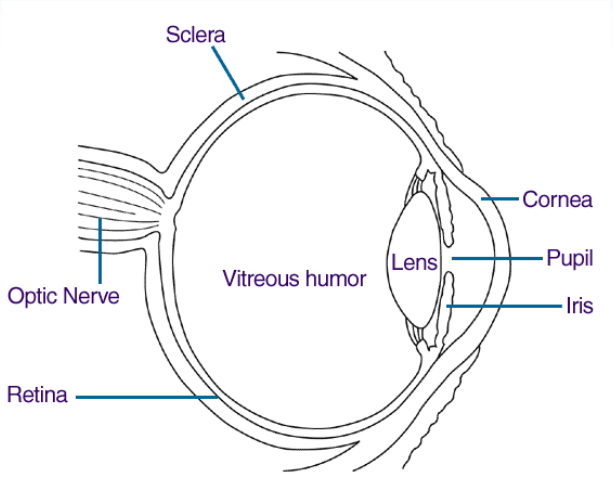
Developing PBPK for Ocular Delivery

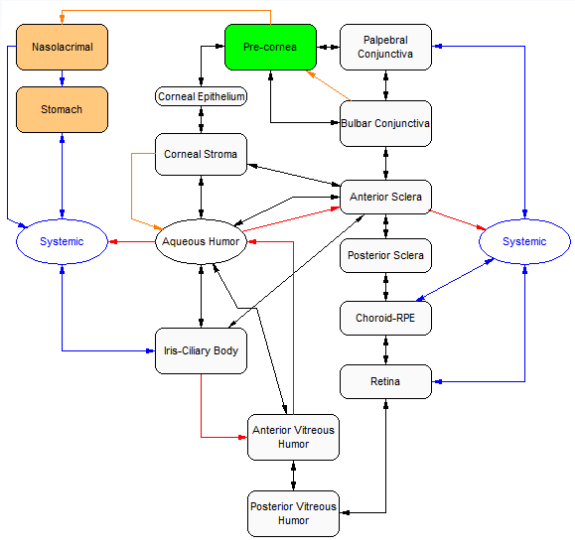
Michael B. Bolger, Ph.D.
Simulations Plus, Inc.

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

Cooperation grant with the FDA (2014-2019)

- 4-year funded collaborative project with the FDA Office of Generic Drugs on the development of mechanistic models for ocular delivery

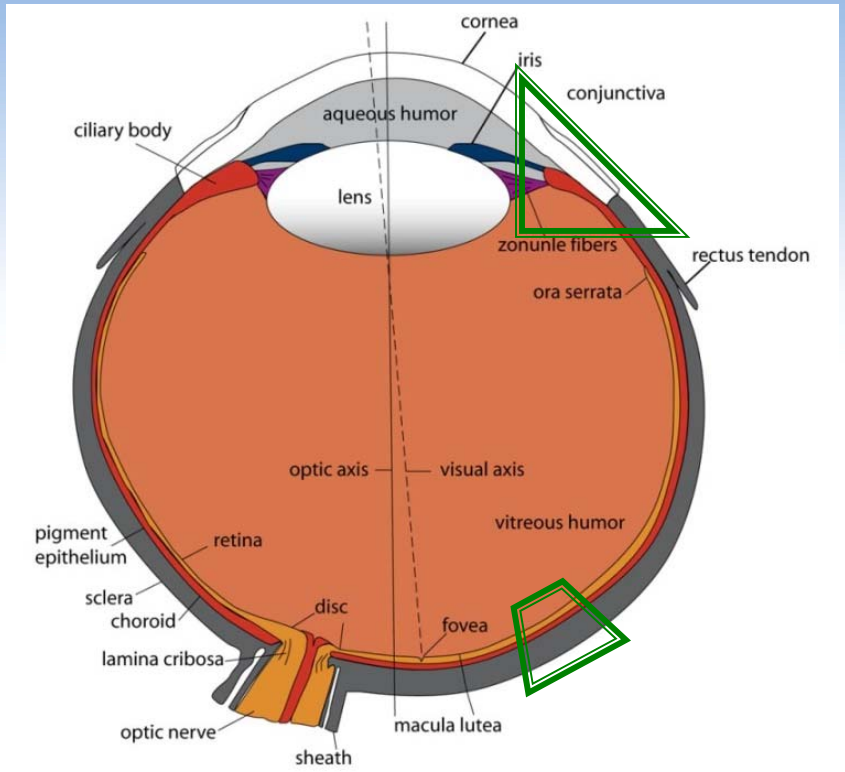


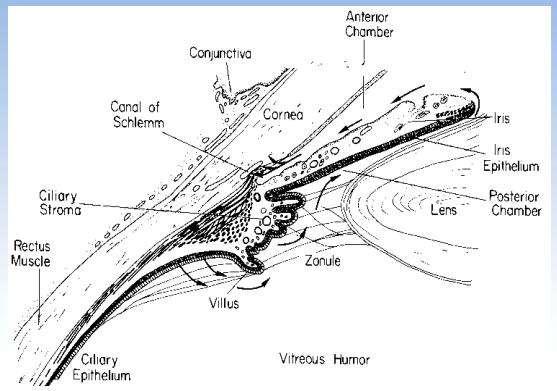


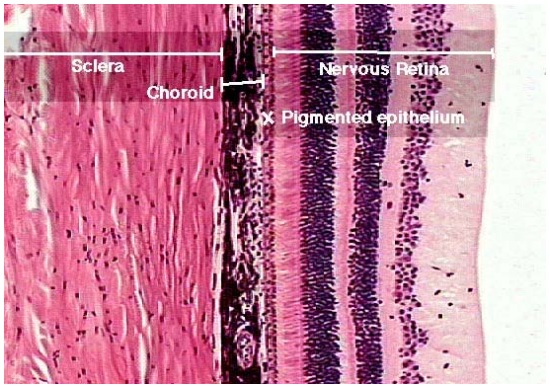
Ocular Dosing

(developed in collaboration with Pfizer)

Anterior – Topical administration (eye-drops)

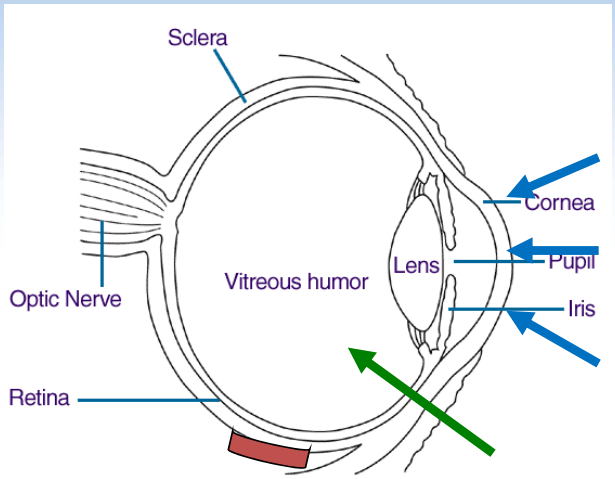






Posterior – Intra-vitreal injections and implants

Modes of Administration in the Eye



Topical

- < 5% reaches anterior segment
- Tiny fraction reaches Retina

Systemic

- Penetration is limited by blood aqueous and blood retinal barriers

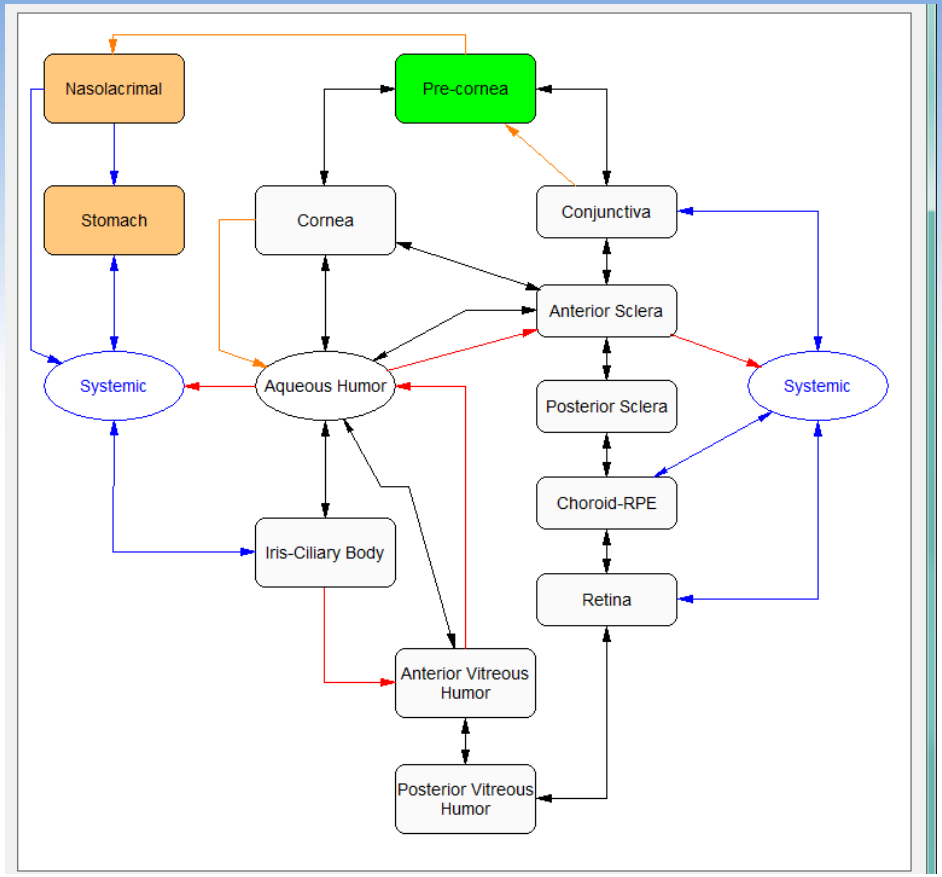
Intravitreal

- Effective mode of administration for achieving therapeutic concentrations in retina

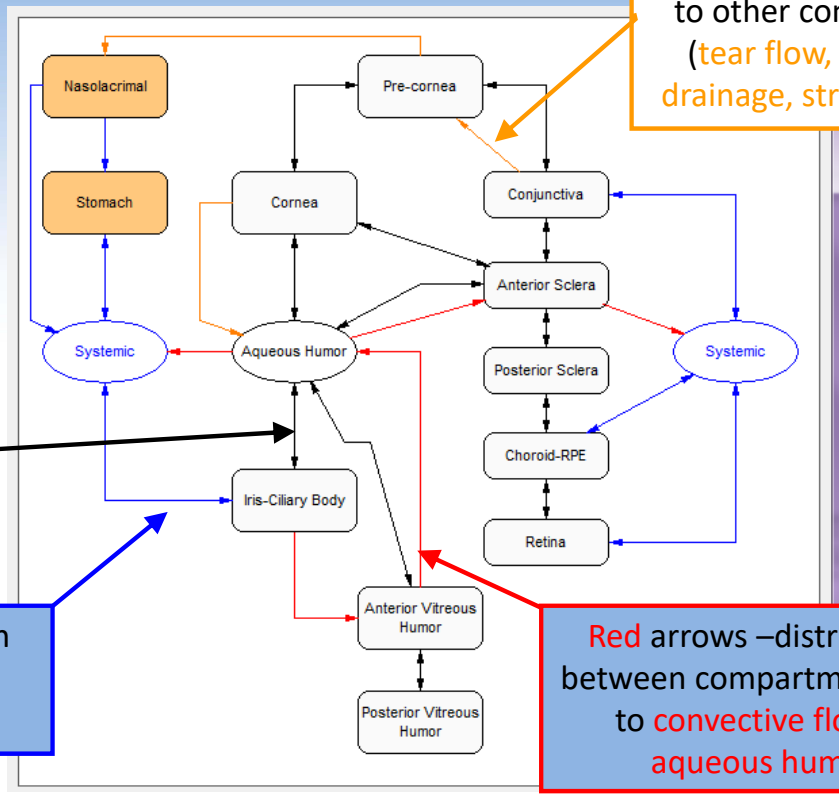
Transcleral

- Noninvasive
- Effectiveness is under investigation

Original Ocular CAT Model (~2013) for human and rabbit



Ocular Compartmental Absorption and Transit Model



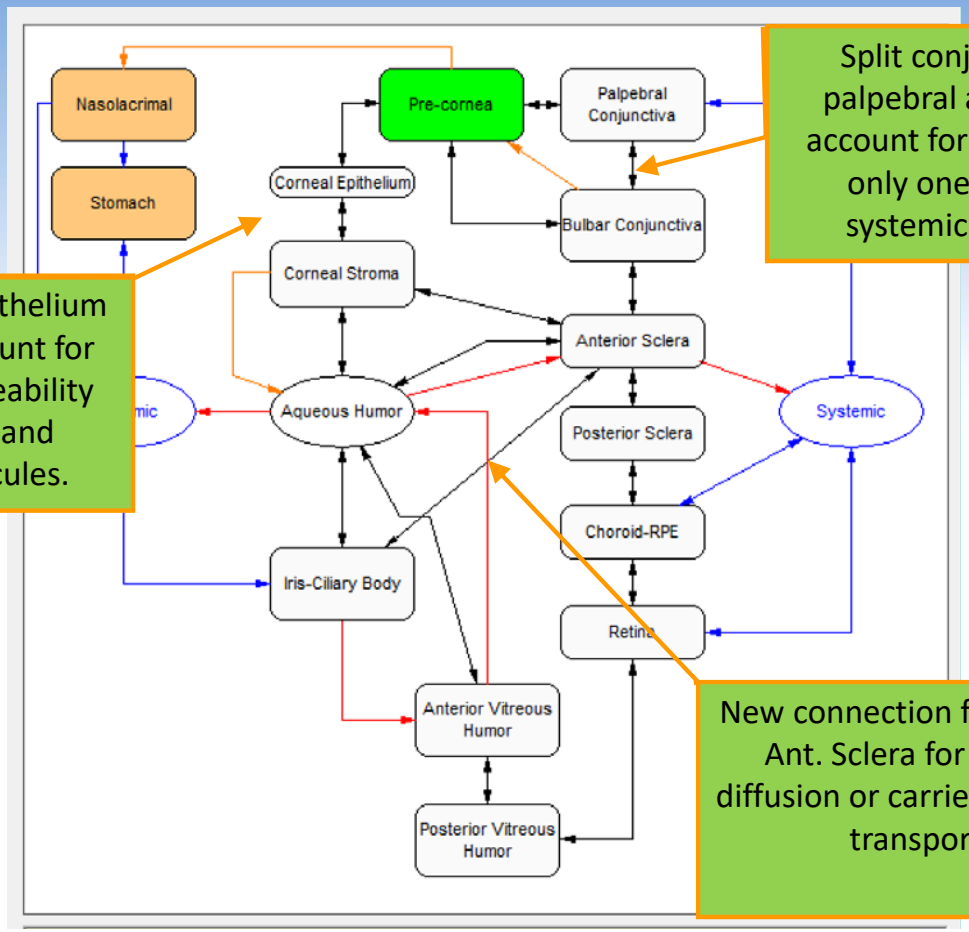
Orange arrows –distribution between compartments due to other convective flows (tear flow, nasolacrimal drainage, stromal thinning)

Black arrows –distribution between eye compartments due to passive diffusion and/or carrier mediated transport

Blue arrows –distribution between ocular and systemic circulation

Red arrows –distribution between compartments due to convective flow of aqueous humor

Newest OCAT Schematic for human, rabbit, and monkey



Split conjunctiva into palpebral and bulbar to account for connection of only one part to the systemic circulation.

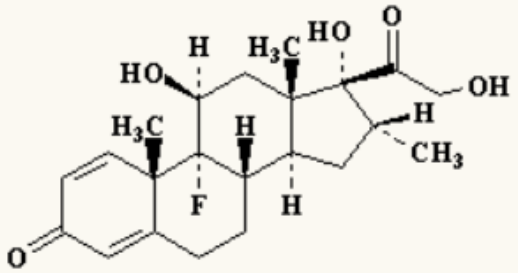
Split cornea into epithelium and stroma to account for difference in permeability for hydrophobic and hydrophilic molecules.

New connection from ICB to Ant. Sclera for passive diffusion or carrier mediated transport.

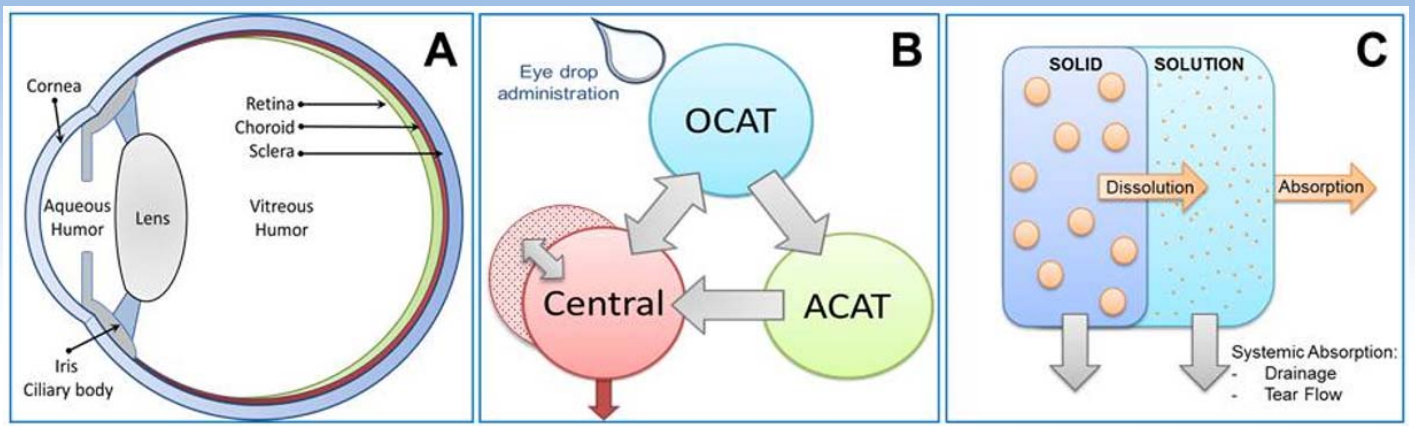
Dexamethasone

- Dexamethasone suspension is indicated for treatment of steroid responsive inflammatory conditions.
- Maxidex (0.1% w/v, eye drops, suspension)

Dexamethasone
$C_{22}H_{29}FO_5$



Dexamethasone Topical Pathways



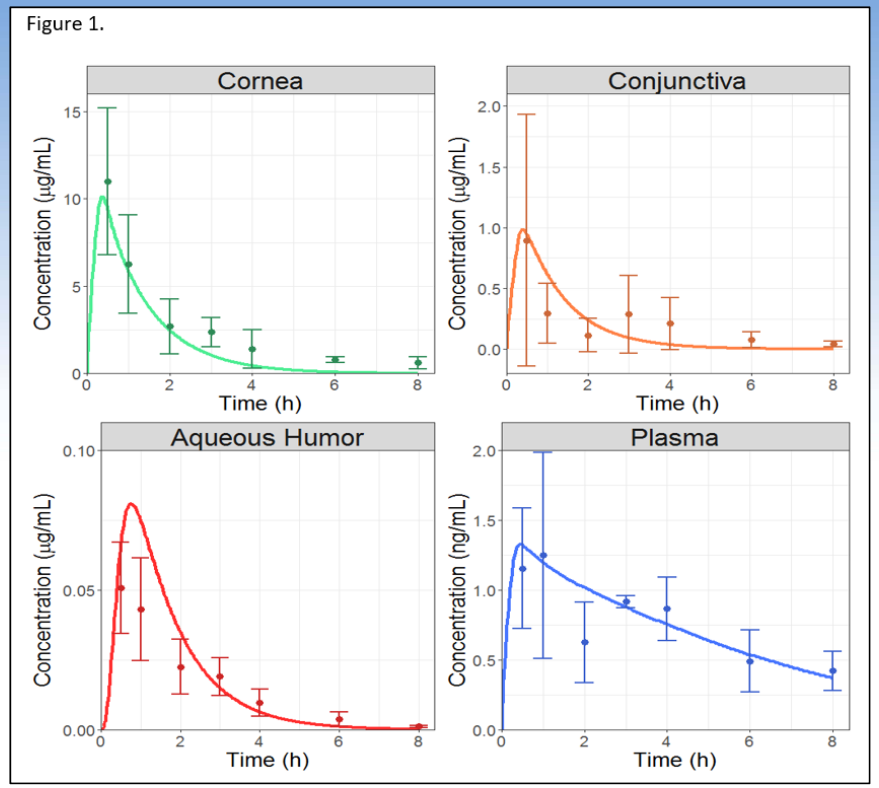
US FDA study of topical ocular administration with distribution to all ocular tissues in rabbits.

US FDA study of topical ocular 30 µL of TOBRADEX ST® 0.1% and 0.05% in a single (right) eye with tissue collection (cornea, conjunctiva and aqueous humor) as terminal procedures at 0.5, 1, 2, 3, 4, 6, and 8 hours.

TOBRADEX ST® 0.05% formulation was treated as a mixture of solution (18%) and solid suspension (82%) based on solubility of 90.3 µg/mL.

Ref. Le Merdy, M. et al. AAPS Journal, submitted 2018, under final review.

Observed and Fitted Rabbit Tissue Distribution



Corneal epithelium and stroma permeabilities (6 E-6 cm/s) were based on the literature data. Conjunctiva, aqueous humor, and ICB permeabilities were optimized by simultaneously fitting the observed ocular and plasma concentration-time profiles of dexamethasone.

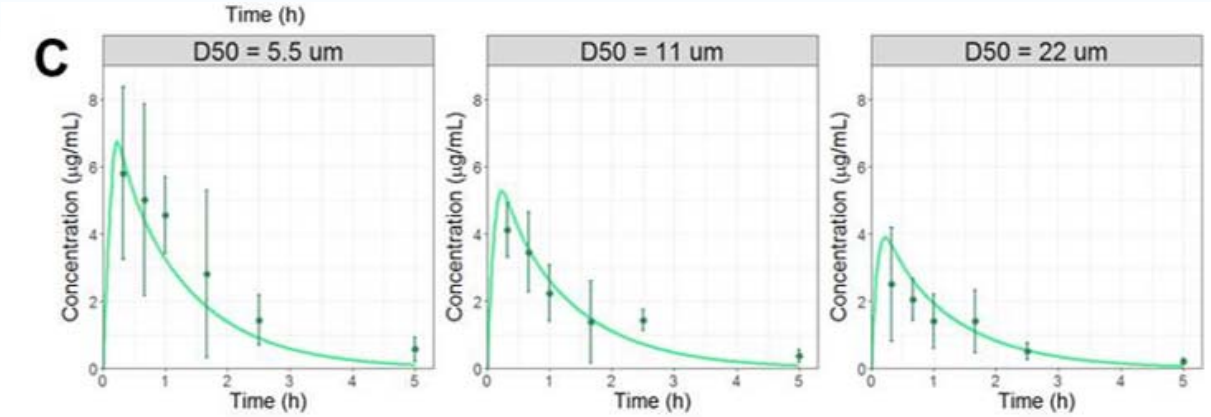
Ref. Le Merdy, M. et al. AAPS Journal, submitted 2018,under final review.

Sensitivity to viscosity and particle size.

Viscosity:
72.9 cP

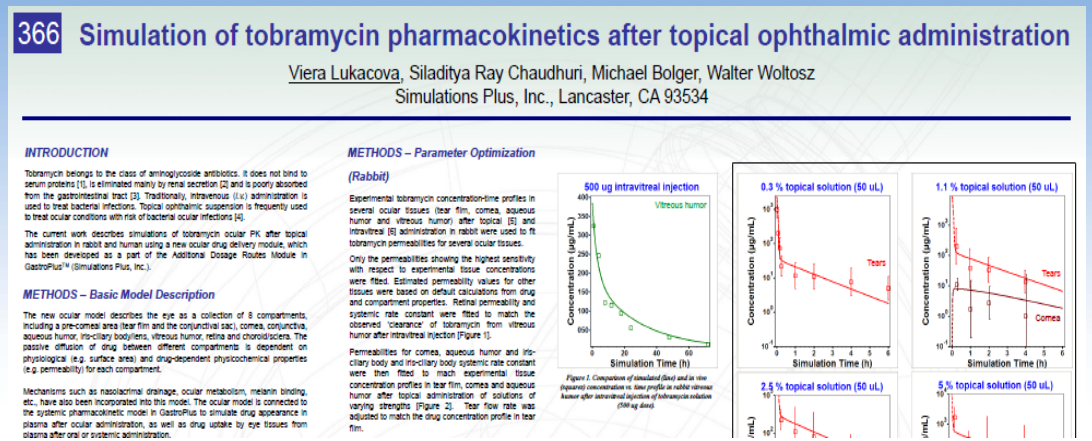
1.67 cP

	C_{max} (µg/mL)		$AUC_{0\to3}$ (µg.h/mL)	
	Observed	Simulated	Observed	Simulated
TOBRADEX ST[c] 0.05%	0.106 ± 0.019	0.081	0.191 ± 0.01	0.13
TOBRADEX[c] 0.1%	0.069 ± 0.022	0.06	0.118± 0.006	0.095



PBPK Model: Le Merdy, M. et al. AAPS Journal, submitted 2018, under final review.
Rabbit data: Schoenwald RD, et al. J. Pharm. Sci. 1980 69(4):391 (1980)

Other Validation Cases



366 Simulation of tobramycin pharmacokinetics after topical ophthalmic administration

Viera Lukacova, Siladitya Ray Chaudhuri, Michael Bolger, Walter Woltosz
Simulations Plus, Inc., Lancaster, CA 93534

INTRODUCTION

Tobramycin belongs to the class of aminoglycoside antibiotics. It does not bind to serum proteins [1], is eliminated mainly by renal secretion [2] and is poorly absorbed from the gastrointestinal tract [3]. Traditionally, intravenous (iv) administration is used to treat bacterial infections. Topical ophthalmic suspension is frequently used to treat ocular conditions with risk of bacterial ocular infections [4].

The current work describes simulations of tobramycin ocular PK after topical administration in rabbit and human using a new ocular drug delivery module, which has been developed as a part of the Additional Dosage Routes Module in GastroPlus™ (Simulations Plus, Inc.).

METHODS – Basic Model Description

The new ocular model describes the eye as a collection of 8 compartments, including a pre-corneal area (tear film and the conjunctival sac), cornea, conjunctiva, aqueous humor, iris-ciliary body/lens, vitreous humor, retina and choroid/sclera. The passive diffusion of drug between different compartments is dependent on physiological (e.g. surface area) and drug-dependent physicochemical properties (e.g. permeability) for each compartment.

Mechanisms such as nasolacrimal drainage, ocular metabolism, melanin binding, etc., have also been incorporated into this model. The ocular model is connected to the systemic pharmacokinetic model in GastroPlus to simulate drug appearance in plasma after ocular administration, as well as drug uptake by eye tissues from plasma after oral or systemic administration.

METHODS – Parameter Optimization

(Rabbit)

Experimental tobramycin concentration-time profiles in several ocular tissues (tear film, cornea, aqueous humor and vitreous humor) after topical [5] and intravitreal [6] administration in rabbit were used to fit tobramycin permeabilities for several ocular tissues.

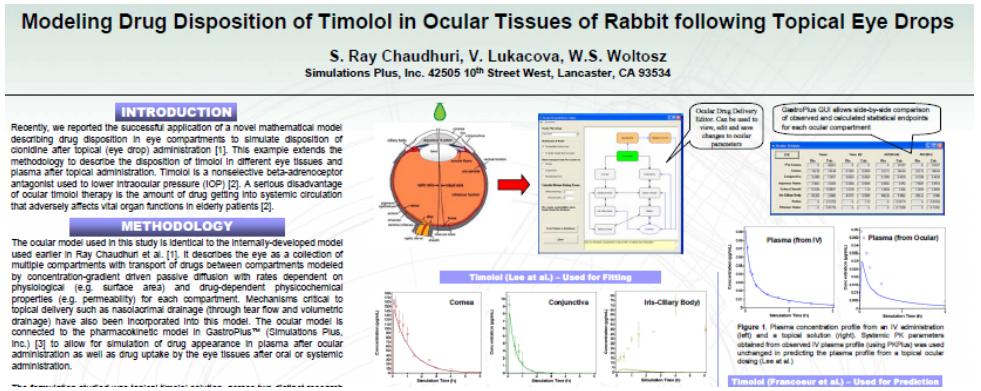
Only the permeabilities showing the highest sensitivity with respect to experimental tissue concentrations were fitted. Estimated permeability values for other tissues were based on default calculations from drug and compartment properties. Retinal permeability and systemic rate constant were fitted to match the observed 'clearance' of tobramycin from vitreous humor after intravitreal injection (Figure 1).

Permeabilities for cornea, aqueous humor and iris-ciliary body and iris-ciliary body systemic rate constant were then fitted to mach experimental tissue concentration profiles in tear film, cornea and aqueous humor after topical administration of solutions of varying strengths (Figure 2). Tear flow rate was adjusted to match the drug concentration profile in tear film.

Figure 1. Comparison of simulated (line) and in vivo (squares) concentration vs. time profile in rabbit vitreous humor after intravitreal injection of tobramycin solution (500 ug dose).

Scaling from rabbit to human when predicting ocular tissue distribution
(Lukacova et al., CRS 2010)

Drug disposition in rabbit ocular tissues following eye drops
(Chaudhuri et al., ISOPT 2009)



Modeling Drug Disposition of Timolol in Ocular Tissues of Rabbit following Topical Eye Drops

S. Ray Chaudhuri, V. Lukacova, W.S. Woltosz
Simulations Plus, Inc. 42505 10th Street West, Lancaster, CA 93534

INTRODUCTION

Recently, we reported the successful application of a novel mathematical model describing drug disposition in eye compartments to simulate disposition of clonidine after topical (eye drop) administration [1]. This example extends the methodology to describe the disposition of timolol in different eye tissues and plasma after topical administration. Timolol is a nonselective beta-adrenoceptor antagonist used to lower intraocular pressure (IOP) [2]. A serious disadvantage of ocular timolol therapy is the amount of drug getting into systemic circulation that adversely affects vital organ functions in elderly patients [2].

METHODOLOGY

The ocular model used in this study is identical to the internally-developed model used earlier in Ray Chaudhuri et al. [1]. It describes the eye as a collection of multiple compartments with transport of drugs between compartments modeled by concentration-gradient driven passive diffusion with rates dependent on physiological (e.g. surface area) and drug-dependent physicochemical properties (e.g. permeability) for each compartment. Mechanisms critical to topical delivery such as nasolacrimal drainage (through tear flow and volumetric drainage) have also been incorporated into this model. The ocular model is connected to the pharmacokinetic model in GastroPlus™ (Simulations Plus, Inc.) [3] to allow for simulation of drug appearance in plasma after ocular administration as well as drug uptake by the eye tissues after oral or systemic administration.

Acknowledgements

Simulations Plus, Inc.
Viera Lukacova (Director)
Jessica Spires
Jim Mullin
Joyce Macwan

External Collaborators
Kenzo Yamamura (Santen)
Hitomi Takanaga (Santen)
Mohammed Tamai (Novartis)
Valeriu Damian-Lordache (GSK)
Xavier Pepin (Sanofi/AstraZeneca)

US FDA
Jianghong Fan
Maxime LeMerdy
Xinyuan Zhang
Eleftheria Tsakalozou
Lanyan Fang
Vincent Li

Supported by FDA OGD grant:
5U01FD005211