

## **Modeling Drug Disposition of Timolol in Ocular Tissues of Rabbit Following Topical Eye Drops**

S. Ray Chaudhuri, V. Lukacova, W.S. Woltosz  
*Simulations Plus, Inc, Lancaster, CA, USA*

Recently, we reported the successful application of a novel mathematical model describing drug disposition in eye tissues to simulate disposition of Clonidine after topical (eyedrop) administration [1]. This example extends the methodology to describe the disposition of Timolol in five different eye tissues and plasma after topical (eyedrop) administration in rabbit [2]. The PKPlus™ module of GastroPlus™ (Simulations Plus, Inc.) was used to fit systemic PK parameters from observed plasma concentration-time profiles after intravenous administration. Concentration-time profiles in different ocular tissues were used to optimize selected ocular parameters (mostly permeabilities into different tissues). The simulated concentrations in plasma and most eye tissues were in good agreement with observed concentrations. The exception was the concentration profile in the Iris-Ciliary body compartment. A similar mismatch for Iris-Ciliary body was also observed for Clonidine, indicating a trend that requires further investigation. Fitted parameters for Timolol were compared to those obtained from the analysis of Clonidine. Continual validation of this model is expected to result in a robust mechanistic model that will have a substantial impact on pharmaceutical, clinical and toxicological studies.

[1] Ray Chaudhuri S et al., Modeling Drug Disposition in Ocular Tissues following Topical Eye Drops and Intravitreal Injection, 2009 ARVO Annual Meeting, 2009, May 3-7, Ft. Lauderdale.

[2] Lee VHL et al., Pharmacokinetic Basis for Nonadditivity of Intraocular Pressure Lowering in Timolol Combinations, *Invest Ophthalmol Vis Sci.* 1991;32:2948-2957.