Integral BioSystems

# OCULAR DRUG DELIVERY: REVIEW OF PRESENT TECHNOLOGIES & STEPS FORWARD

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

## OPHTHALMIC DRUG PRODUCTS MARKET: CLINICAL AND BUSINESS NEED-DRIVEN

Market research estimates performed in the last six months have shown that the market size for ophthalmic medications is expected to reach more than 16 billion, by the year 2018.[1] The ophthalmology drugs market classification is based on the type of drugs: treatment-based drugs, over-the-counter (OTC) drugs and ocular anaesthetics.

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

Combined with these clinical need-driven innovations are a plethora of technologies that are business-driven, aimed at product extensions for life-cycle management of existing products. Each of these extensions offers improvements and benefits over current technologies, such as offering preservative-free options, or "non-settling" formulations, amongst others. From a regulatory perspective, in the US, the number of 505(b)(2) applications claiming differentiated technologies has risen dramatically, with fewer NDA (505(b)(1) applications for new chemical entities (NCEs) than there were in previous years.

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

## ANTERIOR SEGMENT & CHALLENGES TO DELIVERY

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

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disorders of the cornea include episcleritis, uveitis and keratitis.

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

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

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

Another critical obstacle to efficient drug absorption is the corneal and conjunctival barriers. Drugs with log P in the range 2-3 are ideal for absorption through the corneal and conjunctival membranes. Molecules with a low partition coefficient do not penetrate the lipophilic epithelia of the cornea and the conjunctiva. Molecules with a log P value >3.5 do not permeate the hydrophilic stromal layer of the cornea.[3]

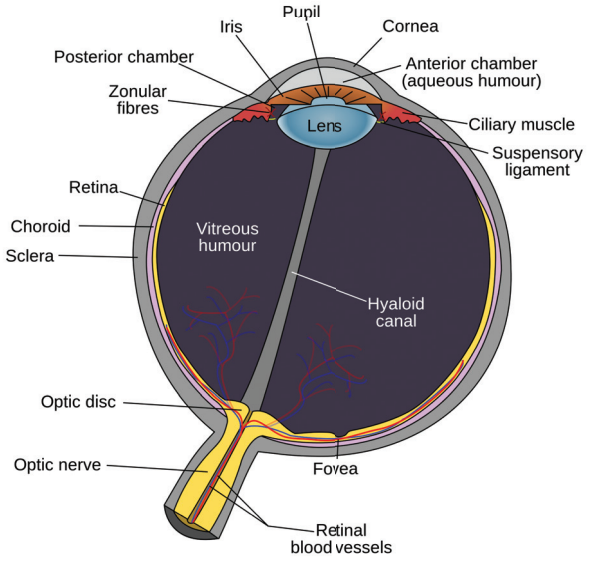


**Figure 1: Simplified schematic of the human eye.**
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However, improvements have been made to render drugs efficient, effective and with fewer side-effects. In fact, the ophthalmic drug industry has witnessed a flood of improved medications with higher drug residence times, higher permeability and lower effective doses. To give just one example, Xibrom, the twice-daily formulation of bromfenac has now been discontinued in favour of the improved version, Prolensa, which is only needed once-daily. Combination products of drugs that have been marketed as separate dosage forms are often now prescribed together to treat inflammation and infections, providing higher probability of patient compliance. For example, Zylet is a combination of loteprednol + tobramycin, which in one product does the job of Lotemax ointment (loteprednol alone) and Tobramycin ointment). However, CMC issues in ensuring stability of co-existing drugs in the same dosage form and regulatory hurdles toward achieving FDA approval can slow down the drug development process.

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

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

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

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

## POSTERIOR SEGMENT: CHALLENGES TO DELIVERY

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

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

disease that causes a progressive loss of central vision. AMD is the most common cause of vision loss in individuals aged over 55. An estimated 10 million people in the US either have AMD or are at substantial risk of developing it. There are two types of AMD, wet AMD and dry AMD. West AMD accounts for about 10% of all cases of macular degeneration. Wet AMD is also called choroidal neovascularisation (CNV), subretinal neovascularisation, or exudative or disciform degeneration. In wet AMD, abnormal blood vessels grow beneath the macula. These vessels leak blood and fluid into the macula that damage photoreceptor cells. Wet AMD often progresses rapidly and can cause substantial loss of central vision. Dry AMD is presented in 90% of the cases with AMD, affects vision less, is non-exudative and characterised by drusen, or fat cells or waste products from cells.

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

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

Innovations with needle technology have provided options for delivering precise microlitre volumes into the vitreous or choroidal space. Companies in this space include: Unilife; iScience Interventional (acquired by Ellex Medical Lasers in January 2014); and Clearside BioMedical. Other innovative methods for delivery include: iontophoresis (e.g. EyeGate II from EyeGate Pharmaceuticals); free-floating intravitreal implants (e.g. Allergan's OzurDex and pSivida's Iluvian); scleral-implanted intravitreal devices (e.g. Retisert also from pSivida); and biodegradable formulations (e.g. Icon Bioscience's Verisome).

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

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

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

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

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

## CONCLUSION

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

## ABOUT INTEGRAL BIOSYSTEMS

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

## PROPRIETARY OCULAR DELIVERY SYSTEMS

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

develop ophthalmic products utilising these delivery systems.

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

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

## ABOUT THE AUTHOR

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

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