Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Moxifloxacin Solution 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
- Identifying the impact of any differences in manufacturing, formulation, or physicochemical characteristics between a generic ocular drug product and its reference listed drug product is critical to maintain safety and efficacy for patients
- Due to their poor sensitivity, associated costs, and ethical limitations, comparative clinical endpoint bioequivalence (BE) studies for a generic ocular drug product are a significant challenge to pharmaceutical industry
- The purpose of this research is to demonstrate the value of ocular mechanistic absorption models (MAM) linked to physiologically based pharmacokinetic (PBPK) models validated against rabbit pharmacokinetic (PK) data to predict clinical ocular exposure

OBJECTIVE

- To develop and validate a MAM-PBPK for moxifloxacin (Mox) administered as an ophthalmic solution in rabbits
- To predict Mox clinical ocular exposure following topical administration in patients undergoing cataract, virectomy, and keratoplasty surgeries

METHODS

- All simulations were performed using GastroPlus® (Version 9.8.2 Simulation Plus Inc., Lancaster, CA, USA)
- Ocular Compartmental Absorption and Transit (OCAT™) model was used to build a MAM for Mox ophthalmic solution. The OCAT accounts for nasolacrimal drainage, ocular absorption, and distribution in the eye
- Cornea epithelium and aqueous humor permeabilities as well as melanin binding were optimized to capture rabbit data. External validations were performed using five additional ocular PK datasets in rabbits
- The OCAT model was subsequently used to predict Mox exposure in humans by adjusting the physiological parameters to match human ocular physiology. All of Mox specific parameters were kept constant between rabbit and human simulations

RESULTS

Table 1: Summary of pre-clinical studies used for Mox ophthalmic solution OCAT model development and validation in rabbit.
NZ = New Zealand Rabbit; DB = Dutch Belted Rabbit; AH = Aqueous Humor, Conj = Conjunctiva, ICB = Iris Ciliary Body; VH = Vitreous Humor

Study code	strain	Doses (%)	Dose	Volume (µL)	Tissue of Interest
Mox.NZ.1	NZ	0.5	single	50	Cornea, AH
Mox.NZ.2	NZ	0.5	single	30	AH
Mox.NZ.3	NZ	0.5	multiple	50	AH
Mox.NZ.4	NZ	0.5	multiple	50	AH
Mox.NZ.5	NZ	0.5	multiple	50	Cornea, ICB, AH, VH
Mox.DB.1	DB	0.3	single	30	Cornea, AH, ICB
Mox.DB.2	DB	0.5	single	50	Cornea, Conj, AH, VH

Model Development

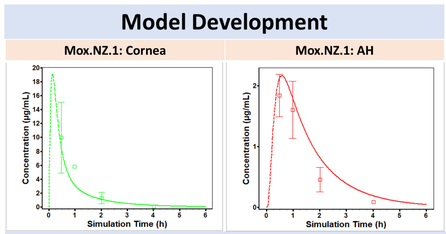
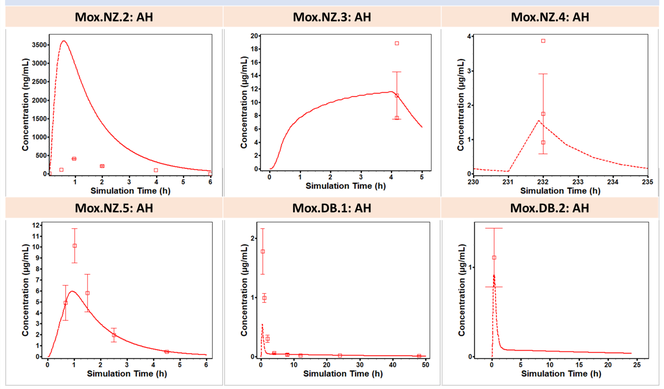


Figure 1: OCAT model development and validation in rabbit: Concentration-time course following the unilateral administration of Mox solution in a rabbit eye. Squares are observed cornea (green) and aqueous humor (AH, red) data and lines are simulated concentration-time courses.

Model Validation



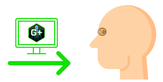


Table 2: Summary of clinical studies used for human extrapolation to predict clinical ocular exposure following topical (solution) Mox administration

Study Code	Surgery	Doses (%)	Dose	Volume (µL)	Tissue of Interest
Mox.Hum.1	cataract	0.5	Single	39	AH
Mox.Hum.2	cataract	0.5	multiple	39	AH
Mox.Hum.3	cataract	0.5	multiple	39	AH
Mox.Hum.4	cataract	0.5	multiple	39	AH
Mox.Hum.5	cataract	0.5	multiple	39	AH
Mox.Hum.6	cataract	0.5	multiple	39	AH
Mox.Hum.7	cataract	0.5	multiple	39	AH
Mox.Hum.8	cataract	0.5	multiple	39	AH
Mox.Hum.9	cataract	0.5	multiple	39	AH
Mox.Hum.10	cataract	0.5	multiple	39	AH
Mox.Hum.11	cataract	0.5	multiple	39	AH
Mox.Hum.12	keratoplasty	0.3	multiple	39	Cornea, AH
Mox.Hum.13	keratoplasty	0.5	multiple	39	Cornea, AH
Mox.Hum.14	virectomy	0.5	multiple	39	AH, VH
Mox.Hum.15	virectomy	0.5	multiple	39	AH, VH
Mox.Hum.16	virectomy	0.5	multiple	39	VH
Mox.Hum.17	virectomy	0.5	multiple	39	VH
Mox.Hum.18	healthy	0.5	Single	39	Conjunctiva
Mox.Hum.19	healthy	0.5	Single	39	Conjunctiva

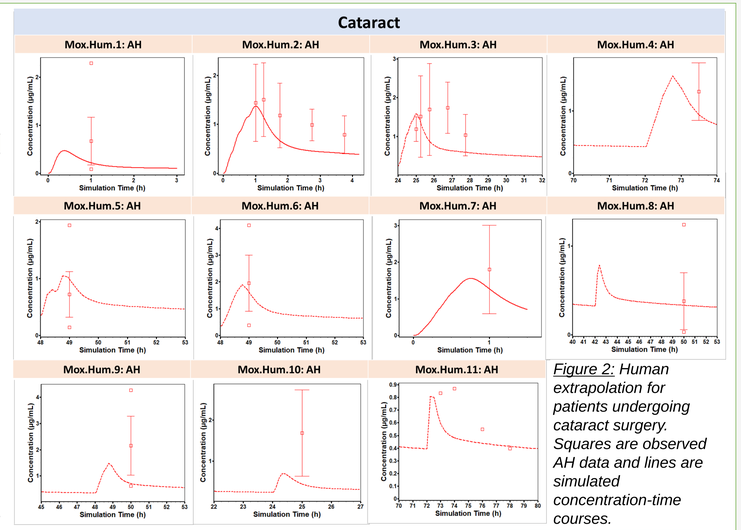


Figure 2: Human extrapolation for patients undergoing cataract surgery. Squares are observed AH data and lines are simulated concentration-time courses.

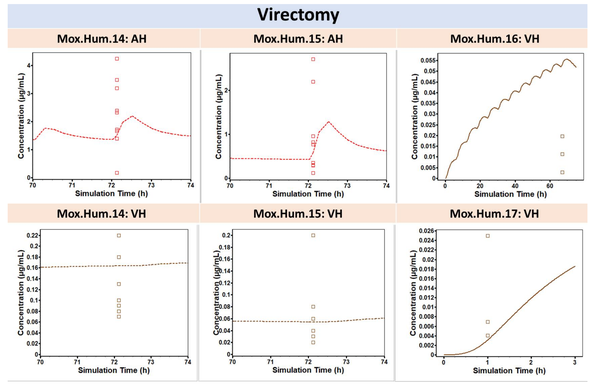


Figure 3: Human extrapolation for patients undergoing Virectomy surgery. Squares are observed AH (red) and vitreous humor (brown) data and lines are simulated concentration-time courses.

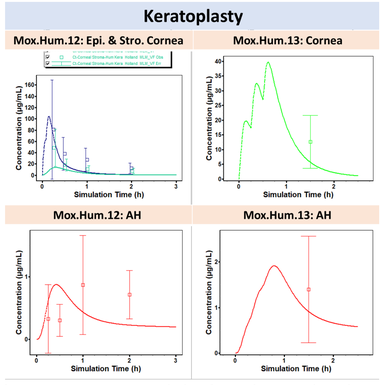


Figure 4: Human extrapolation for patients undergoing Keratoplasty surgery. Squares are observed AH (red) and cornea (epithelium: Blue, stroma: green, total: light green) data and lines are simulated concentration-time courses

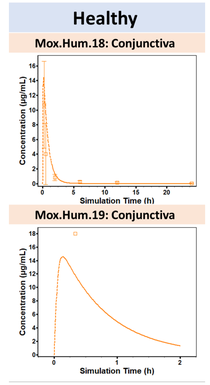


Figure 5: Human extrapolation for healthy subjects. Squares are conjunctiva data and lines are simulated concentration-time courses.

CONCLUSION

- Preliminary data suggest that the OCAT model reasonably predicts human ocular exposure once validated with rabbit ocular PK data for MOX ophthalmic solutions
- The model reasonably predicts observations sampled from patients with cataract, virectomy, and keratoplasty surgeries
- Due to the significant intersubject and interstudy variability in observed human ocular exposure, extrapolation from more case studies is necessary to validate the MAM-PBPK extrapolation method
- Successful clinical extrapolation of MOX ophthalmic solution represents an important step in validating the use of MAM-PBPK models for prediction of human ocular exposure for ophthalmic drug products
- The approach described in this study is expected to have a significant impact on ophthalmic generic drug product development

REFERENCES

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