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Application of Ocular Physiologically Based Pharmacokinetic Modeling to Understand the Impact of Particle Size and Viscosity on Ophthalmic Bioavailability of TOBRADEX ST© Suspension in Rabbits

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BACKGROUND

- Generics represent 88% of prescriptions for a cost of 28% of drug market[1].
- From 2011 through 2016, suspension formulations represented 29% of the FDA approved topical ophthalmic formulations[2].
- Demonstrating therapeutic bioequivalence (BE) for ophthalmic suspensions is challenging, costly and time consuming.
- Critical formulation attributes for ophthalmic suspensions such as particle size (PS) and viscosity could impact *in vivo* performance.
- However these formulation attributes repercussion on drug ocular disposition has not been well characterized.
- Quantitative methods such as physiologically-based pharmacokinetic modeling (PBPK) can support regulatory decisions regarding BE.

OBJECTIVES

- Verify an Ocular Compartmental Absorption & Transit (OCAT)-PBPK model predicting the concentration-time course of dexamethasone (Dex) in ocular tissues and plasma after an injection of TOBRADEX ST© in the rabbit eye.
- Investigate model abilities to simulate the impact of PS and viscosity on Dex disposition in ocular tissues.
- Understand the impact of PS and viscosity on maximum concentration (Cmax) and area under the curve (AUC) for different bio-phases.

METHODS

- *In vivo* analysis of Dex ocular disposition following the unilateral administration of 30 µL of TOBRADEX ST© (Dex, 0.05%/tobramycin, 0.3%, η= 72.7 cP) in rabbit eye.
- OCAT-PBPK verification (GastroPlus™ 9.5) → TOBRADEX ST© *in vivo* data.
- Analysis of PS (literature data[3]) and viscosity (TOBRADEX© (Dex, 0.1%/ tobramycin, 0.3%, η= 1.67 cP, NDA 50-818 Pharmacology review[4])) impact on Dex ocular disposition.
- Sensitivity analysis was conducted to understand the impact of PS and viscosity on Cmax and AUC in aqueous humor and plasma.

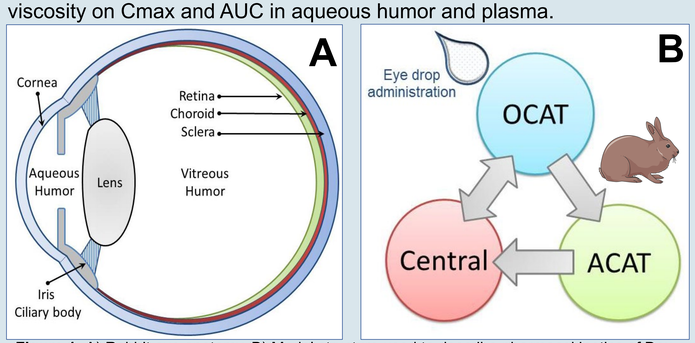

Figure 1: A) Rabbit eye anatomy. B) Model structure used to describe pharmacokinetics of Dex. OCAT: Ocular Compartmental Absorption & Transit ; ACAT: Advanced Compartmental and Transit

RESULTS

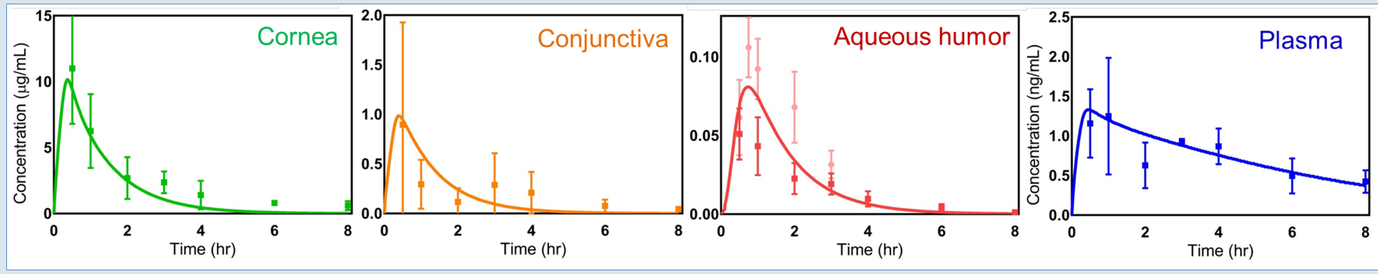

Figure 2: Concentration-time course following the unilateral administration of 30 µl of TOBRADEX ST© 0.05% in a rabbit eye. Dots represent experimental data for cornea (green), conjunctiva (orange) aqueous humor (red) and plasma (blue). Aqueous humor data from NDA 50-818 pharmacology review[4] (pink) were also used to calibrate the model. Lines represent model simulations after manual optimization of tissue permeabilities. Cornea permeability was fixed based on *in vitro* permeation test. Drainage rate (DR) was set to 0.1 min^{-1} to account for TOBRADEX ST© viscosity (η= 72.7 cP) according to literature[5].

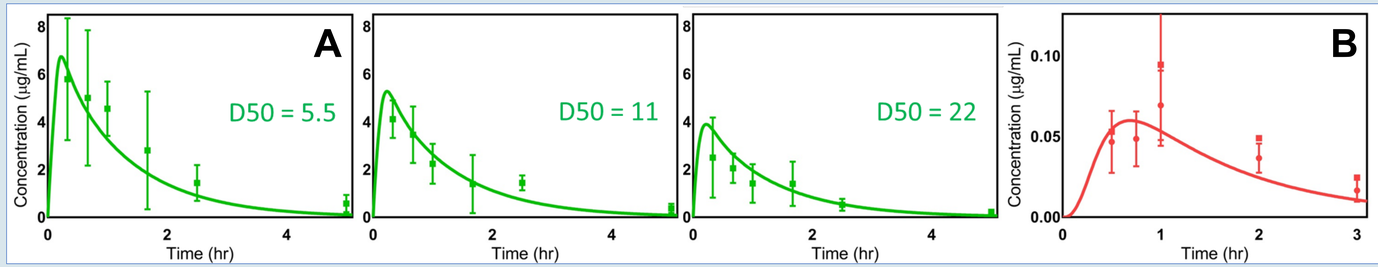

Figure 3: A) Model-based simulation for cornea concentration-time course after unilateral administration of three Dex 0.1% formulations to rabbit with different mean PS (D50= 5.5 ; 11 ; 22 µm)[3].
B) Concentration-time course in aqueous humor following the unilateral administration of 30 µl of TOBRADEX© 0.1% (D50=4, η=1.67cP) in a rabbit eye. DR was estimated to be 0.4 min^{-1} to account for reduced viscosity of this formulation[4].

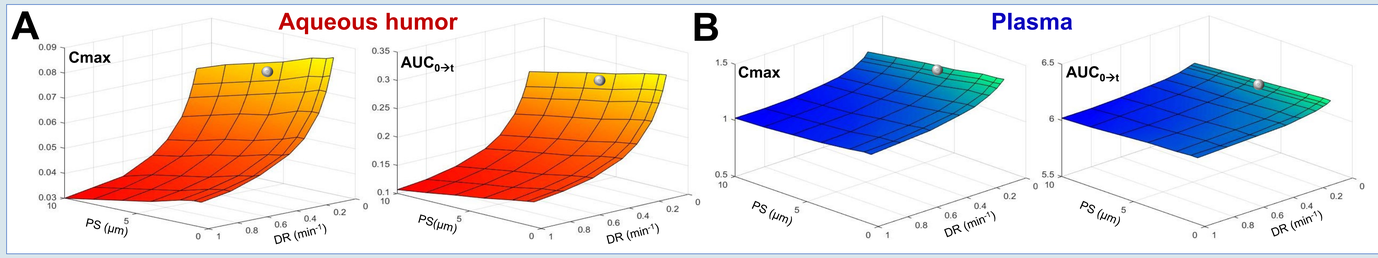

Figure 4: Impact of mean PS (0.5< D50 <10 µm) and viscosity (0.1< DR <1 min^{-1}) on Dex Cmax and $AUC_{0\rightarrow t}$ in A) aqueous humor and B) plasma, following the unilateral administration of 30 µl ophthalmic suspension 0.05% in a rabbit eye.
Baseline values for TOBRADEX ST © are presented by the grey dots (DR=0.1 min^{-1} and D50=5 µm).

CONCLUSIONS

- An OCAT-PBPK model using Gastroplus 9.5 was verified based on *in vivo* rabbit data for Dex ocular distribution following TOBRADEX ST© administration (Fig 2).
- The developed OCAT-PBPK model well-predicts the impact of particle size and viscosity on Dex disposition in rabbit eyes (Fig 3) .
- Model-based simulations indicate (Fig 4):
  - Limited impact of a reasonable particle size modification (0.5< D50 <10µm) on aqueous humor Cmax & AUC.
  - Significant impact of viscosity (0.1< DR <1 min^{-1}) on aqueous humor Cmax & AUC.
  - Plasma exposure cannot be used as a surrogate for ocular exposure, because the rate and extent of Dex appearing in the systemic circulation do not reflect the rate and extent of Dex delivery to the ocular tissues.

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