Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Ofloxacin Ointment Case Study

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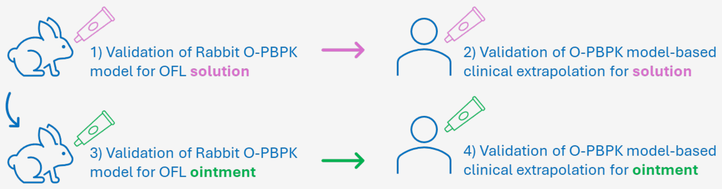
PURPOSE

- Development of generic ophthalmic drug products is challenging due to the complexity of the ocular system and a lack of sensitive testing tools to evaluate its interplay with ophthalmic formulations
- Due to their poor sensitivity, and associated costs, comparative clinical endpoint bioequivalence (BE) studies for a generic ocular drug product are a significant challenge to the pharmaceutical industry
- Ocular physiologically based pharmacokinetic (O-PBPK) modeling is an alternative to support regulatory assessment of ophthalmic drug products
- O-PBPK models have already demonstrated their value in predicting clinical pharmacokinetics (PK) for ophthalmic solutions
- The purpose of this research is to demonstrate the ability of O-PBPK models, validated against rabbit PK data, to predict clinical ocular exposure, following topical administration of ophthalmic ointments

OBJECTIVES

- To develop and validate an O-PBPK for Ofloxacin (OFL) administered as an ophthalmic solution and ointment in rabbits
- To predict OFL clinical ocular exposure following topical administration in healthy subjects and patients undergoing ophthalmic surgery

METHODS



- All simulations were performed using GastroPlus® (Version 9.9 Simulation Plus Inc., Lancaster, CA, USA). The Ocular Compartmental Absorption and Transit (OCAT™) model was used to build an O-PBPK model for OFL solution and ointment. The OCAT accounts for nasolacrimal drainage, ocular absorption, and distribution in the eye.
- The model was initially validated using rabbit PK data following OFL topical solution administration. Cornea epithelium and conjunctiva permeabilities, and iris-ciliary body systemic absorption rate were optimized (5E-7 cm/s, 1.05E-5 cm/s, and 1.25E-3 1/s, respectively).
- The OCAT model was subsequently used to predict OFL ophthalmic solution exposure in humans by adjusting the physiological parameters to match human ocular physiology. All OFL-specific parameters were kept constant between rabbit and human simulations.
- The model was then validated for ointment application in rabbit by fitting the application time (0.4 hr) and Higuchi release constant (7.5*E-5 mg/($s^{1/2}$ cm^2)). In a similar fashion to the topical solution, clinical prediction following ointment administration was performed.

RESULTS

Preclinical studies used for OFL ophthalmic solution OCAT model development and validation in rabbits were based on single or multiple dose administrations of 0.3% (w/v) OFL solution in New Zealand White (NZ), or Dutch Belted (DB) rabbits. The administered volumes were either 100 uL (0.3 mg dose), 50 uL (0.15 mg dose) or 30 uL (0.09 mg dose).

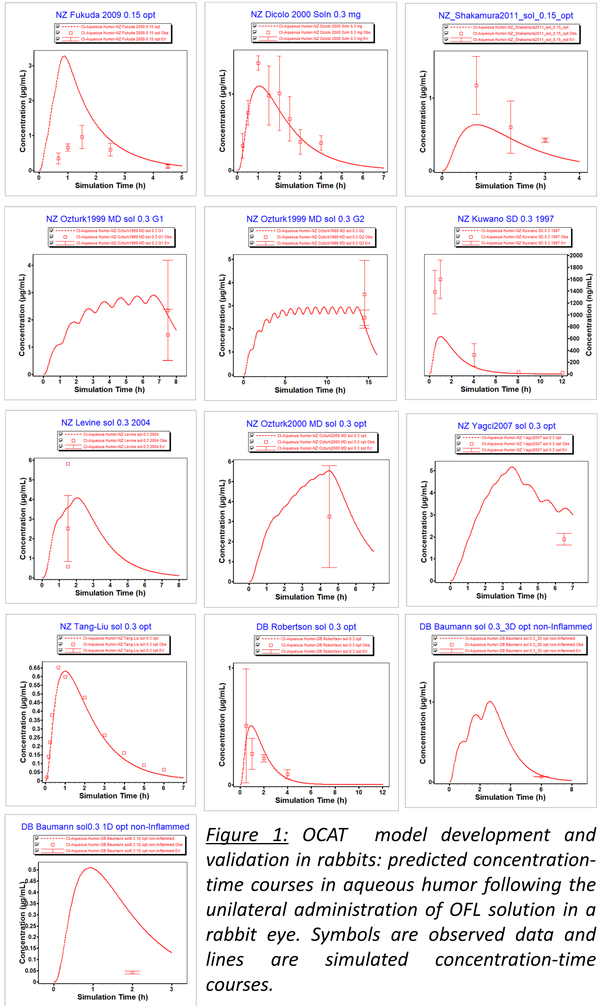


Figure 1: OCAT model development and validation in rabbits: predicted concentration-time courses in aqueous humor following the unilateral administration of OFL solution in a rabbit eye. Symbols are observed data and lines are simulated concentration-time courses.

Clinical studies used for human extrapolation were based on single or multiple dose administrations of 100 uL (0.3 mg dose), 50 uL (0.15 mg dose) of 0.3% (w/v) OFL solution in healthy subjects.

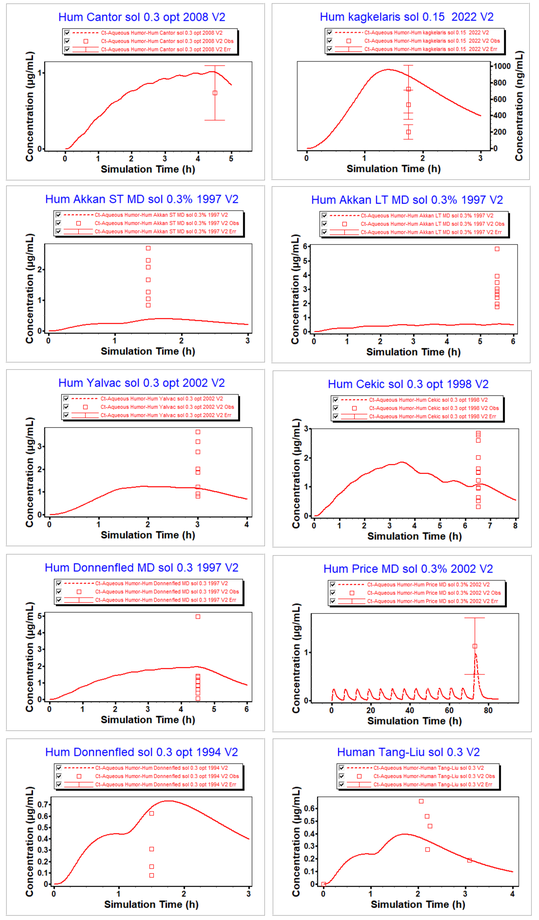


Figure 2: OCAT Human extrapolation: predicted concentration-time courses in aqueous humor following the unilateral administration of OFL solution in human eyes. Symbols are observed data and lines are simulated concentration-time courses.

For the ointment formulation, the Higuchi release rate and the residence time were fitted to describe the observed data.

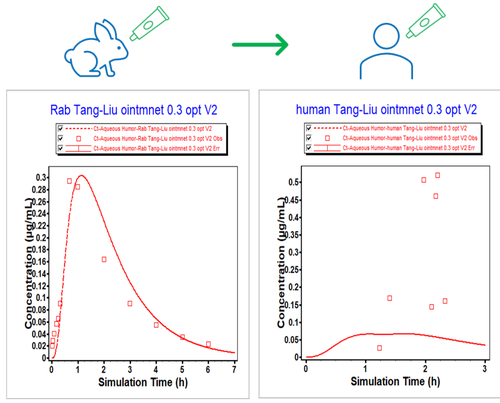


Figure 3: Rabbit Validation and Human extrapolation following single administration of Ofloxacin 0.3 % ointment. Symbols are observed data and lines are simulated concentration-time courses.

CONCLUSION

- Preliminary data suggest that the OCAT model reasonably predicts human ocular AH exposure once validated with rabbit ocular PK data for OFL ophthalmic solution and ointment
- Due to the significant intersubject and interstudy variability in observed human ocular exposure, extrapolation from more case studies is necessary to validate the O-PBPK extrapolation method
- Successful clinical extrapolation of OFL ophthalmic ointment represents an important step in validating the use of O-PBPK models for the prediction of human ocular exposure following topical administration of ophthalmic ointment drug products

REFERENCES

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