A PB-QSP module for ocular applications for the Open Systems Pharmacology - A vancomycin example

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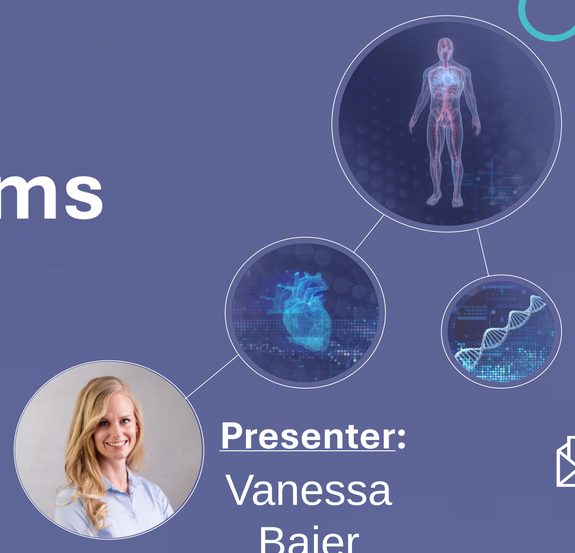

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Introduction

Treatment of ocular disorders (e.g., eye infection or macular degeneration) often requires optimization of delivery of drugs to the ocular tissues by either intravitreal infusion or topical administration. Physiologically-based pharmacokinetics (PBPK) modeling could combine a predictive framework for local biodistribution with cross-species extrapolation, drug-drug-interaction, or extrapolation to special populations simulation [1], but most PBPK models lack a detailed description of the eye physiology.

The open-source PBPK and Quantitative Systems Pharmacology (QSP) modeling software "Open Systems Pharmacology Suite" (OSPS) introduces the concept of model modularization, offering a structured framework to facilitate model integration and extension [2]. This modularized approach is showcased based on a published physiological PBPK structure [3,4] on the example of vancomycin, an antibiotic glycopeptide, as an ocular administration for the treatment of eye infection in two species rabbit and human.

Methods

The modeling has been performed with the Open Systems Pharmacology Software version 12. The PBPK model of vancomycin was downloaded from the freely accessible OSP model library [5] (validation report available on GitHub) and loaded in MoBi as a PK-Sim module.

The previously developed extension modules were loaded into the project and combined with the PK-Sim module to create the prediction models. The PD module describes an Emax model:

$$E = mu - \frac{E_{max} * (C/MIC)^h}{(EC_{50})^h + (C/MIC)^h}$$

The eye physiology module [6] has the following structure

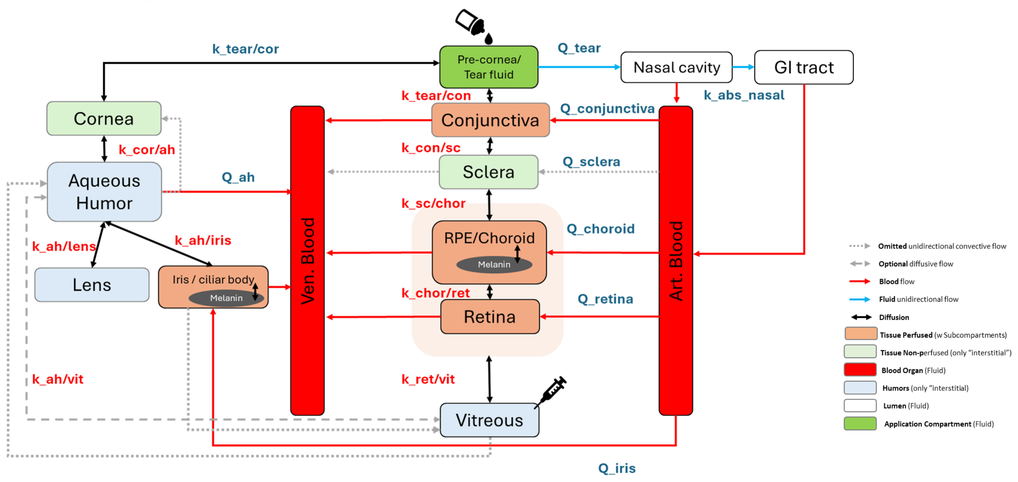


Fig 1: Compartmental structure of the ocular PBPK absorption model comprises an application compartment ('pre-cornea/tear fluid') and different types of absorption/distribution compartments, which are defined as full PBPK tissue organ structures (highlighted in orange, including 'plasma,' 'interstitial,' and 'intracellular' space), as non-perfused tissue (highlighted in light green, as an 'interstitial'-like space), or as humorous tissue (highlighted in light blue, as a primarily water-containing space).

Results

A previously developed eye physiology module has been combined with a PBPK model of vancomycin from the OSP model library on GitHub to predict ocular exposure of vancomycin.

A PD module was plugged in to the model to predict the drug effect on bacterial growth in the vitreous under eye infection.

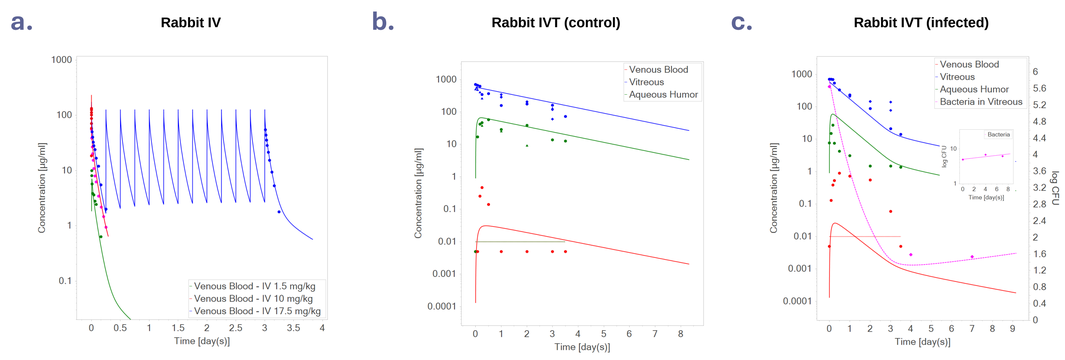


Table 1: Fitted parameters of the integrated PBPK-QSP model

Parameter	Value
Fraction unbound rabbit [-]	0.56 (0.67)
GFR rabbit [-]	1.5 (1)
Emax [log10 of CFU]	0.02
EC50 [µmol/l]	16.5
k_diffusion Aqueous Humor to Vitreous [1/min]	1000

Human reference values in ()

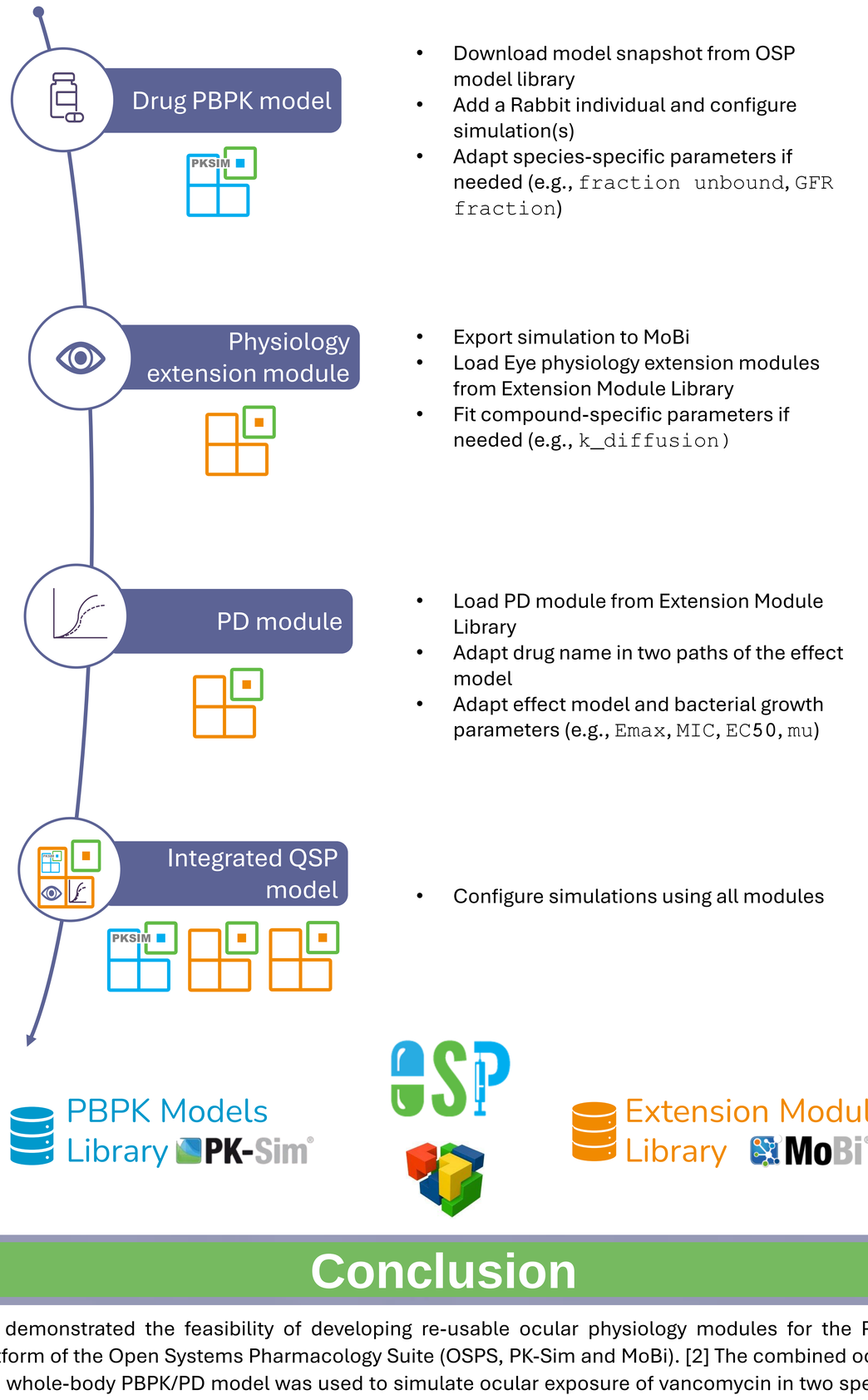
Fig 2: Simulations of vancomycin concentrations in plasma, aqueous humor, and vitreous in rabbits (a-c) and humans (d+e). Solid/dashed lines represent simulated data, symbols represent observed data points. a. - green = IV 1.5 mg/kg [7], red = IV 17.5 mg/kg [8] (single dose), blue = IV 17.5 mg/kg (every 6h, 3 days)[8], pink = IV 10mg/kg [9], b. - IVT 1mg, dots from [9], triangle from [10], diamonds from [11]; c. - IVT 1mg, dots from [9], diamonds from [11], plus from data [12]; d. - IV 1g, data from [13]; e. - IVT 1mg, data from [13]

The final model was able to reproduce systemic and eye tissue concentrations of vancomycin in rabbits and humans after intravenous and intravitreal administrations [7-11]. The model confirmed that ocular concentrations after IV administrations were insufficient to sterilize the vitreous.

Enabling the end-to-end Model-Informed Drug Development (MIDD) ecosystem [14]:

How to use the OSPS modularization approach to build an integrative QSP model in 15 minutes:

PBPK model + ocular physiology + PD model



- Download model snapshot from OSP model library
- Add a Rabbit individual and configure simulation(s)
- Adapt species-specific parameters if needed (e.g., `fraction unbound`, `GFR fraction`)
- Export simulation to MoBi
- Load Eye physiology extension modules from Extension Module Library
- Fit compound-specific parameters if needed (e.g., `k_diffusion`)
- Load PD module from Extension Module Library
- Adapt drug name in two paths of the effect model
- Adapt effect model and bacterial growth parameters (e.g., `Emax`, `MIC`, `EC50`, `mu`)
- Configure simulations using all modules

Conclusion

We demonstrated the feasibility of developing re-usable ocular physiology modules for the PBPK platform of the Open Systems Pharmacology Suite (OSPS, PK-Sim and MoBi). [2] The combined ocular and whole-body PBPK/PD model was used to simulate ocular exposure of vancomycin in two species and predicted therapeutic efficacy for eye infection after different administration protocols.

The model workflow can easily be applied to other compounds and extended to more complex PD or QSP models.

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