Developing PBPK for Ocular Delivery

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Simulations Plus, Inc.
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

- **Blue arrows** – distribution between ocular and systemic circulation
- **Orange arrows** – distribution between compartments due to other convective flows (tear flow, nasolacrimal drainage, stromal thinning)
- **Red arrows** – distribution between compartments due to convective flow of aqueous humor
- **Black arrows** – distribution between eye compartments due to passive diffusion and/or carrier mediated transport
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 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.

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.

Sensitivity to viscosity and particle size.

Viscosity:
- 72.9 cP
- 1.67 cP

### Table

<table>
<thead>
<tr>
<th>Viscosity</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>AUC&lt;sub&gt;0→3&lt;/sub&gt; (µg·h/mL)</th>
</tr>
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<tbody>
<tr>
<td><strong>TOBRADEX ST&lt;sup&gt;α&lt;/sup&gt;</strong> 0.05%</td>
<td>0.106 ± 0.019</td>
<td>0.081</td>
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<tr>
<td><strong>TOBRADEX&lt;sup&gt;α&lt;/sup&gt;</strong> 0.1%</td>
<td>0.069 ± 0.022</td>
<td>0.06</td>
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**Notes:**
Other Validation Cases

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)
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