



APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER

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DRUG DELIVERY EVENTS

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- + **3rd European Workshop on Protein Aggregation and Immunogenicity (KN 6661)** [Details](#)
January 30-31, 2017, Innsbruck, AT
- 8th Global DDF Summit - Drug Delivery & Formulation** [Details](#)
March 27-29, 2017, Berlin, DE
- 2nd European Conference on Pharmaceutics - Novel dosage forms, innovative technologies** [Details](#)
April 03-04, 2017, Krakow, PL

[Suggest a meeting to be announced!](#)

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosenmayr-Templeton

VIEKIRA® XR

Viekira XR from Abbvie was approved by the FDA in July 2016 [1]. This dosage form is a film-coated bilayer tablet with one immediate release and one sustained release layer. In total it contains 4 different active moieties:

- Dasabuvir, a non-nucleoside inhibitor of the hepatitis C virus (HCV) NS5B palm polymerase. This enzyme is critical to virus replication.
- Ombitasvir, an inhibitor of HCV NS5A protein which is involved in viral RNA replication and modulation of the host cell physiology [2].
- Paritaprevir is a HCV NS3/4A protease inhibitor. It is essential for the proteolytic cleavage of the HCV encoded poly-protein into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins.
- Ritonavir, an HIV protease inhibitor, whose role in this formulation is to inhibit the CYP3A breakdown of paritaprevir and enable increased plasma concentrations of the NS3/4A protease inhibitor. It has no activity against HCV but is an HIV protease inhibitor approved for the treatment of HIV infection

Viekira XR is indicated for chronic Hepatitis C infection of genotype 1a and 1b with or without compensated liver cirrhosis. For treatment of genotype 1a or mixed infections Viekira XR is co-administered with ribavirin. It is not suitable for patients with advanced liver cirrhosis. The product is a co-formulation of the components of the previously approved Viekira Pak which contained ombitasvir, paritaprevir, and ritonavir tablets and dasabuvir tablets. The dose is three tablets taken once daily for 12 weeks with each tablet containing 200 mg dasabuvir (in the form of 216.2 mg of dasabuvir sodium monohydrate), 8.33 mg ombitasvir (on an anhydrous basis), 50 mg paritaprevir (on an anhydrous basis), and 33.33 mg ritonavir. In the case of patients infected with HCV genotype 1a and diagnosed with compensated cirrhosis treatment with Viekira XR plus ribavirin can be extended to 24 weeks.

VIEKIRA XR must be taken with a meal because of significantly reduced bioavailability under fasting conditions due to the poor aqueous solubility of its active constituents. In pharmacokinetic studies it was found that the increase in

bioavailability following a high fat meal was approximately two-fold for ombitasvir and ritonavir, 4.5 fold for paritaprevir and 6 fold for dasabuvir compared with that achieved under fasting conditions. The reduction in bioavailability if Viekira XR is taken on an empty stomach could result in a reduction in efficacy and potentially development of resistance to the medication. In addition, release of dasabuvir is influenced by alcohol and therefore alcohol should not be consumed within 4 hours of taking Viekira XR.

The ER layer contains 216.2 mg of dasabuvir sodium monohydrate plus copovidone, K value 28, hypromellose 2208, 17,700 (mPa*s), colloidal silicon dioxide and magnesium stearate. The IR layer contains 8.33 mg ombitasvir, 50 mg paritaprevir and 33.33 mg ritonavir plus copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate, sorbitan monolaurate, colloidal silicon dioxide. The pale yellow tablets are coated with a hypromellose-based film coat.

Approval was based on the results of seven Phase II clinical trials in which 1076 subjects received the recommended dose of the components of Viekira with/without ribovarin for 12 weeks, or for 24 weeks in patients with compensated cirrhosis. The components of Viekira were administered twice daily with a meal. Three months after the treatment ended 95 to 100 % of those treated had non-detectable levels of HCV in their blood [1,3].

The co-formulated tablet with its once daily dosing will help Viekira compete with the Gilead's Sovaldi® (sofosbuvir) and Harvoni® (ledipasvir and sofosbuvir), which are also dosed once daily, in the lucrative US market which accounts for over 40% of the estimated global market for Hepatitis C treatment of \$11.52 billion [4].

XELJANZ® XR

In July 2016 the FDA approved Xeljanz XR, an oral sustained release formulation of tofacitinib [5]. Tofacitinib is a Janus kinase inhibitor marketed by Pfizer for the treatment of moderate to severe active rheumatoid arthritis in patients who have had an inadequate response or intolerance to methotrexate. Tofacitinib may be prescribed as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs. The formulation, which contains 11 mg tofacitinib as the citrate salt, enables once daily dosing of this drug which was first approved in the US in 2012 as an immediate release tablet for twice daily administration.

Xeljanz XR is a pink, oval, extended release film-coated tablet with a drilled hole at one end of the tablet band indicating that release from the dosage form is controlled by an osmotic pump mechanism. In addition to 17.77 mg tofacitinib citrate salt the tablets also contain sorbitol, hydroxyethyl cellulose, copovidone, magnesium stearate, cellulose acetate, hydroxypropyl cellulose, HPMC 2910/Hypromellose, titanium dioxide, triacetin, and red iron oxide.

Approval was based on a study showing Xeljanz XR 11 mg once daily to be bioequivalent to Xeljanz 5 mg administered twice daily. The absolute oral bioavailability of Xeljanz is 74% and both immediate and sustained release products can be administered with or without food [5].

The approval of Xeljanz XR will help bolster sales of tofacitinib in the US which got off to a slow start due to concerns about its safety and help protect it against future generic competition. The global sales of the immediate release product climbed 72% to a high of \$523 million in 2015 [6].

Both Xeljanz and Xeljanz XR are not approved within the European Union. In 2013 the European Medicines agency refused to give Xeljanz a product license based on the safety profile of tofacitinib whose immuno-suppressant activity can lead to patients suffering serious infections and its association with other major adverse events such as gastrointestinal perforations. A re-submission to the EMA earlier this year did not reverse the earlier decision that the benefits of therapy did not outweigh the risks [7].

References and Further Information

- [1] Entry for Viekira XR on Drugs@FDA <http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208624> (Accessed 6.11.2016)
- [2] Pawlotsky J-M (2013) NS5A inhibitors in the treatment of hepatitis C. *Journal of Hepatology* Vol. 59 j 375–382
- [3] AbbVie Receives U.S. FDA Approval of Once-Daily VIEKIRA XR™ (dasabuvir, ombitasvir, paritaprevir and ritonavir) for the Treatment of Genotype 1 Chronic Hepatitis C. <https://news.abbvie.com/news/abbvie-receives-us-fda-approval-once-daily-viekira-xr-dasabuvir-ombitasvir-paritaprevir-and-ritonavir-for-treatment-genotype-1-chronic-hepatitis-c.htm> (Accessed 6.11.2016)
- [4] Global Hepatitis C Drug Market Poised to Surge from USD 11.81 Billion in 2015 to USD 27.63 Billion by 2021 – MarketResearchStore.Com. <https://globenewswire.com/news-release/2016/07/20/857331/0/en/Global-Hepatitis-C-Drug-Market-Poised-to-Surge-from-USD-11-81-Billion-in-2015-to-USD-27-63-Billion-by-2021-MarketResearchStore-Com.html> (Accessed on 6.11.2016)
- [5] Entry for Xeljanz XR on Drugs@FDA http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208246s000lbl.pdf (Accessed on 6.11.2016).

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[7] Xeljanz http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002542/human_med_001662.jsp&mid=WC0b01ac058001d124 (Accessed 6.11.2016).

DRUG DELIVERY TECHNOLOGIES

Provided by Dr. Kaspar van den Dries

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IONIC LIQUID TECHNOLOGY (Capsugel, Belgium)

Capsugel and Monash University announced in January 2015 that Capsugel has acquired the intellectual property pertaining to proprietary Ionic Liquids Technology developed at the Monash Institute of Pharmaceutical Sciences (MIPS), Monash University. This novel technology uses lipid-like counter-ion salts to improve the solubility of drugs in lipid-based liquid, semi-solid and multiparticulate formulations. One of the challenges with lipidic formulations is that poor aqueous solubility not necessarily means that the solubility in lipid excipients is sufficient to obtain sufficient drug loading to formulate an enabling formulation in lipids. By employing the concepts of lipidic salts drug loading of and above 150-200 mg/g in solution could be achieved.

Fact sheet:

Founded:	2015
Location:	Capsugel, Belgium
Ownership:	Capsugel
Employees:	Unknown
Key technology:	Ionic liquid technology
Products:	No products have been marketed, but proof of principle has been established for molecules like Cinnarizine and Itraconazole
Development status:	Proof of concept/principle
Partnerships:	Monash Institute of Pharmaceutical Sciences, Monash University
Website:	www.capsugel.com
Contact:	CAPSUGEL BORNEM Rijksweg 11 B-2880 Bornem, Belgium Telephone: +32 (0) 3-890-05-11 Fax: +32 (0) 3-889-26-22

DRUG DELIVERY PEOPLE

Provided by Dr. Lea Ann Dailey

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DAVID BRAYDEN, BSc, MSc, PhD, is Professor of Advanced Drug Delivery at the School of Veterinary Medicine and a Fellow of the University College Dublin Conway Institute. Following a Ph.D. in Pharmacology at the University of Cambridge, UK (1989), and a post-doctoral research fellowship at Stanford University, CA (1991), he set up Elan Corporation's pharmacology laboratory in Dublin (1991). At Elan Biotechnology Research, he became a senior scientist and project manager of several of Elan's Joint-Venture drug delivery research collaborations with US biotech companies. He joined University College Dublin as a lecturer in veterinary pharmacology in 2001 and was appointed Full Professor in 2014.

His main research interests include improving peptide delivery across intestinal epithelia using in vitro and in vivo bioassays, developing nanoparticle constructs for oral peptides, conducting high content toxicology assays in cells exposed to nanoparticles, biomaterials and polymers, designing polymeric peptide conjugates for long-acting injectables, investigating nanoparticle transport across Peyer's patch M cells for oral vaccines, understanding the interaction of human and veterinary drugs with efflux transporters, and developing nanoparticle formulations for intra-articular injection for osteoarthritis.

In addition to his research interests, Professor Brayden is the current Deputy Coordinator of an EU 7th Framework grant on oral nanomedicines (www.TRANS-INT.eu), 2012-2017. He is a Co-lead Principle Investigator on the new Science Foundation Ireland CURAM Centre for Medical Devices (www.curamdevices.ie) and has authored more than 200 research



publications and patents. He serves on the Editorial Advisory Boards of Drug Discovery Today, European Journal of Pharmaceutical Sciences, Advanced Drug Delivery Reviews, the Journal of Veterinary Pharmacology and Therapeutics, and Therapeutic Delivery. Professor Brayden also works as an independent consultant for drug delivery companies. In 2012, he was the first Irish academic to be inducted into the College of Fellows of the Controlled Release Society.

OCULAR DRUG DELIVERY – STATE-OF-THE-ART AND NEW CONCEPTS

By Lutz Franzen and Florian Unger; Formulation Development, Bayer Pharma AG

1. General Overview

On 20th and 21st of June 2016 the *International Association for Pharmaceutical Technology* (APV) hosted a “high-toned seminar” on ocular drug delivery. At the venue in Berlin an audience from academic and industrial research listened to a comprehensive mix of overview talks and case studies. In the following article we give a brief introduction to the topic of ocular drug delivery and summarize the key findings presented at the seminar.

Arto Ursti from *Helsinki University* opened with an introductory talk on “*Ocular anatomy, physiology, pharmacokinetics & pK modeling*”. Pascal Furrer from the *University of Geneva* followed with a comprehensive overview on ocular dosage forms and the accompanying regulatory requirements.

From a drug delivery perspective the eye can be separated in two parts, the anterior and the posterior segment. The anterior segment includes the cornea, aqueous humor, iris, lens and the conjunctival tissue. The posterior segment is comprised of the vitreous humor surrounded by the choroid, the retina including the macular and adjoining vasculature. In order to account for the anatomical differences a distinction between treatments of diseases in the anterior and posterior segment has to be made.

Drugs can be delivered to most parts of the anterior segment through topical application of eye drops, gels or inserts. For diseases of the posterior segment, intra-ocular or systemic administration is necessary. Figure 1 depicts the basic anatomy of the human eye and illustrates the various barriers relevant for ocular drug delivery.

After topical application a substance has to overcome the corneal barrier to penetrate into the anterior chamber. In the precorneal area a high elimination rate by tear flow, blinking and a significant loss to the systemic circulation limits the residence time of applied drugs. The most common formulations for topical drug delivery are eyedrops. As aqueous solutions, emulsions or suspension eyedrops have to fulfill strict requirements for osmotic pressure and pH-values.

A three compartment model of the pharmacokinetics after topical instillation of eye drops was presented by A. Ursti. It involves the tear fluid as donor compartment after drug application. Drainage, tear turnover and systemic absorption compete with the aqueous humor as the acceptor compartment. The cornea acts as a penetration barrier to limit perfusion. This model illustrates the significant loss of topical applied drugs and the low availability in the target tissue [1].

Ocular ointments and crèmes can help to increase residence time and contact area on the cornea. Hydrogels composed of carbomer or hyaluronic acid are, due to their bioadhesive properties, among the most commonly used semisolid formulations. Recently, *in situ* activated gels were introduced to overcome the drawback of difficult instillation of viscous gels and crèmes. *In situ* activated systems thicken under certain conditions like changes in temperature or pH. This method combines the easy administration of fluids with the delayed elimination of viscous gels. P. Furrer presented Timoptic XE® as an example of *in situ* gelling. Timoptic XE® contains gellan gum, which thickens in presence of double charged cations like Mg²⁺ or Ca²⁺, both present in tear fluid.

In order to further increase the residence time of the drug on the precorneal site, drug delivery systems with prolonged release were developed e.g. ocular inserts. The solid or semisolid formulations shaped like rods or shields are designed to be inserted in the conjunctival sac. The biodegradable or non-biodegradable inserts provide accurate dosing by controlled long term release and reduced systemic absorption. On the downside ocular inserts are costly and provoke low patient compliance as a result of complicated insertion, foreign body sensation and with a constant risk of loss of the insert. Further advances in topical ophthalmic drug delivery might involve the use of permeation enhancers and produgs [2].

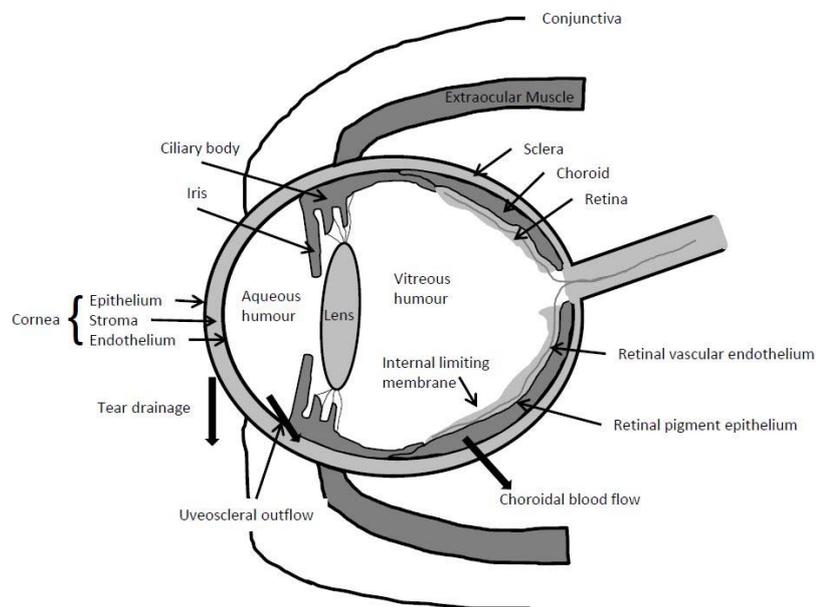


Figure 1: Basic anatomy of the human eye and main barriers for drug delivery

In contrast to the transcorneal route, periocular drug transport to the posterior segment is potentially feasible. However, complex models suggest a very high clearance by choroidal blood flow and a resulting low bioavailability in the vitreous after sub-conjunctival application [3]. The pharmacokinetic models of drug delivery to the posterior segment include clearance to the anterior chamber and a systemic loss via the blood-retinal barrier. To predict clearance in the human posterior segment, rabbit eye is reported as the preferred model [4]. A simple structure-activity-relation model can calculate *in silico* the clearance of small molecules from vitreous humor [5].

Due to the high clearance rates intravitreal injection is the preferred way to reliably reach the posterior segment of the eye. Although state-of-the-art for the treatment of diseases affecting the retina, this painful and complex procedure carries a high risk of unwanted side effects like infections and changes of the intraocular pressure. To reduce the number of injections needed, drug delivery systems with controlled and sustained release have proven to be beneficial. Virtasert®, a non-biodegradable intravitreal implant was introduced in 1996. The surgically implanted device delivers Ganciclovir for up to 8 Months before it has to be removed. The drawback of surgical removal can be avoided by the use of biodegradable polymers. Ozurdex® is a PLGA based rod shaped implant, which can be injected with a special applicator and degrades and releases the incorporated drug allowing for reinjection intervals of 6 months.

As complex and versatile drug products ophthalmics have to fulfill an extensive panel of regulatory requirements. The aspects of efficacy, sterility, tolerance and stability are in combination referred to as "Goldmann Criteria" and comprise the most important quality attributes [6]. Ocular tolerance plays a special role in ophthalmology. Intolerance causes irritation, which induces a vicious circle that leads to reduced patient compliance. Ocular intolerance of applied formulations can be provoked by many factors. Therefore the quality requirements for ophthalmics are rigid. Eyedrop solutions and emulsions must be free of particles and suspensions cannot contain particles larger than 90 µm. The pH has to be between 5 and 9 and the buffer capacity of the applied formulation volume should not exceed the buffer capacity of tears. Furthermore, eyedrops need to be isotonic to prevent adverse effects upon topical instillation [7]. To assess tolerability of ophthalmic formulations the Draize test is state-of-the-art and will be discussed more detailed in Section 2 of this article. Furthermore, *in vitro* testing on isolated cornea, fertilized hens eggs or cell culture models are possible. Due to the high sensitivity and limited immune capacity of the eye infections have to be prevented at all cost. This includes absolute sterility of applied formulations. To assure absence of microorganisms multi-dose ophthalmics require preservatives.

In the second part of the introductory session Francine Behar-Cohen from the *University Hospital of Lausanne* introduced the most relevant ocular diseases and summarized challenges and unmet needs of novel drug delivery systems.

From industry perspective a growing market in ocular therapeutics promises to generate value for patients and shareholders. The highest potential to achieve significant benefits for the patient are seen in Dry Eye, Glaucoma, Bacterial Keratitis, Diabetic Retinopathy, Age-related Macular Degeneration (AMD), Myopia and Uveitis.

With a high prevalence Dry Eye is a disease of major interest to ophthalmologic research. Among the unmet needs is still a "real" treatment that surpasses the mere wetting of the cornea and replacement of tear fluid. As for most topical ocular treatments the fast elimination rate demands a high dosing frequency. A reduced frequency of instillations and improved application devices for elderly and disabled patients are urgently needed. After Cataract is Glaucoma the second-leading cause of blindness. Glaucoma therapy still lacks the employment of neuroprotective agents and a simplified treatment with reduced dosing frequency is desired. To improve the formulations and reduce the dosing frequency is

also an unmet need in the treatment of Bacterial Keratitis. Moreover, improved bioavailability and new antimicrobial strategies should be pursued.

In Diabetic Retinopathy the ultimate goal is, to maintain the patients' vision. In order to achieve this earlier diagnosis combined with improved drug treatment is vital.

In AMD the dry form is the most common clinical manifestation and dry AMD is characterized by a slow progressing central vision loss due to retinal atrophy. No surgical or medical treatment of dry AMD is currently available. In 10-20% of dry AMD patients the degeneration advances into a fast progressing wet form. Wet AMD is characterized by neovascularization and subsequent leakage of blood and protein causing permanent damage to photoreceptors. As a retinal disease wet AMD requires intravitreal drug application. By improved drug delivery methods a reduction of the dosing frequency would facilitate patient compliance and convenience and decrease adverse effects from the precarious injection procedure. In the treatment of Uveitis intravitreal application of corticosteroids is currently state-of-the-art. Considering the adverse effects, a therapy without corticosteroids via a non-invasive delivery route would be highly anticipated.

Not considered as a disease but identified as risk factor for other eye diseases is Myopia. A therapy to prevent ocular growth is still missing and would benefit a large population.

As unmet needs for drug delivery to the anterior segment F. Behar-Cohen highlighted the reliable delivery of hydrophobic drugs, sustained release and reduced toxicity and tolerability. For the posterior segment the development of sustained release formulations is also of major interest. Furthermore, the delivery of proteins and gene therapy are in focus of current studies. A huge leap forward would be the possibility to non-invasively deliver drugs to the retina.

To evaluate the necessary improved drug delivery systems, a strong need for valid pharmacokinetic data remains. Up to date, no relevant animal model and no *in silico* method can predict distribution in and transport to the posterior segment. Major drawback is the lack of a clear correlation between drug concentration levels in ocular tissues and media.

Furthermore, F. Behar-Cohen claimed that topical delivery to the posterior segment is plausible for proteins <50kDa [8]. Derived from the known permeability data of the inner limiting membrane and sclera, a passive transport of macromolecules would be possible [9, 10]. However, delivery to the retina is additionally impeded by unknown target concentrations and passive diffusion as the only transport mechanism. Alternatives to topical delivery are intravitreal, subconjunctival or subretinal injection. While the intravitreal injection is subject to a high elimination rate, as previously discussed, subconjunctival intrusions lack reproducibility and subretinal implantation is a complex procedure with low tolerability.

2. Animal Models for ocular drug delivery

A meaningful evaluation and optimization of ocular drug delivery depends on valid models. Besides *in vitro* and *in silico* methods, animal models for *in vivo* testing are important tools to predict efficacy and potential side effects in human.

Laurence Ferraile from *IRIS Pharma* and Margaret E. Collins from *Charles River Laboratories* elaborated on animal models to evaluate drug delivery to the eye. For drug delivery to the front of the eye, L. Ferraile distinguished a static and a dynamic anatomical barrier. The static barrier consists of cornea and sclera. The cornea has three layers with alternating polarity and therefore only amphiphilic substances can easily penetrate all layers. In contrast only charged small molecules and macromolecules can penetrate the sclera. The capabilities of rabbit models to mimic the permeability through the static barrier in human are limited. For example, the cutoff of the sclera for macromolecules is three times higher in rabbit (150 kDa) in comparison to human (50 kDa) [8].

The dynamic barrier properties of human and rabbit eye are comprised of tear turnover, blinking, peripheral blood flow, metabolism and turnover of the aqueous humor. While the tear turnover is 16% per minute in human and 8% per minute in rabbit, tear volume and pre corneal volume are comparable. A significant difference was reported in a blinking rate of 5-15 seconds in human and 6 minutes in rabbit. Aside from these differences numerous features support rabbits as most relevant animal model for topical ocular delivery.

Comparable values between human and rabbit are reported for the corneal surface, central corneal thickness and tear volume. In addition the similarity in aqueous humor volume and turnover supports the previously mentioned suitability of rabbit eyes as model for drug elimination [5]. However in another example, microparticles were observed to migrate to the anterior segment after intravitreal application and thus clouding the vision. This effect was only observed in *in vivo* studies in primates. This highlights the importance of selecting the right animal model.

To assess ocular toxicity in rabbits the *in vivo* Draize test is the international standard assay approved by the FDA and OECD. The procedure involves the topical application of the test formulation to rabbit eyes. After 72h of exposure signs of irritation are evaluated and presented in a summarized score. Conventional examination by slit lamp, pachymetry (the measurement of corneal thickness as a predictive measure of edema) and tonometry (intraocular pressure) complement the assessment of formulation safety.

For ocular diseases the model has to be developed and selected specifically by symptoms and anatomical similarity. For example for Glaucoma an increase of the intraocular pressure is provoked by water loading of rabbit eyes or topical application of corticoids in young rats. To mimic the Dry Eye, lacrimal gland insufficiency and evaporation are forced by treatment of mice with transdermal scopolamine in a cage with elevated airflow.

M. Collins focused on the aspects covering back of the eye drug delivery. The most common ways to deliver drugs to the back of the eye are intravitreal and subretinal injection. Both methods require the formulation to be free of endotoxins with a tolerable pH near 7.4. In large species like human intravitreal injections are performed with 25-30G needles and 50 µL can be applied. In small species a 32 G needle is used to inject 2-5 µL. The advantages of intravitreal injection include a delivery near mid-vitreous close to the retina as target tissue. On the downside, the method is painful and risks infections as mentioned earlier.

For delivery of intravitreal implants a delivery device or surgical implantation is needed. Challenges are a potential interference with vision and the influence of location and movement. Biggest advantage is the significantly reduced number of applications in a therapeutic regime.

To establish valid *in vivo* animal models is a vital step in the evaluation of ocular drug delivery. However, the complexity of the eye as an organ impedes cross-species testing and the outcome is often limited in transferability to the clinical situation.

3. Challenges and new concepts in ocular drug delivery

Ocular drug delivery is one the most challenging tasks in pharmaceutical formulation development. The complex structure and protective anatomy and physiology of the human eye significantly impede the design of effective therapies for ocular diseases. Especially novel therapeutic approaches like biologically derived active ingredients and gene therapy have to overcome extensive drawbacks in order to be successfully implemented in ophthalmology [11, 12]. The previously elaborated limitations of topical delivery force researchers to find alternative ways for targeted and sustained delivery. Recently the complex invasive methods for back-of-the-eye drug delivery have been challenged by inventive approaches to improve drug penetration and prolong drug availability. Transporter targeted exploitation of pro-drugs as well as nanotechnology demonstrated the potential to impact ocular drug delivery [13-15]. In addition, sophisticated drug delivering devices like inserts or implants are developed and harness the advancement in polymer technology and engineering [6].

Sustained delivery of biologics

Biologically derived active ingredients and therapies have gained a lot of interest in pharmaceutical research in general and especially in ophthalmology. Despite successful positioning in the market of biopharmaceutical products like Eylea® and Lucentis® further improvements and better understanding are demanded.

Ann Daugherty from *Genentech* elucidated the challenges of delivering proteins to the back of the eye. Currently biologics require intravitreal application as most do not cross all ocular barriers. Intravitreal injection is associated with numerous disadvantages as previously discussed. The development of sustained delivery systems for biologics to reduce the number of applications is impeded by a number of factors. First of all, the stability of the active ingredient has to be guaranteed. Furthermore, the relevance of available animal models is questionable. For humanized antibodies for example, a cross-species testing in rabbits can induce immune reactions not likely to occur in humans. Moreover, longer safety studies are required to assess the impact of breakdown products of the active and the delivery system itself. However, several promising approaches for improved drug delivery like liquid depots, biodegradable implants and advanced delivery devices are already available or on their way to the market.

To evaluate the tolerability of these novel drug delivery systems extensive placebo studies are irremissible. Rabbits have shown to be most sensitive in terms of tolerability with the previously mentioned reaction to human fab-fragments for example impeding the use of rabbits for protein tolerability studies. However, due to anatomical similarities the rabbit-model remains the gold-standard [16].

Gene delivery

Jean-Phillippe Combal from *GenSight* presented a case study highlighting recent advances in gene therapy. In general gene therapy is considered well suited for ocular implementation and a potential treatment for Retinitis Pigmentosa (RP), Geographic Atrophy in AMD and Lebers Hereditary Optic Neuropathy (LHON). To reach the target cells in the retina a viral vector can be injected intravitreally or subretinally [17]. A schematic drawing of the general principle of ocular gene therapy is presented in figure 2. In the presented study gene therapy of LHON is based on intravitreal injection of an adeno-associated viral vector containing the human wild type gene ND4 (GS010). In Phase II the treatment improved vision by 17 letters in treated vs untreated eye in 15 patients. Currently the GS010 therapy has entered Phase III in spring 2016 [18]. The presented approach is a promising advancement in gene delivery and a fitting showcase study for gene therapy of ocular diseases.

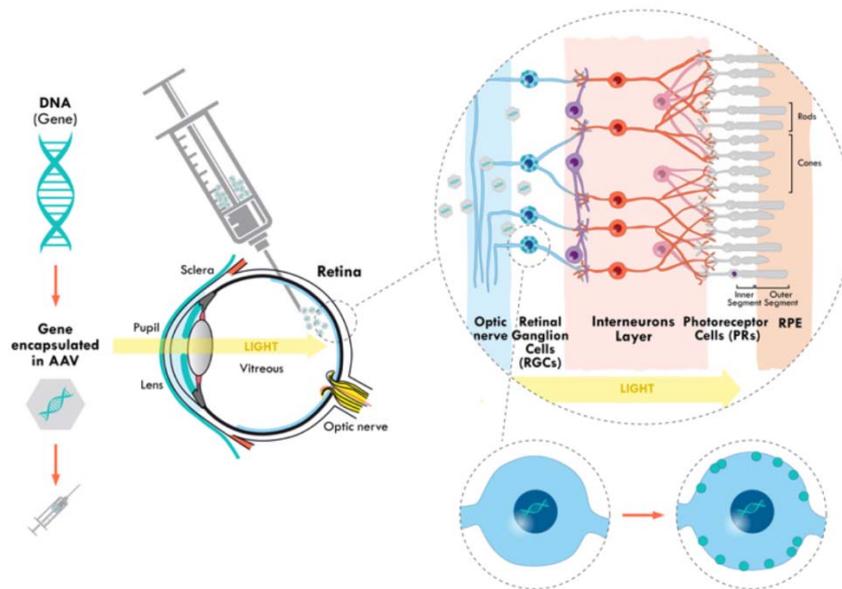


Figure 2: Schematic depiction of ocular gene therapy targeting the Retinal Ganglion Cells [gensight-biologics.com]

Novel device approaches

As previously mentioned, ophthalmology is in vast need of advanced approaches in drug delivery. Improved penetration rates, targeted drug delivery and sustained release are the major aims.

Signe Erickson from *ForSight* presented two novel device approaches for sustained drug delivery to the eye. "Vision4 Port Delivery System" is a refillable implant which resembles a scleral plug. Once subconjunctivally implanted a customizable membrane controls the drug release from a reservoir. The reservoir holds 20-100 μL of formulation and can be emptied and refilled painlessly for years. Solutions and suspensions for ocular back-of-the eye treatment can be loaded into the reservoir. In a representative study the refillable implanted device reduced the number of necessary applications of Lucentis® from 6 to 4.8 in one year. The location of the implant in the sclera and the refill procedure are illustrated in figure 3.

ForSight is developing "Vision 5", an ocular insert that assures sustained topical delivery. The silicone ring rests on the eye without interference with vision. In a phase II study the intraocular pressure was reduced by approx. 20% for 6 months by one Timolol loaded ocular insert [19].

Nanotechnology for ocular drug delivery

Other novel approaches for improved drug delivery can be found in the promising field of nanotechnology [14]. Frederic Lallemand from *Santen* presented cationic emulsions, marketed as Novasorb®. With Cetalkoniumchloride as cationic surfactant, an oil in water emulsion is created. Due to the bioadhesive and penetration enhancing properties of Cetalkoniumchloride the corneal bioavailability was increased by a factor of 2-4. In 2015 ciclosporin loaded eyedrops employing the cationic emulsion were approved by the FDA as Ikervis®.

Doris Gabriel from *Apidel SA* presented nano-scaled micelles (ApidSOL®) with a size of 20-50 nm. The micelles formed by the polymeric surfactant mPEGhexPLA can encapsulate poorly-water soluble drugs and facilitate penetration.

The presented approaches resemble a wide range of innovations suitable to significantly improve drug delivery to the eye. Especially the requirement to improve sustained drug delivery is currently in focus of formulation development in academia and industry.

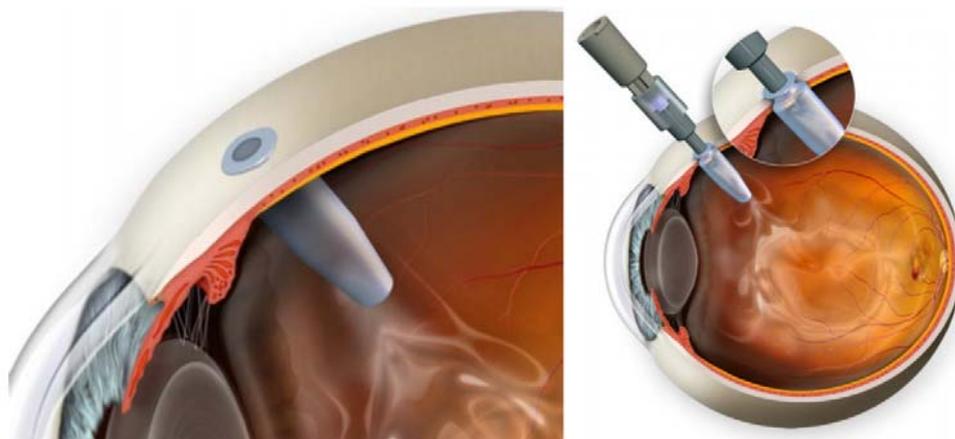


Figure 3: Illustration of the refillable *ForSight* Vision 4 scleral plug [forsightlabs.com]

4. Recent advances in Packaging Development

With the task to assure stability and sterility and improve patient compliance packaging plays an important role in ophthalmology. By harnessing recent advancement in process technology and polymer development packaging can facilitate therapeutic success. Blow-Fill-Seal (BFS) technology was presented by Otto Schubert from *Maropack* as an advanced method to manufacture packaging for ophthalmics. The Blow-Fill-Seal process involves the blow molding of a polymer melt with sterile air and subsequent filling and sealing of the container. This procedure minimizes the risk of contamination and prevents the necessity to sterilize the final product. By BFS a variety of shapes and sizes of containers can be produced. Besides standard multidose containers, sophisticated systems that spare the need for preservatives can be manufactured. In the Novelia® system the drops are delivered through a valve that blocks backflow of air. The air-intake for pressure compensation passes through a filter and contamination is prevented.

Another interesting approach to prevent the need for preservatives is the exploitation of new materials. Loic Marchin from *Pylote* introduced the Pyclear® system. *Pylote* presents a new additive to packing material that reduces contamination. By including micronized ceramic spheres in the packaging material, an antimicrobial effect upon contact of microorganisms with the container is achieved. This reduces the microbial liability of the container tip and prevents contamination of the formulation. The claimed antimicrobial effect is based on interstitial ions and reactive oxygen-species that form locally upon direct contact of the microspheres with microorganisms.

The presented approaches for advanced packaging tackle the pressing objective to reduce the use of preservatives and prevent infections.

5. Summary and Outlook

The APV Seminar on Ocular Drug Delivery provided a solid knowledge base and valuable insights into current advances and new concepts. Besides overview talks, details on animal models, protein delivery, novel delivery systems and packaging technologies were presented. In general the acquisition of valid pK-Data, further establishment of representative animal models and the ongoing development of sustained drug delivery systems are the main challenges in developing innovative treatments for ophthalmic diseases. The diverse audience at the seminar assured increasing interest in academia and industry to tackle these upcoming tasks.

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DRUG DELIVERY LITERATURE

Provided by Dr. Carsten Timpe

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COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

OUR MISSION STATEMENT:

Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

Our mission includes in particular the following tasks:

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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