Fluorometholone Ocular Suspension PBPK simulations using the OCAT™ model in GastroPlus™

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Abstract

Purpose:
Development of generic formulations of ophthalmic corticosteroids and regulatory acceptance of bioequivalence can be facilitated by analysis of the mechanisms of ocular dissolution, absorption, distribution, and elimination. For this purpose we developed an *in silico* ocular PBPK model for fluorometholone (FML), a commonly preferred ophthalmic corticosteroid.

Methods:
The Ocular Compartmental Absorption and Transit™ (OCAT™) model within GastroPlus 9.0 was used to build a mechanistic compartmental model to account for extraocular loss of the administered dose, dissolution, ocular absorption, and distribution in the albino rabbit eye. Due to the lack of literature data for intravenous and oral delivery of FML, we built a systemic distribution and clearance model using biopharmaceutical properties estimated by ADMET Predictor™ 7.1. We used experimental permeability for cornea (Hull, 2002). Permeability for conjunctiva, aqueous humor, and iris-ciliary body, and systemic elimination rate for iris-ciliary body, were fitted to match the observed aqueous humor concentrations for the saturated solution dose. The OCAT model simulation results for FML administered as a 0.1% suspension were then compared to the experimental aqueous humor concentrations reported in the literature (Sieg, 1975). Particle size sensitivity analysis was also performed.

Results:
The OCAT model simulations matched the observed aqueous humor concentrations for both the saturated solution and the 0.1% suspension. The duration and AUC of the aqueous humor concentrations for the suspension formulation were sensitive to the particle size distribution.

Conclusions:
The OCAT model resulted in important insights into the mechanisms of dissolution, absorption, and distribution of an ocular solution and suspension formulations.

Biopharmaceutical and Clinical Data

Table 1 lists the experimental properties of FML that were found in the literature with references. For any properties that were not available, we used ADMET Predictor™ ver. 7.1 (AP, Simulations Plus, Inc.) to estimate the property.

Table 1. Fluorometholone Properties

Biopharmaceutical Property	Value	Source/Reference
Log $P_{o/w}$	2.0	Grass, 1984
Aq. Solubility	16 µg/mL	Hui, 1986,
S+Rbp	0.90	AP (ver. 7.1)
fup	20.7%	Absorption Systems Lighthouse Database
Caco-2 Papp	3.23 x 10^{-5} cm/s	Absorption Systems Lighthouse Database
HLM Stability	39.3 min	$t_{1/2}$ Abs. Sys. Lighthouse Database

Where:
S+Rbp = Blood-to-plasma concentration ratio
AP ver 7.1 = ADMET Predictor ver. 7.1
Fup = percent unbound in plasma

The aqueous humor concentrations in male albino rabbits are from the work of Sieg and Robinson, 1975.

Methods

The physiologically based pharmacokinetic (PBPK) model of FML ocular delivery was simulated using GastroPlus™ 9.0 (Simulations Plus, Inc., Lancaster, CA) and it's PBPKPlus™ module to estimate the tissue distribution and systemic clearance. Rabbit physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR™) Physiology™ module (Agoram, et al. 2001; Bolger, et al. 2006; Bolger, et al. 2009). Tissue/plasma partition coefficients were calculated using Lukacova's algorithm based on tissue composition and *in silico* physicochemical properties (Table 2) (Lukacova, 2008). The systemic metabolic clearance of FML in liver was based on experimental *in vitro* unbound intrinsic clearance calculated from half-life in human liver microsomes (Table 1). The final PBPK model utilized fitted permeabilities for several ocular tissues (Table 2.). The OCAT model is depicted in Figure 1.

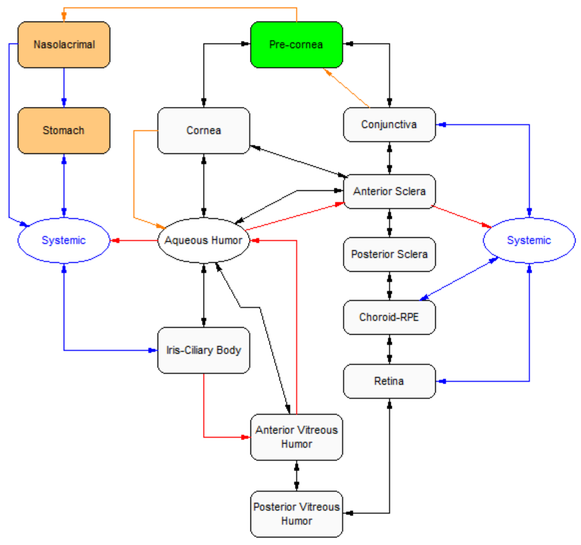

Figure 1 Schematic diagram of the OCAT model in GastroPlus. Black lines represent permeability pathways, Red and Orange lines represent fluid flow convection pathways, and Blue lines represent pathways to and from the systemic circulation.

Results:

Figures 2 and 3 illustrate a poor prediction of aqueous humor concentration as a function of time when using purely in silico estimates of tissue permeability for both solution and suspension formulations.

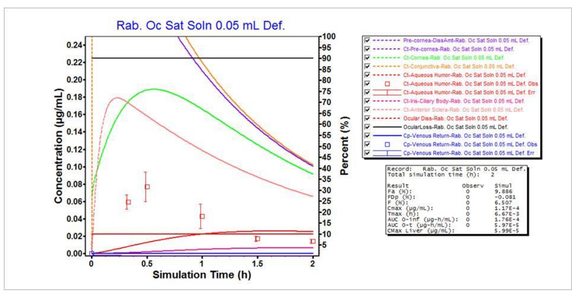

Figure 2 Observed (points) and simulated (lines) aqueous humor concentration vs. time for a saturated solution dose of FML using purely *in silico* parameters.

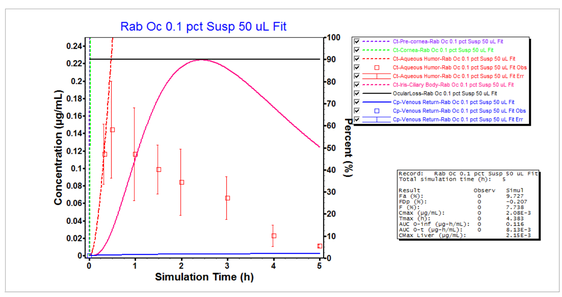

Figure 3 Observed (points) and simulated (lines) aqueous humor concentration vs.. time data for a 0.1% suspension dose of FML using purely *in silico* parameters.

Results continued:

Figures 4 and 5 illustrate the improved simulation of aqueous humor concentration as a function of time when tissue permeability and systemic elimination rates have been fitted to match the observed data.

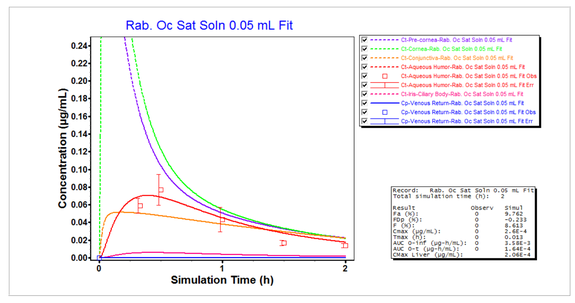

Figure 4 Observed (points) and simulated (lines) aqueous humor concentration vs. time for a saturated solution of FML using the fitted permeabilities from Table 2. The rate of transfer from conjunctiva and iris-ciliary body to the systemic circulation was set to 4E-3 s^{-1} for all simulations.

Table 2. Fitted OCAT tissue permeability (cm/s) Sat. Soln.

Ocular Tissue	Initial Value	Fitted Value	Ratio
Cornea	1.6E-5	1.7E-5	1.06
Conjunctiva	5.1e-5	5.1E-7	0.01
Aqueous Humor	6.6E-6	3.6E-5	5.45
Iris-Cliary Body	1.7E-5	4.8E-5	2.82

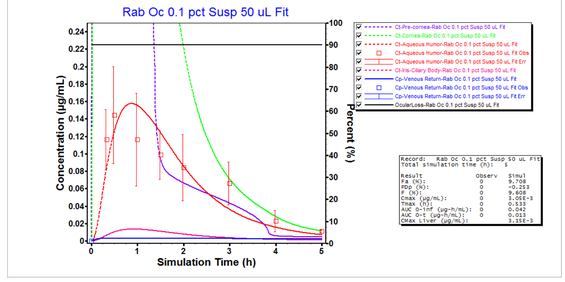

Figure 5 Observed (points) and simulated (lines) aqueous humor concentration vs. time data for a saturated solution of FML using the fitted permeabilities from Table 3.. The rate of transfer from conjunctiva and iris-ciliary body to the systemic circulation was set to 4E-3 s^{-1} for all simulations.

Table 3. Fitted OCAT tissue permeability (cm/s) 0.1% Suspension

Ocular Tissue	Initial Value	Fitted Value	Ratio
Cornea	1.6E-5	1.7E-5	1.06
Conjunctiva	5.1e-5	5.1E-5	1.00
Aqueous Humor	6.6E-6	6.6E-6	1.00
Iris-Cliary Body	1.7E-5	4.8E-5	2.82

Conclusions:

Analysis of the OCAT model simulations provided important insights into the mechanisms of dissolution, absorption, and distribution of ocular solution and suspension formulations. The fitted permeabilities suggest that the solution dose is absorbed primarily through the cornea and into the aqueous humor, and that the suspension dose is primarily absorbed through prolonged contact with the conjunctiva.

References:
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