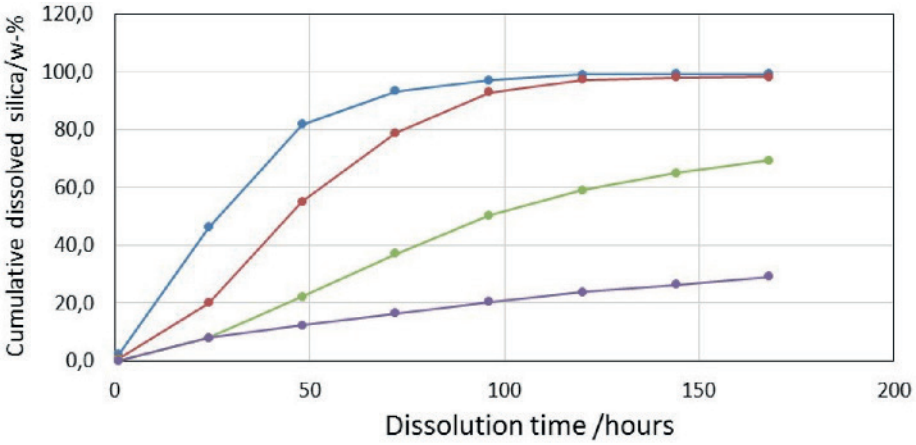

Figure 1: Cumulative in vitro silica dissolution rates in Tris buffer pH 7.4 (in sink) of four silica microsphere formulations which differ only in the water-to-TEOS ratio in the sol-gel reaction. The ratio is (from up to down) 3:1, 5:1, 10:1 and 15:1.

Figure 1 shows an example of how a simple change in water-to-TEOS ratio in the sol-gel process affects the dissolution rate of silica microspheres in aqueous buffer, i.e. the biodegradation time. The other manufacture and microsphere parameters were kept constant (sol pH, spray-drying parameters, and particle size distribution which was 1.5-10 µm, D50=3-4 µm).

Spray-drying is the main form-giving method to produce API-containing silica microspheres. It is inexpensive, fast and an easily scaleable manufacturing method that can be operated in a GMP environment, even in aseptic conditions. The spray-drying parameters are optimised for each API and formulation. Spray-drying is also gentle enough to preserve the biological activity and therapeutic effect of the encapsulated proteins and peptides. The temperatures in the process are kept low and the presence of silica protects sensitive molecules.

After spray-drying, the API-silica microspheres are mixed with a flowing aqueous silica sol and the mixture is transferred into a syringe before the sol turns into a hydrogel. The filling of the syringes is controlled by careful rheological measurements to ensure homogeneous product, long-term stability and good injectability. Shear rate-dependent viscosity is measured to study the shear-thinning behaviour, to ensure easy injectability, and oscillation measurements (for elastic and viscous modulus and their ratio, loss factor that describes the stiffness of the hydrogel) are conducted to ensure a non-flowing, gel-like structure at rest in the syringe.

The goal of the rheological optimisation is to form a non-flowing composite hydrogel structure, which remains stable for prolonged times, but at the same time, the structure has to be loose enough to be injectable through thin needles when shear stress is applied by pushing the plunger of the syringe. The resulting unique silica-silica composite hydrogel is easily injectable with needle sizes of 27-30G as illustrated in Figure 2. Although the hydrogel part of the silica-silica composite most often controls the injectability and homogeneity, it may also fine-tune the release of API from microspheres by controlling/removing the burst, the initial fast phase of the release.

Figure 2: Injectable silica-silica hydrogel composite depot.

The injectable silica hydrogel composites can be used both in IVT and subconjunctival delivery where at least one month's sustained release of the API is needed. It is also possible to develop much longer acting composite formulations with 3-6 months' controlled release of API. As with all drug delivery systems, the development of an ultra-long acting dosage form with silica matrix technology is limited by the required daily dose of the active compound, which directly impacts the volume of the IVT injection material (typically maximum 0.1 ml). With a very potent molecule, it would be possible to design products with a release profile of more than 12 months.

Topical application of the silica-silica hydrogel composite formulation in the conjunctival cul-de-sac represents another drug delivery opportunity in the treatment of the front part of the eye. The silica composite material is sticky enough to stay in the conjunctiva where it releases API in a controlled fashion. Prototype formulations have been produced where fluorescein as a surrogate molecule is encapsulated into silica microspheres that are further embedded in the silica hydrogel. When these "eye drops" are administered in the rabbit eye, they release fluorescein steadily for 24 hours without any signs of local irritation.

SILICA OCULAR MICRO-IMPLANTS

Traditionally, drug-eluting implants have been the first type of controlled-release dosage forms used in ocular drug delivery. Most implant technologies are based on non-biodegradable materials that have their limitations especially in repeated administration, as they should be removed after use. DelSiTech has developed micro-implant technology for IVT delivery of drugs that is based on biodegradable silica matrix (Figure 3).

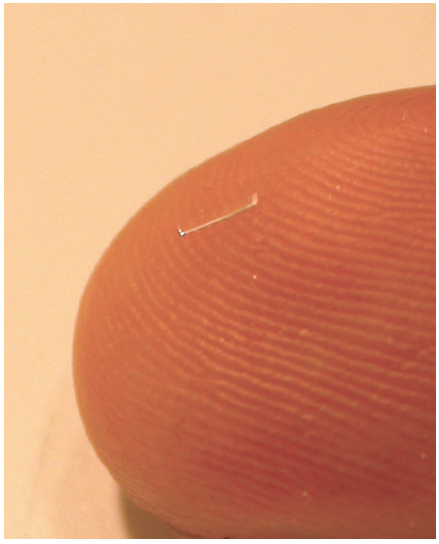

Figure 3: Intravitreal biodegradable silica micro-implant (diameter 0.4 mm) on top of a finger.

Silica implants are typically transparent, especially when in contact with water. The biological activity of biopharmaceuticals and viral vectors can be maintained because the water content inside the implant can easily be controlled.

The silica microimplants are prepared by casting the API-containing silica sol into a mould before the silica sol turns into a gel. The gel is formed in the mould followed by a controlled drying. Silica microimplants offer an attractive alternative to injectable dosage forms in cases where the API is not suitable for spray-drying form-giving.

CONCLUSION

Different biodegradable silica matrix based dosage forms can be used for ophthalmic drug delivery. The technology provides potential formulation solutions both for the anterior and posterior parts of the eye in the form of eye drops, injectable silica-silica composite hydrogels, and micro-implants. Also, the technology is mature enough to fulfil the pharma industry requirements such as GMP manufacture and sterilisation. Currently, DelSiTech is actively working on several projects developing novel drug formulations for ocular delivery.

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MIDATECH PHARMA

OPSISPORIN: A LONG-ACTING DRUG DELIVERY APPROACH FOR UVEITIS

Here, Paul Seaman, PhD, Head of Sustained Delivery, and Daniel Palmer, PhD, Chief Scientific Officer, both of Midatech Pharma, discuss the company's next-generation treatments for auto-immune ocular diseases, which use a combination of innovative, sustained-release drug products that are active for several months and designed for delivery through ultra-fine injections into the eye. The article focuses on OpsiSporin, an encapsulated sustained-release cyclosporin formulation for the treatment of uveitis.

Current treatments for eye diseases often do not achieve the required level of effect. Topical therapies have low efficacy and bioavailability as a result of factors such as anatomical and physiological barriers, tear formation, and lymphatic drug clearance. Systemic therapies have high incidence of adverse effects, poor tolerability, and limited efficacy. Frequently, patients are non-compliant due to unpleasantness, pain, or inconvenience of the treatment options.

Midatech's sustained-release technology, delivered directly to a specific ocular space, addresses these challenges. Localised long-acting delivery of API offers marked advantages and consistency over oral administration since drugs are delivered to the target site in therapeutic concentrations, off-target side effects of high-dose systemic delivery are avoided, and patient experience is improved via minimally-invasive, convenient and infrequent administration.

TECHNOLOGY

Our proprietary microsphere engineering platform can use a wide range of biomaterials to encapsulate ocular drug candidates into micron sized particles (of diameter ~25µm). These include glucocorticoid anti-inflammatories, anti-VEGFs and immunosuppressants for diseases such as glaucoma, AMD and non-infective uveitis. Long-acting treatment is achieved using formulations of biodegradable polymers (including polylactides) to control the release of API over a period of 3-6 months following a single intravitreal or subconjunctival injection. Monodisperse microspheres may be readily injected via minimally-invasive needles as fine as 30G.

In formulating small molecules, biopharmaceuticals and PEGylated species, Midatech focuses on developing products that provide high drug loading, with minimal initial burst release. These characteristics are essential to the development of safe and effective ophthalmic therapies. The formulation tuning and process control to achieve this requires precision know-how and novel technology to ensure control over particle size, morphology and drug kinetics.

Our technology represents a step-change in control for microsphere manufacturing, enabling emulsion-free synthesis with both product monodispersity and processing efficiency built-in. Further, the encapsulation process is engineered to avoid the use of poorly-tolerated organic solvents such as dichloromethane. The manufacturing system has been designed for total compatibility with the aseptic production environment and standard isolator technol-

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ogy, and is proven for sterile synthesis and filling of clinical trial materials.

This level of flexibility enables Midatech to formulate products to provide release profiles and dosage regimes that treat ocular disease states in the most efficacious manner.

UVEITIS

One such application of the Midatech technology is for the treatment of posterior uveitis, an intra-ocular inflammatory condition affecting one or more parts of the uvea which includes the iris, the ciliary body, and choroid of the eye, although other ocular structures such as the retina and the vitreous body may also be secondarily involved. Aetiology is varied and includes infectious causes (e.g. tuberculosis, toxocara) and non-infectious pathogenesis. Non-infectious causes include systemic auto-immune disorders (e.g. rheumatoid arthritis, sarcoidosis, Lupus, Behçet's disease), trauma, and rarely can also be drug induced. However, many cases of uveitis are idiopathic in nature.

Uveitis is a major cause of significant visual loss in young and middle aged adults in the Western world. The burden, to society and the patient, resulting from uncontrolled uveitis is significant. Uveitis is a major cause of new cases of blindness; in the US, it is estimated that uveitis causes an estimated 30,000 new cases of legal blindness and results in 2.8-10% of all blindness annually. Uveitis can be classified on the basis of the aetiological factors (e.g. infectious, non-infectious, drug induced etc), or most commonly, on the anatomical location of the disease, anterior, intermediate, posterior, and panuveitis. Until recently, not all EU countries had uveitis as a listed indication and it is still not an approved indication in the US.

The presenting symptoms tend to vary with the type of uveitis and the severity, and may affect one or both eyes. Anterior uveitis is often accompanied by ocular pain and photophobia. Blurring of vision is less of a characteristic of anterior uveitis, but may be reported in severe cases or by patients with secondary cataracts or macular oedema. Posterior uveitis may be accompanied by some degree of pain and photophobia, but these may not be the predominant symptoms. However, blurred vision is common due to involvement of the macula (inflammation and macular oedema) and opacity of vitreous humour (flare and cell infiltration). Vasculitis and retinal edema are also notable features. It is important to establish the correct diagnosis so that specific treatment to address the underlying aetiology can be initiated, along with treatment to reduce ocular inflammation.

The inflammatory process in the eye(s) must be reduced quickly to avoid long-term consequences. The treatment options for non-infectious uveitis affecting the posterior or intermediate segment of the eye include the use of local and systemic corticosteroids, systemic immunosuppressants, and off-label use of anti-VEGF agents and systemic biologic agents. Patients are routinely initiated on systemic steroids, the mainstay of posterior uveitis therapy, at high doses of up to 1 mg/kg/day and then tapered to ideally less than 5 mg/day. If, after a period of time (ranging from 2-3 months), the steroids cannot be reduced or eliminated, systemic immunosuppressives are started such as cyclosporin, or off-label adalimumab, azathioprine, cyclophosphamide, infliximab, methotrexate, tacrolimus and others. Each of these has the potential for causing serious systemic adverse effects that limit the dose or their use altogether. Intra-ocular administration of sustained release steroids like fluocinolone and dexamethasone are an advance, but risk causing cataracts, glaucoma, and increased intraocular pressure; and the duration of effect seems to be limited and with high relapse rate. The systemic use of cyclosporin for the treatment of non-infectious uveitis of the posterior segment is common practice among uveitis specialists. However, systemic drugs (corticosteroids and immunosuppressive therapy) often fail because of the presence of the blood-retinal barrier that limits drug delivery into uveal tissues.

The important, sometimes life threatening, adverse effects of these drugs limit the maximum dose that can be recommended. The dose given may, therefore, be suboptimal in terms of control of inflammation in the eye even when maximum dosing is prescribed.

In summary, although the treatment options available for patients with non-infectious uveitis of the posterior segment of the eye have recently improved, none is ideal. Topical steroids often do not work and systemic corticosteroid or immunotherapy is limited by the risks of adverse events with protracted use. Ocular inflammation may require the addition of intravitreal steroid injections to prevent permanent damage to vision. These are effective, but have a relatively short duration of action as well as side effects. This medical need has been recognised and implants for the intravitreal administration of steroids have been developed, but again side effects are problematic and efficacy inconsistent. A product that achieves control of inflammation without serious steroid-related side effects would constitute a significant benefit.

> "Depot-based drug delivery is strongly required in ocular disease, due to the burden of frequent intravitreal injections and lack of any satisfactory treatments to date."

OPSISPORIN

OpsiSporin is a treatment under development by Midatech. It comprises encapsulated cyclosporine, a cyclic peptide of 11 residues that has been routinely used as an oral immunosuppressor for organ transplantation since first approval in 1983. The drug's mode of action is well understood, being the selective inhibition of interleukin-2 release during the activation of T-cells, suppressing cell-mediated immune response. Cyclosporin forms a complex with the cytosolic protein cyclophilin of lymphocytes, especially T cells. This complex inhibits calcineurin, which, under normal circumstances is responsible for activating the transcription of interleukin-2. This results in an immunosuppression that is reversible when treatment is ceased. Therefore, diseases that involve cytokines or immune–related disorders, such as non-infectious uveitis, are potential indications for cyclosporin. Through prevention of T-cell activation and proliferation, cyclosporin has been hypothesized to be a suitable treatment for non-infectious uveitis.

Sustained-release of cyclosporin within the posterior eye is expected to reduce or spare the need for oral drug treatments

used in the treatment of uveitis, in particular oral glucocorticosteroids and immunosuppressants; and the literature indicates that the use of intravitreal cyclosporin is effective and well tolerated as described above. Hence, OpsiSporin is expected to be effective in the treatment of uveitis affecting the posterior segment of the eye. In treating the disease and preventing recurrence, its use could remove the need for long-term steroid cover required to treat ocular inflammation avoiding the complications of chronic systemic or intravitreal corticosteroids. Systemic immunosuppression may still be required to address the aetiology of the uveitis, but the dose may be tailored to this objective and not raised excessively in an effort to suppress ocular inflammation with systemic dosing.

Sustained delivery of the cyclosporin is achieved by encapsulation with bioresorbable polymer excipients, such that the endecapeptide is physically entrapped in the polymer matrix. Cyclosporin is released as the poly-ester backbone of the polymer undergoes hydrolysis and is broken in to its constituent monomers, resulting in the gradual erosion of the polymer matrix.

The development of the product targeted a sustained release (SR), microparticle formulation, with the following product attributes:

- Cyclosporin drug loading >15% w/w
- Cyclosporin encapsulation efficiency >80%
- Formation of stable suspension, injectable via ½" 30G needle
- Linear release kinetics maintained for 90-100 days.

Early formulation development focused on identifying parameters for satisfactory drug encapsulation (suitable drug loading and stability) and applying knowledge of SR formulations to produce early formulations aimed at a three-month release duration (established via *in vitro* release modelling). Formulations have been focused on polymers from the polylactide-co-glycolide family, specifically those containing a high ratio of lactide to glycolide (typically 75-100%).

Additionally, review of the literature indicated that higher-molecular-weight polymers were also well suited to this application. It is known that drug loosely bound to the surface of microspheres can give rise to a rapid drug dissolution profile immediately upon administration; i.e. an undesirable burst release of cyclosporin. Therefore, the manufacturing process involves a post-processing step during which the surface drug is removed and this burst release significantly attenuated. Particle-drug loading was generally very high (~19-21% w/w), and was not significantly affected by particle post-processing.

Similar to many microsphere-based SR products, OpsiSporin is presented as a powder that is formed into a suspension prior to dosing. Due to the intravitreal route, where injection volume is limited to 0.1 mL, and the hydrophobic nature of cyclosporine-loaded microspheres, formation of a simply and reproducibly injectable suspension required significant development. Midatech has worked to develop the formulation to make reconstitution rapid, consistent and safe.

The application of microsphere processing expertise has resulted in the introduction of technology that enables OpsiSporin to be reconstituted rapidly with nothing more than water. The formulation excludes novel excipients whilst preventing microsphere aggregation during storage and reconstitution, and maximising suspension stability. As a result, homogenous suspensions can be formed in under 30 seconds and remain stable for several minutes, meaning preparation in the clinic is minimal and the dosing need not be rushed. Data gathered to date indicate that OpsiSporin is injectable through ½" 30G needles.

PROOF OF CONCEPT

An *in vivo* study has illustrated the efficacy of OpsiSporin in the treatment of experimental auto-immune uveitis (EAU) in a murine model. EAU was induced in groups of ten C57/BL6 mice by challenge with retinal antigens interphotoreceptor retinoid binding protein peptide (IRBPp) and Freund's adjuvant (subcutaneous administration) and pertussis toxin (intraperitoneal administration). Due to the sustained-release properties of the OpsiSporin product, intravitreal treatment was administered on a single occasion only (day zero) via 33G needle. A negative control group receiving vehicle only was also injected at day zero. In addition, two groups of ten animals received different doses of oral cyclosporin (in car-

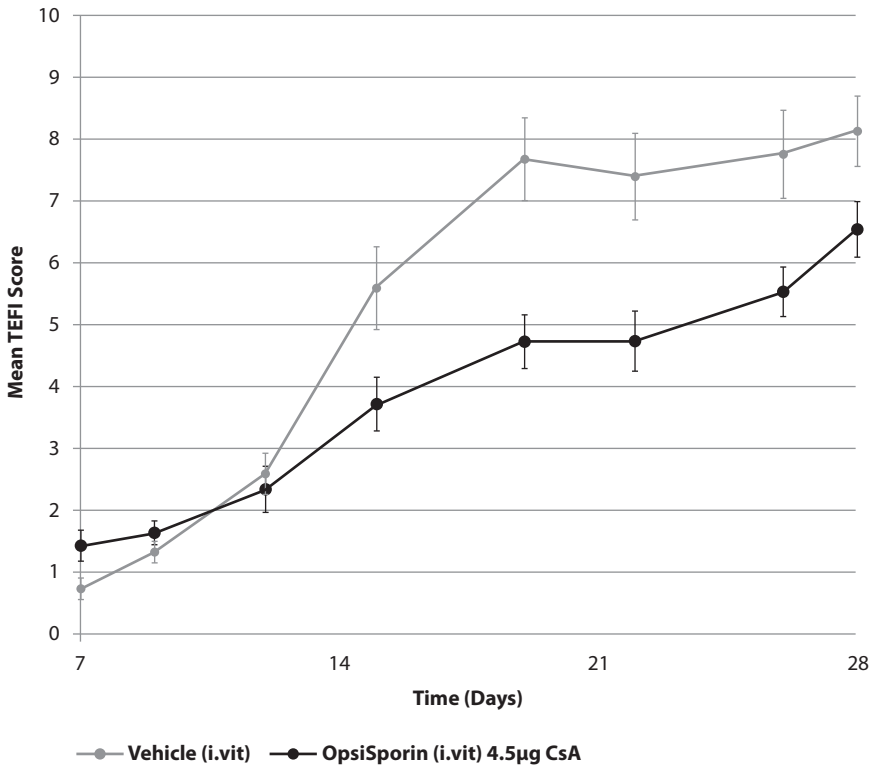

Figure 1: Proof of concept in murine model.

Increasing TEFI score of retinal imaging indicates worsening of the EAU disease state. Mice receiving intravitreal injection of OpsiSporin (4.5µg cyclosporin) showed a significant reduction in EAU severity compared to those animals that received vehicle alone.

boxylmethylcellulose solution), once daily, as positive control treatments.

Increasing TEFI score of retinal imaging indicates worsening of the EAU disease state. Mice receiving intravitreal injection of OpsiSporin (4.5µg cyclosporin) showed a significant reduction in EAU severity compared to those animals that received vehicle alone (Figure 1).

Topical endoscopic fundal imaging (TEFI) is a technique used to monitor the progression of retinal degradation in ocular disease. In this study it was used to track the progress of EAU after administration of the IRBPp / pertussis toxin insult. An increasing TEFI score denotes the advancement of the EAU disease state, and hence can be used to observe recovery or reduction in retinal damage and inflammation. Mice receiving intravitreal injection of OpsiSporin (4.5µg cyclosporin) showed a significant reduction in EAU severity compared to those animals that received vehicle alone ($p<0.002$), supporting the hypothesis that delivery of cyclosporin via the OpsiSporin product has potential for the treatment of non-infectious uveitis in man. A significant reduction in disease development was observed at the later time points, as severity of disease increased in the untreated and negative control groups. Multiple t tests between untreated animals and those receiving cyclosporin either as OpsiSporin or orally showed a significant reduction in disease from day 15.

In addition, a significant reduction was observed between those animals receiving intravitreous injection of vehicle with those receiving OpsiSporin containing 4.5 µg cyclosporin. An equivalent reduction in disease development was observed following daily oral administration of 6.7 mg/kg/day cyclosporin, as compared with intravitreous injection of 4.5µg OpsiSporin; efficacy was equivalent whilst total amount of cyclosporine administered was 1000-fold lower with OpsiSporin. The EAU model is self-limiting, and as such is only able to indicate efficacy for up to 28 days.

In vitro modelling of drug release kinetics indicated that the rate of cyclosporin release shown to be efficacious *in vivo*, were maintained for three months (see Figure 2). It is therefore hypothesised that efficacy will be maintained over the entire target period, facilitating a three-monthly dosing regimen.

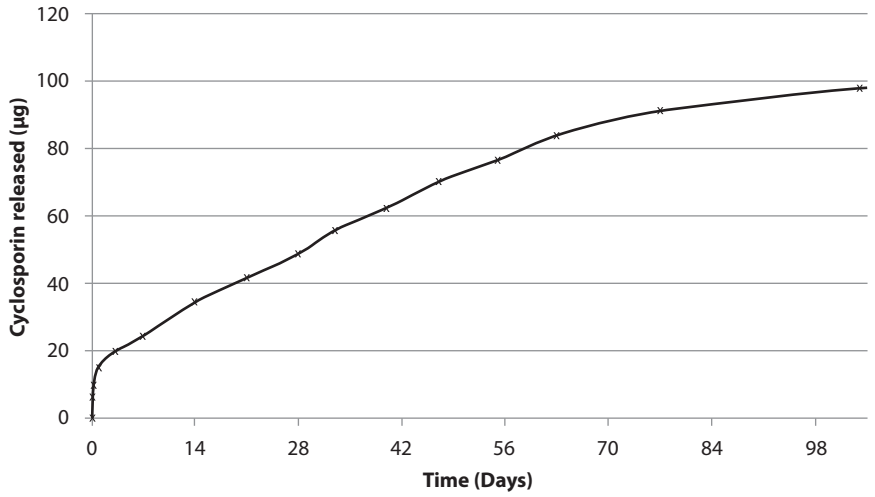

Figure 2: In vitro testing of OpsiSporin models the release of API from the drug product, with the data plotted as a cumulative mass of drug released. Highly linear release of cyclosporin lasting three months was observed with OpsiSporin. These data show the mass of cyclosporin released per mg of OpsiSporin drug product, and predict a linear release of 0.96 µg/mg/day. Data are the mean of three replicates, and error bars represent standard deviation.

CONCLUSION

Depot-based drug delivery is strongly required in ocular disease, due to the burden of frequent intravitreal injections and lack of any satisfactory treatments to date. Solid formulations that are precisely defined, easy to administer into the eye, and able to provide steady drug release over 3-6 months are ideal alternatives for chronic conditions such as non-infective posterior uveitis. In developing its ocular drug delivery platform, Midatech technology may provide a compelling and unique platform to bring significant benefits to patients suffering from uveitis by providing a long-acting, easy-to-use efficacious product that spares the use and thus side effects of treatment with systemic or local steroids, or immunosuppressants.

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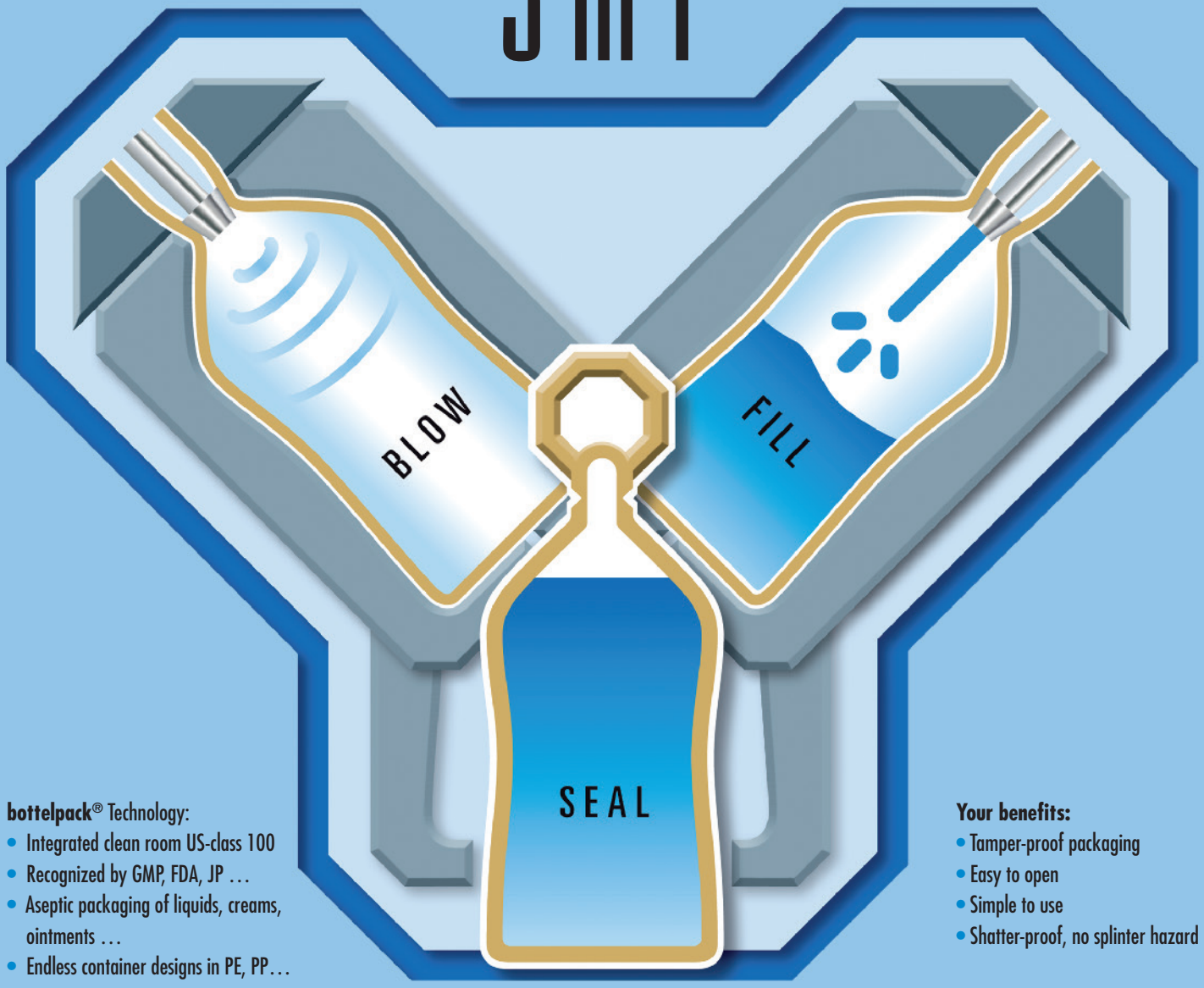

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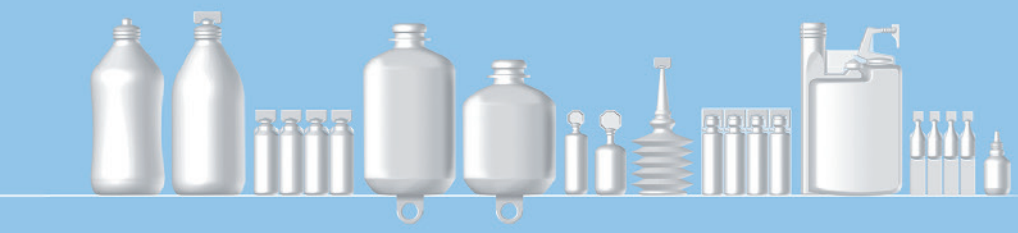

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