

OPHTHALMIC DRUG DELIVERY



ONdrugDelivery Issue N° 54, January 30th, 2015

Ophthalmic Drug Delivery

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

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 The Candlemakers, West Street, Lewes,
 East Sussex, BN7 2NZ, United Kingdom

ONdrugDelivery Magazine is published by Frederick Furness Publishing Ltd. Registered Office:
 The Candlemakers, West Street, Lewes,
 East Sussex, BN7 2NZ, United Kingdom.

Registered in England: No 8348388.
 VAT Registration No: GB 153 0432 49.
 ISSN 2049-145X print
 ISSN 2049-1468 pdf

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Front cover image: "Eye Drop and Bottle", provided by Psivida (see this issue, page 18). Credit: Borke/CrystalGraphics.com.

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HUGE THERAPEUTIC ADVANCES: BIGGER DRUG DELIVERY OPPORTUNITIES

By Paul Ashton, PhD

The landscape for ophthalmic pharmaceuticals has been undergoing a seismic shift as drug development has turned its focus to treatment diseases of the retina. The two biggest products in the field, with more than US\$5 billion (£3.3 billion) in annual sales between them, both treat retinal disease and were approved in the US only within the last eight years. Diseases of the retina, a thin layer of photosensitive tissue at the back of the eye responsible for generating

“The challenge and opportunity facing the ophthalmic pharmaceutical world is to take the next steps to develop effective long-term (months or years) delivery systems for the current and expected increasing number of drugs, particularly biologics, designed to prevent or treat retinal disease”

electrical impulses, are the major causes of irreversible vision loss and blindness in the developed world, affecting hundreds of thousands of people each year.

For decades, ophthalmologists (and their patients) realised that diseases of the retina represented a huge, unsolved problem, but little research went into developing anything that wasn't an eye drop. Twenty years ago, eye drops for glaucoma were the best-selling ophthalmic products. While eye drops can be a very effective way to get drugs into the front of the eye (the target for all approved glaucoma drugs), it has thus far been impossible to achieve therapeutic concentrations of drug in the back of the eye, where the retina is located, with topically applied drops in humans (although there are many reports in the literature of eye drops being used to treat retinal disease models effectively).

The only ways to deliver adequate concentrations of drugs to the retina have historically been by administration of systemic doses or by injections directly into the eye. Unfortunately, both can be problematic. Since ocular clearance rates are fast, the half-life of small molecules is typically less than 12-24 hours, while biologics such as antibodies have half-lives of up to 4-6 days. In addition, systemic delivery requires large doses to overcome the blood-eye barrier with attendant side effects. Complications of injections include intraocular infection, perforated sclera, vitreous haemorrhage and cataract formation. As a result, seeking to develop effective treatments for retinal disease has brought significant challenges of effective drug delivery.

Delivery of drug to the retina began to change with the AIDS epidemic and the development of Vitrasert®, the first ophthalmic sustained release product. Patients in the late stage of AIDS often developed cytomegalovirus (CMV) retinitis, a member of the herpes family that led to blindness. There were drugs available to control CMV retinitis, most importantly ganciclovir, but it needed to be administered as an IV infusion every day. Not only did the regular infusions have a risk of infection (particularly in immune-compromised patients) but the high systemic doses (necessary to overcome the blood-eye barrier) caused life-threatening neutropenia. Small doses of ganciclovir could also be delivered as intraocular injections every three days. Long term, both of these options were untenable.

The unmet need led to the very rapid development of Vitrasert, a small core of ganciclovir coated in a series of polymers surgically implanted into the back of the eye. Vitrasert provides sustained release for more than six months. Systemic exposure is minimal, and intraocular drug levels are higher than those achievable by



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systemic administration. When Vitrasert was approved by the US FDA in 1996, six years after the initial animal studies were performed, it was the first drug approved to treat retinal disease.

The next advance in ophthalmic sustained delivery was Retisert®, which extended the duration of sustained delivery to 30 months. Marketed by Bausch + Lomb, it delivers fluocinolone acetonide to treat posterior uveitis, a serious retinal disease that can lead to gradual or sudden vision loss. Also a drug core coated with polymers, Retisert is smaller than Vitrasert. However, it still needs to be surgically implanted. This product was approved in the US in 2005.

Next came Allergan's Ozurdex® (0.7 mg dexamethasone PLGA matrix), which provided the advances of being both bio-erodible and injectable. It was first approved in 2009 for vein occlusion, then in 2010 for uveitis, and in 2014 for diabetic macular edema. This implant is small enough to be injected into the eye. Being a matrix drug, release is relatively rapid. Over 90% of the drug is generally released in the first month) but in uveitis, the pharmacodynamic effect can last three to six months. However, as the device is bio-erodible, it can be administered frequently without the build-up of depleted devices in the eye, but still has the risks associated with frequent intraocular injections.

The most recent advance in sustained drug delivery for the eye is Iluvien®, also injectable but with extended duration of 36 months. It was approved in 2014 for the treatment of diabetic macular edema. It is composed of 0.19 mg fluocinolone acetonide in a polyimide tube the ends of which are capped to control release.

Currently this is where things stand. Sustained delivery systems have been approved for two steroids and an anti-viral. However, none of these systems deliver biologics. The three most-used drugs for retinal disease right now are biologics: the antibody Avastin® (approved for oncology but used off-label), the antibody fragment Lucentis® (a fragment of Avastin) and the trap molecule Eylea®, all of which target vascular endothelial growth factor (VEGF). These drugs have revolutionised the treatment of wet age-related macular degeneration (AMD), the leading cause of vision loss in people over 65 years old, and other retinal diseases. Unfortunately, these biologics must be injected directly into the eye typically eight times per year to control the disease. This

is tolerable, but perhaps only because the alternative is rapid deterioration of vision and blindness.

Another very common disease is dry AMD, which is approximately eight times more prevalent than the wet form and is

“Sustained delivery systems have been approved for two steroids and an anti-viral. However, none of these systems deliver biologics”

characterised by a slow atrophy of the retina. There is currently no approved treatment for dry AMD, and most observers believe that frequent intraocular injections will not be a viable treatment option for this disease.

COMMON EYE DISEASES: SUMMARY

Glaucoma affects 1.5-2% of the population. It is normally characterised by high intraocular pressure (IOP), which leads to progressive damage to the optic nerve and blindness. Drugs that reduce pressure can slow down or halt this process. Two strategies are either to reduce the production of aqueous humour (drugs such as Timolol®) or speed up its drainage from the eye (drugs like Xalatan® (latanoprost). Since the process that governs both aqueous production and outflow are located in the anterior chamber, topically applied eye drops are a convenient way to achieve therapeutic concentrations of drug and assuming good patient compliance, glaucoma is generally a well-managed disease.

Posterior uveitis is inflammation of the back of the eye, and is estimated to affect 175,000 people in the US. It is responsible for about 30,000 cases of blindness in the US. While it can be associated with other autoimmune diseases such as lupus, multiple sclerosis and rheumatoid arthritis, approximately 50% of the time, posterior uveitis is idiopathic. In some relatively rare instances, it can be genetic. The mixed aetiology and chronic nature of the disease can make it difficult to manage effectively. Posterior uveitis can also be associated with other ophthalmic conditions such as cataract, glaucoma (thought to be due to particulate matter blocking the normal outflow channels) and paradoxically hypotony (too-low eye pressure), due to reduced ability of the eye to make aqueous

humour. Approved treatments include oral and injected corticosteroids and immunosuppressants and Retisert.

Retinal vein occlusion is the second most common vascular disease of the eye, estimated to affect over one million people in

the US. Occlusion of the retinal veins causes elevated pressure in the vessels of the eye and impairs oxygen supply to the retina. The immediate result is swelling of the macula (macular edema) and a slow death of the affected region of the macular. Left untreated, the retina will usually re-perfuse and the swelling resolve. However, any death of the retina is irreversible. Approved treatments include regular intraocular injections of anti-VEGFs (Lucentis and Eylea) and intraocular injections of sustained release steroids (Ozurdex).

Diabetic macular edema (DME) is the most common cause of vision loss in people under 65 years of age and the most common vascular disease of the eye. Approximately 10% of people with diabetes will develop DME. It is caused by progressive failure of the micro blood vessels feeding the retina, in much the same way as blood vessel failure causes other conditions associated with diabetes such as ulcers leading to limb amputations and other vascular perfusion problems. As the blood supply to the retina becomes insufficient, stressed tissues exude cytokines (including vascular permeability factor or VEGF), which makes the vessels more leaky and leads to swelling of the macula (edema). DME can be treated by burning the macula and retina by laser. More recently the treatment of DME has been revolutionised by intra-vitreous injection of the anti-VEGF drugs, Lucentis and Eylea. When injected into the eye on a regular basis (typically every 4-8 weeks), these can be very effective in resolving edema with significant increases in visual acuity. However, the DME of the majority of patients is not optimally managed with VEGF drugs and long-term (over five-years) results are less impressive, since these treatments merely mask the effects of diabetes. Finally, in 2014, both Ozurdex and Iluvien were approved in the US for DME.

Age-related macular degeneration is characterised by a progressive breakdown of the retinal pigmented epithium (RPE), a layer of cells under the retina and resulting atrophy of the retina. Although this process can be very slow, it leads to irreversible loss of vision. There are no FDA-approved treatments for dry-AMD, the most prevalent incidence of AMD. In approximately 15% of cases, new blood vessels grow under and through the RPE, which are leaky and fragile, causing bleeding and edema. This can result in a rapid loss of vision. Fortunately, the two anti-VEGFs, Lucentis and Eylea, have been recently approved and found to be remarkably effective at least in the short to mid-term in treating wet AMD. The major downside for these agents is that they must be injected into the eye approximately every four to eight weeks.

CONCLUSION

The size of the market for effective treatments of serious retinal eye diseases should drive a flow of potential drug candidates to treat them. The challenge and opportunity facing the ophthalmic pharmaceutical world

“In the not too distant future, we will hopefully look back and wonder that patients had to resort to monthly injections into their eyes to preserve their vision”

is to take the next steps to develop effective long-term (months or years) delivery systems for the current and expected increasing number of drugs, particularly biologics, designed to prevent or treat retinal disease.

Many companies and academic groups are working on this problem. In the not too distant future, we will hopefully look back and wonder that patients had to resort to monthly injections into their eyes to preserve their vision. The challenge for drug delivery scientists is to make this happen soon; the prize is enormous, helping the millions of people who suffer from blinding eye diseases.

ABOUT THE AUTHOR:

Paul Ashton, PhD, has been President & Chief Executive officer of pSivida since January 2009, having previously served as Managing Director of the Company from January 2007 to January 2009 and Executive Director of Strategy from December 2005 to January 2007. Dr Ashton was the President & Chief Executive Officer of Control Delivery Systems (CDS) from 1996 until its acquisition by pSivida in December 2005. CDS was a drug delivery company that Dr Ashton co-founded in 1991. Prior to co-founding CDS, Dr Ashton was a Joint Faculty Member in the Departments of Ophthalmology and Surgery at the University of Kentucky, served on the faculty of Tufts University, and worked as a Pharmaceutical Scientist at Hoffman-La Roche. Dr Ashton received a BSc in Chemistry from Durham University (UK), and a PhD in Pharmaceutical Science from the University of Wales.

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| December | Delivering Biotherapeutics | November 9th |
| January 2016 | Ophthalmic Drug Delivery | Dec 14th |



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SECTOR OVERVIEW

OCULAR DRUG DELIVERY TECHNOLOGIES: EXCITING TIMES AHEAD

By Ilva D Rupenthal, PhD

SMALL ORGAN – BIG MARKET

The 2010 global cost of vision loss was nearly US\$3 trillion (£2 trillion) for the 733 million people living with low vision and blindness,¹ with this number expected to increase significantly due to the aging population and the increasing incidence of metabolic disorders such as diabetes. This makes eye disorders one of the costliest health conditions worldwide. The major blinding disorders currently include age-related macular degeneration (AMD), diabetic retinopathy /

Type I diabetics and 60% of Type II diabetics show signs of retinopathy and according to the 2014 Prevent Blindness report, more than eight million people are currently affected by DR with this number projected to increase to nearly 11 million by 2032. Moreover, diabetes patients are 60% more likely to get cataracts and 40% more prone to develop glaucoma than those without diabetes, further increasing the incidence of ocular disorders in diabetics. Glaucoma currently affects over 2.8 million Americans with an estimated increase of 92% (a total

of 5.5 million cases) expected by 2050. Today more than \$6 billion is spent to treat glaucoma and optic neuropathies, with costs expected to double by 2032 and to rise to \$17.3 billion by 2050 according to the 2014 Prevent Blindness report.

While there are many effective medications to treat ocular conditions the challenge remains to deliver these drugs effectively with minimal side effects. Glaucoma eye drops, for example, usually need to be applied once or twice daily, often as a combination of multiple products, to achieve suf-

“The number of companies working on ocular drug delivery platforms, especially for the posterior segment, has skyrocketed over the past decade, with the reformulation of previously approved molecules offering the advantage of available long-term safety data in humans and therefore a facilitated approval process”

ficiently high drug concentrations while intravitreal injections of antibodies against vascular endothelial growth factor (VEGF) in AMD treatment are generally given every 4-8 weeks. Therefore, achieving sufficiently high concentrations at the target site and maintaining these over prolonged periods with minimal side effects, offers great opportunities for new product development, especially when using already US FDA-approved drugs with well-known safety and efficacy.¹

macular edema (DR/DME) and glaucoma, with these conditions offering great opportunities for innovation in drug delivery technologies. According to the Bright Focus Foundation, over 11 million people in the US have diagnosed AMD, with this number expected to double to nearly 22 million by 2050. Worldwide around 18 million injections of anti-VEGF agents were given in 2014 to treat AMD with an estimated global cost of visual impairment due to AMD being \$343 billion, including \$255 billion in direct health care costs. According to the International Diabetes Federation, around 387 million people are currently affected by diabetes with this number projected to increase by 205 million until 2035.

Within 20 years of diagnosis virtually all

The global ophthalmology drug and device market was estimated at \$36 billion in 2014 and is expected to increase to \$52.4 billion by 2017. The pharmaceutical segment of this market was \$19.8 billion last year, with AMD and DR drugs accounting



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for \$5.84 billion.¹ When comparing disease cases and revenue, anterior segment conditions (45% of cases) accounted for 95% (\$4.9 billion) of the revenue in 2001. While the proportion of disease cases (45% anterior and 55% posterior segment) has not changed significantly since then, the revenue for posterior segment diseases is expected to increase from \$0.3 billion in 2001 to about \$9.9 billion by 2018 (reaching 43% of eye care costs) with the anterior segment accounting for the remaining 57% (\$13.2 billion). Keeping these figures in mind it is no surprise that the number of companies working on ocular drug delivery platforms, especially for the posterior segment, has skyrocketed over the past decade, with the reformulation of previously approved molecules offering the advantage of available long-term safety data in humans and therefore a facilitated approval process, which will hopefully result in a number of innovative products on the market within the next few years.

SMALL ORGAN – BIG CHALLENGES

One would think that a small organ such as the eye which is readily accessible from the outside of the body would be easy to treat. However, the eye is a rather isolated organ with a number of barriers in place to protect it from the environment, which pose major challenges to effective drug delivery. When applying eye drops, for example, the most common method of treating anterior segment diseases, generally less than 5% of the applied drug reaches the ocular tissues. This is mainly due to the fast nasolacrimal drainage and the poor permeation of the remaining drug across the sandwich-like structure of the cornea, with the lipophilic corneal epithelium being the main barrier to ocular entry for most drugs. While this leads to excessive waste of costly drugs as well as low efficacy and patient compliance, it also poses a significant side effect risk due to systemic absorption of the majority of the dose given.

To overcome issues with topical ocular drug delivery researchers have focused predominantly on two strategies:

- 1) Increasing the corneal residence time using viscosity enhancers, mucoadhesive, particulate and/or *in situ* gelling systems; and
- 2) Increasing the corneal permeability using penetration enhancers, prodrugs and colloidal systems such as nanoparticles and liposomes.

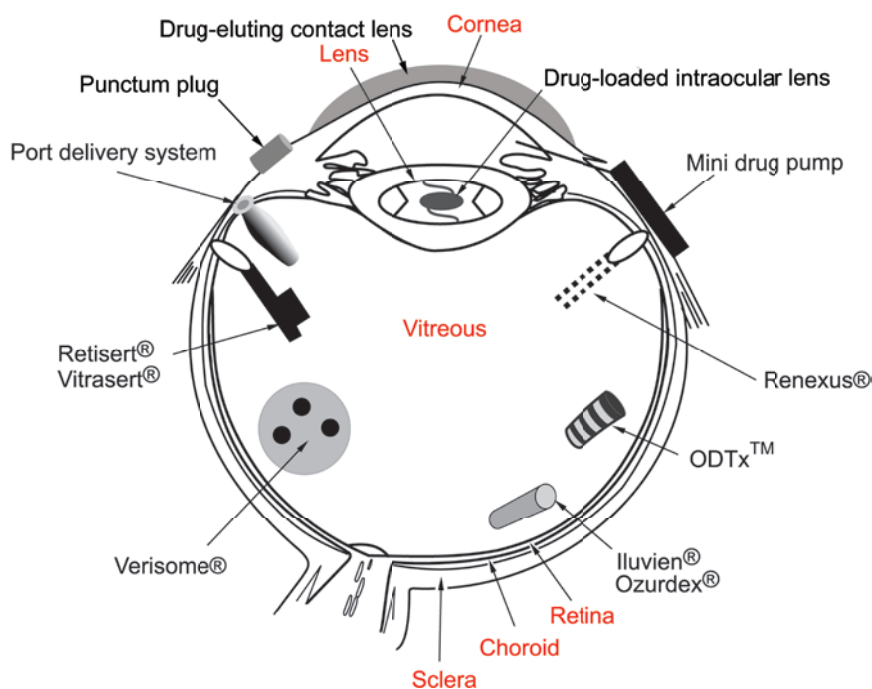


Figure 1: Overview of the ocular structures and recent delivery technologies. (Modified with permission from Yasin et al.³)

While these have shown some improvements in the treatment of anterior segment diseases, they are unable to deliver sufficiently high concentrations to the back of the eye to treat most posterior segment conditions.

The gold-standard to treat conditions such as AMD is intravitreal injection of the drug-containing solution, although a few implants which are either sutured into the sclera or injected into the vitreous have also made it onto the market over the last two decades to treat a variety of retinal conditions (these will be further discussed below). However, although confined to the relatively small vitreal space, the drug faces elimination processes and needs to diffuse through the vitreous (with diffusion of large positively charged molecules hindered by the dense negatively charged vitreous meshwork) before crossing the inner limiting membrane to reach the retina with the RPE and Bruch's membrane posing yet another permeation barrier for delivery into the choroid.

Other options to reach the choroid include periocular injections with the sclera allowing molecules up to 20 kDa to permeate (compared to ≤ 5 kDa across the cornea) as well as the possibility to inject larger volumes (≤ 1 ml compared with ≤ 100 μ l intravitreally). Even more localised are suprachoroidal injections via precise microneedles which allow the drug solution to spread between the sclera and choroid around the eye ball, almost forming a drug-containing liquid 'bandage' around the eye. Again, there is a

volume restriction (≤ 35 μ l can be injected without leakage) and solutions are eliminated relatively quickly. However, injecting particles with a size smaller than 100 nm and/or *in situ* gelling systems into this space could offer sustained release possibilities.²

Finally, the active could also be administered systemically (oral or parenteral) and although choroidal blood flow is extremely high (up to 2000 μ l/min/100 g of tissue with most other tissues having a rate of < 500 μ l/min/100 g), generally less than 2% of the administered dose reaches the ocular tissues mainly owing to the tight blood-retinal barrier. However, a number of posterior segment diseases are characterised by leaky blood vessels which may result in higher drug concentrations in the effected ocular tissues and may increase the overall benefit to risk ratio after systemic administration, especially if the drug is encapsulated into a particulate system to protect it from degradation within the bloodstream. An overview of the ocular structures and recent delivery technologies, which will be further discussed below, is given in Figure 1.

RECENT ADVANCES IN ANTERIOR SEGMENT DELIVERY

Anterior segment diseases include blepharitis, conjunctivitis, corneal keratitis, dry eye, corneal infections and glaucoma with most of these currently treated with conventional eye drops such as solutions (β -blockers, prostaglandin analogues

(PGA), β -agonists, carbonic anhydrase inhibitors and some antibiotics) or suspensions (steroids).

When taking anti-glaucoma medications as an example, only a limited number of advanced delivery systems have made it onto the market over the last decades. Allergan's Propine® was the first prodrug-based eye

deliver loteprednol for a number of ocular conditions, with a twice-daily administration of the MPP-formulation as effective as four daily doses of the conventional suspension. Focusing again on novel anti-glaucoma technologies, Envisia Therapeutics is investigating a PGA loaded PRINT-based biodegradable polymer rod intended for

(Sensimed), but also have great potential to measure other clinical biomarkers in the tear film.⁶ The Triggerfish® from Sensimed AG, for example, is able to monitor the IOP telemetrically over 24 hrs.⁶ Similar to currently utilised glucose-sensing insulin pumps, one could therefore imagine a combination of sensing and drug eluting contact lens capabilities to achieve more efficient treatment of high pressure induced glaucoma. A similar concept is currently utilised in the Replenish MicroPump™ system, which contains a fluidic flow sensor, a bi-directional telemetry system for wireless programming and a microcontroller allowing pre-programmed administration of nanolitre-sized doses. With the addition of a pressure sensor, this technology could serve as a closed-loop system whereby an increase in the IOP would initiate on-demand drug release.⁷

"A recent study investigated nanodiamond-embedded contact lenses capable of lysozyme-triggered release of timolol maleate enabling drug release only once in contact with the tear fluid and therefore preventing premature drug release during storage"

drop to enter the market in the 1970s, with a 0.1% dipivalyl epinephrine solution lowering the intraocular pressure (IOP) as effectively as the 2% conventional solution. The closest to a microparticulate glaucoma formulation is Betoptic® S, which contains betaxolol hydrochloride bound to ion-exchange resin particles, with the 0.25% particle formulation found to be equivalent to a 0.5% Betoptic solution. A couple of *in situ* gelling systems are also available, including gellan gum based Timoptic® XE and xanthan gum based Timolol GFS®, both reducing the eye-drop application frequency from twice to once daily. Ocuser®[®], a pilocarpine-containing membrane-controlled reservoir system inserted into the conjunctival sac, offered sustained drug release over seven days. It was, however, relatively difficult to insert and often resulted in irritation and ejection.

In addition to these, a large number of exciting approaches are currently being researched or have entered into clinical trials. Novaliq GmbH, for example, is developing topical ocular formulations based on semi-fluorinated alkanes particularly suitable for the delivery of poorly soluble drugs such as Cyclosporin A (see this issue, Page 21). While enhancing drug dissolution and permeation and therefore increasing the overall drug bioavailability, the formulation does not require preservatives and lubricates the ocular surface, both aspects which are of particular benefit when treating dry-eye conditions. Kala Pharmaceuticals is developing mucus penetrating particles (MPP) which allow efficient penetration of the tear film mucin layer, the first defense mechanism encountered after topical administration of eye drops (see Issue 48, Page 16). This technology is currently under investigation to

intracameral injection for three to eight months drug delivery (see Issue 48, Page 10), while GrayBug is developing proprietary PLGA particles (see this issue pp 24), which can release the IOP-lowering agent (GB-201) in a controlled fashion over several months, without causing any inflammation, a problem commonly associated with conventional particles.⁴ Currently in clinical trials are also three PGA-containing punctum plugs. The travoprost-containing plug from Ocular Therapeutix currently in Phase II clinical trials releases drug for up to 90 days and contains a visualisation aid to monitor plug retention. Both the QLT and Mati Therapeutics punctum plugs deliver latanoprost over three months and are currently in or have completed Phase II clinical trials.

Drug-eluting contact lenses have also recently gained considerable interest for drug delivery to the anterior segment of the eye with the lens trapping the pre-corneal tear film and thus reducing its nasolacrimal drainage. Drug-loading approaches hereby include simple soaking of the lens in the drug solution (with limited sustained-release potential), incorporation of particles into soft contact lenses or molecular imprinting with the last two having shown drug delivery for up to one month. To reduce the initial burst and achieve controlled release, a recent study investigated nanodiamond-embedded contact lenses capable of lysozyme-triggered release of timolol maleate enabling drug release only once in contact with the tear fluid and therefore preventing premature drug release during storage.⁵

Besides refractive and drug delivery capabilities, soft contact lenses have also been investigated as sensors for glucose levels (Google) and intraocular pressure

RECENT ADVANCES IN POSTERIOR SEGMENT DELIVERY

Posterior segment diseases are the most prevalent cause of visual impairment in the developed world and include degenerative conditions such as AMD and retinitis pigmentosa, vascular diseases such as DR, retinal vein/artery occlusion and retinopathy of prematurity, inflammation such as seen in uveitis, infectious conditions including endophthalmitis and cytomegalovirus (CMV) retinitis as well as optic neuropathies arising from glaucoma.

The gold-standard to treat posterior segment conditions remains intravitreal injection which delivers the drug directly into the eye but may be associated with poor patient compliance and possible complications such as a cataract formation and retinal detachment. Besides intravitreally injected solutions, four sustained-release implants have made it onto the market so far. These include non-biodegradable Vitrasert®, a ganciclovir containing scleral implant approved in 1996 for the treatment of CMV retinitis, and Retisert®, based on the same technology but smaller in size, which contains fluocinolone acetonide and was approved for the treatment of non-infectious posterior uveitis in 2005. Just recently US FDA-approved, Iluvien®, also a non-biodegradable implant (polyimide tube with membrane caps), is injected into the vitreous with a 25G needle rather than being sutured into the sclera. It can deliver fluocinolone acetonide over three years for the treatment of DME, but little is currently known about its fate after drug depletion.

The first ever biodegradable intravitreal implant, Ozurdex®, was approved in 2009 and consists of a PLGA-based rod containing dexamethasone for the treatment of DME, retinal vein occlusion and posterior uveitis. The same technology is currently also under investigation for the delivery of brimonidine to treat dry AMD and retinitis pigmentosa, with the drug aimed at preventing cell death in the retinal pigment epithelium. It remains to be seen whether inflammation due to the low pH of PLGA degradation products, potentially masked when delivering an anti-inflammatory steroid (Ozurdex), may become more apparent with the brimonidine implant. GrayBug has therefore developed a proprietary PLGA-based technology proven to reduce the inflammation seen with conventional PLGA particles, with their lead product for wet AMD treatment (GB-102), exhibiting both anti-VEGF and anti-PDGF properties, targeted to last up to six months.⁴ The GrayBug technology allows relatively high drug loading and may also be capable of delivering large molecules including proteins, aptamers and biologics for several months.

In addition to Envisia's intracameral implant discussed in the previous section,

the PRINT technology has also been used for posterior segment systems. In the ENV705 implant a trehalose/bevacizumab mixture is dispersed within a polyglycolic acid matrix allowing drug release of effective concentrations over 3-6 months. While the Envisia particles are preformed, the Verisome® technology, based on carbonates, tocopherol and citrate esters, allows implant formation *in situ* once in contact with the aqueous vitreous environment. Depending on the volume of the formulation injected, drug levels can be maintained for up to 12 months with current clinical trials including dexamethasone and triamcinolone acetonide formulations.

A rather different concept is utilised by Zordera which has developed a nanoporous film device with zero-order sustained drug release after intravitreal injection (see Issue 48, Page 20). This device consists of a drug pellet, sandwiched between two thin layers of impermeable biodegradable membrane, with adjustable nano-pores on one side permitting only one drug molecule to leave the reservoir at a time. The impermeable polymer layers degrade at a later time-point when most of the drug has been released, eliminating the need for device

removal. This system has been shown to deliver ranibizumab over four months in a sustained manner.

While all of the above implantable systems may achieve sustained release, the release rate can generally not be altered if the condition worsens or aborted in the case of serious side effects. A refillable (to increase the device's life span) and flushable (to abort drug delivery) functionality has, however, been included in the port delivery system, a scleral plug consisting of a porous container, a semi-permeable non-biodegradable membrane with a refill port and one or more exit ports to release the drug into the vitreous humour. This implant has been tested with ranibizumab and exhibited significant positive clinical outcomes when compared with monthly intravitreal injections of the same drug. With advances in polymer science and nanomaterial development for biomedical applications over recent years there has been a paradigm shift from conventional to stimuli-responsive or tunable devices, with such systems also having great potential in the area of ocular drug delivery.³

Whilst, to date, only open-loop systems responsive to light (e.g. ODTx), or an elec-

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tric or magnetic field (e.g. micro-electro mechanical systems (MEMS)), have been explored for the purpose of drug delivery to the posterior segment of the eye,³ pressure-

Tunable systems with the addition of a sensing capability may therefore offer more effective treatment of ocular diseases in the future. The major hurdle with success-

“Whilst, to date, only open-loop systems responsive to light, or an electric or magnetic field have been explored for the purpose of drug delivery to the posterior segment of the eye pressure-responsive closed-loop systems may have great potential in the treatment of glaucoma and optic neuropathies”

responsive closed-loop systems may have great potential in the treatment of glaucoma and optic neuropathies. Similar to the anterior MicroPump discussed in the previous section, the posterior Replenish system may be suitable to deliver neuroprotective agents to the posterior segment to prevent retinal ganglion cell loss resulting from elevated IOP. In the future, other sensing capabilities such as the measurement of VEGF levels, inflammatory markers or fluid build-up in the macula combined with a feedback mechanism and stimuli-responsive drug release could offer tailored and efficient treatment of posterior segment diseases.

CONCLUSION

A number of innovative drug delivery technologies are currently in the pipeline to treat ocular diseases more efficiently while minimising side effects, with the majority aiming to sustain drug release over prolonged periods. This would reduce the overall administration frequency and the need for specialist visits in the case of intravitreal injections, significantly reducing treatment costs and improving the quality of life for those affected by vision-impairing and blinding diseases. However, long-term effects of low sustained drug levels especially in the posterior segment are currently unknown and tunable drug release may be of advantage if the condition improves to avoid side effects such as the increased incidence of geographic atrophy seen when comparing monthly to as needed intravitreal injections of ranibizumab over 24 months.⁸ Thus, while sustained release is certainly of great advantage, variations in the disease progression, individual patient response to treatment and concurrent conditions may require alterations in the drug release pattern.

ful development of such tunable implants remains the device size restriction, which in turn limits the amount of drug loading. Thus, to achieve sustained release over prolonged periods, such devices are generally limited to highly potent drugs such as steroids and may become difficult to adapt to macromolecules such as anti-VEGF agents. Moreover, matching these new technologies with drug pharmacokinetics and translating pre-clinical studies into human clinical trials remains a challenge. Nevertheless, novel ocular drug delivery technologies offer great market potential and it is certainly a very exciting area to be working in at the present time.

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ABOUT THE AUTHOR

Dr Ilva Rupenthal is a Senior Lecturer in the Department of Ophthalmology, University of Auckland, and the inaugural Director of the Buchanan Ocular Therapeutics Unit, which aims to translate ocular therapeutic related scientific research into the clinical setting, whether pharmaceutical, cell or technology based. Dr Rupenthal obtained a Pharmacy degree from Philipps-University of Marburg, Germany, and completed a PhD on “Ocular Delivery of Antisense Oligonucleotides” in the School of Pharmacy and the Department of Ophthalmology, University of Auckland. She now has more than 10 years of experience in the area of ocular drug delivery and has worked on a number of polymer-based, *in situ* gelling and nanoparticulate systems for ocular peptide and nucleotide delivery. In 2010, Dr Rupenthal was awarded a New Zealand Science and Technology Postdoctoral Fellowship to establish an ocular pharmaceuticals group within the New Zealand National Eye Centre and she is presently a Sir Charles Hercus Health Research Fellow of the New Zealand Health Research Council. Her current research focuses on tunable ocular delivery systems with projects investigating light-responsive and conducting polymer-based implants for the treatment of posterior segment diseases such as AMD and DR. She has published over 20 articles and one book chapter in the area of ocular drug delivery and has won Commercialization Challenge Awards for her innovative ideas on stimuli-responsive ocular implants.

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MODELLING OCULAR DELIVERY USING COMPUTATIONAL FLUID DYNAMICS

In this piece, Paul Missel, PhD, Therapeutic Area Modeller, Modelling & Simulation, Global Clinical and Regulatory Affairs, Alcon Research Ltd, and Marc Horner, PhD, Lead Technical Services Engineer, Healthcare, ANSYS, Inc, describe the use of computational fluid dynamics simulations to predict drug flow and temperature inside the eye, and provide examples of applications modelling: delivery following topical application; delivery from an intra-ocular depot; and delivery from juxtascular devices.

INTRODUCTION

Effective drug delivery to internal ocular tissues must overcome significant barriers imposed by fluid flow and clearance within the eye. Fluid flow processes include production, circulation and elimination of both tear fluid and aqueous humour, and hydraulic-assisted flow through porous media such as the vitreous humour, iris root, and outer sheath tissues. Clearance occurs as dissolved drug flows past or percolates through vascular tissues such as the conjunctiva, iris, ciliary body, retina and choroid or into the lymphatic system. Computer modelling is helping pharmaceutical scientists understand the interplay between drug formulation, fluid flow and clearance, which is leading to the development of more effective ocular drug delivery systems.

Classical pharmacokinetic (PK) models were among the first models developed for predicting ocular drug disposition. These models are comprised of well-mixed compartments representing specific ocular tissues with various interconnections. A series of first-order transfer equations describes transport between and elimination from each compartment. Physiologically-based pharmacokinetic (PBPK) approaches improve on PK models by incorporating the flow processes that facilitate drug distribution within the eye and drug clearance through vascular tissues. This is accomplished by constructing model compartments explicitly reflecting the volumes of the tissues they represent, by replicating the physiological production and elimination of tear fluid and aqueous humour and by assigning transfer coefficients between compartments reflecting physicochemical drug properties.¹

The PBPK approach can be more powerfully applied using computational fluid dynamics (CFD), which uses numerical methods to provide approximate solutions to the differential equations that describe fluid flow, heat transfer, and species transport. Today's CFD software tools are general enough such that the same software used to model product performance in such diverse fields as automotive, nautical, aeronautical, civil, and petroleum engineering can be applied to predict the flow of fluid, heat and drug in the eye. A primary advantage over compartmental approaches is that CFD models the spatial distribution of drug within each compartment through time. Such detailed numerical experimentation can help establish the safety and efficacy of a delivery system while reducing the number and/or size of clinical studies required.

OCULAR CFD MODEL SUMMARY

This section provides an introduction to the physical processes that govern fluid flow, heat transfer, and drug motion in the eye and their implementation into a CFD model, please see Missel *et al*, 2010 for a complete description.²

A CFD simulation begins with the construction of a geometric model that includes all structures involved in fluid, heat, and drug transport. The geometry is typically constructed in CAD or a geometry tool specific to the CFD software. Figure 1 shows anatomical human and rabbit ocular models. The rabbit is frequently used as a preclinical model for evaluating ophthalmic drug products before human clinical testing. Conducting simulations in both ocular



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geometries enables translating results from preclinical experiments in rabbits into predictions for clinical outcomes in humans.

The aqueous humour region consists of the fluid zones between the cornea and vitreous, excluding the iris and ciliary body. Aqueous humour is a clear, non-viscous, water-like fluid that is secreted by cells on the outer lining of the ciliary body. Aqueous humour flows around the iris and exits the eye through the trabecular meshwork, a ring-shaped structure of connective tissue. Aqueous humour following this path eventually returns to the blood via a fine venous network surrounding the outer layer of the sclera, the shell encasing most of the eye. A small fraction of aqueous humour percolates through the sclera and cornea. The resistance of the sclera to fluid permeation produces the intra-ocular pressure. The trabecular meshwork also provides some resistance to fluid flow and in glaucoma this resistance increases, thus increasing the pressure.

All structures apart from aqueous humour were treated as porous media. Experimental measurements have established the hydraulic resistance of the sclera is about 15,000 times higher than that of the vitreous. All other porous media tissues, apart from the trabecular meshwork and the vitreous, are assigned the same resistance as the sclera. The hydraulic resistance of the trabecular meshwork was a parameter in the model whose value was adjusted such that the maximum pressure inside the eye matched an intraocular pressure of 15 Torr. A band along the ciliary body behind the iris produces aqueous humour at a rate appropriate for each species. The pressure

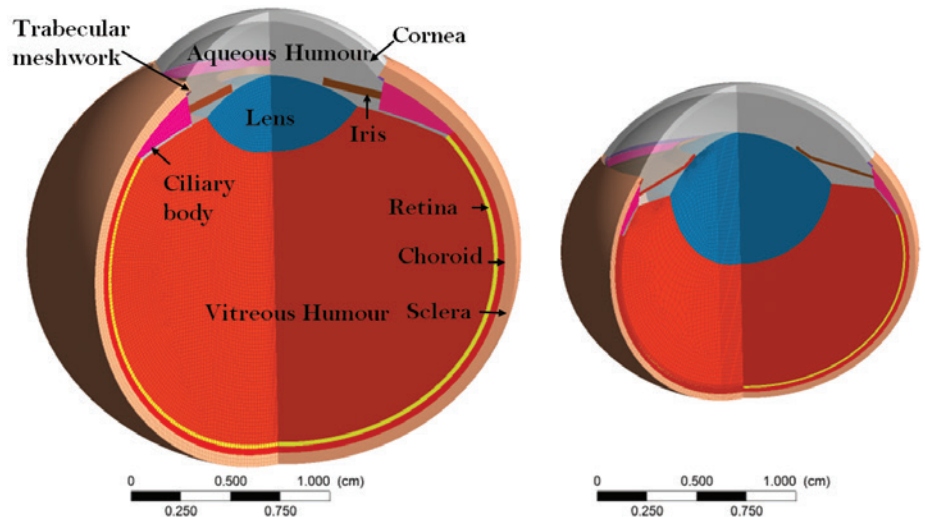


Figure 1: Comparison of geometric ocular models for human and rabbit, shown on the same scale; the horizontal bar below each panel corresponds to 1 cm.⁸

boundary condition on the outer sclera and the surface behind the trabecular meshwork was specified as 10 Torr, matching the episcleral venous pressure, whereas there was zero (atmospheric) pressure applied on the outer cornea. The sclera, choroid, retina, iris and ciliary body were set to a fixed temperature of 37°C and the cornea was set to 34°C. The thermal gradient between the cornea and internal tissues creates density gradients in the aqueous humour, which significantly impact aqueous flow patterns.

The fluidic and thermal transport processes were simulated using the ANSYS Fluent CFD solver. Figure 2 shows simulation results of pressure, temperature and fluid flow in the rabbit ocular model. In Figure 2a, most of the ocular interior is at the maximum pressure of 15 Torr; the pressure drop occurs almost entirely across

the outer sheath surfaces. Figure 2b shows the variation of temperature within the eye. Since the aqueous humour density is allowed to vary with temperature, density gradients give rise to thermal convection, which creates a circulating flow pattern with a maximum fluid velocity on the order of 10^{-4} m/s, as illustrated in Figure 2c. The maximum velocity for the hydraulic flow in the vitreous is four orders of magnitude lower than the maximum velocity within the aqueous humour region. This fluid-thermal solution forms the baseline convective flow pattern upon which the modes of drug delivery presented in the next three sections occur.

MODEL APPLICATION: PK FOLLOWING TOPICAL DELIVERY

Topical dosing is commonly used to treat glaucoma. The target of anti-glaucoma drugs is typically the iris / ciliary body. Mechanisms of action include reducing the production rate for aqueous humour and reducing the hydraulic resistance of the iris root to facilitate outflow. Topically administered anti-inflammatory drugs also target the iris / ciliary body to reduce pain and inflammation following cataract surgery. These drugs can also exert an important influence on deeper ocular tissues such as the retina and macula to prevent edema, which occurs occasionally in diabetic patients following surgery.

Drug transport in the eye was also simulated using ANSYS Fluent, which can model the interaction between drug convection, diffusion and elimination. Convection is the motion of drug due to bulk flow of aqueous humour; diffusion is the rate of passive mass transport through the medium down

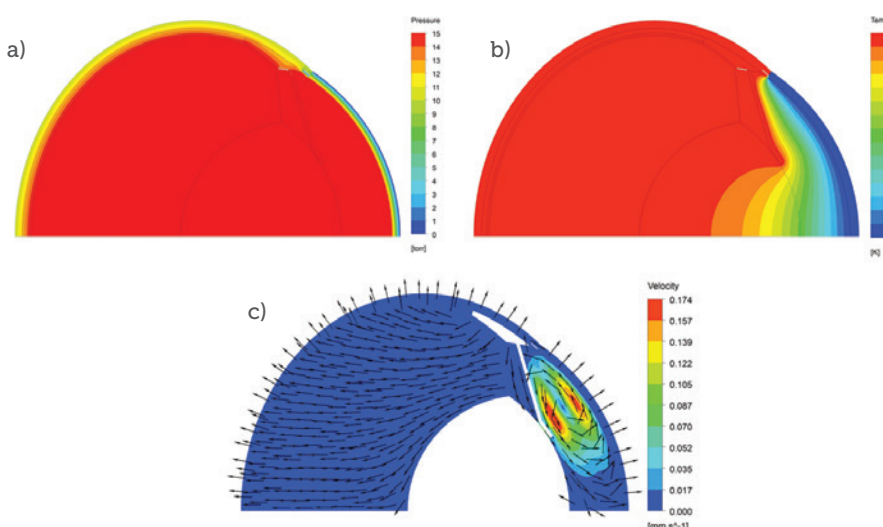


Figure 2: CFD simulation results in the rabbit eye model. a) Pressure (Torr). b) Temperature (Kelvin). c) Vector velocity, arrows show direction of flow and are colour-coded to match the scale for the superimposed contour plot (m/s).

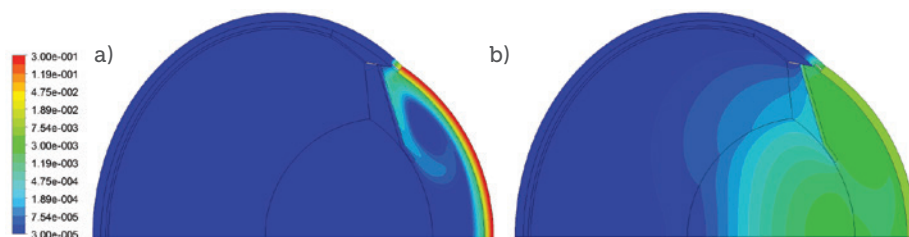


Figure 3: Simulated advection of drug into ocular tissue following topical dosing with timolol maleate (concentration plotted on a logarithmic scale where 1 corresponds to the concentration of drug in the topical dose). a) Three minutes after instillation of a topical dose. b) Four hours after instillation.

a concentration gradient, and sink terms account for removal of drug by vascular or lymphatic clearance. Chemical partitioning, which gives rise to discontinuities in drug concentration at boundaries between tissues having different lipophilic / hydrophilic properties, is also included in the model through the use of jump conditions at tissue interfaces. Each tissue is assigned its own unique set of values for the partition coefficient, diffusion coefficient, sink term, and equilibrium drug concentration.

Drug application to the outer corneal surface can be modelled by a time-varying function approximating the tear concentration resulting from instillation of a topical dose. The tear film concentration decays exponentially with time, the concentration dynamics being influenced by the initial rapid decrease in pre-corneal fluid volume after dosing and by the continuous influx of fresh tears. Since our models do not include tissues outside the eye such as the conjunctiva and eyelids, our drug input function will most likely overestimate the flux of drug into the eye. Thus we include a single

adjustable parameter to enable tuning the amplitude of the drug input function. The model predicts that rapid mixing of aqueous humour in the anterior chamber creates a wisp of higher drug concentration just a few minutes after drug instillation (Figure 3a). Mixing has rendered the aqueous humour drug concentration to be approximately uniform four hours later (Figure 3b).

Figure 4 compares simulation results with experimental measurements of mean tissue concentrations following the topical dosing of a drug solution. The concentrations in the anterior compartments initially increase with time, then decrease as drug distributes throughout the remaining tissues. Applying an amplitude prefactor of one quarter for our drug input function, the simulation accurately predicts the time dependence of the concentrations for anterior tissues such as the iris / ciliary body, the tissue affected by the drug. Thus, CFD is quite useful for predicting the time course of drug distribution. Simulated concentrations in the vitreous and lens lag behind the experimental values, however. Additional fluid currents

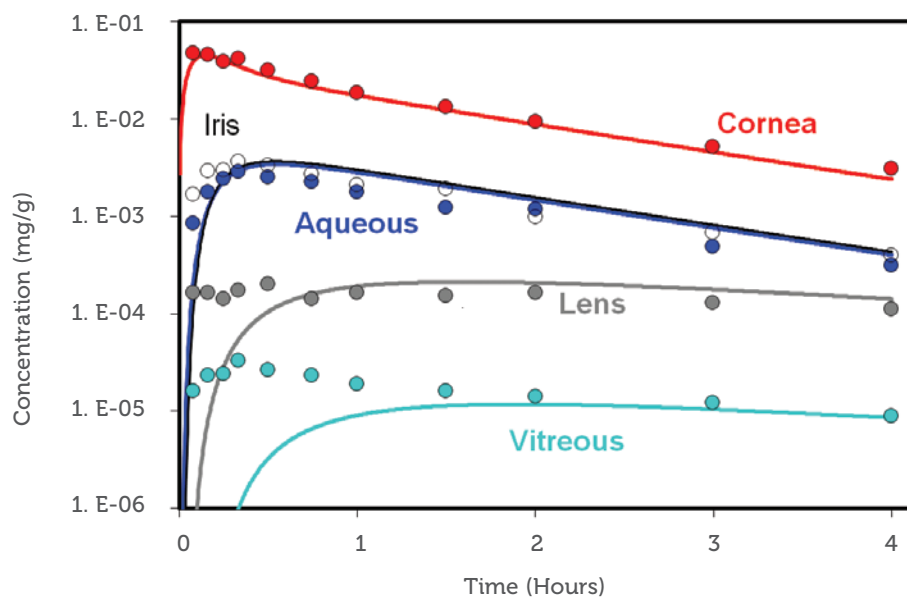


Figure 4: Comparison of simulated & experimental mean tissue compartment concentrations following topical instillation of 25 µL 0.65% timolol maleate.⁹

or vascular circulation pathways capable of transporting drug between tissue compartments may be at work. Identifying and incorporating these missing fluidic and circulatory currents could improve the model.

MODEL APPLICATION: DELIVERY FROM INTRAOCCULAR DEPOTS

Much effort has been expended in development of bio-erodible dosage forms that will sustain drug release over time. However, a suspension may perform suitably as a sustained release depot if injected in a region of quiescent vitreous which has retained its gel-like consistency, provided that the drug solubility is low enough to dissolve slowly but high enough to deliver a therapeutic level of drug. Drug release rate and duration can be controlled by adjusting the suspension drug concentration. This behaviour is a consequence of a local concentration effect, in which drug dissolved from one particle suppresses the dissolution of drug from nearby particles. The formulation will need to be engineered to immobilise the particles until they are completely dissolved for this approach to be most effective.

Figures 5 and 6 show simulation results from various model suspensions of triamcinolone acetonide (TAC). In each simulation, identically sized particles are initially arranged in an evenly spaced array inside a spherically shaped depot.

Figure 5 illustrates how the duration of the suspension (defined as the time after injection at which all solid drug has dissolved) varies with particle size. Figure 6 shows the time dependence of drug content for two different suspensions. These simulations utilised the volume of fluid (VOF) method in ANSYS Fluent, which enables the tracking of phase boundaries through a stationary mesh. In this case, the VOF method tracks the boundary between solid, undissolved drug crystals and drug dissolved in solution. The concentration at the dissolving surface was set to 36 ppm, the drug solubility limit.

The insets in Figure 5 show the quasi steady-state drug distributions a few days after intravitreal injection. The contours show the drug concentration in the region containing the particles is very close to the solubility limit (denoted by the red colour). The concentration decreases at a rate that is approximately inversely proportional to distance outside the suspension depot. If the therapeutic window (the difference between the minimum effective

concentration and the maximum concentration allowable before toxic side effects are manifested) is wide enough, the entire eye may be treated effectively.

For an oral suspension dissolving in the stomach, drug particles dissolve at a rate proportional to the total particle surface area, as specified by the Noyes-Whitney equation.³ This strong dependence of dissolution rate on particle surface area is observed in certain *in vitro* dissolution experiments which expose drug particles to copious amounts of dissolution medium under substantial agitation.⁴ Each particle is uniformly accessible to the release medium in these methods. This is not the case for the intravitreal depot, because the particles on the exterior shield interior particles from dissolution. Instead, the dependence of dissolution rate on particle size exhibits an asymptote. The arrow in Figure 5 at 428 μ m identifies the diameter at which the dissolution rate is within 1% of the value in the limit of infinitesimally small particle size. Since this diameter is 30-100 times the diameter of particles in a typical ophthalmic suspension, dissolution rate of an intravitreal depot will not depend on particle size.

Figure 6 shows a comparison between simulated dissolution-*versus*-time profiles for suspensions containing either 4 or 16 mg TAC confined to a 100 μ L spherical depot *versus* simulations in the infinitesimally small particle size limit. The predictions match the experimental data fairly well for the 16 mg depots, but under-predict the duration of the 4 mg depots. If we allow for the depot to condense to a smaller volume after day 10, as was observed in the 2006 study by Kim *et al.*,⁵ the simulation curve for 4 mg comes in closer agreement with the data.

MODEL APPLICATION: JUXTASCLERAL DEVICES

Our last example is a juxtasclear device for anecortave acetate (AAc), a low-molecular-weight lipophilic compound which at one time was being developed to treat macular degeneration. The prototype device, shown in Figure 7a, is a silicone holder for placing a drug tablet adjacent to the sclera. A simulation for steady-state drug distribution in ocular tissue is shown in Figure 7b. Drug partition and diffusion coefficients were obtained from *in vitro* experiments equilibrating ocular tissues with drug solution and measuring drug permeability through excised tissues.⁶ Partition coefficients for drug are 2.2 and 4 for sclera and

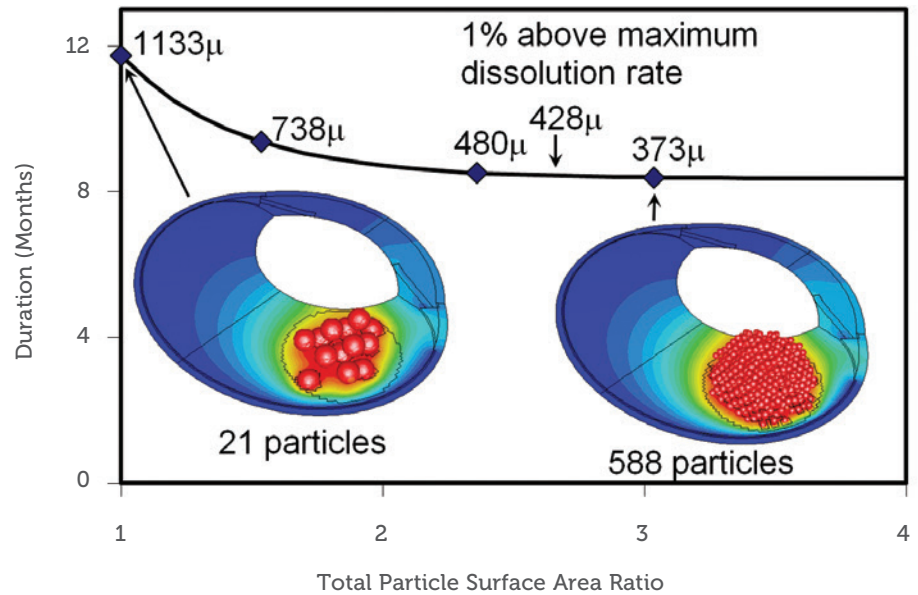


Figure 5: Influence of particle size on duration of suspensions of 16 mg TAC confined to a 100 μ L spherical vitreous depot. The units of the horizontal axis denote the ratio in total particle surface area compared to the model suspension with the largest particle size simulated. The insets show model suspensions dividing the drug into either 21 (left) or 588 (right) equally sized spherical particles. The colour spectrum denotes drug concentration, red corresponding to the solubility limit and blue corresponding to zero drug concentration. Duration becomes quite insensitive to particle size when the size falls below 428 μ m in diameter. This simulation used an earlier rendition of the rabbit eye geometry in which the lens was represented by an appropriately shaped void.²

retina/choroid respectively; this partitioning is apparent in the figure contours. The strength of the choroidal drug sink was adjusted to match drug clearance rate after

intravitreal injection of a dilute AAc solution. This sink localises delivery to a region immediately beneath the tablet.

Juxtasclear devices containing AAc

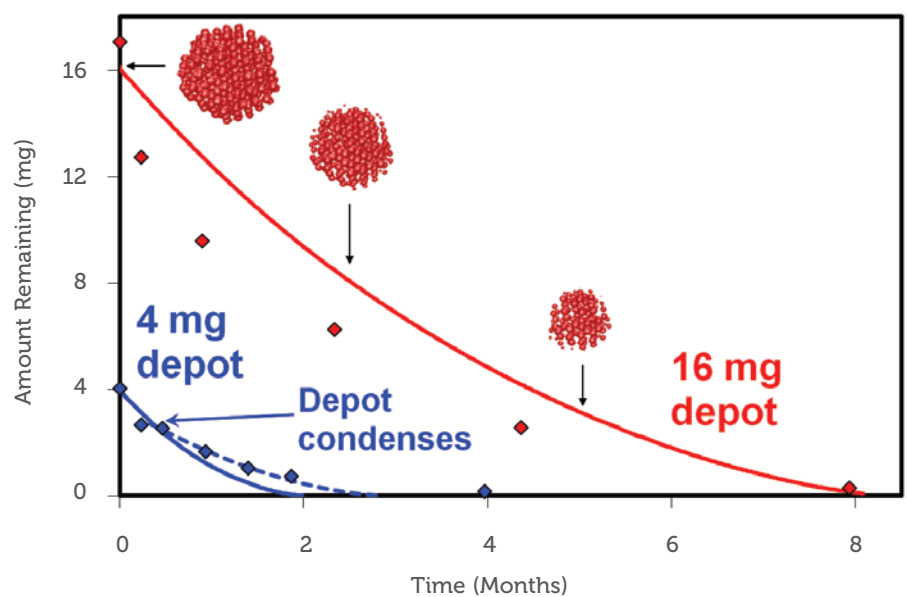


Figure 6: Dissolution versus time profiles for 4 mg and 16 mg TAC confined to a 100 μ L spherical vitreous depot compared with experimental data from Kim 2006 (diamonds).⁵ Curves represent simulation predictions in the limit of infinitesimally small particles. The appearance of the 276-particle suspension model at various times is shown in the insets. The dashed curve for 4 mg restarts the simulation by distributing 2.7 mg of drug in a 25 μ L depot on day 10 to approximate the influence of depot condensation observed *in vivo*.²

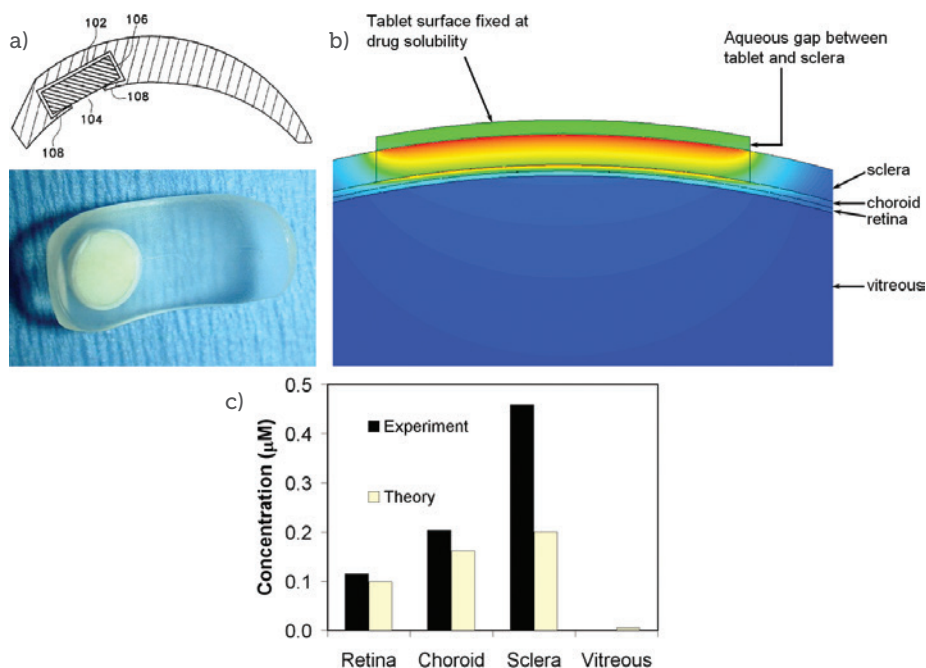


Figure 7: a) Upper panel: Schematic for juxtасlеral device 10: 102 – cavity; 106 – drug source; 104 – exposed opening; 108 – circumferential rim to retain the drug source. Lower panel: photo of prototype device. b) Simulated steady-state drug concentration in ocular tissue resulting from delivery of AAC from the device. c) Comparison between experimental and simulated average concentrations in the measured tissues at the one year following implantation of juxtасlеral devices containing AAC in rabbits.^{7,11}

implanted in rabbits maintained constant ocular tissue drug levels for two years. Figure 7c shows average drug levels in retina, choroid and sclera in a 10 mm circular dissection beneath the depot one year after insertion. Since the device provides for unidirectional release of drug towards the ocular interior, and shields from non-productive loss behind the eye, the payload duration is extended. The simulated tissue concentration is ranked Sclera > Choroid > Retina >> Vitreous. Using no additional adjustable parameters, simulations predict the appropriate rank order and come close to the values measured in the retina and choroid. The values for sclera match less well, but less is known about the exterior scleral sinks.

CONCLUSION

The examples described in this article illustrate some of the capabilities of computational fluid dynamics to model ocular drug delivery. Its application is limited, however, by the accuracy and completeness of the ocular anatomy and by the particular features of ocular physiology incorporated into the model. For example, the lack of external anterior ocular anatomical features limits the ability to apply the current model to topical delivery.

The number of publications utilising methods similar to what is described here are increasing. Many additional aspects have been explored, such as the effects of age and disease on liquefaction of the vitreous, eye movements, and variability in permeability of the outer tissue layers. Simulations may also provide insights into the effect of various disease states on drug delivery. Such work needs to be guided and qualified by appropriate preclinical and clinical observations to maximise the insights provided.

The design of ophthalmic drug delivery therapies can be improved as the fluidic and vascular clearance barriers are better understood through careful *in vivo* experiments illuminated through simulation.

ACKNOWLEDGEMENT

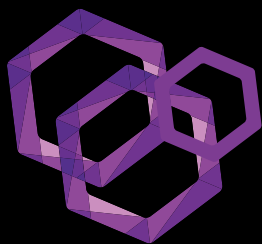
The authors would like to thank Lasya Reddy of ANSYS, Inc, for her assistance creating some of the images for this article.

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PSIVIDA AND OPHTHALMIC DRUG DELIVERY

Here, Paul Ashton, PhD, President & Chief Executive Officer, pSivida, describes how much of the progress that has been made recently in the treatment of ophthalmic diseases can be ascribed to effective drug delivery systems, and outlines some of the delivery technologies and resulting products for which pSivida has been responsible. pSivida's new platform technology, Tethadur, for the sustained, long-term delivery of biologics in the eye, is also described.

The ophthalmic pharmaceutical market has been expanding at a truly remarkable pace with the potential for even faster growth in the next decade. This expansion has been driven by the development of innovative, effective therapeutics for common devastating diseases. Many of these diseases such as diabetic macular edema (DME) and wet age-related macular degeneration (AMD) once blinded hundreds of thousands of people but now treatments are available, slowing or

required to overcome this barrier increase adverse side effects. The back of the eye where the retina is located is even more challenging for drug delivery, because it is inaccessible to eye drops used to treat front-of-the-eye diseases. Intraocular injections are now generally used to deliver therapeutics to the back of the eye but the repeated injections required (sometimes as frequently as every month) can have adverse consequences, most commonly intraocular

infection. Further, both systemic dosing and intraocular injections face challenges in sustaining the appropriate concentrations of drug in the eye.

There are currently only two approved drug delivery systems capable of delivering drug to the eye on a sustained basis – pSivida's three Durasert™-based products and Allergan's Ozurdex®. Fortunately, more products designed to address the challenges and opportunities of retinal drug delivery are now under development.

halting the progression of the diseases. Other serious conditions such as dry AMD and retinitis pigmentosa (RP) remain the subjects of intensive research, and optimism is high that effective treatments for these conditions will soon be developed.

This torrent of good news (and good products) reflects increased understanding of the biological processes underlying these diseases and, increasingly, growing awareness of the importance of effective drug delivery.

The eye has traditionally been an extremely difficult target for drug delivery as the efficacy of the blood-eye barrier limits the therapeutic effectiveness of systemic drug delivery, particularly as the dosages

pSivida is seeking to develop a series of new sustained release ophthalmic products based on its proprietary Durasert and Tethadur™ platform technology systems. These systems are designed to provide controlled release for periods of months to years for small drug molecules and biologics to treat eye disease.

pSivida's Durasert technology can be used to deliver different drugs for periods of months to years with a single application. The first generation of this technology is Vitrasert®, which delivers ganciclovir to treat CMV retinitis for over six

"This torrent of good news (and good products) reflects increased understanding of the biological processes underlying these diseases and, increasingly, growing awareness of the importance of effective drug delivery"



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Figure 1: Iluvien[®], pSivida's most recently approved iteration of Durasert technology.

months. Approved almost 20 years ago, this implant was partnered with Bausch + Lomb and was the first drug approved for retinal disease. pSivida developed a second generation of Durasert technology for Retisert[®], the first therapeutic approved for the treatment of posterior uveitis (partnered with Bausch + Lomb and approved in 2005). This product, also an implant, delivers the corticosteroid fluocinolone acetonide (FA) and extended the duration of delivery to 30 months.

pSivida's most recently approved iteration of Durasert technology is Iluvien[®] (Figure 1), partnered with Alimera Sciences and approved in the US in 2014 following EU approval in 2012. This product is injectable and delivers FA for three years. Iluvien was the fourth sustained delivery product approved by the US FDA for back-of-the-eye disease. The third was Allergan's Ozurdex[®] (dexamethasone in a PLGA matrix), approved in 2009.

Successive generations of Durasert products have lengthened the sustained release of the drugs they deliver and simplified the delivery of drugs to the back of the eye. With a single application, Vitrasert is effective for five to eight months, Retisert for 30 months and Iluvien for three years. While pSivida's first two products, Vitrasert and Retisert, are implanted into the eye in a surgical procedure, both Iluvien and Allergan's Ozurdex are injected in an office visit. Ozurdex is bioerodible, releasing more than 90% of its drug in the first month, but the pharmacodynamics effect is longer, up to six months in some cases.

pSivida is developing Durasert-based devices that provide long-term sustained release from a bioerodible system as, one would assume, are Allergan and others.

Durasert and Ozurdex technologies will not be capable of delivering all ophthalmic therapeutics for all applications. For example, sustained release of water-soluble drugs will likely be difficult from matrices like



Figure 2: In diseases such as glaucoma that require daily self-administration of eye drops effective therapy can be limited by poor patient compliance.

Ozurdex, although this is not an issue for Durasert. More important, neither system is well suited for the delivery of biologics, such as proteins and antibodies. Treatment of retinal disease with biologics such as Eylea[®], Lucentis[®] and Avastin[®] and delivery of biologics to the back of the eye is increasingly important in ophthalmology.

pSivida's Tethadur, a new platform technology, is designed to provide long-term sustained ophthalmic delivery of biologics. Tethadur is a suspension of micronised particles of oxidised meso-porous silicon with a therapeutic drug or biologic, which is injected into the eye. The material slowly dissolves to form silicic acid and is thus slightly acidic, providing an electrostatic attraction with

therapeutics. Loading the therapeutics into the pores prevents them from aggregating prior to delivery. Furthermore, the attraction between the therapeutic and the pore is a function of the proximity of the pore walls to the therapeutic. This allows the size of the pores to control the release rate. The tighter the fit, the more slowly the therapeutic is released. Using this technology, pSivida has developed systems designed to provide sustained delivery of biologics and drugs for months.

In ophthalmology, there are many potential applications for longer-term sustained release. In traditionally well-managed diseases such as glaucoma that require daily self-administration of eye drops (Figure 2), effective therapy can be limited by poor patient compliance. In more recently treatable disease such as wet AMD, current therapy necessitates regular, as frequently as monthly, injections into the eye. These injections have potential risks such as infection and also present patient compliance issues, but the alternative currently is rapid loss of vision. A sustained-release system for the biologics that treat wet AMD and other retinal diseases should be a significant advance for patients and physicians alike.

“pSivida's Tethadur, a new platform technology, is designed to provide long-term sustained ophthalmic delivery of biologics”

proteins such as Eylea and Lucentis (which have an isoelectric point of over 8). As the material dissolves, the drug or biologic is absorbed into the eye on a sustained basis.

The surface area of Tethadur is extremely large (>200 m²/g) so the material has a high binding capacity (typically over 10% wt/wt). Further, the diameter of the pores of Tethadur can be manufactured to sizes ranging from 2 to 30 nm to accommodate differently sized

For some presently untreatable diseases, such as dry AMD, which results in a slow loss of vision, the slow progression of the disease makes sustained-release treatment even more desirable.

New therapies are expected to transform treatment of retinal disease in the coming years. Effective sustained release delivery will be key to the success and efficacy of these therapies.

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Unique Drug And Oxygen Delivery Systems



AN INTEGRATED PIPELINE OF OPHTHALMIC PRODUCTS BASED ON EYESOL™ DELIVERY TECHNOLOGY

In this piece, Dieter Scherer, PhD, Chief Scientific Officer, Novaliq, describes two of the company's most advanced products. NovaTears® OTC is ready to be marketed as a wetting agent for the ocular surface and for stabilisation of the tear film for the relief of dry-eye and irritated-eye symptoms, and CyclASol®, a clear formulation of Cyclosporin A, which has completed a Phase I clinical trial. Both products use Novaliq's semifluorinated alkane technology, EyeSol®.

Novaliq GmbH, based in Heidelberg, Germany, is a drug delivery company developing a superior generation of ocular formulations for poorly soluble drugs. These patented ocular formulations are based on semifluorinated alkanes (SFAs), which can be easily applied in the form of eye drops or as an eye spray.

Since its establishment in 2007, Novaliq has obtained five rounds of funding totaling US\$42.2 million (£28 million) from its major shareholder, Dievini Hopp Biotech Holding, a venture capital company focusing on biopharmaceutical companies in Europe.

BUSINESS STRATEGY

Novaliq's strategy is to establish a portfolio of consumer and prescription products in the field of ophthalmic diseases including evaporative dry-eye disease. These multi-dose products are intended to cover unmet medical needs with one major advantage of being preservative free.

MECHANISMS OF ACTION & TECHNOLOGY

Novaliq's technology platform is based on highly purified SFAs. These biocompatible liquids can dissolve poorly soluble drugs and have excellent wetting properties.

Their amphiphilic profile makes SFAs ideal for the production of purely physical active drug solutions or homogenous suspensions for ocular applications.

PRODUCT PIPELINE

Novaliq GmbH currently has several product candidates with excellent market potential in various stages of development (see Figure 1).

THE TECHNOLOGY

EyeSol® is Novaliq's proprietary ophthalmic drug delivery technology based on SFAs. For the treatment of complicated retinal detachment, these compounds have been used in patients intra-ocularly as temporary endotamponades for more than 10 years. They are well tolerated and have an excellent safety profile. SFAs are chemically and biologically inert and thus do not cause ocular tissue irritation.

PHYSICAL PROPERTIES

Their extraordinary spreading properties support the drug distribution on the corneal surface. In addition, their low viscosity and low surface tension result in much smaller droplet size compared with water leading to improved administration, superior kinetics and reduction of systemic side effects.

Due to their amphiphilic nature, SFAs can dissolve poorly water soluble compounds or create stable ophthalmic suspensions. As a non-aqueous system, they do not require preservatives and support the long term stability of the formulation.



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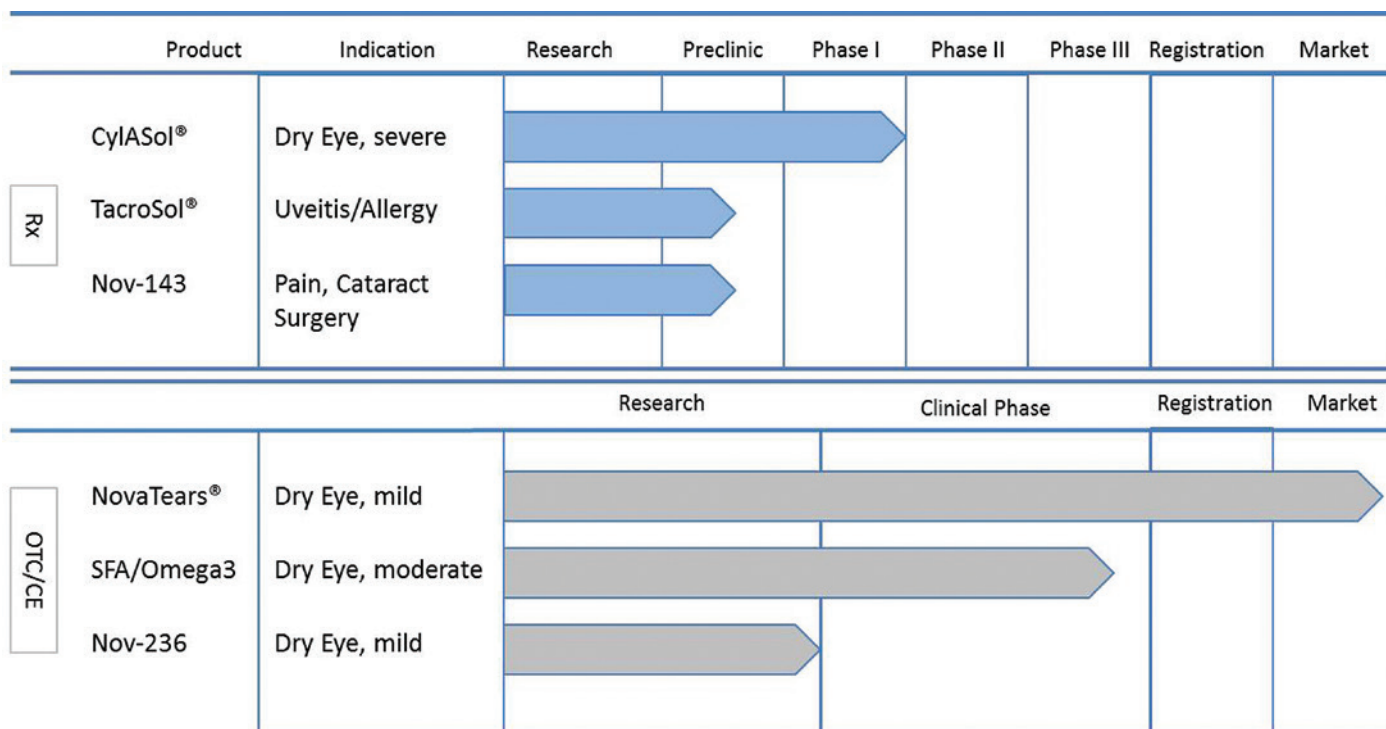


Figure 1: Novaliq’s Pipeline of Prescription Only and Over-the-Counter Products.

NOVATEARS®

NovaTears® OTC, the first product based on Novaliq’s proprietary EyeSol® Technology, is an innovative multi-dose, non-aqueous, non-blurring and preservative-free topical eye drop formulation for lubrication of the ocular surface. It is intended for use as a wetting agent for the ocular surface and for stabilisation of the tear film for the relief of dry-eye and irritated-eye symptoms. Due to its significantly reduced surface and interface tension NovaTears® has a superior wettability compared with all other available eye drop technologies. NovaTears® has been classified as a class IIa medical device and received CE mark approval in Europe in July 2013.

NOVATEARS® POSITIVE CLINICAL RESULTS

In an observational clinical study, NovaTears® OTC eye drops showed

excellent clinical performance and safety in patients with hyperevaporative dry-eye disease. The study (NT-001), which placed NovaTears® OTC eye drops in 30 patients with symptoms of mild-to-moderate evaporative dry-eye disease, was successfully completed in July 2014 and demonstrated efficacy and safety in relief of dry-eye symptoms.

The primary objective of the open, prospective, uncontrolled post-market clinical follow-up study (treatment survey) was to confirm whether NovaTears® was able to lubricate the ocular surface

tolerability and safety of NovaTears® was assessed when used in accordance with its approved labelling.

Tear film stability improved over the study period (measured using industry-standard Schirmer I and TFBUT tests), tear osmolarity remained unchanged and assessment by a subjective dry-eye questionnaire revealed that patient symptom severity decreased after use of NovaTears® over a 5-7 week period.

Corneal staining (measured using the Oxford Grading Scheme) indicated less corneal damage after treatment, as demon-

“These biocompatible liquids can dissolve poorly soluble drugs and have excellent wetting properties”

successfully, stabilise the eye’s tear film, and relieve adverse symptoms associated with dry-eye disease. Additionally, local

strated by patient shift towards Grade 0 at follow-up. No changes were observed in either visual acuity or intraocular pressure,



IN WHICH EDITION COULD YOUR COMPANY APPEAR?

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indicating that use of NovaTears® eye drops is safe.

Novaliq is currently preparing NovaTears® for market entry in several geographic regions with dedicated ophthalmic partners. (NovaTears® is not approved for marketing or distribution in the US.)

CYCLASOL®

Based on Novaliq's proprietary Eyesol® technology, CyclASol® is the only Cyclosporin A ophthalmic solution.

pharmaceutically relevant APIs. In July 2014, Phase I clinical study was successfully completed.

CYCLASOL® CYS-001 CLINICAL STUDY SUMMARY

CYS-001, a two-arm, double-blind, randomised, placebo-controlled, cross-over Phase I study investigated the safety, local tolerability and systemic exposure of Cyclosporin A compared with a placebo (perfluorobutylpentane) following single

particular no dryness, grittiness, burning, stinging, tiredness, blurred or foggy vision, redness, watery eyes, eye mucus or crusting. In slit-lamp examinations, no subjects revealed any clinically abnormal signs of the anterior and posterior eye structures. With dosing of up to four drops per eye per day, no systemic levels of Cyclosporin A were detected after any dose or at any time point when using a highly sensitive assay with a LLOQ as low as 0.1 ng/ml. Novaliq has a granted patent position in most relevant markets. (CyclASol® is not approved for marketing or distribution in the US.)

CyclASol® is the first clear Cyclosporin A solution in clinical trials to treat dry-eye syndrome. Whilst conventional Cyclosporin A formulations are emulsions, CyclASol® is the first and only 0.05% clear Cyclosporin A solution based on Novaliq's proprietary Eyesol® platform technology.

- CyclASol® eye drops are safe and well-tolerated
- No burning or other adverse effects
- Available in preservative-free multi-dose bottles
- Excellent spreading and wettability
- Superior biocompatibility
- Proven long-term stability
- Broad patent protection.

“Based on Novaliq's proprietary Eyesol® technology, CyclASol® is the only Cyclosporin A ophthalmic solution”

CyclASol® is developed as a clear solution in multi-dose, preservative free bottles for patients with dry-eye syndrome and has demonstrated long term stability plus pre-clinical data indicating superior wettability, pharmacokinetics and biocompatibility compared with conventional emulsions.

CyclASol® is the second Novaliq product with positive data in humans, for the first time addressing poorly soluble

and multiple ocular doses of CyclASol and Placebo solution in healthy volunteers.

Objectives of the 18-patient trial were to investigate safety, local tolerability and systemic exposure of CyclASol® (Cyclosporin A solution) eye-drops and vehicle following single and multiple ocular doses in healthy volunteers. No drug-related signs or symptoms of ocular discomfort or irritation were reported; in



NovaTears®

Lubricant Eye Drops

The first Preservative-Free and non aqueous eye drops for the relief of evaporative Dry Eye Symptoms

Unique and superior properties of NovaTears®

- Non Aqueous
- Preservative-Free
- No Blurring
- Superior Wetting
- Excellent Safety and Efficacy Profile^{1,2,3,4,5}

The Company

Novaliq GmbH, based in Heidelberg (Germany), is a drug delivery company which is developing a superior generation of ocular formulations for poorly soluble drugs. These patented ocular formulations are based on semifluorinated alkanes (SFAs), which can be easily applied in the form of eye drops or as an eye spray. Since its establishment in 2007, Novaliq has obtained five rounds of funding totaling 42.2 million US\$ from its major shareholder, Dievini Hopp Biotech Holding, a venture capital company focusing on biopharmaceutical companies in Europe.

1) Observational Study NT-001
2) Semifluorinated alkanes as a liquid drug carrier system for topical ocular drug delivery Dutescu RM, Panfil C, Merkel OM, Schrage N. Eur J Pharm Biopharm. 2014 May 15.
3) EyeSol: a Novel Topical Ocular Drug Delivery System for Poorly Soluble Drugs Scherer D, Pettigrew A, Alvarez-Gonzales E. Drug Delivery Tech. Issue 2013 Jan
4) Use of perfluorohexyloctane as a long-term internal tamponade agent in complicated retinal detachment surgery.
5) Meinert H, Roy T. Semifluorinated alkanes—a new class of compounds with outstanding properties for use in Ophthalmology. Eur J Ophthalmol. 2000;10(5):189-197

Not FDA Approved or For Sale in the USA



Unique Drug And Oxygen Delivery Systems

NOVALIQ

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COMPANY PROFILE: GRAYBUG



GRAYBUG OVERVIEW

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

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

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

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

VALUE PROPOSITION

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

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

PROOF-OF-CONCEPT

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

Our world-class team and advisors have over 100 peer-reviewed publications on the long-term, controlled delivery of biologics.

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

Figure 1: Development pipeline showing milestone achievements.

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



Michael O'Rourke
President & CEO
Former GM, VP Global Strategy
Bausch + Lomb, Chiron Vision,
Alza, Pfizer, and 3M



Justin Hanes, PhD
Founder & CSO
Lewis J. Ort Professor of Ophthalmology
& Biomedical Engineering, Director of the
Center for Nanomedicine at the Wilmer Eye
Institute, Johns Hopkins School of Medicine

GRAYBUG'S TECHNOLOGY

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

Pipeline products include GB-102, which is a single drug agent that inhibits multiple pathogenic angiogenesis signals, and innovative glaucoma therapies GB-201-204 for the controlled-release of intraocular pressure-lowering drugs and for long-term protection of the optic nerves to prevent blindness.

SUMMARY

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

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

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

ABOUT GRAYBUG

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

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

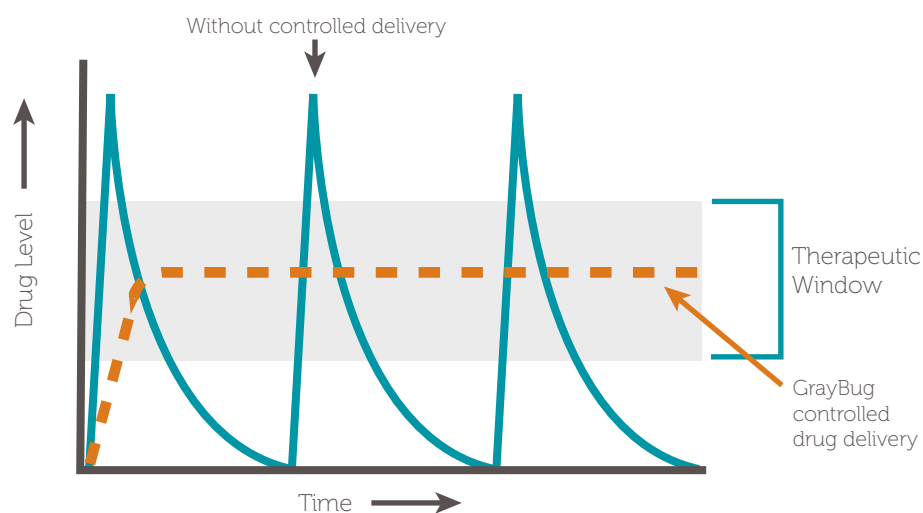


Figure 2: GrayBug controlled-release drug delivery.



Peter Campochiaro, MD

Founder

George S and Dolores Doré Eccles Professor of Ophthalmology & Neuroscience, Wilmer Eye Institute, Johns Hopkins School of Medicine



Peter McDonnell, MD

Founder

William Holland Wilmer Professor and Chair of Ophthalmology, Director of the Wilmer Eye Institute, Johns Hopkins School of Medicine

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SUSTAINED DRUG DELIVERY TO THE POSTERIOR SEGMENTS OF THE EYE

In this article, Shikha Barman, PhD, Chief Executive Officer & Chief Technology Officer, Integral BioSystems, reviews approaches for delivering drugs for diseases of the back of the eye, and introduces EySite-InjecT™, a biodegradable, precisely tunable sustained-release delivery system which can be administered to suprachoroidal, intravitreal, subconjunctival sites by injections through a 31G needle.

DELIVERY TO TREAT DISEASES OF THE POSTERIOR SEGMENT

Diseases that occur in the back-of-eye that, potentially, can result in serious visual impairment and blindness include age-related macular degeneration (AMD), macular edema, uveitis, choroidal neovascularisation (CNV), retinitis pigmentosa, and cytomegalovirus retinitis (CMV).

Among these, AMD is a leading cause

“EySite-InjecT encapsulates are designed to be non-aggregating and maintain shape due to a proprietary treatment prior to injection”

of blindness among the elderly. In the US, more than eight million people suffer from this disease; this number is projected to increase many-fold by 2020.¹ AMD can be of the dry and wet form and is a consequence of excessive aging associated with alterations in the retinal pigment epithelium (RPE). In wet AMD, CNV occurs with fluid build-up in the sub-retinal space. The dry form of AMD is associated with drusen formation and RPE atrophy.² Diabetic Retinopathy often leads to neovascularisation and macular edema and is the third leading cause of blindness in the US. Macular edema is the swelling of the macula and occurs in approximately 10% of all diabetics.³ Endophthalmitis is another cause of blindness. It is characterised by infection of the interior ocular space by micro-

organisms, due to post-operative infections. These include gram positive bacteria such as *Staphylococcus aureus* and *streptococci*.^{4,5}

The clinical and experimental drugs for the posterior segment treatments include both small and large molecules (such as siRNA, antibodies, growth factors, DNA), but delivering these molecules to the target sites is problematic. When administered topically, drug concentrations in the retina and choroid are many-fold lower than the tear fluid. Drug delivery to the posterior segment of the eye is most efficiently achieved by local, ocular routes of administration, which includes intravitreal, subretinal, suprachoroidal and periocular injections.^{6,7}

Intravitreal injections and implants deliver drugs effectively to the retina and the choroid.

For example, intravitreal injections of therapeutics are routinely used in the treatment of wet AMD (Lucentis™, Macugen, Vitravene™), macular inflammation (Triesence™), etc.⁸ This mode of administration while efficacious is highly invasive; considerable risks exist to developing infections (endophthalmitis) and retinal detachment with repeated injections over a person's lifetime. However, high concentrations of drug can be achieved with intravitreal injections with sustained presence due to the relative lack of fluid flow in the vitreous humour. Triamcinolone acetonide is the most commonly used steroid treatment for AMD and vitreoretinal disorders. To achieve a dose for prolonged duration and to minimise repeated injections, triamcinolone acetonide suspension must be injected at high concentrations. Due to the presence of high



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concentrations of drug in the vitreous, lateral drug diffusion into the aqueous humour leads to significant adverse events such as cataract formation, glaucoma induced by increased intra-ocular pressure and blurred vision due to blocking of the visual field.

In contrast, the periocular route is less invasive than intravitreal administration and it provides higher retinal and vitreal drug concentrations than eye-drops. Periocular delivery of therapies can be accomplished through injections or implantation of the drug to the sub-conjunctival, sub-tenon, or parabulbar space. However, the drug must penetrate through several barriers: sclera, choroid and RPE. Relatively high permeability of sclera to macromolecules has resulted in renewed interest in this route.

Macromolecules such as anti-angiogenic antibodies, oligonucleotides, trans-gene expression products and growth factors are proving to have immense therapeutic value in the treatment of back-of-the-eye diseases. Scleral permeability is dependent upon the molecular radius as opposed to the innate lipophilicity of the drug; macromolecules up to 70,000 Da can readily penetrate the sclera.^{7,9}

However, one technical challenge with delivery via the periocular route is the enhanced clearance of drugs due to fluid flow in these vascularised tissues. When injected into periocular tissues, both small molecules (ophthalmic steroids) and macromolecules (proteins) have been determined to be rapidly eliminated into conjunctival lymphatics and episcleral veins. On a positive note, though, long-term trans-scleral delivery can be obtained by utilising drug-containing microspheres; retention of microspheres has been demonstrated at the site for approximately two months.⁹

SUSTAINED RELEASE PRODUCTS: APPROVED AND IN-CLINIC

Ocular implants have been the principle platform for the sustained release of therapeutics, either from biodegradable or non-degradable matrices. Non-biodegradable implants can provide more accurate control of drug release and longer release periods than the biodegradable polymers do, but require surgical implant removal with its associated risks.¹

The polymers commonly used for non-biodegradable implants are polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA) and silicone, whereas for biodegradable implants, a variety of polymers can be used (PLA, PGA,

PLGA, polycaprolactones, polyanhydrides and polyorthoesters). The erosion rate and spontaneous degradation of these polymers can be modulated to allow for the desired intraocular kinetics of drug release to take place. Moreover, biodegradable polymers can be used to form solid or injectable viscous/semi-solid implants in various shapes, which do not require their removal.

Vitrasert® and Retisert® (Bausch + Lomb, US) are clinically used non-biodegradable implants. Vitrasert® was the first implantable ganciclovir delivery device, approved by the US FDA in 1996 for the treatment of cytomegalovirus (CMV) retinitis for up to eight months, and is the primary line of care of patients with CMV. However, occasional endophthalmitis and an increased rate of retinal detachments have been associated with this implant. Retisert® contains fluocinolone acetonide; this product is utilised in the treatment of chronic non-infectious posterior uveitis. However, Retisert has been shown to increase intraocular pressure and cataract progression. Both of these indications could benefit from a re-formulation of the drug into precise micro-delivered matrices delivered into periocular space. Illuvien™ (Phase III trials) is a rod-shaped implant containing fluocinolone acetonide. The product releases the drug for up to three years. Another product, I-vation™ (releasing triamcinolone acetonide for two years) is in Phase I clinical trials to treat diabetic edema.

Recently, a biodegradable intravitreal implant, Ozurdex™ has been approved for the treatment of macular edema secondary to retinal vein occlusion and for non-infectious uveitis. This implant is comprised of PLGA and releases incorporated dexamethasone over 4-6 weeks.

EYSITE-INJECT™: INJECTABLE, BIODEGRADABLE, PRECISELY MODULATED, NANO-ENGINEERED DRUG DELIVERY

EySite-InjecT™ encapsulates have been developed by Integral BioSystems as a platform drug delivery system for all therapies that can benefit from sustained-release treatment.

The delivery system has been engineered specifically for injection into target ocular tissues and spaces, including suprachoroidal, intravitreal, subconjunctival sites. The delivery system, optimised for the specific drug molecule, has certain cassette-like features that include proprietary compositions,

“Key considerations in developing an appropriate therapy for a posterior eye condition are: the disease being treated (acute, or chronic); and drug properties”

process engineering methods, surface treatments and vehicle traits that allow injection through a 31G needle and long-term, precise and predictable release of drug in the ocular space. The system utilises only excipients that are present in approved parenteral injectable drug products.

The process has been successfully enabled for the fabrication of EySite-InjecT™ encapsulates for water-soluble, small-molecular-weight and higher-molecular-weight peptides, oligonucleotides, DNA, proteins, ophthalmic steroids, antifungals, antibacterials and NSAIDs. Critical process parameters for larger scale production of EySite-InjecT have been developed for an ophthalmic steroidal drug and a water-soluble peptide.

HIGH LOADING

The process to fabricate EySite-InjecT™ encapsulates has been optimised to have high drug content within the matrices. A maximum volume of 50 µL can be injected into the vitreous humour or suprachoroidal space safely. Thus, the entire dose needs to be contained in that volume. This requires the drug to be potent, and the delivery system to be injected at a high concentration. For EySite encapsulates containing an ophthalmic steroid can be injected at a concentration of 400-500 mg matrix/mL, with 90% drug encapsulation achieved per gram of matrix, allowing release of 1-6 µg of steroid per day, for 180 days *in vitro* (USP4 *in vitro* release model).

SUSTAINED RELEASE, PREDICTABLE RELEASE

One of the issues of sustained release from standard PLGA microspheres is erratic release of the drug *in vivo* due to instant aggregation and eventual coagulation post-injection and the failure to maintain shape. Furthermore, drug release

profiles from PLG matrices are sigmoidal with low concentrations of drug released initially, followed by large “bursts” as the matrix starts to degrade. Proprietary EySite-InjecT PLG encapsulates have near-constant release for the entire duration. Unpredictable release can result in sub-therapeutic drug levels, or dose dumping. EySite-InjecT™ encapsulates are designed to be non-aggregating and maintain shape due to a proprietary treatment prior to injection.

INJECTABILITY, DISPERSABILITY, BIODEGRADABILITY

For achieving a target release of an ophthalmic steroid for six months *in vivo*, relatively large PLGA microspheres or implants are required – neither mode of administration is injectable through 31G needles. EySite InjecT encapsulates are injectable through a 31G needle in any ocular space (suprachoroidal, intravitreal, periocular). Steroid-containing EySite-InjecT™ encapsulates have been engineered to bioabsorb in generally an equivalent time frame for 100% drug release.

The feasibility of long-term release of an ophthalmic steroid from biodegradable EySite-InjecT™ formulations, tested *in vitro* at 37°C, pH 7.4 is shown in Figure 1. The release profiles demonstrate modulation of release rates to meet target specifications.

Figure 2 demonstrates release modulation of a highly water-soluble peptide from EySite-InjecT™ encapsulates, tested *in vitro*,

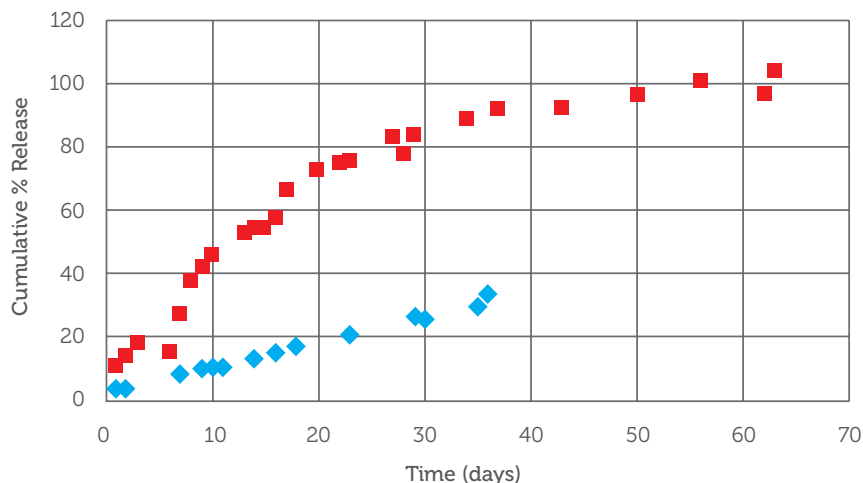


Figure 1: In vitro release of an ophthalmic anti-inflammatory steroid from two different formulations of injectable (31G), biodegradable encapsulates (EySite-InjecT™). (In vitro release conditions: phosphate buffered saline + 0.1% Tween 20, 37°C.)

at 37°C, pH 7.4. The data demonstrates that the internal microstructure of encapsulates influence the release rate of a drug.

While this can be utilised as a handle to control release, achievement of reproducible internal structure is no small feat. The proprietary process to fabricate EySite-InjecT™ encapsulates produces reproducible microstructure.

Studies are underway to further test and characterise these products.

THE BIG PICTURE

A balanced, realistic and strategic approach must be adopted by clinicians to achieve therapeutic concentrations of drug at the target site, considerations that must

depend upon the acuteness of the disease and the need for repeated injections.

For example, an acute and severe infection in the posterior chamber may require treatment via direct injection into the vitreous to enable efficient eradication of the infection by achieving high drug concentrations at the target site. Acute inflammatory reactions should likely be treated in a similar manner, to enable a rapid and efficient effect. However, therapy of chronic conditions like diabetic edema and AMD should be addressed via injections to periocular tissue spaces such as the choroid, sub-tenon, parabolbar, sclera, etc, and a strategy for disease management developed. For example, an intravitreal injection of the drug every six months may be considered minimally invasive and feasible, if such sustained-release options exist and have been validated. Likewise, treatment of retinoblastoma should likely be addressed by direct intravitreal injection, as opposed to risking rapid drug clearance rates seen in barrier-compromised cancer patients.

On the other hand, continuous presence of an anti-inflammatory drug at high concentrations in the vitreous can induce glaucoma and cataract formation; treatment of inflammation for a chronic condition is best approached via suprachoroidal delivery. Thus, key considerations in developing an appropriate therapy for a posterior eye condition are: (a) the disease being treated (acute, or chronic) and (b) drug properties. Highly water-soluble small-molecule-therapeutics such as peptides are extremely difficult to encapsulate with high loading in biodegradable polymer matrices, due to process challenges.

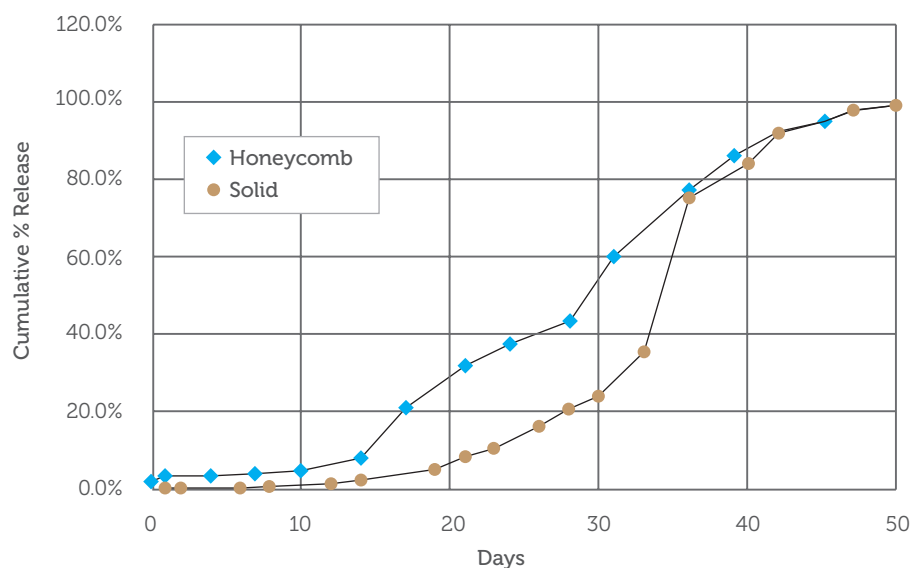


Figure 2: In vitro release of a highly water soluble peptide from two different formulations of injectable (31G), biodegradable micro-encapsulates (EySite-InjecT™). (In vitro release conditions: phosphate buffered saline + 0.1% Tween 20, 37°C.)

Additionally, a highly water soluble compound has limited extraction into lipophilic ocular tissues; thus, clearance rates are typically much higher for these molecules than lipophilic molecules. A highly water-soluble small-molecule drug for a retinal disorder may be best suited for intravitreal injections to achieve sustained levels at the target site. In contrast, highly lipophilic molecules such as triamcinolone acetonide and dexamethasone can be successfully delivered to the suprachoroidal space to treat inflammation in the vitreous. Mechanical microneedle-based devices can be utilised to deliver to the suprachoroidal space.

In envisioning drug delivery systems, matching the biodegradability of the matrix to the drug release profile is relevant; the matrix should be cleared from the site to ensure that components from the matrix do not cause adverse effects of local toxicity. The ideal target profile of an injectable, sustained release product for the treatment of posterior chamber diseases is: (a) injectable via a 27-31G needle, (b) precise, predictable drug release and (c) bioabsorbable and biocompatible.

ABOUT INTEGRAL BIOSYSTEMS

Integral BioSystems specialises in biodegradable, sustained-release dosage forms for proteins, peptides, nucleic acids and small molecules. Additionally, Integral BioSystems has assisted companies with formulation development of topical ophthalmic drug products.

Microspheres, liposomes, micro-nano suspensions are Integral's niche specialisation. Integral BioSystems invites collaborations that can be strictly on a CRO-basis to create drug products with compounds that already have IP protection, or as a co-developer with pharmaceutical companies to render repurposed drugs IP-protectable with Integral's proprietary drug delivery innovations. Integral scientists have developed a proprietary ocular delivery system (EySite™) that releases precise, predictable concentrations of drug over time. The composition of the EySite delivery system can be modulated for a drug regimen that lasts a week, to one that can be designed to last 3-6 months. The company invites collaborations with drug companies to co-develop ophthalmic products utilising these delivery modalities.

As a CRO, Integral BioSystems offers formulation development, process engi-

neering, scale-up, technical transfer and CMC writing services for US FDA submissions.

Integral BioSystems, LLC, is based in the Boston area, with offices and fully equipped laboratories at Bedford, MA, US.

ABOUT THE AUTHOR

Named as one of "20 Women to Watch in Massachusetts High Technology in 2014", Shikha P Barman, PhD, has over 20 years of experience in the translation

"EySite Inject™ encapsulates are injectable through a 31G needle in any ocular space (suprachoroidal, intravitreal, periocular)"

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of concepts from the lab into clinical and commercial drug products. She is a founding member of Integral BioSystems, LLC, a CRO/innovation-based company.

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, 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, 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, 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. She has a PhD in Polymer Science and in 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.

EXCIPIENT SELECTION FOR OPHTHALMIC OINTMENTS

In this piece, Janice Cacace, PhD, Director of Formulation, and Travis Webb, MsPharm, Senior Research Formulation Associate, both of CoreRx, describe the physical properties of petrolatums as they relate to the comfort and efficacy of formulations of ophthalmic ointments.

One would think that, in the 21st century, dosage forms would be more advanced and that the ophthalmic ointment would have gone by the wayside. Anyone who has had to use one knows that they are “gooey and sticky”, leave a film, and often “glue” your eyelids together. And based on recent US FDA product approvals they do not appear to be very prevalent (<https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/13/>

“What can be done to optimise the elegance of a petrolatum based ointment?”

ophthalmology). However, the ophthalmic ointment still plays an important part in the ophthalmic market overall as there are at least a dozen products on the market in the US (<https://masshealthdruglist.ehs.state.ma.us/MHDL/pubtheradetail.do?id=34>), primarily for antibiotic and anti-inflammatory products.

The base for an ophthalmic ointment is primarily petrolatum. This is what gives them that characteristic “gooey, sticky” feeling. But this is also what gives them desirable properties for some ophthalmic applications. Their advantages include:

- Pseudoplastic – solid state behaviour at low shear increases stability and prevents phase separation and settling of suspended particles
- Thixotropic – excellent for retaining drug in suspension, and yet capable of spreading in the eye. As shear force is applied (when blinking) the product becomes more fluid and retains fluidity, which helps coat the eye
- Non-Aqueous – spreads and softens but won't be flushed out of the eye with tears. Ensures it gets delivered and stays where you want it. Doesn't get “rinsed away” like aqueous solutions

- Non-aqueous and non-hygroscopic – eliminates issues with hydrolysis as compared to aqueous solutions, and protects active components from hydrolytic degradation
- Insoluble – May limit the treatment to local delivery with very little systemic absorption. The latter can be important for minimising side effects.

So, in certain instances, such as with drugs that are susceptible to hydrolysis, the petrolatum-based ointment is ideal. And also for indications where prolonged contact with the infected area in the eye is important, they are ideal.

Petrolatums for pharmaceutical products are classified as Petrolatum USP and White Petrolatum USP. For ophthalmic products, the white petrolatums are preferred. However, even within white petrolatums, there are differences, they vary in:

- Colour and clarity
- Consistency
- Flow
- Yield Stress.

So what can be done to optimise the elegance of a petrolatum based ointment?

As can be seen in Figure 1, White Petrolatum can differ in colour and clarity. The petrolatum on the left is the clearest and most “white” as

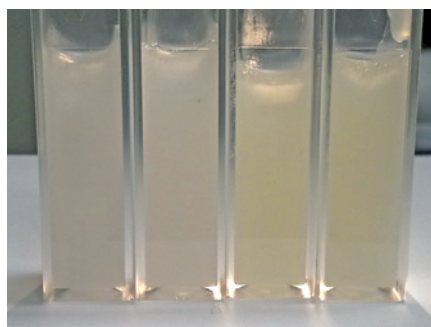


Figure 1: Colour and Clarity of four petrolatums.



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compared with the other three petrolatums, with the sample on the right having a distinct yellow hue. Any of these can be used but the most “white” may provide more elegance from an appearance perspective.

The last three properties – consistency, flow and yield stress, are related to product rheology. These properties can be used to assess effects of formulation variables in order to attain the desired physical properties or benchmark a product for comparison with another product. These can be assessed using a rheological model such as the Power Law (or Ostwald) Model. This will fit a typical viscosity *versus* shear rate, or shear stress *versus* shear rate curve within the range of about one to a few hundred reciprocal seconds.

| Petrolatum | Yield Stress, Pa | Flow Index | Consistency Index |
|------------|------------------|------------|-------------------|
| A | 30 | 0.30 | 25318 |
| B | 60 | 0.22 | 59244 |
| C | 36 | 0.34 | 36050 |
| D | 22 | 0.54 | 22111 |

Table 1: Flow Index and Consistency Index for four different petrolatums.

The Power Law model takes the form of:

$$\tau = Ky^n$$

Where: shear stress (τ) is the cross-sectional stress experienced by the material and is expressed in Pascals (Pa); consistency index (k), is simply the viscosity (or stress) at a shear rate of reciprocal second. and describes, in a sense, how thick (viscous) a material is at low shear; and shear Rate (y), is the rate at which a progressive shearing deformation is applied to some material expressed in reciprocal seconds (1/s).

These values can be used to obtain yield stress, which is the amount of force that must be applied to induce plastic deformation; and the viscosity, which describes a material’s resistance to flow. All of these values can then be used to evaluate the physical characteristics and

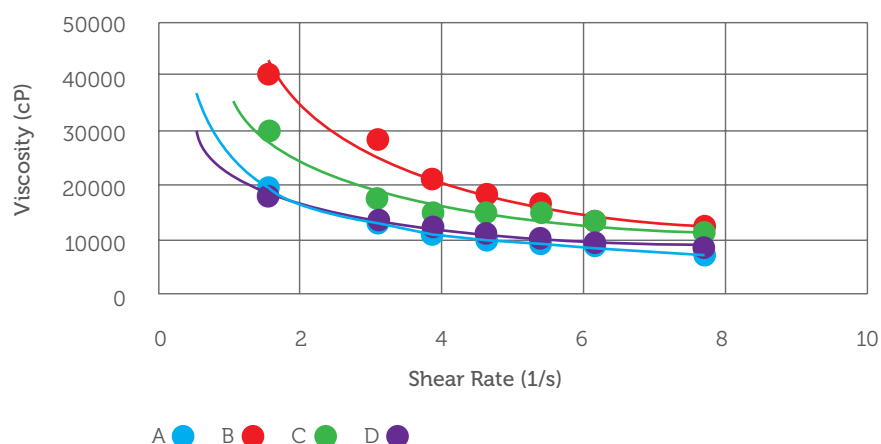


Figure 2: Graph showing Shear Rate against Viscosity for four different petrolatums.

flow behaviour of a product.

They can also be used to calculate flow index (n). This is a measure of non-Newtonian-ness, in essence, the magnitude of shear thinning or shear thickening.

For a Newtonian fluid Flow Index = 1; for a shear-thinning fluid it is between 0 and 1 and for a shear thickening fluid it is greater than 1.

In Table 1, the Flow Index, or shear thinning index, indicates how smoothly the ointment will flow as shear is applied. Materials with a high degree of shear thinning tend to feel softer and spread more smoothly. As can be seen in the table, all of the petrolatums tested had a Flow Index between 0 and 1, and therefore are shear-thinning. Petrolatum D has the lowest consistency index but it also has the highest Flow Index, and thus is the least shear thinning of the four materials so it tends to have much more of a waxy feel than petrolatums A or B. However, the higher consistency index of petrolatums A and B may lead to difficulty in dosing smaller quantities and feel more “goopy” in the eye. These can be important factors in dose effectiveness as well as patient compliance.

Another important factor to consider when choosing which type of petrolatum to use is the formulation composition. Additional excipients such as mineral oil, surfactants, and preservatives can lower the apparent viscosity and yield stress relative to their concentration in the formulation.

“Additional excipients such as mineral oil, surfactants, and preservatives can lower the apparent viscosity and yield stress”

thinning. By plotting the natural log of the shear rate and shear stress according to the Power Law model we can obtain the Flow index and approximate yield stress of each material. Figure 2 and Table 1 show the comparison of the shear thinning behaviour and viscosity at low shear rates.

This is an important factor for the formulator when deciding which type of petrolatum to use. An ointment with a high yield stress and viscosity might feel very thick and sticky in the eye. However, if these parameters are too low the medication will not be retained and the effectiveness of delivery will suffer.

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