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Development of an ocular physiologically-based pharmacokinetic model to describe the impact of formulation attributes on the disposition of an antibiotic applied on the rabbit eye

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PURPOSE

"Bottom-up" modeling approaches such as physiologically-based pharmacokinetic (PBPK) modeling allow the evaluation of the impact of formulation components and body physiology parameters on in vivo drug product performance. This is increasingly important for locally-acting products for which drug exposure information at the site of action is not available or not feasible to obtain. Several antimicrobial agents have been approved by the FDA for the treatment of bacterial conjunctivitis. Here, we leveraged drug application data and other literature sources towards the development of a mechanistic ocular PBPK model to describe the ocular and systemic disposition of an ophthalmic antibiotic (Drug A) following the application of Drug A ophthalmic suspension in rabbits.

OBJECTIVES

To develop and verify an ocular PBPK model of an antibiotic applied on the rabbit eye as a suspension that can be utilized:

- To identify formulation attributes impacting ocular and systemic exposure
- To quantitatively describe the impact of the previously identified formulation attributes on ocular and systemic disposition

METHODS

The Ocular Compartmental Absorption & Transit (OCAT™) module built within GastroPlus™ 9.6 was used to describe ocular absorption of Drug A. A two-compartment model was chosen to describe systemic exposure. Dose volume was 50 µL. Physicochemical parameter values were obtained from literature sources[1] and the ADMET™ Predictor v6.1. Solubility and particle size distribution data for Drug A were retrieved from information submitted to the FDA. High viscosity was assumed for this drug and, to reflect that assumption, the drainage rate constant was set equal to 0.1 min^{-1} [2]. Saturable melanin and precornea volume information (30 µL) were incorporated into the model. Default model parameter values were utilized for model building with the exception of conjunctiva and sclera optimized permeabilities which were set equal to $2.39 \cdot 10^{-5}$ and $3 \cdot 10^{-4}$ cm/sec. The iris-ciliary body systemic absorption rate constant was optimized and set to $5.01 \cdot 10^{-2}$ 1/sec. The conjunctiva surface area was modified based on literature sources[3]. Iris-ciliary body, retina, choroid and sclera melanin protein content (mg of protein) were modified based on literature sources[4,5]. Parameter optimization was performed manually. The final model parameter values were within a physiological range reported in the literature[6]. The parameter sensitivity analysis module within GastroPlus™ was used to identify model parameters of increased impact on ocular/systemic bioavailability.

RESULTS

Model Verification: the predictions generated using the ocular PBPK model described Drug A concentrations versus the time profiles in various ocular tissues reasonably well.

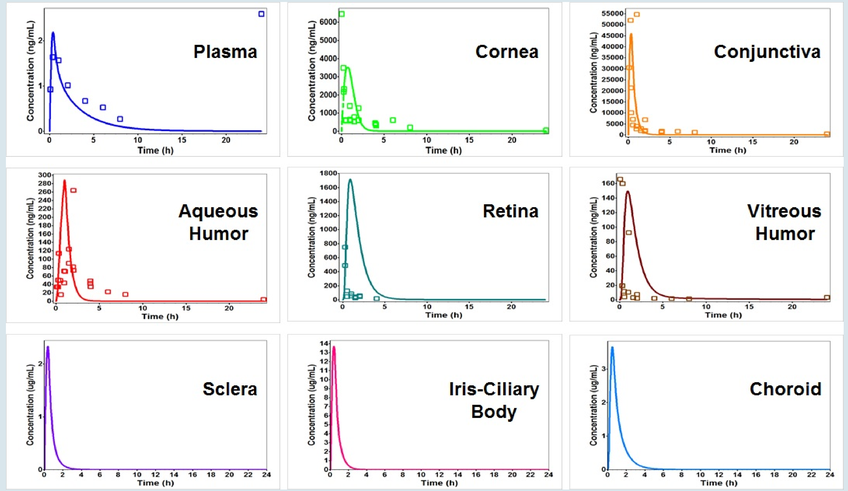

Figure 1. Predicted (mean, solid line) versus observed (mean, symbols) pharmacokinetic (PK) profiles of Drug A in plasma, cornea, conjunctiva, aqueous humor, retina and vitreous humor following instillation of 50 µL of ophthalmic suspension of Drug A in rabbits. Predicted (mean, solid line) PK profiles of Drug A in sclera, iris-ciliary body and choroid are provided. Simulated profiles were generated utilizing the developed ocular PBPK model in rabbits. Observed data were retrieved from information submitted to the FDA.

Viscosity, not particle size, impacts Drug A exposure in conjunctiva.

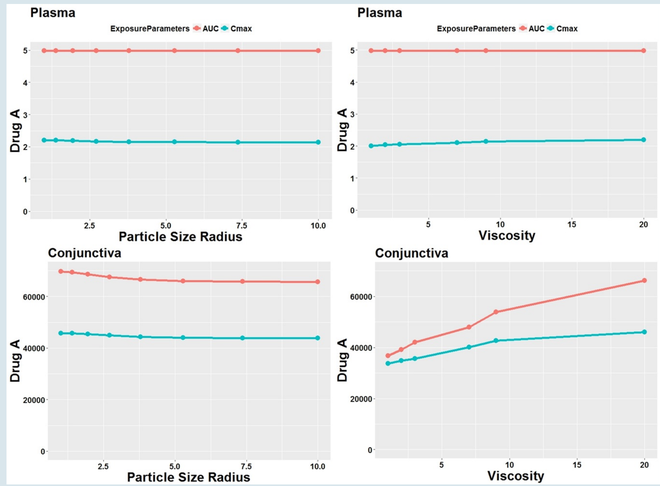

Figure 2. Sensitivity analysis of the impact of particle size (radius, µm) and viscosity (cps) on Drug A exposure (C_{max} and AUC) in plasma and conjunctiva. Conjunctiva C_{max} and AUC decreased by 36.5% and 80.3%, respectively, in response to a decrease in viscosity (20 cps). A slight decrease in exposure in conjunctiva (4.5 % for C_{max} and 6.1 % for AUC) was observed when particle size was assumed to change from 1 to 10 µm.
C_{max} (ng/mL): maximum concentration, AUC (ng· h/mL): area under the concentration versus time curve.

Melanin binding is critical for predicting drug disposition in aqueous humor.

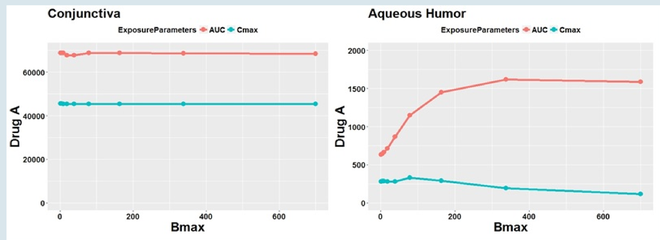

Figure 3. Sensitivity analysis of the impact of Bmax and Kd (data not shown) on Drug A exposure (C_{max} and AUC) in conjunctiva and aqueous humor.

CONCLUSIONS

The developed model can be used to quantitatively describe the impact of formulation components and physiology parameters on the in vivo performance of Drug A administered as ophthalmic suspension in rabbits.

- Viscosity appeared to have a noteworthy impact on ocular bioavailability in conjunctiva and AUC was more sensitive to viscosity changes than C_{max}. The impact of particle size on simulated local exposure was minimal.
- Neither viscosity nor particle size were predicted to impact systemic exposure of Drug A.
- Protein (melanin) binding impacted Drug A distribution in aqueous humor, but not in conjunctiva.
- Future endeavors will focus on further model verification and model scale-up to predict the disposition of Drug A in humans.

REFERENCES/DISCLAIMER

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