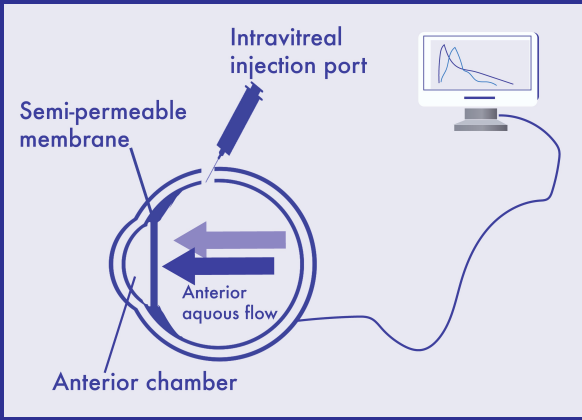
Introducing the PK-Eye™

The PK-Eye™ for intraocular drug development

OPTCEUTICS
RESEARCH • INNOVATE • DEVELOP



The PK-Eye™ can be used to:

- Identify the best formulation technology
- Determine PK parameters (t_{max}, C_{max}, $t_{1/2}$)
- Determine impact of physiological variables (age)
- Assess stability and functional maintenance of activity
- Optimize the selection of dose and dose frequency
- Generate unique data to support additional patent coverage
- Compare activity and duration to known products
- Speed development of biosimilar/biobetter products
- Reduce program risk BEFORE moving into costly animal and human studies

What is the PK-Eye™?

The PK-Eye™ is a 2-compartment, aqueous outflow model scaled to the 2 interior compartments of the human eye.

Human clearance times for biologics can be accurately determined in real time.

Implants of retinal permeable drugs can be accurately estimated by IVIVCs.

Stability studies for extended release candidates during optimisation are much more easily conducted than in animals.

PK-Eye™ (Ver 2) has been developed.

RESEARCH ARTICLE – *Pharmaceutics, Drug Delivery and Pharmaceutical Technology*

The PK-Eye: A Novel *In Vitro* Ocular Flow Model for Use in Preclinical Drug Development

SAHAR AWWAD,[1,2] ALASTAIR LOCKWOOD,[1,2] STEVE BROCCHINI,[1,2] PENG T. KHAW[1]

[1]National Institute for Health Research (NIHR) Biomedical Research Centre at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London EC1V 9EL, United Kingdom
[2]UCL School of Pharmacy, London WC1N 1AX, United Kingdom

Received 13 February 2015; revised 8 April 2015; accepted 8 April 2015
Published online 24 June 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24480

ABSTRACT: A 2-compartment in vitro eye flow model has been developed to estimate ocular drug clearance by the anterior aqueous outflow pathway. The model is designed to accelerate the development of longer-acting ophthalmic therapeutics. Dye studies show aqueous flow is necessary for a molecule injected into the vitreous cavity to clear from the model. The clearance times of proteins can be estimated by collecting the aqueous outflow, which was first conducted with bevacizumab using phosphate-buffered saline in the vitreous cavity. A simulated vitreous solution was then used and ranibizumab (0.5 mg) displayed a clearance time of 8.1 ± 3.1 days, which is comparable to that observed in humans. The model can estimate drug release from implants or the dissolution of suspensions as a first step in their clearance mechanism, which will be the rate-limiting step for the overall resident time of a candidate dosage form in the vitreous. A suspension of triamcinolone acetonide (Kenalog®) (4.0 mg) displayed clearance times spanning 26–28 days. These results indicate that the model can be used to determine *in vitro–in vivo* correlations in preclinical studies to develop long-lasting therapeutics to treat blinding diseases at the back of the eye. © 2015 The Authors. *Journal of Pharmaceutical Sciences* published by Wiley Periodicals, Inc. and the American Pharmacists Association] Pharm Sci 104:3330–3342, 2015
Keywords: Intraocular fluid flow; in vitro/in vivo correlations (IVIVC); in vitro model; pharmacokinetics; proteins; protein delivery; intraocular drug suspension; ocular drug delivery; intravitreal injection

INTRODUCTION

Prolonging therapeutic levels of a drug within the vitreous to treat blinding diseases is one of the most important goals in ophthalmic drug development. Intravitreal (IVT) injections of therapeutic proteins and the use of steroid implants in the vitreous are currently the best clinical methods to achieve prolonged exposure in the back of the eye. With increased life expectancy and an aging population, more people will require treatment for longer periods to manage blinding conditions that would otherwise rapidly progress.

Therapeutic biologics registered for ophthalmic use by IVT injection comprise a PEGylated-aptamer (Pegaptanib), antibody fragment (ranibizumab), and a Fc fusion (aflibercept).[1] These medicines bind to VEGF and are administered by IVT injection every 1–2 months. Although IVT injections are a costly, invasive procedure that is associated with a low risk for vision threatening complications,[2] many health systems around the world cannot cope with the increasing demands for IVT injection of the current anti-VEGF treatments,[3,4] even when administered every 1–2 months. The increased knowledge of the molecular mechanisms involved in blinding ocular diseases[5,6] will continue to drive the development of protein-based medicines,[7] which tend to be potent and have a rapid onset of action. This will further drive the development[7–11] of longer-lasting IVT injection dosage forms such as implants that require less frequent administration.

Mass exchange within the eye is dominated by the aqueous that is secreted into the vitreous from the ciliary body (2.0–2.5 μL/min).[12–16] The vast majority of this aqueous passes the anterior hyaloid membrane and flows into the front of the eye (anterior chamber) to then leave the eye via trabecular and uveoscleral pathways.[16,17] Drug elimination from the vitreous occurs by (1) the aqueous outflow into the anterior chamber and (2) permeation through the retina via retinal-choroid-sclera (RCS) pathways.[14,17] Therapeutic proteins clear predominantly through the anterior route because they are high-molecular-weight, charged molecules.[18–21]

Proteins have longer half-lives (i.e., days to weeks)[8,13,20,21] in the vitreous than RCS[20] permeable molecules (e.g., lipophilic molecules ≤500 Da), which generally are a matter of hours.[16,17,20] Reasons for this include (1) lower molecular weight permeable molecules diffuse more rapidly in the vitreous than proteins,[16,19,21,22] (2) the surface area of the retina is large compared to the anterior hyaloid membrane, and (3) permeable molecules can clear via several routes through the RCS (e.g., passive diffusion, active transport, binding to melanin, loss to conjactival lymphatics and episcleral veins, and metabolism).[16] *In vitro* cell permeation models have been developed to evaluate RCS permeability.[20] It is thought that the physicochemical properties of a drug can often be used to predict RCS permeability.[19,20–24]

Correspondence to: Peng T. Khaw (Telephone: +44 207 608 6867; Fax: +44 207 608 6967; E-mail: p.khaw@ucl.ac.uk); Steve Brocchini (Telephone: +44 207 753 5832; Fax: +44 207 753 5942; E-mail: steve.brocchini@ucl.ac.uk)
Journal of Pharmaceutical Sciences, Vol. 104, 3330–3342 (2015)
© 2015 The Authors *Journal of Pharmaceutical Sciences* published by Wiley Periodicals, Inc. and the American Pharmacists Association

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

PK-Eye™ (Ver 1)

The PK-Eye™ enables:

- Accelerated formulation and late preclinical dose escalation studies that are not feasible using *in vivo* models to be conducted.
- High throughput formulation development and stability analysis of intraocular drug candidates at all stages of preclinical development.
- Identifies only the best candidates for radio-labelling studies and detailed *in vivo* and stability studies.
- Real time, 24/7 monitoring of the outflow of candidate drug formulations at controlled temperature.

Email: admin@optceutics.com
Website: www.optceutics.com