Integral BioSystems

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

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

GLOBAL OPHTHALMIC MARKET

Globally, the ophthalmic drugs market is witnessing significant growth due to increasing prevalence of ophthalmic disorders, both for the anterior and posterior segments of the eye. As a result, this market is expected to grow at a compound annual growth rate (CAGR) of about 5.2% during 2013-2018.[1] Accordingly, the ophthalmic drug industry has witnessed a plethora of technologies that are business driven and aimed at product extensions for lifecycle management of existing products. Each of these extensions offers improvements and benefits over current technologies, such as offering preservative-free options, or "non-settling formulations," amongst others. From a regulatory perspective, in the US, the number of 505(b)(2) applications claiming differentiated technologies has risen dramatically, with fewer NDA 505(b)(1) applications for new chemical entities (NCEs) than there were in previous years.

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

THE 505(B)(2) STRATEGY

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

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

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

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KEY STRATEGY FOR GENERICS

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

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

NANOSTRUCTURED EYE-DROP WITH HIGH OCULAR PERMEABILITY

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

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

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

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

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

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

Integral BioSystems is developing a series of ophthalmic products with the OcuSurf

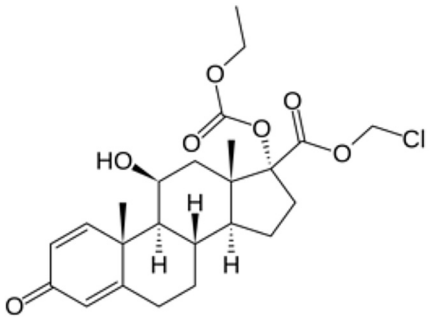

Figure 1: Chemical structure of loteprednol etabonate (OcuSurf-LP).

platform, employing a 505(b)(2) strategy on the reformulation of existing products.

In particular, a loteprednol etabonate topical product (OcuSurf-LP) (Figure 1) for the prevention of inflammation post cataract surgery is underway. An elegant structural design improvement, loteprednol etabonate is a novel carbon 20 (C-20) ester-based corticosteroid [6] that has been developed as a topical treatment for ocular inflammation. Loteprednol etabonate was developed using retro-metabolic design, in which an inactive and nontoxic metabolite of a reference compound is used as the starting point for the synthesis of a therapeutically active, but metabolically unstable, compound that can

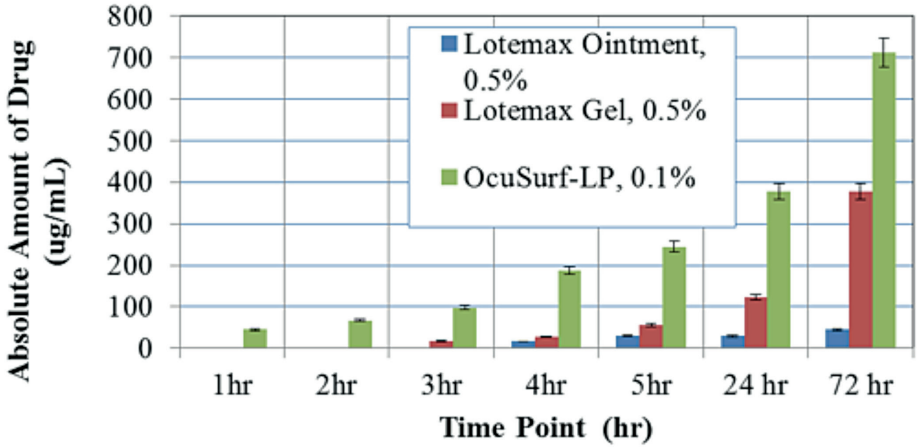

Figure 2: High permeability of loteprednol etabonate formulated in OcuSurf nanodispersion.

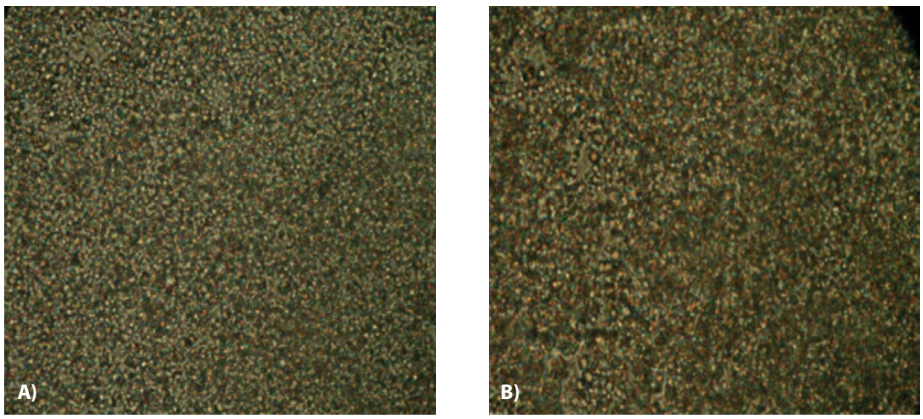

Figure 3: Optical microscopy of OcuSurf formulations using an Olympus BX51P, using an oil immersion objective at 1100X; A= OcuSurf-LP (LP=loteprednol etabonate); B=OcuSurf-DX (DX=dexamethasone).

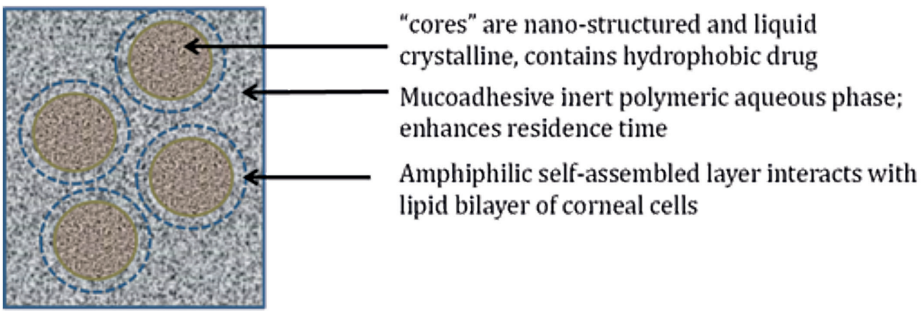

Figure 4: OcuSurf™ nanostructured dispersion.

be rapidly deactivated. In the case of loteprednol etabonate, the drug is rapidly deactivated to inactive metabolites by nonspecific tissue esterases in the ocular tissue, thereby limiting its potential to cause adverse effects such as ocular hypertension and glaucoma, side effects commonly known to occur with steroids. Products containing loteprednol etabonate (LoteMax™ Ointment, 0.5%, LoteMax™ Gel, 0.5%) have been FDA approved, with high patient acceptance. Both product formulations contain micronised drug. OcuSurf™-LP is non-settling, membrane-adherent, stable for room temperature storage and demonstrates high bioavailability.

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

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

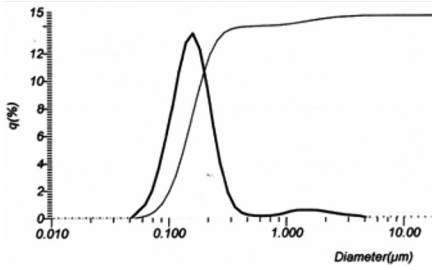

Figure 5: OcuSurf-LP particle size distribution measured by laser light diffraction.

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

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

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

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

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

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

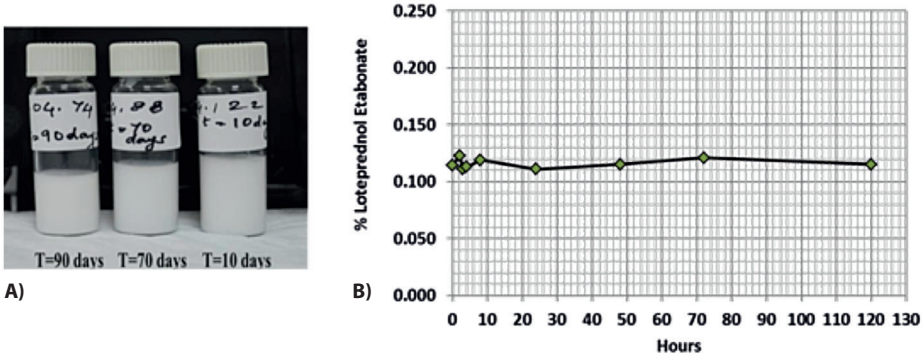

Figure 7: (A) Vials were stored at room temperature and visually assessed periodically. (B) Settling kinetics was assessed by measurement of drug concentrations over 120 hours at room temperature.

ABOUT THE AUTHOR

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

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

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

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

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ABOUT INTEGRAL BIOSYSTEMS

Integral BioSystems specialises in biodegradable sustained-release dosage forms for proteins, peptides, nucleic acids and small molecules. Microspheres, liposomes, and micro-nano suspensions are Integral's niche specialisation.

Integral BioSystems invites collaborations that can be strictly on a CRO-basis to create drug products with compounds that already have IP protection, or as a co-developer with pharmaceutical companies to render repurposed drugs IP-protectable with Integral's proprietary drug delivery innovations.

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

The company also announces OcuSurf™, a proprietary nanostructured delivery system designed to deliver drugs to the ocular surface, enhancing permeation into ocular tissues. The company invites collaborations with drug companies to co-develop ophthalmic products utilising these delivery modalities.

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