Physiologically-based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development

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OBJECTIVES

To use a rabbit ocular physiologically-based pharmacokinetic (PBPK) model to compare a suspension to a solution for ophthalmic products

BACKGROUND

- Development of new therapeutics or generic drugs for ocular disease is a challenging task due to the complexity of the ocular system.
- To optimize the therapeutic drug level reaching the biophase, multiple formulation strategies have been used to prolong the tear residence time of topical ophthalmic drug products by increasing the viscosity or enhancing the amount reaching the target site by dosage modification[1].
- For most ophthalmic suspension products, we calculate that 90% or more of the active ingredient remains undissolved.
- Previously, a dexamethasone (Dex) ocular PBPK model (OCAT module in GastroPlus™ V9.6, Simulations Plus, Inc.) was developed and verified in rabbit for Dex suspension formulations with differences in particle size, strength, and viscosity (manuscript submitted[2]).

METHODS

- Using the verified OCAT-PBPK model, the following simulations (S1-S11) were performed:

	Suspension Dose (%)	Solution amount (µg)	Solid amount (µg)	Particle clearance mechanism	DR (min^{-1})
Suspended particles clearance process from the ocular surface					
S1	0.1	2.67	27.33	DR + TFR	1
S2	0.1	2.67	27.33	DR	1
S3	0.1	2.67	27.33	TFR	1
S4	0.1	2.67	27.33	-	1
Suspension advantages compare to a saturated solution					
S5	0.05	2.67	12.33	DR + TFR	0.1
S6	*	2.67	-	-	0.1
Dose increase for ophthalmic suspensions					
S7	0.01	2.67	0.33	DR + TFR	0.1
S8	0.05	2.67	12.33	DR + TFR	0.1
S9	0.1	2.67	27.33	DR + TFR	0.1
Dose-viscosity relationship					
S10	0.1	2.67	27.33	DR + TFR	0.4
S11	0.1	2.67	27.33	DR + TFR	0.1

Table 1: List of simulations performed in GastroPlus™ for rabbit to understand (1) the suspended particles clearance process from the ocular surface; (2) the advantages of suspension as compared to a saturated solution; (3) the impact of dose increase for ophthalmic suspensions; and (4) the relationship between dose and viscosity for ophthalmic suspensions.

DR = drainage rate
TFR = tear flow rate

- Viscosity of formulations are controlled by adjusting the DR

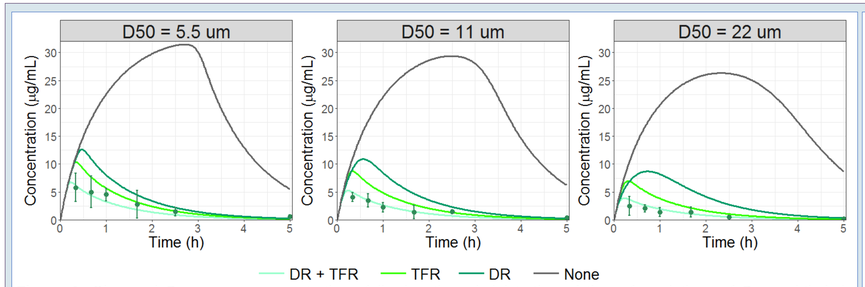

Figure 1: Observed Dex cornea concentrations following the administration of three formulations of Dex ophthalmic suspensions 1% to rabbit eye[3]. The formulations differ in median particle size (D50; 5.5, 11 and 22 µm) (green dots). Lines represent simulations for different elimination mechanisms from ocular surface.

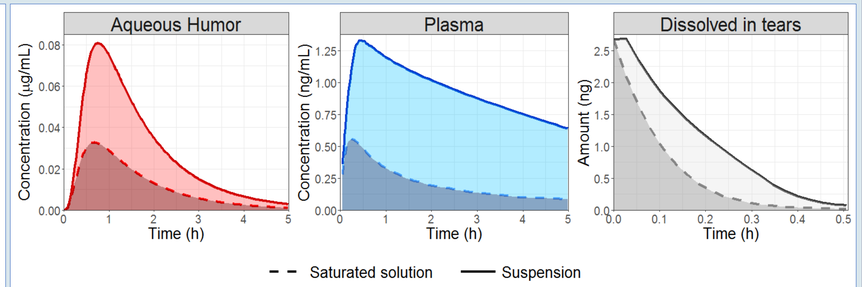

Figure 2: Dex concentration in aqueous humor and plasma and dissolved amount in tears following the administration of Dex suspension 0.05% (solid lines) or saturated solution (dashed lines).

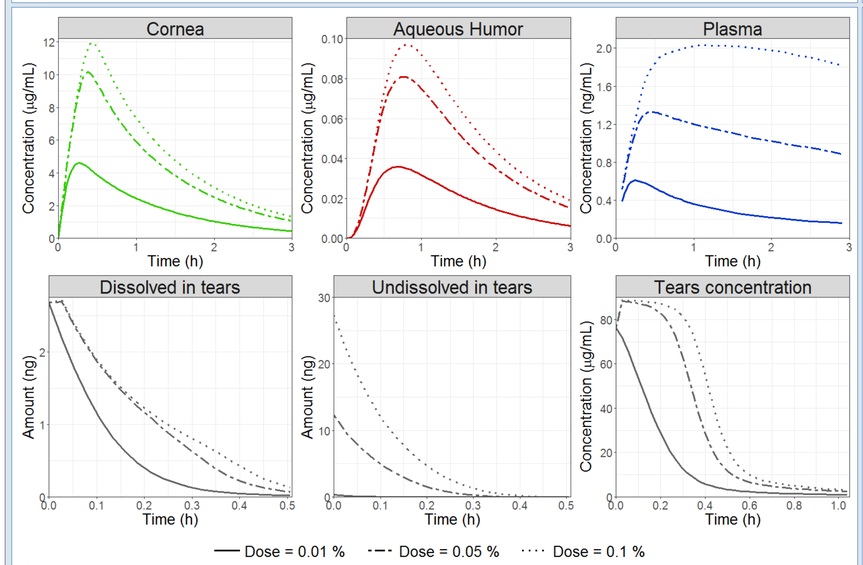

Figure 3: Dex cornea, aqueous humor, plasma and tears concentrations following the administration of 3 different strengths of Dex suspension: 0.01, 0.05, 0.1%. Dissolved and undissolved amount of Dex tears are also presented

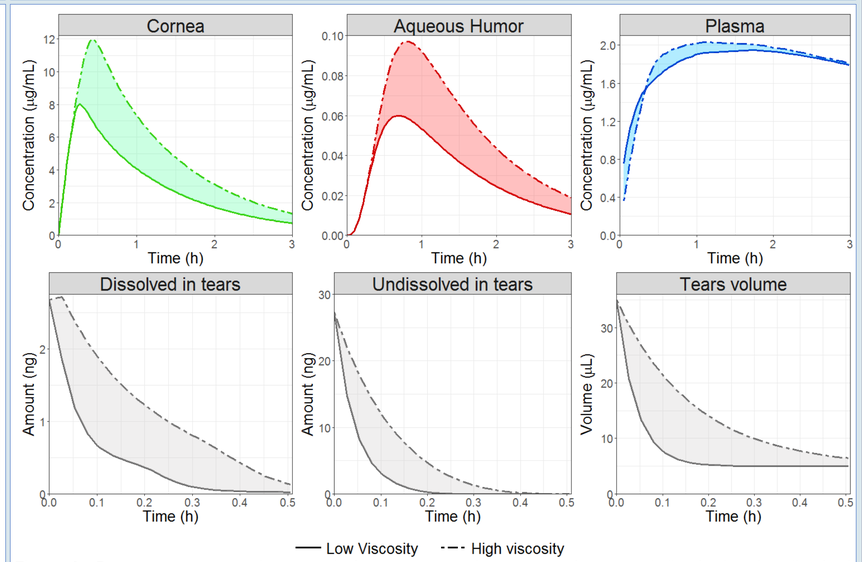

Figure 4:. Dex cornea, aqueous humor and plasma concentrations, tears volumes, and dissolved and undissolved amounts of Dex in tears following the administration of Dex 0.1% suspensions with high or low viscosity (Table 1).

RESULTS/CONCLUSIONS

- Both DR and TFR are critical to adequate corneal predictions.
- Dex suspension 0.05% has a 2.5- and 5-fold higher aqueous humor and plasma AUC, respectively, compared to saturated solution.
- Strength increase by 5- or 10-fold induces a respective 2.2- or 3.3-fold increase in aqueous humor and 4.4- or 8.6-fold increase in plasma Cmax and AUC
- Increasing formulation viscosity (from 1.6 to 75 cP) causes an overall increase in Dex available for absorption in the cornea resulting in a higher ocular Cmax and AUC with no significant impact on systemic exposure.
- A model able to correlate formulation changes to both ocular and plasma exposure is a necessary tool to support ocular product development taking into consideration the pharmacodynamic and toxicology aspects.

REFERENCES & FUNDING

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3. Schoenwald RD, Stewart P. Effect of particle size on ophthalmic bioavailability of dexamethasone suspensions in rabbits. J Pharm Sci. 1980;69(4):391-4.

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