An Integrated Multiscale-Multiphysics Modeling of Ocular Drug Delivery and Pharmacokinetics pharmacological protection and treatment

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PPBPK Modeling for The Development and Approval of Locally Acting Drug Products

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Modeling Session – Goal, challenges, solutions

Develop the multiscale computational framework, CoBi, for modeling **in vitro and in vivo** ocular drug delivery, PK/PD and to establish protocols for model-based assessment of BE of generic drugs.

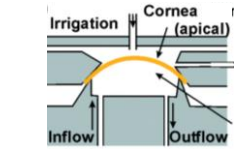
- **Multiscale modeling tools dissolution of ophthalmic products**
- **Modeling of Dissolution Devices and Protocols**
- **Improves of the Anterior Eye Model**
  - **Anatomic Geometry**
  - **Tear Film**
  - **Models of Topical Delivery of Suspension Products**
- **Validation of the Cornel Model on Iv Vitro data**
- **Whole Eye Model Q3D – 3D**
- **Simulation of Timolol PK – PD**
- **Posterior Eye Model**

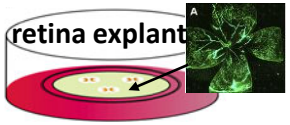
Acknowledgements:
FDA: Dr. Andrew Babiskin, Dr. Ross Walenga, Dr. Jianghong Fan
CFDRC: Dr kay Sun, Mr Joseph Pak, Dr ZJ Chen
Supported by FDA. FDA/OGD (5U01FD005219-02, HHSF223201810151C)

Overview

High-Resolution Ocular Models

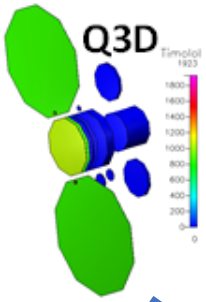
In Vitro/Ex Vivo Validation



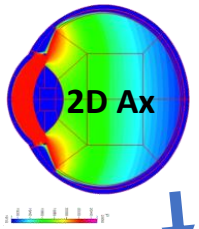


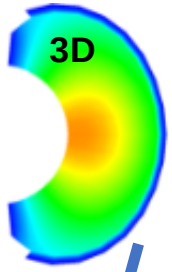
In Vivo Validation

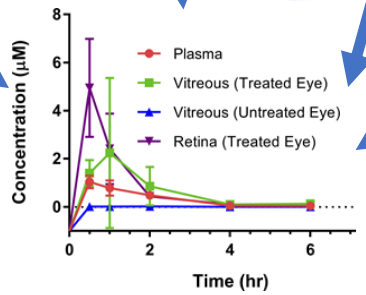
Anterior Eye



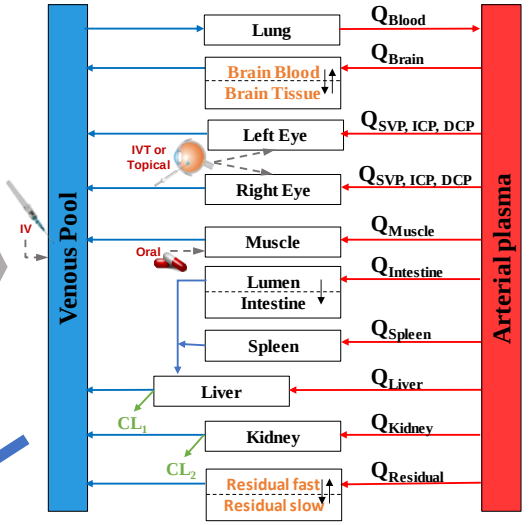
Posterior Eye





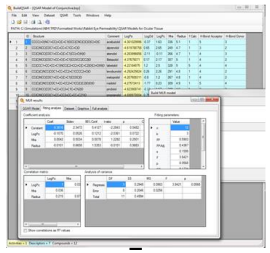


PBPK Whole-Body Model

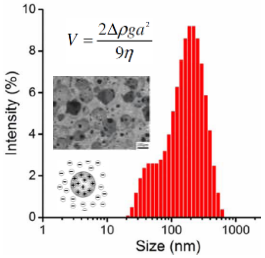


Formulation Properties

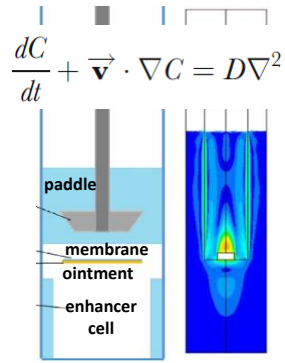
Biochemical

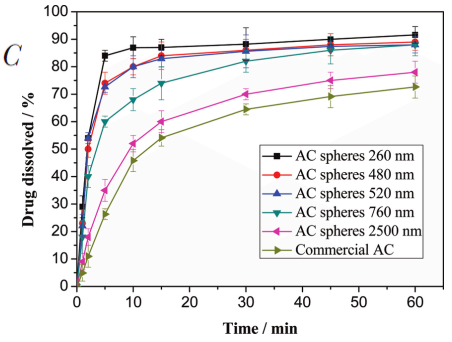


Biophysical



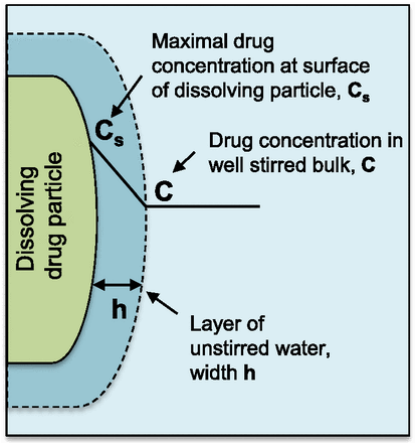
Dissolution Model

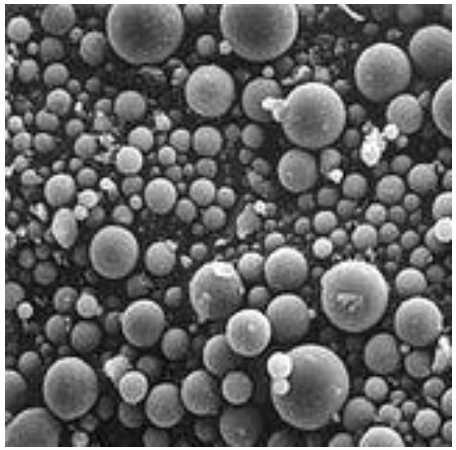




Dissolution Models: Particle Suspensions

Solid Particles





Dissolution: Change in Particle Mass

$$\frac{dM_p}{dt} = -D \cdot A \cdot (C_s - C_b) \cdot \left[\frac{1}{h} + \frac{1}{R}\right]$$

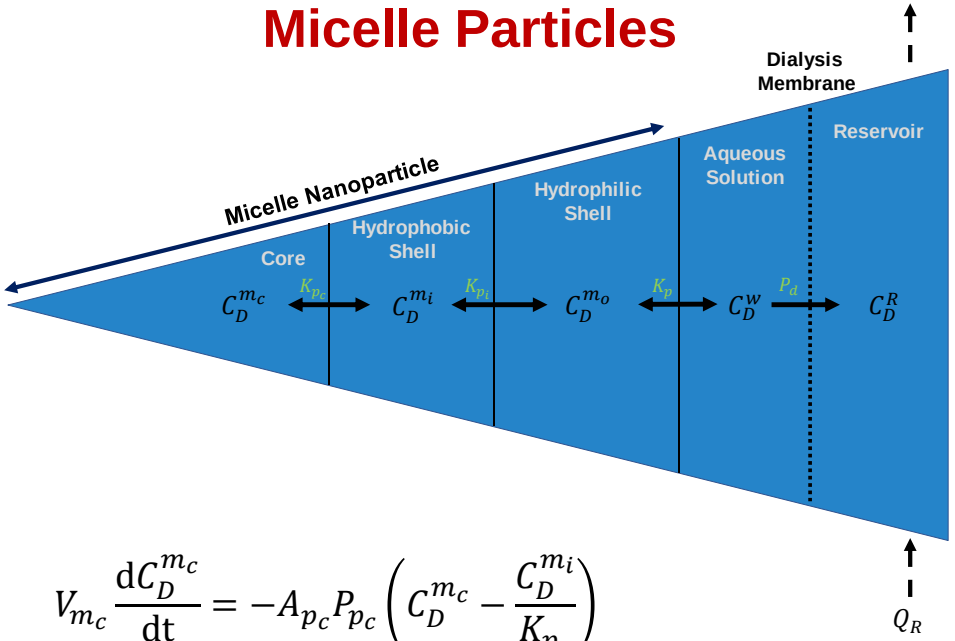
Change in Particle Radius

$$r_{p,i} = \left(\frac{3}{4\pi} \cdot \frac{M_{p,i}}{N_i \cdot \rho}\right)^{1/3}$$

Dissolution: Change in Bulk Media Conc.

$$\frac{dC_b}{dt} = \frac{D \cdot A}{V_{media}} \cdot (C_s - C_b) \cdot \left[\frac{1}{h} + \frac{1}{R}\right] \cdot N_i$$

Micelle Particles



$$V_{m_c} \frac{dC_D^{m_c}}{dt} = -A_{p_c} P_{p_c} \left(C_D^{m_c} - \frac{C_D^{m_i}}{K_{p_c}}\right)$$

$$V_{m_i} \frac{dC_D^{m_i}}{dt} = A_{p_c} P_{p_c} \left(C_D^{m_c} - \frac{C_D^{m_i}}{K_{p_c}}\right) - A_{p_i} P_{p_i} \left(C_U^{m_i} - \frac{C_D^{m_o}}{K_{p_i}}\right)$$

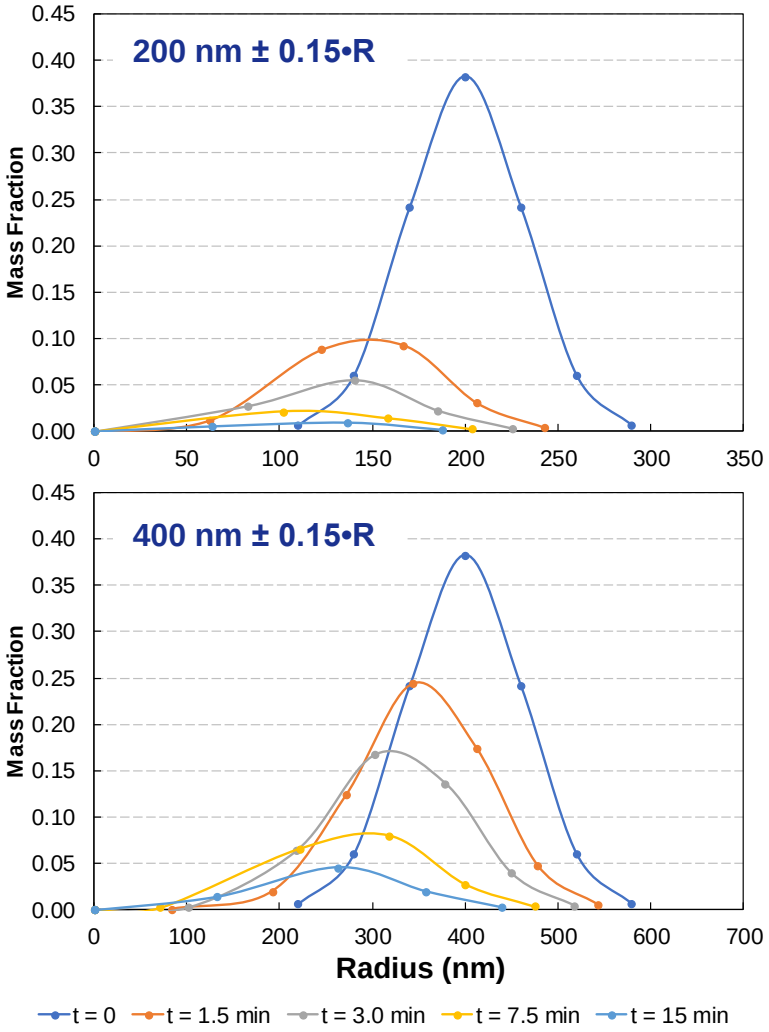
$$V_{m_o} \frac{dC_D^{m_o}}{dt} = -A_p P_p \left(C_D^{m_o} - \frac{C_D^{w}}{K_p}\right) + A_{p_i} P_{p_i} \left(C_D^{m_i} - \frac{C_D^{m_o}}{K_{p_i}}\right)$$

$$V_w \frac{dC_D^{w}}{dt} = A_p P_p \left(C_D^{m_o} - \frac{C_D^{w}}{K_p}\right) - A_d P_d \left(C_D^{w} - C_D^{R}\right)$$

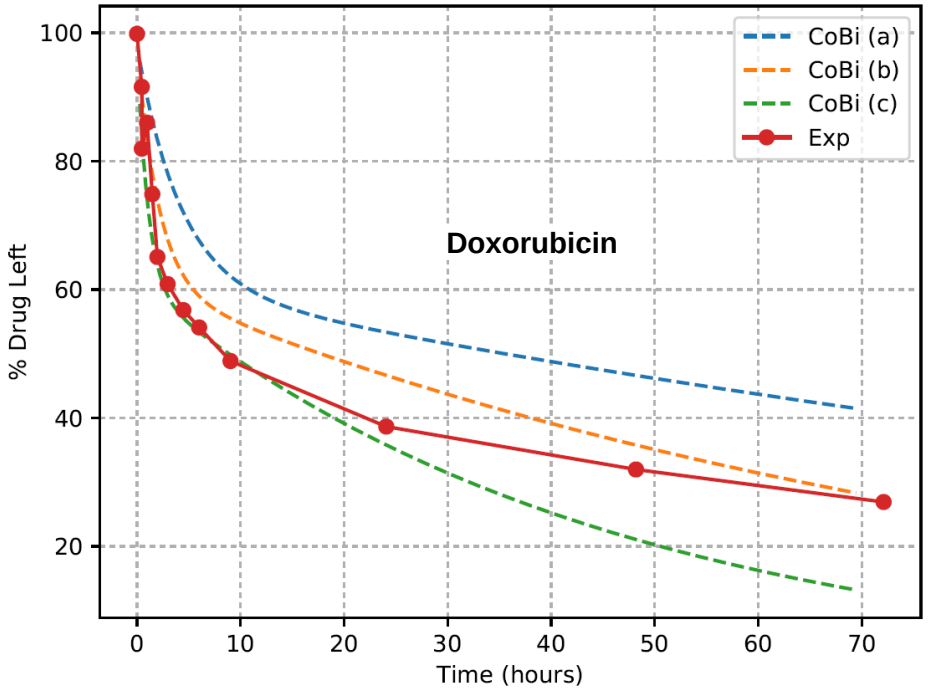
$$V_R \frac{dC_D^{R}}{dt} = Q_{R,in} \left(C_{D,in}^{R} - C_D^{R}\right) + A_d P_d \left(C_D^{w} - C_D^{R}\right)$$

Dissolution Models: Particle Suspensions

Solid Particles



Micelle Particles



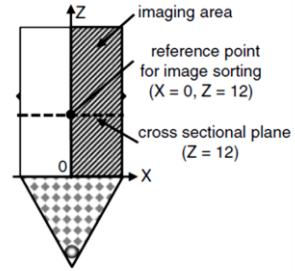
Calibration Parameters

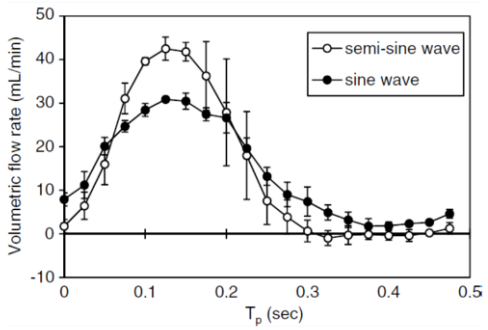
	k_s ($\times 10^{-2}\ h^{-1}$)	k_f (h^{-1})
(a)*	0.55	0.24
(b)	1.1	0.48
(c)	2.2	0.96

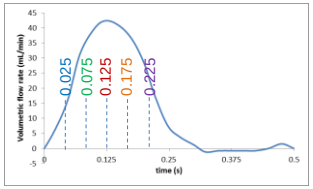
Ponta A. (2015) Release, Partitioning, and Conjugation Stability of Doxorubicin in Polymer Micelles Determined by Mechanistic Modeling. Pharm Res 32:1752–1763

Dissolution Models: In Vitro Systems

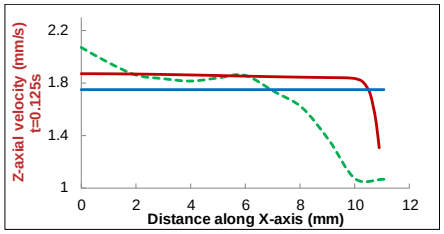
USP 4 Apparatus

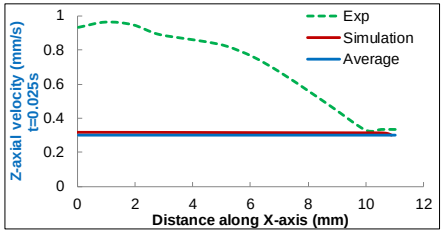


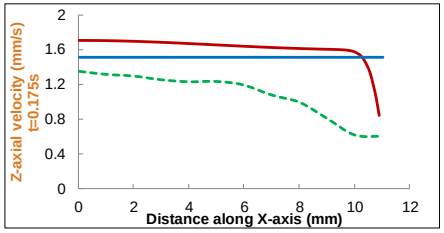


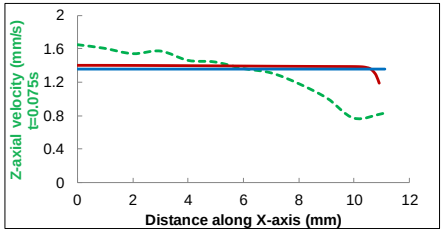


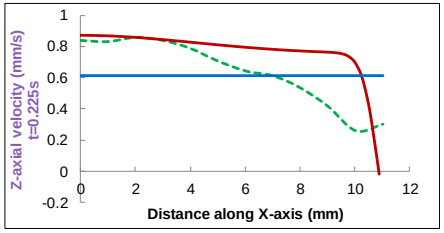
Discharge:
t=0.025 to 0.225s





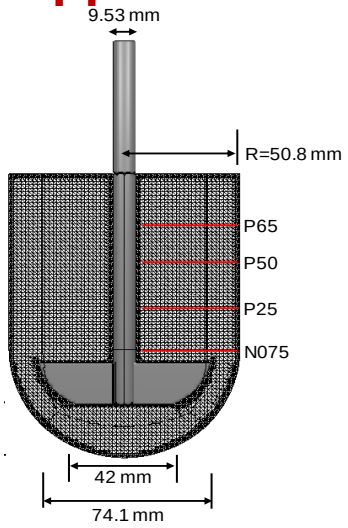


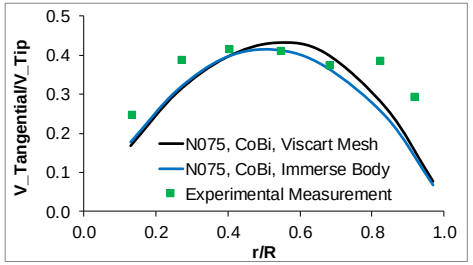


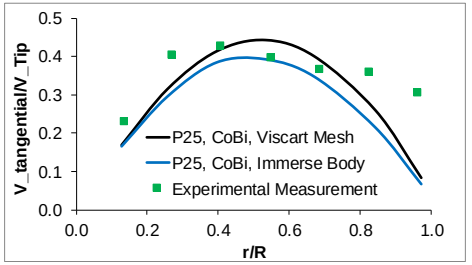


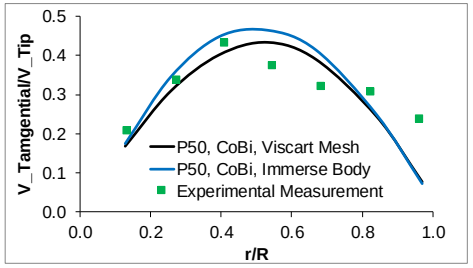
H. Yoshida, et al Effects of Pump Pulsation on Hydrodynamic Properties and Dissolution Profiles in Flow-Through Dissolution Systems (USP 4)," *Pharm. Res.*, vol. 33, no. 6, pp. 1327–1336, 2016.

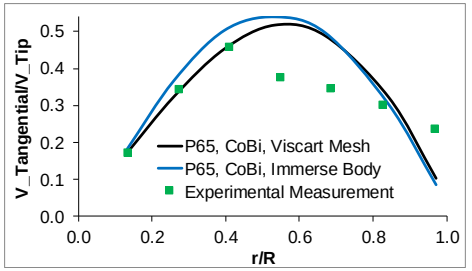
USP 2 Apparatus







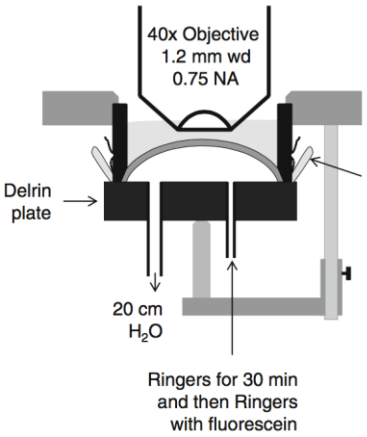




G. Bai, P. M. Armenante, et al. Hydrodynamic investigation of USP dissolution test apparatus II, *J. Pharm. Sci.*, 96(9)2327–2349, Sep. 2007

In Vitro/Ex Vivo Modeling Approach

Experimental Setup



Tear and AH baths had the same volume:

h ≈ 150 μm

A ≈ 1.53 cm^2

Governing Equations

Cell Membrane Flux

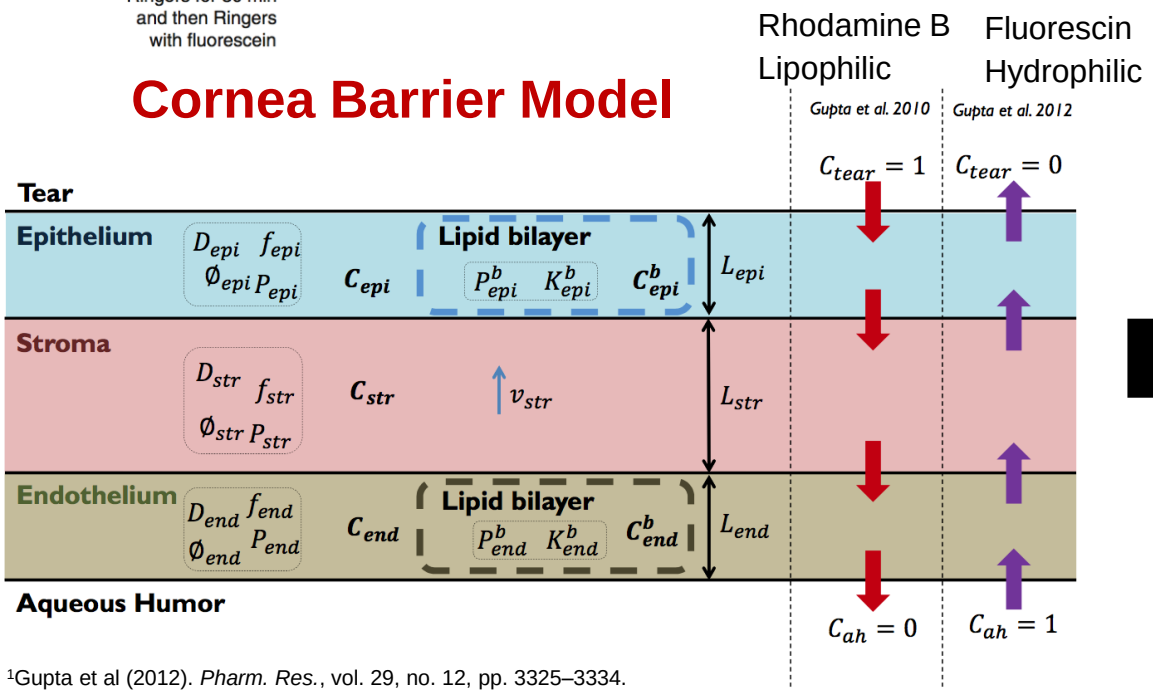
$$J = -D\nabla C - J^B$$

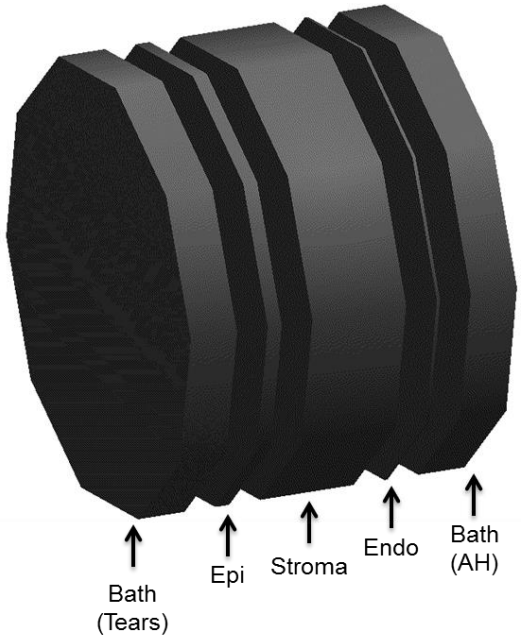
Intracellular Flux

$$J^B = k^B\left(C - \frac{C^B}{R^B}\right)$$

- k^B: cytoplasmic permeability rate constant
- R^B: ratio of equilibrium concentration

Cornea Barrier Model

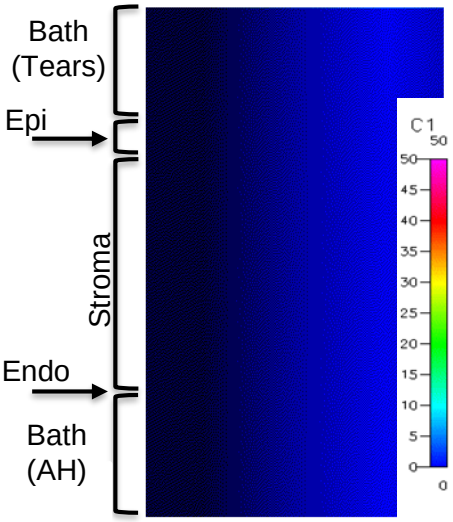




[1]Gupta et al (2012). *Pharm. Res.*, vol. 29, no. 12, pp. 3325–3334.
[2]Gupta et al (2010). *Pharm. Res.*, vol. 27, no. 4, pp. 699–711, Apr.

In Vitro/Ex Vivo Validation

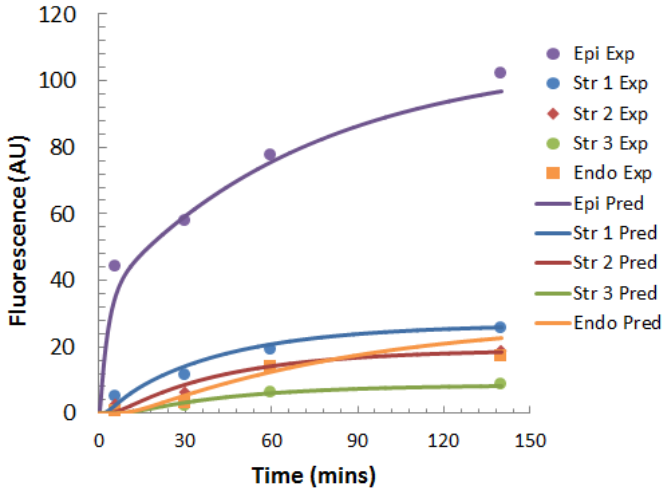
Animation

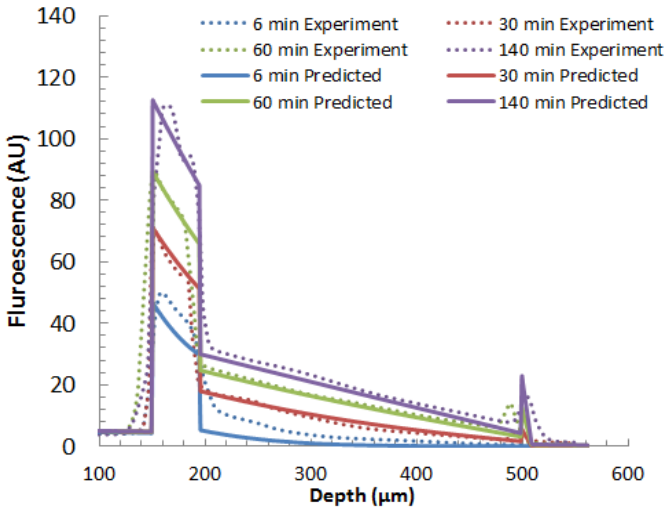


*scaled in x-axis

Gupta et al 2010

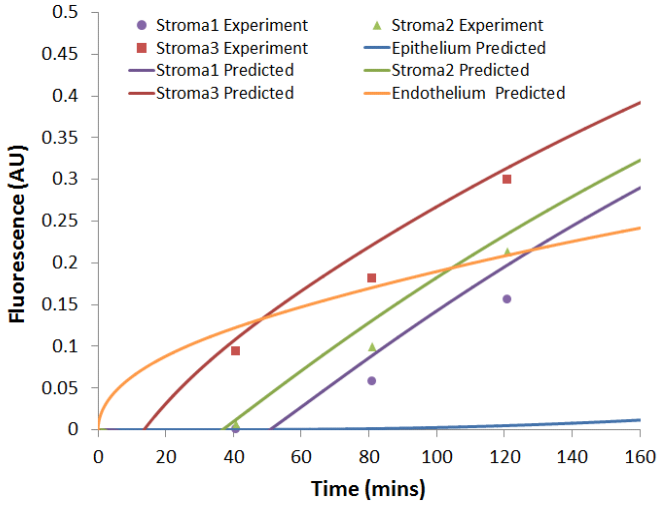
Rhodamine B

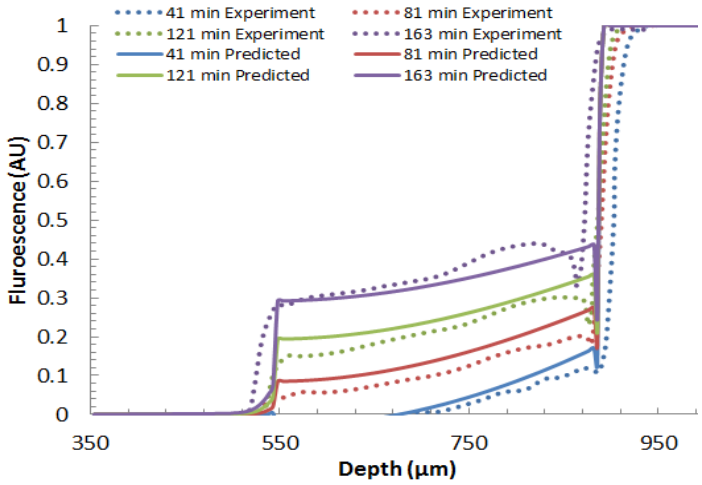




Gupta et al 2012

Fluorescin

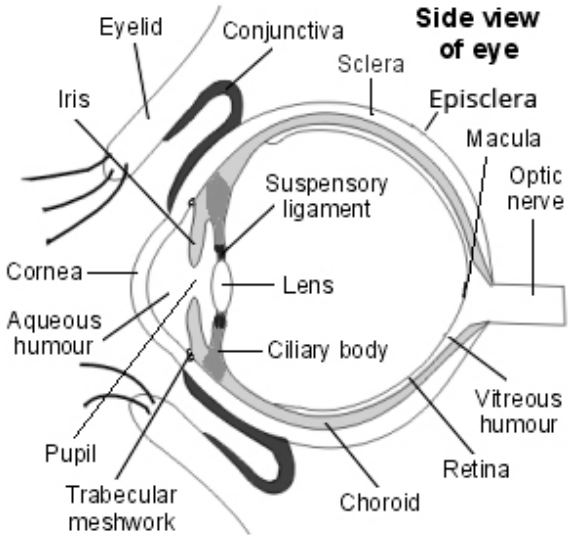




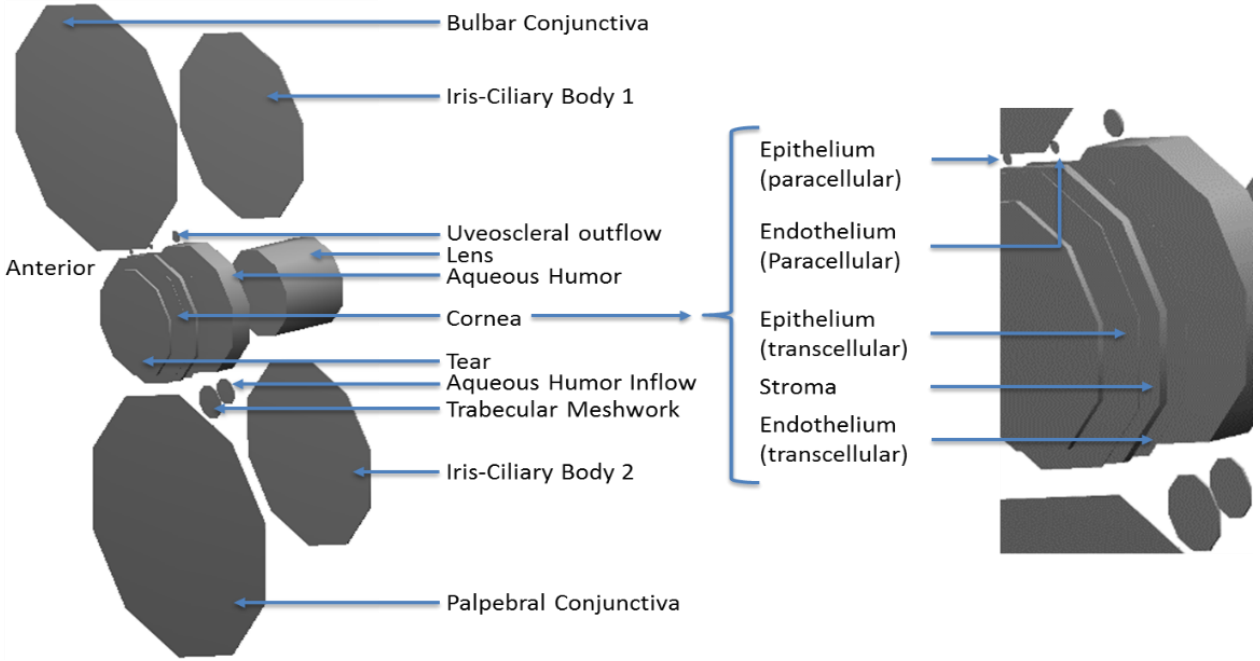
Gupta et al (2010). *Pharm. Res.*, vol. 27, no. 4, pp. 699–711, Apr.

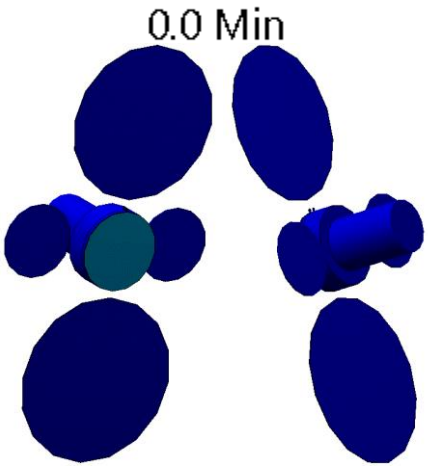
Gupta et al (2012). *Pharm. Res.*, vol. 29, no. 12, pp. 3325–3334.

In Vivo Modeling Approaches: Q3D

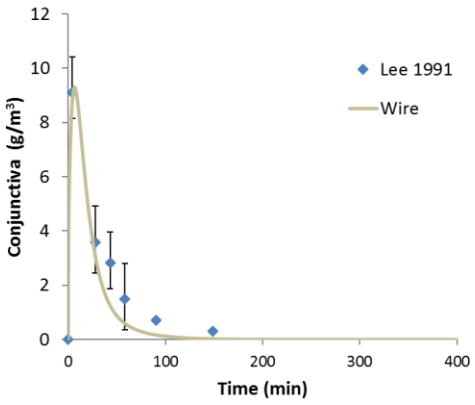


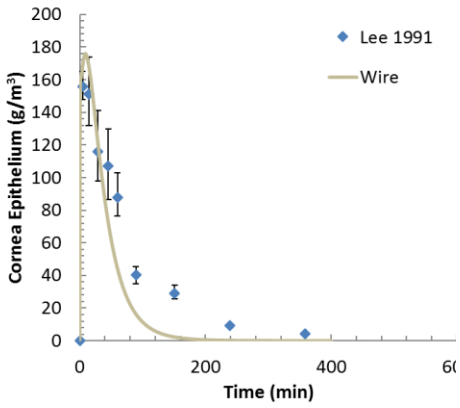
Animation

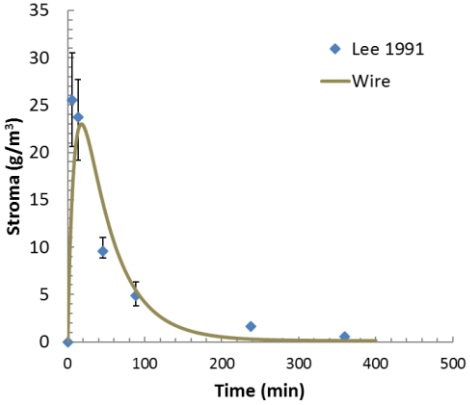




Timolol in the Rabbit Eye



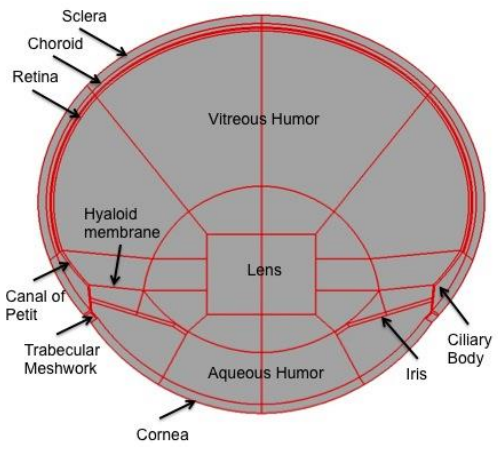




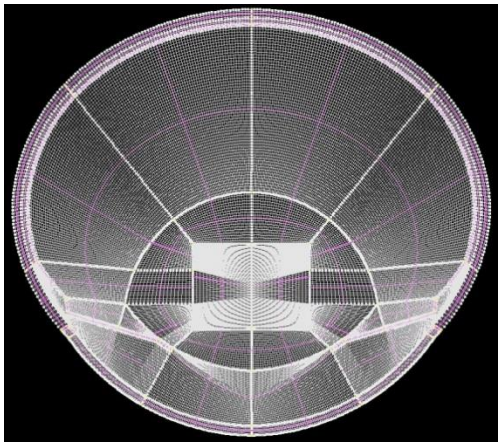
Lee at al (1991) Pharmacokinetic basis for nonadditivity of intraocular pressure lowering in timolol combinations. Invest. Ophthalmology & Visual Sci. Vol.32,2948-2957

In Vivo Modeling Approaches: 2D Axisymmetric

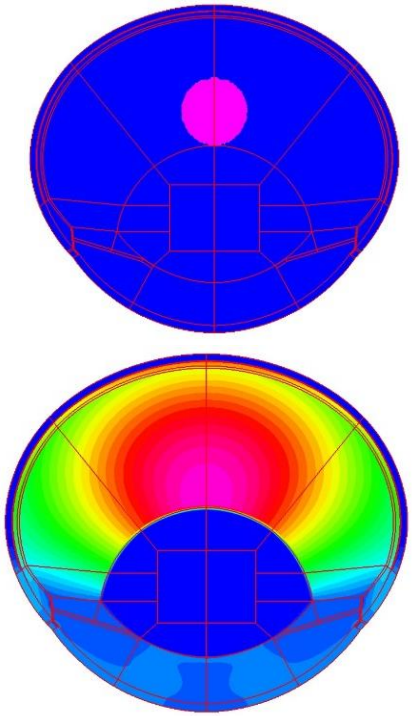
Rabbit Eye Model



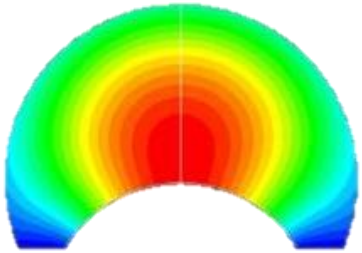
Computational Mesh



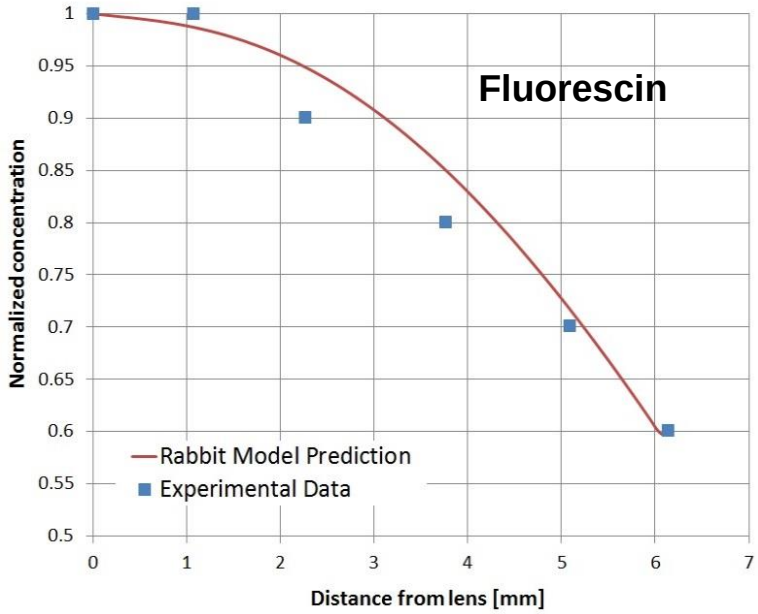
CoBi Predictions

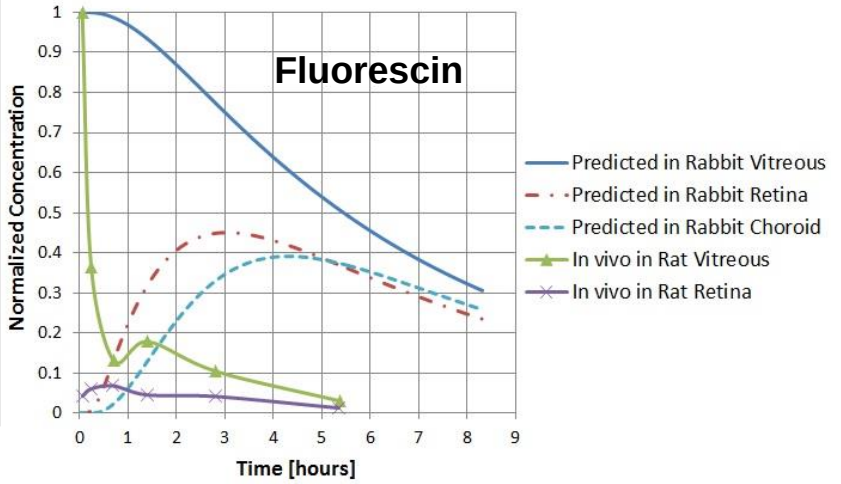


Haghjou et al Predictions



Validation

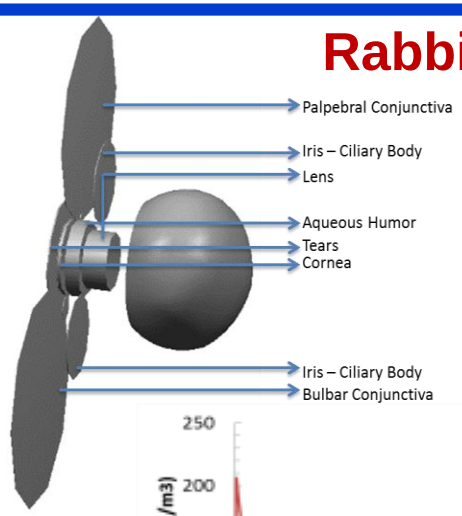




Haghjou N. et al (2011) Computer Modeling of Drug Distribution after Intravitreal Administration. Int J Pharm. & Pharmaceutical Sci. Vol:5, No:5,
M. Araie and D. M. Maurice, (1991) The loss of fluorescein, fluorescein glucuronide and fluorescein isothiocyanate dextran ….*Exp. Eye Res*., vol. 52,;27–39

Whole-Eye Model: Q3D-3D Coupling

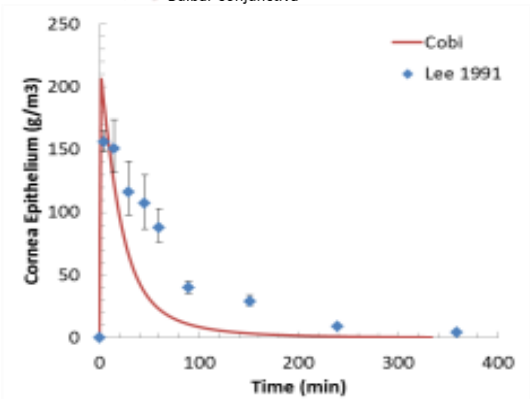
Rabbit Model

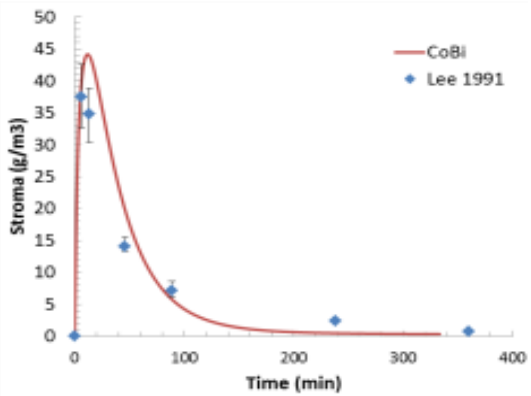


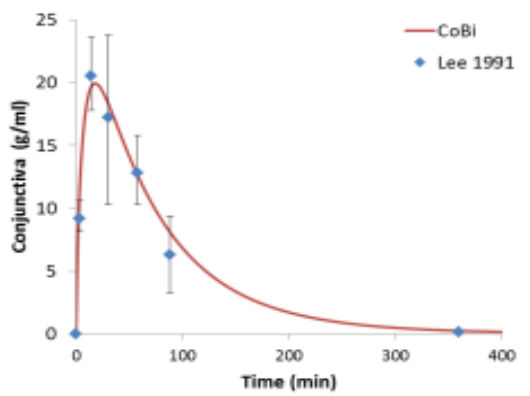
Q3D-3D Coupled Model:

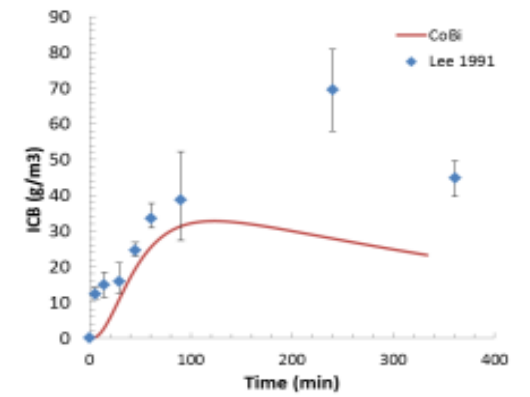
- Anterior Eye – Q3D
- Posterior Eye – 3D

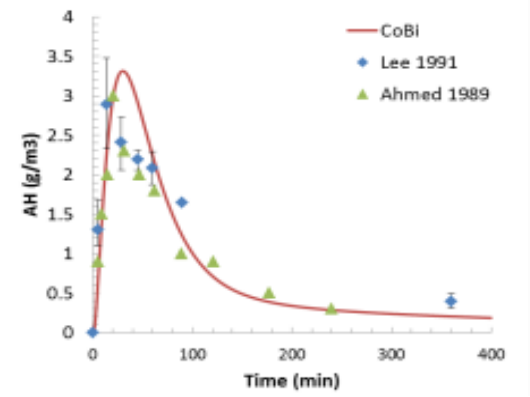
PK Profiles - Timolol

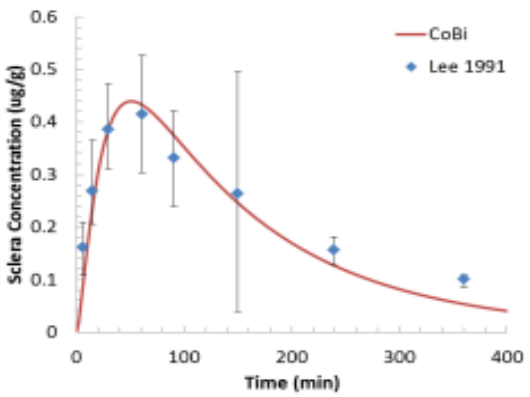












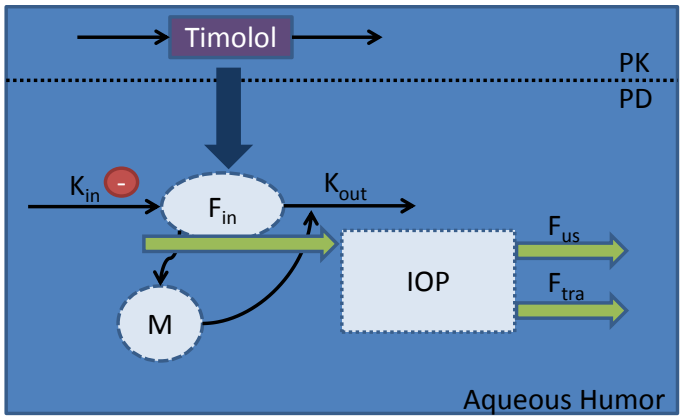
Lee at al (1991) Pharmacokinetic basis for nonadditivity of intraocular pressure lowering in timolol combinations. Invest. Ophthalmology & Visual Sci. Vol.32,2948-2957

Pharmacodynamic Modeling

PD model:

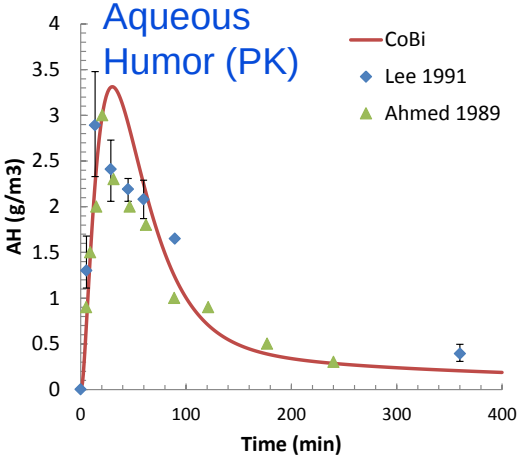
- 5 mg/ml instillation of Timolol causes IOP drop
- Increasing Timolol concentration extends duration of IOP drop, but IOP will not dip below ~17.6mmHg due to M regulator

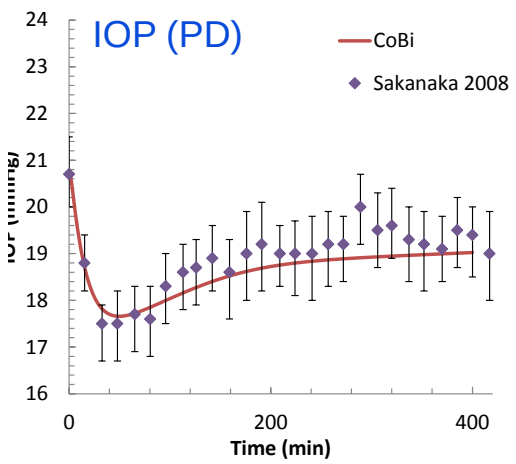
PD Model Schematic



PD Model Parameters

Constant	Value	Description	Units
IC_{50}	5.71E-3	Drug amount needed to inhibit F_{in}	nmol/ml
I_{max}	0.268	Timolol max inhibitory effect	
C_{of}	0.170	outflow facility	µl/min/mmHg
P_v	9	Episcleral Venous Pressure	mmHg





PD Model Equations

$$F_{tra} = C_{of}\left(IOP - P_V\right)$$

$$IOP = Pv + \frac{F_{in} - F_{us}}{C_{of}}$$

$$\frac{dF_{in}}{dt} = K_{in}\left(1 - \frac{I_{\max}\cdot C_A}{IC_{50} + C_A}\right) - K_{out}\cdot F_{in}\cdot(1+M)$$

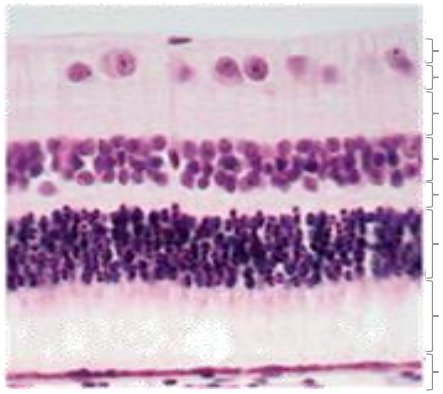
$$\frac{dM}{dt} = K_t\left(F_{in} - M\right)$$

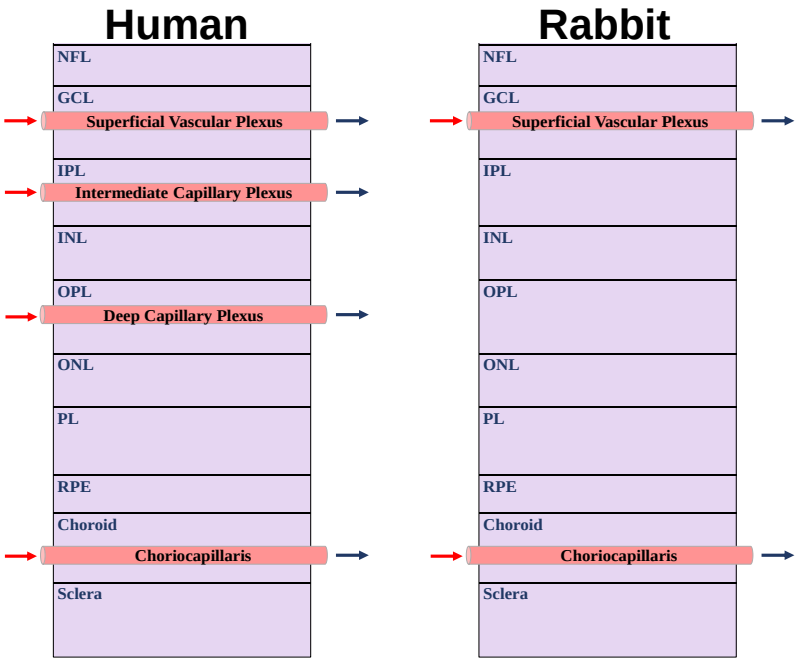
$$\frac{dIOP}{dt} = \frac{1}{C_{of}}\left[K_{in}\left(1 - \frac{I_{\max}C_A}{IC_{50} + C_A}\right) - K_{out}\left(F_{tra} - F_{us}\right)(1+M)\right.$$

Sakanaka et al. (2008). *Biological & Pharmaceutical Bulletin*, *31*(5), 970–5.

High-Resolution Modeling of the Retina

Anatomy





Model Equations

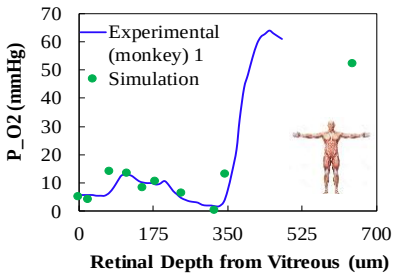
Tissue:

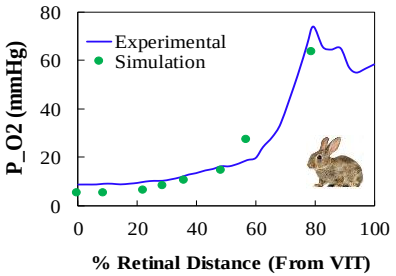
$$\frac{\partial C_i}{\partial t} = J_{D\_i-1\_i} - J_{D\_i\_i+1} + \frac{A_{retina} \cdot \psi_{b-t} \cdot \left(C_j - C_i\right)}{V_i}$$

Blood:

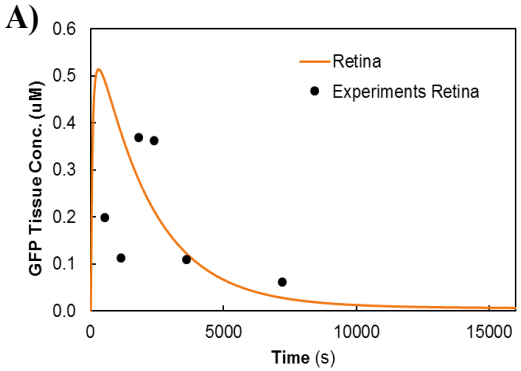
$$\frac{\partial C_j}{\partial t} = \frac{Q_j \cdot \left(0 - C_j\right)}{V_j} - \frac{A_{retina} \cdot \psi_{b-t} \cdot \left(C_j - C_i\right)}{V_j}$$

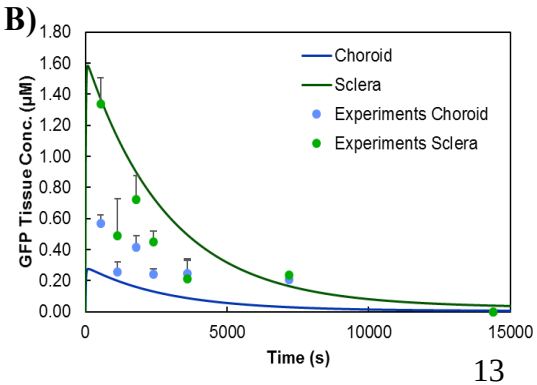
Oxygenation Profiles





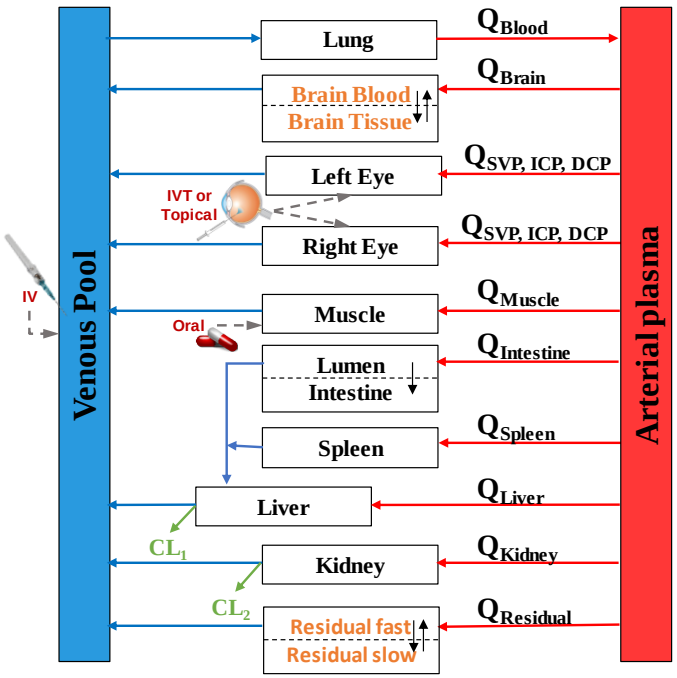
Tracer PK Profiles (GFP) Periocular Pnjection in the Rabbit Eye





PBPK-High-Resolution Eye Modeling/Validation

Mouse PBPK Model



Organ Model Eqs.

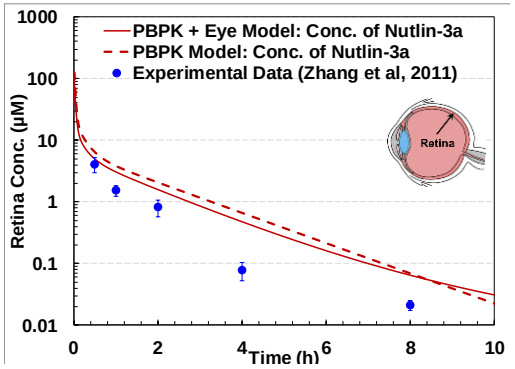
Perfusion-Limited

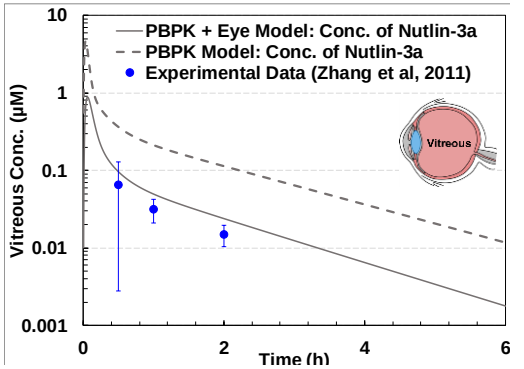
$$V_i \cdot \frac{dC_i}{dt} = Q_i \cdot \left(C_{ART\_PL} - \frac{C_i}{K_i} \right)$$

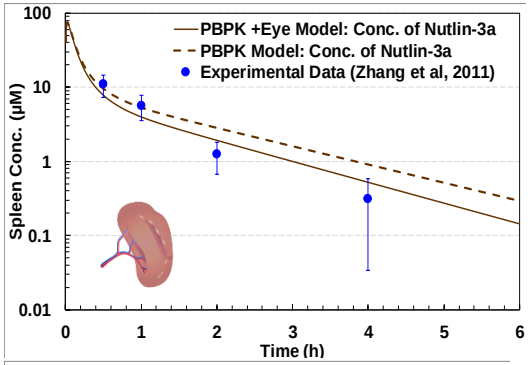
Permeability-Limited

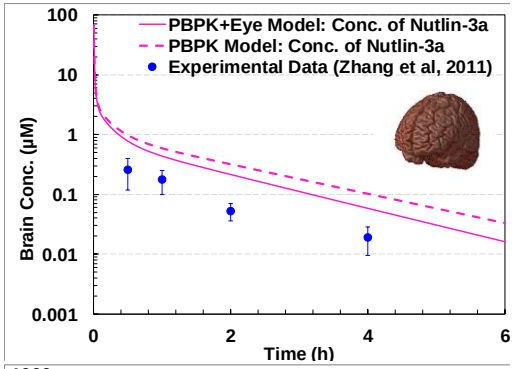
$$V_j \cdot \frac{dC_j}{dt} = PA_j \cdot \left(C_i - \frac{C_j}{K_j} \right)$$

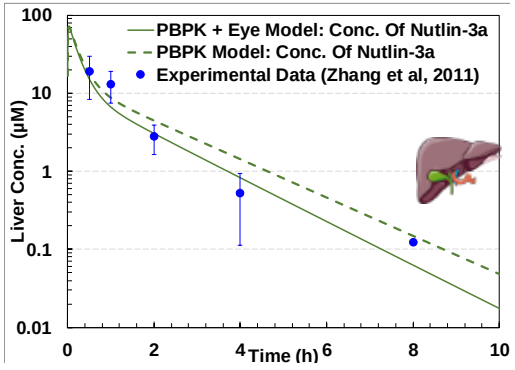
Nutlin-3A

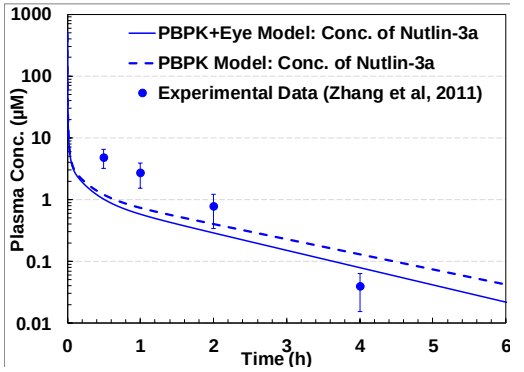












Summary and Plans

- Developed components of a multiscale computational framework, CoBi, for modeling in vitro and in vivo ocular drug delivery, PK/PD
- Developed a framework for modeling in vitro dissolution of
  - ophthalmic products (suspensions, micelles, …) validation in progress
  - dissolution equipment (USP2 USP 4, Transwell,…)
- Developed Q3D models of the anterior eye , posterior eye (retina)
- Performed initial validation of model components

- Ongoing
  - Improves of the Anterior Eye Model (anatomic geometry, tear film)
  - Development and validation of dissolution model for complex drug products
  - Models of Topical Delivery of Suspension Products
  - Integration of the In vitro and In vivo models
  - Development of model based IVIVE

CoBi tools and all models available on Open Source