CURRENT AND FUTURE OPHTHALMIC FORMULATION AND PROCESS DEVELOPMENT TRENDS

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

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

Uveitis can ultimately lead to conditions and disease states such as cataracts, glaucoma and retinal edema. At the time of development, the Retisert platform offered a great technological advancement over contemporary therapies which included injectable technologies with extreme side effects.

The dosage form included micro-tablet technology (tablets were 1.5 mm wide and a few mg in weight), encapsulated by a silicon layer covered with a water soluble polymer, designed to deliver the corticosteroid for approximately 30 months to the posterior segment of the eye.

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

Working on this development platform with the group of scientists at Bausch + Lomb made me realise that as a whole the ophthalmic industry had not yet evolved. Early Retisert prototypes lacked sophistication as far as both the formulation matrix itself and the crude methods with which we had to manufacture the product at the time. Analytical testing of prototypes also presented unique challenges such as in vitro release testing of the product using novel dissolution systems. Other challenges included uniform coating of the polymeric system onto the micro-tablets, and incorporation of the micro-tablets into the silicon tubing. The process was hardly automated and presented troublesome processing and validation issues from a manufacturing standpoint.

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

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

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

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

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

PROCESS DEVELOPMENT & MANUFACTURING

From the process development and manufacturing side of ophthalmic development, many companies which develop and manufacture sterile products are using disposable process technologies which incorporate single-use components. This is often useful for compounds with special handling considerations. In these cases, traditional manufacturing vessels and components utilising stainless steel are replaced by polymeric materials which must be sterilised using commonplace sterilisation techniques.

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

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

The vendor will need to offer validation packages for the product and insight into the materials the systems are made from. Generally these types of disposable systems might be gamma irradiated for sterilisation purposes so the components of the systems would need to be immune to changes in their physical properties after irradiation. When CoreRx purchased the LevTech mixer the company supplied a great amount of compatibility data, however, many of the drug molecules utilised in ophthalmic systems will need compatibility studies performed with the bag structure, bag neck and mixing wand of the bag system. Evaluation of these components will be critical to any successful study. The CoreRx scientific team recently performed detailed compatibility studies for one particular dosage form with the active ingredient, excipient technology and bag components of the LevTech mixer. In this case the active ingredient and formulation matrix were fully compatible with the bag and mixer components.

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

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

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

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

FORMULATIONS & DELIVERY

As with any industry, as ophthalmic drug developers move into the future it will be a necessity to incorporate innovative formulation and process techniques in an effort to develop efficacious products leading to profitable markets.

Formulation matrices using cutting-edge excipient technologies and delivery systems yielding fewer side effects should be future goals of drug development platforms. At Bausch + Lomb we saw the side effects of repeated injections of corticosteroids for delivery to the rear of the eye, including extreme increase in intra-ocular pressure and ultimately development of cataracts. We saw how new delivery systems and technologies could negate these side effects when dosing the same drug molecule via a different platform. Development of novel dosage forms for delivery to the posterior segment of the eye will be critical in coming years with the current escalation of type 2 diabetes in the US.

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

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

ABOUT THE AUTHOR:

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