

Modeling Drug Disposition in Ocular Tissues following Topical Eye Drops and Intravitreal Injection

S. Ray Chaudhuri, J.R. Crison, V. Lukacova, M.B. Bolger, W.S. Woltosz
 Simulations Plus, Inc. 42505 10th Street West, Lancaster, CA 93534

INTRODUCTION

The purpose of this study was to model the ocular absorption, distribution and clearance of clonidine and voriconazole from topical and intravitreal applications, respectively. Clonidine is a potent hypotensive agent used to lower intra-ocular pressure (IOP) in the treatment of Glaucoma [1]. Voriconazole has been known to provide for a treatment for post-operative fungal endophthalmitis [2].

METHODOLOGY

Our model describes the eye as a collection of 8 compartments, including a pre-corneal area (tear film and the conjunctival sac), cornea, conjunctiva, aqueous humor, iris-ciliary body/lens, vitreous humor, retina and choroid/sclera. The passive diffusion of drugs between different compartments is assumed to be concentration-gradient driven with rates dependent on physiological (e.g. surface area) and drug-dependent physicochemical properties (e.g. permeability) for each compartment. Mechanisms such as nasolacrimal drainage (through tear flow and volumetric drainage), ocular metabolism, melanin binding etc. have also been incorporated into this model. The ocular model is connected to the pharmacokinetic model in GastroPlus™ (Simulations Plus, Inc.) [3] to allow for simulation of drug appearance in plasma after ocular administration as well as drug uptake by the eye tissues after oral or systemic administration. Simulation parameters were fitted to best explain the results from literature studies for two drugs dosed as solutions into two different compartments: pre-corneal area and vitreous humor.

The formulations studied were: a topical clonidine solution (eye drops dosed at 0.06 and 0.12 mg) [4] and an intravitreal injection of voriconazole (0.035 mg) [5]. For clonidine, selected model parameters (relevant ocular permeabilities, volumetric drainage constant and tear flow rate) were fitted using *in vivo* data from rabbit in six eye compartments for the lower dose. The fitted set of parameters was then used to predict the ocular distribution of clonidine for the higher dose. A similar framework was used to fit a model for intravitreal administration of voriconazole for which data were available for only one dose.

RESULTS

Figure 1 represents the concentration vs. time profiles in individual eye compartments from a topical clonidine eye-drop for the lower dose (0.06 mg), while Figure 2 gives the same for the higher dose (0.12 mg). The volume of the eye-drop was 30 microliters. Figure 3 represents the concentration vs. time profiles in two eye compartments from an intravitreal injection of voriconazole (0.035 mg). In all of these figures, squares (with error bars) represent experimental data points while solid lines represent the simulated profiles.

REFERENCES

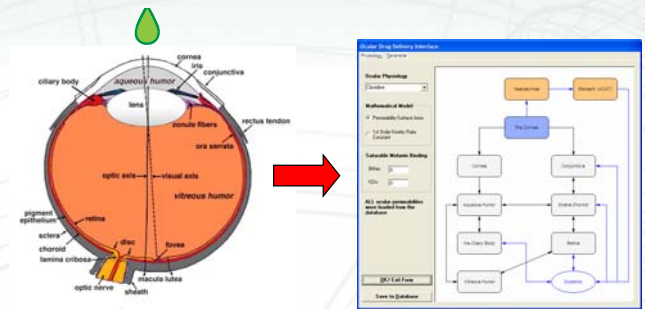
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CONCLUSIONS

For both doses of clonidine, the simulated concentrations were in agreement with the observed concentrations in the eye compartments for which the *in vivo* data were available. Similarly, our ocular model was able to provide a good fit to the voriconazole *in vivo* data in two eye compartments. Such mechanistic models will be a useful tool for scientists in development of new drug candidates, novel dosage forms and devices with specific release rates, new sites of administration, as well as assessment of eye tissue distribution of drugs administered via ocular and other routes.



Clonidine 0.06 mg Dose - Used for Fitting

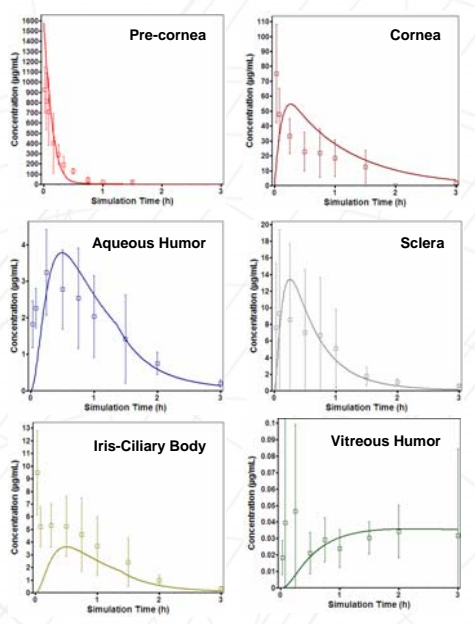


Figure 1. Concentration vs. time profiles in different eye compartments from a 0.06 mg topical eye-drop of clonidine

Clonidine 0.12 mg Dose - Used for Prediction

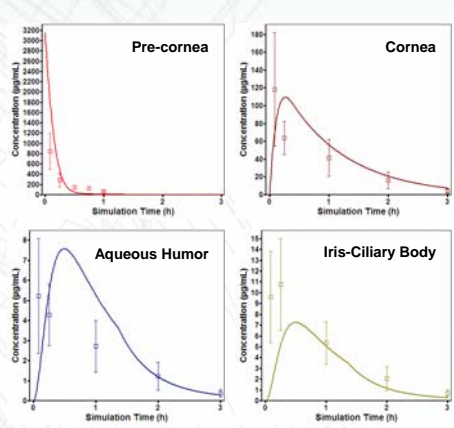


Figure 2. Predicted concentration vs. time profiles in different eye compartments from a 0.12 mg topical eye-drop of clonidine

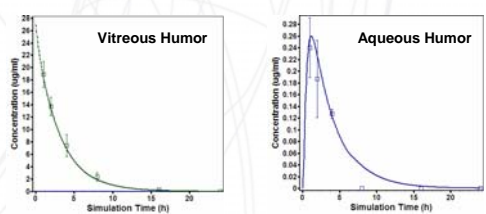
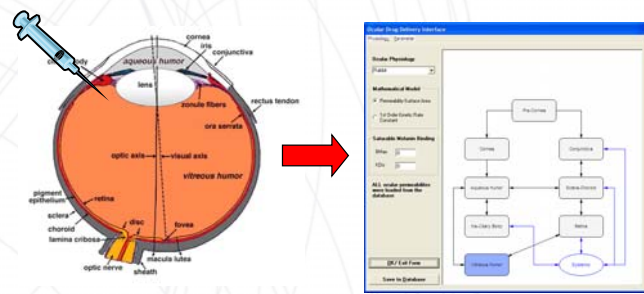


Figure 3. Concentration vs time profiles in different eye compartments from a 0.035 mg intravitreal injection of voriconazole