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.

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.
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 formulations 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 nanosuspensions 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 antibacterial 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 sterisation purposes so the components of the systems would need to be immune to changes in their physical properties after irradiation.

“New delivery systems and technologies could negate these side effects when dosing the same drug molecule via a different platform.”

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.

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 tradi-
tional 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 formu-
lation 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 plat-
form. Development of novel dosage forms for
delivery to the posterior segment of the eye
will be critical in coming years with the cur-
rent escalation of type 2 diabetes in the US.

Macular swelling, inducing blurred vision and ultimately loss of visual acuity
may be attributed to diabetic retinopathy.
Corticosteroids are often used as a treat-
ment option for this condition leading
to the previously mentioned side effects.
Thus, it will be up to pharmaceutical sci-
entists 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
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Bausch + Lomb and MDS Pharma Services
prior to joining CoreRx in 2006. In his
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uid oral, ophthalmic, parenteral, semi-sol-
ids and topicals (creams, gels, ointments,
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![DIABETES SUMMIT](image)

The Diabetes Summit has evolved to be the go-to conference to learn about the latest research & partnership opportunities. The program brings together over 150 experts and includes plenty networking opportunities with academia, venture capital, government, small/medium size biotech, big pharma and healthcare organizations. **There is nothing quite like the Diabetes Summit - the combination of research and partnering makes attending worthwhile!**

**Past Attendee Demographics**

<table>
<thead>
<tr>
<th>By Title:</th>
<th>By Industry:</th>
</tr>
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<tbody>
<tr>
<td>25% Director &amp; Head</td>
<td>45% Biotech</td>
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<tr>
<td>20% President &amp; C-Level</td>
<td>20% Big Pharma</td>
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<tr>
<td>15% VP Level</td>
<td>20% University</td>
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<tr>
<td>15% Researcher/Scientist</td>
<td>5% Research Hospital/Institute</td>
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<tr>
<td>15% Professor &amp; Postdocs</td>
<td>5% Non-Profit/Government</td>
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<tr>
<td>5% Consultant/VC</td>
<td>5% Consulting/VC Group</td>
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<td>5% Other</td>
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