Ocular drug delivery: Fundamentals, challenges, and technologies

Organizers
Ash Jayagopal, PhD, Kodiak Sciences Inc. and Uday Kompella, PhD, University of Colorado, Anschutz Medical Campus

Description
Ocular drug delivery is an evolving field featuring cutting-edge advances in devices, formulations, and paradigms for design and characterization. This course will draw upon experts in the various disciplines of the field in order to instruct attendees on how to apply key concepts in drug delivery to improve upon the translational value of their research endeavors.

Key topics will include fundamentals and pharmacokinetics of drug delivery to the anterior and posterior segment, anatomical and tissue barriers for ocular drug biodistribution, models for evaluating drug delivery systems, as well as advances in device, formulation, polymer, and lipid technologies, as well as regulatory and clinical considerations for incorporation of drug delivery technologies in the clinic.

Learning objectives
After attending this course, participants will be able to:

- Identify significant ocular tissue barriers for drug delivery and clearance in the eye
- Develop competency in comparing ocular drug delivery systems and formulations to propose optimal strategies for delivery of small molecules and macromolecules including oligonucleotides, gene therapies, and protein drugs
- Describe the regulatory process for approval of drug delivery devices and formulations
- Identify and apply state-of-the-art platform technologies for ocular drug delivery in anterior and posterior segment diseases, including those based on polymer, lipid, implant, and nanoparticulate technologies

Agenda
Presenters and presentations may change.

8 – 8:20am  Introduction and history of ophthalmic product development  
Sesha Neervannan, PhD, Pharmaceutical Development, Allergan, Irvine, CA  
General introduction to the day and topic.

8:20 – 8:45am  Overview of fundamentals of ocular drug delivery  
Uday B. Kompella, PhD, FARVO, Professor, University of Colorado, Anschutz Medical Campus, Aurora, CO  
This presentation will provide an overview of the fundamentals determining the selection and development of various types of drug molecules, routes of administration, and delivery systems for treating eye diseases. Special emphasis will be placed on the rate limiting biological factors for ocular drug delivery and how they can be overcome, at least in part, by using conventional and novel delivery systems.
8:45 – 9:10am  Ocular drug delivery technologies: A clinical perspective  
Diana V. Do, MD, Professor of Ophthalmology, Stanford University School of Medicine, Palo Alto, CA  
Intravitreal vascular endothelial growth factor (VEGF) inhibitors have revolutionized the treatment of retinal vascular diseases such as neovascular age related macular degeneration, diabetic macular edema, diabetic retinopathy, and retinal vein occlusion. Continuous monthly or bimonthly treatments are required to obtain the greatest visual acuity benefits. However, in the real world, patients receive significantly fewer intravitreal injections resulting in suboptimal visual acuity outcomes compared to clinical trials. There remains an unmet need to develop new therapies with a longer duration of action to inhibit VEGF and other angiogenic targets. We will discuss current and emerging drug delivery technologies.

9:10 – 9:35am  Potentials and pitfalls of animal models  
John S. Penn, PhD, FARVO, Snyder Professor & Vice Chairman, Vanderbilt University School of Medicine, Nashville, TN  
The goal of this presentation is to describe common rodent models of eye disease, with an emphasis on diseases of the retinal and choroidal vasculatures. The focus of the presentation will be on the pitfalls associated with certain experimental eye disease models, how they work, their clinical relevance, and what they can and cannot tell us about the pathogenesis of human eye diseases. Specific models to be discussed include oxygen-induced retinopathy (OIR), laser-induced choroidal neovascularization (LCNV), diabetic retinopathy, retinal vein occlusion, ischemia reperfusion injury. Brief mention will made of models of glaucoma and inherited retinal dystrophies.

9:35 – 9:50am  Morning break

9:50 – 10:15am  Computational modeling of drug delivery to the eye  
Jessica Spires, Simulations Plus, Inc., Lancaster, CA  
Delivery to the anterior portion of the eye is heavily affected by the properties of the topical formulation. Through mechanistic computational modeling, these properties, as well as the properties of the administered compound and the physiological properties of the eye, can be used to simulate and predict the effects of formulation properties on ocular bioavailability. This talk will discuss the characterization of these formulations and the impact of key formulation parameters, and examine their application in a case study of topical dexamethasone suspensions.

10:15 – 10:40am  Pharmacokinetics and modeling of drug delivery to the back of the eye  
Arto Urtti, PhD, Professor, Centre for Drug Research, University of Helsinki, Helsinki, Finland  
The lecture will describe the main factors in the posterior eye segment pharmacokinetics, test models, their clinical relevance and modeling approaches for generalized understanding of the processes.

10:40 – 11:05am  Eye drop formulations for drug delivery  
Clive G. Wilson, PhD, J.P. Todd Professor of Pharmaceutics, University of Strathclyde, Glasgow, Scotland, UK  
The objectives are to examine the barriers for efficient topical dosing of the eye in the context of anatomical and physiological differences between species. The presentation will
show how lacrimal scintigraphy can be used to relate physical features of formulations to
dispersion and clearance and will also examine how dosing bottle characteristics can
influence compliance and ease of use for patients. Imaging techniques, especially gamma
scintigraphy where a component of the formulation is labelled with a suitable
radiopharmaceutical such as technetium-99m was utilised for animal and human testing.
Dynamic sequences over 1 to 20 minutes are usually sufficient to reveal viscosity-driven
differences in residence and this can be correlated to clinical efficacy. For non-aqueous
vehicles such as perfluorodecalin which are poor solubilisers, technetium-99m labelled
carbon microparticulate, formed as a stable suspension with colloidal silica in the vehicle
were used. Applications of techniques such as scintigraphy show that there is a critical limit
to viscosity in the performance of formulations with poor spreading due to cohesive
behaviour and slow hydration of the polymeric excipients. There are also marked animal-
man differences that result in a failure to predict clinical performance. The spectrum from
simple unthickened drops through gels and non aqueous vehicles will be presented and key
learnings on the advantages and disadvantages will be presented.

The human eye clears non-viscous solutions effectively by blinking, with 90% clearance from
the eye in 1 minute. Above a certain viscosity, the mixing action of the upward sweep of the
lid is insufficient to break the cohesive forces and the material then forms a reservoir in the
lower fornix. In contrast, conventional particulate formulations tend to become aggregated
in tear mucins after topical delivery and form a plug that accumulated in the inner corner of
the eye. This plug is later ejected on to the skin. With a particulate suspended in a non-
aqueous formulation such as perfluorodecalin, the particles were swept to the conjunctiva-
lid margins during the reflex blink and remained there for a considerable time.

Thickening solutions may cause problems In the elderly patient, the grip strength is
decreased and dosing with thickened solutions becomes difficult because the pressure has
to be sustained to encourage the formulation to flow.

11:05 – 11:30am  Ocular suspension and nanosuspension products: Formulation
development, scale up and manufacturing considerations

Onkar N. Singh, PhD, MBA, Director, Pharmaceutical Development, CONRAD,
Eastern Virginia Medical School (EVMS), Norfolk, VA

Drug delivery to the ocular diseases requires strategic approaches due to the existence of
several anatomical/static and physiological/dynamic barriers. Several ophthalmic
conventional topical formulations are designed as solutions, suspensions, nanosuspension,
ointments or emulsions to achieve an effective drug dose to the ocular tissues. In addition,
various novel nanoformulation-based delivery systems have been explored through various
routes of administration and showed promising results. I will also present how the various
routes of ocular administrations play a key role in designing and developing a suspension
formulation and other drug delivery systems. The considerations in formulation
development of suspension dosage forms will be presented to facilitate the development of
safe, stable, and efficacious drug products meeting ideal target product profile (TPP).
Stability studies per ICH guidelines will be summarized. I will also touch upon process scale
up and manufacturing of a sterile ocular suspension products.

11:30 – 12:30pm  Lunch
12:30 – 12:55pm  Emulsions for drug delivery to the eye

Frederic Lallemand, PhD, Lallemand Conseil SAS, Rambouillet, France

This presentation will firstly present a brief state of the art on the use of emulsions in ophthalmology either as artificial tears for the relief of dry eye or as vehicle for active molecules. We will review the main physicochemical and thermodynamic parameters driving the stability and efficacy of the emulsions after topical application. Manufacturing processes will be examined and discussed with their pros and cons as well as sterilization processes. A good physicochemical characterization is key in understanding the emulsion and appropriate in vivo model should be chosen. The course will be concluded by listing the gaps to be filled to better understand the behavior of emulsions after ocular administration. During the talk, reference to regulatory standards will be done to ensure that emulsion developments are done according to ICH, FDA and EMA requirements.

12:55 – 1:20pm  Slow release drug products for ocular delivery

Susan S. Lee, PhD, Director, Clinical Development, Allergan, Inc., Irvine, CA

Drug delivery for ophthalmic diseases is limited and often difficult due to the anatomy and physiology of the eye. Limited absorption and the layers of ocular tissue inhibit adequate amounts of topically applied ocular drops from reaching the target tissue of the eye. The blood-aqueous and blood-retinal barriers prevent an adequate amount of systemically administered drugs from reaching the eye as well. While intravitreal injection can bypass some of these limitations, these injections are invasive and must be performed often. Implantable drug delivery devices have been designed to avoid many of the difficulties associated with other ocular treatment options. These devices can be biodegradable, soluble, or nonbiodegradable, and can be placed in different parts of the eye depending on the target tissue, and are a great alternative that can reduce treatment burden, provide more targeted delivery, and minimize systemic side effects.

1:20 – 1:45pm  Nanoparticles and microparticles for ophthalmic drug delivery

Rocio Herrero-Vanrell, PhD, Professor, Complutense University, Madrid, Spain

Nanoparticles and microparticles are intended to provide controlled delivery of therapeutic agents. For ophthalmic purposes they can be administered by topical, intraocular or periorcular routes. Depending on the biomaterial used for their preparation, particles can be biodegradable or non bioerodible. The right choice of the appropriate drug delivery system depends on the ophthalmic disease, route of administration and the site of action. There are several methods to fabricate nanoparticles and microparticles. Once prepared they are characterized in terms of size, morphology, encapsulation efficiency and release profile.

1:45 – 2:00pm  Afternoon break

2:00 – 2:25pm  Hydrogels and novel materials for ocular delivery

Hu Yang, PhD, Professor, Virginia Commonwealth University, Glen Allen, VA

Challenges to ocular drug delivery come from the physiological barriers of the eye. Hydrogels have been widely explored to address the medication challenges of the ocular environment. In this workshop, I will review the latest hydrogel formulations and their associated chemistries for use in oculary therapies, spanning from external anterior to internal posterior regions of the eye in order to evaluate the state of recent research. I will discuss the utility of hydrogels in soft contact lens, wound dressings, intraocular lens, vitreous substitutes, vitreous drug release hydrogels, and cell-based therapies for regeneration. Additional focus
is placed on the pre-formulation, formulation considerations of the hydrogels as well as new materials based on individual components (polymer chains, linkers, and therapeutics).

2:25 – 2:50pm  **Molecular engineering of ocular therapeutics for retinal diseases**

*Ashwath Jayagopal, PhD, Executive Director, Discovery Medicine, Kodiak Sciences Inc., Palo Alto, CA*

Emerging engineering approaches on the molecular scale for biologics and other therapeutic modalities, including small molecules and gene therapies, have promising clinical applications toward improving clinical outcomes in retinal disease. We will discuss key preclinical and clinical examples of how engineering approaches can be used to develop therapeutics with prolonged ocular half-life, reduced dosing frequency, targeting of multiple disease mediators, rapid systemic clearance, and favorable ocular safety profiles.

2:50 – 3:15pm  **Regulatory considerations for drugs and devices (FDA/EMA)**

*Speaker request pending*

3:15 – 3:45pm  **Q&A: Panel Discussion: Focus on anterior segment**

3:45 – 4:15pm  **Q&A: Panel Discussion: Focus on posterior segment**

4:15 – 4:30pm  **Wrap and key takeaways**

*Ash Jayagopal, PhD, and Uday Kompella, PhD*