A review of OSP suite PBBM capabilities: looking ahead

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Introduction

PK-Sim® is an open-source solution for physiologically based biopharmaceutics modeling (PBBM). PBBM applications integrate physiology, population data, and drug-specific characteristics to mechanistically describe a drug product's pharmacokinetic (PK) and/or pharmacodynamic (PD) behavior.

The main objectives of this work are to:

a) showcase of the versatility and efficiency of the OSP suite in relevant research scenarios;

b) to outline future directions for enhancing its utility in predicting oral drug absorption.

Methods

A literature review focused on PBBM studies employing OSP® (PK-SIM® or MoBi®) as modeling software (1).

A case study was developed for metoprolol to showcase a mechanistic IVIVC workflow using PK-SIM®. PK after administration of an oral solution was used to estimate permeability and CYP2D6-related metabolism (kcat) (2). In vitro dissolution of three formulations with different release rates (slow, medium, fast) and respective PK profiles were collected from the literature (2). The parameter identification module of PK-SIM® was used to deconvolute Weibull dissolution parameters for 3 extended-release formulations: slow, moderate, and fast. The estimated *in vivo* dissolution was extracted from PK-SIM® and correlated with *in vitro* dissolution collected from the literature.

PBPK reference formulation (i.e., oral solution) model ⇒ Deconvolution & correlation ⇒ PK prediction & evaluation

The convoluted dissolution profiles were input into the model to predict plasma concentration profiles. Predictability criteria were based on the FDA guideline (2):

- Average absolute percent prediction error (% PE) of 10% or less for Cmax and AUC;
- For each formulation % PE should not exceed 15%.

After evaluation, the IVIVC was used to establish a dissolution-safe space for metoprolol. Virtual in vitro dissolution profiles were converted to in vivo dissolution using the developed mechanistic IVIVC model.

To establish the dissolution safe space, a maximal difference of 20% in the predicted Cmax and AUC was accepted between the fastest and slowest dissolution rates, as suggested by FDA guidelines (3). The absolute error was calculated as the difference of each PK parameter (AUC and Cmax) between the upper and lower limit virtual profile.

Results

One key feature of the Open Systems Pharmacology (OSP) suite is the default implementation of a detailed gastrointestinal (GI) absorption model that simulates the complex physiological environment of the GI tract (Figure 1).

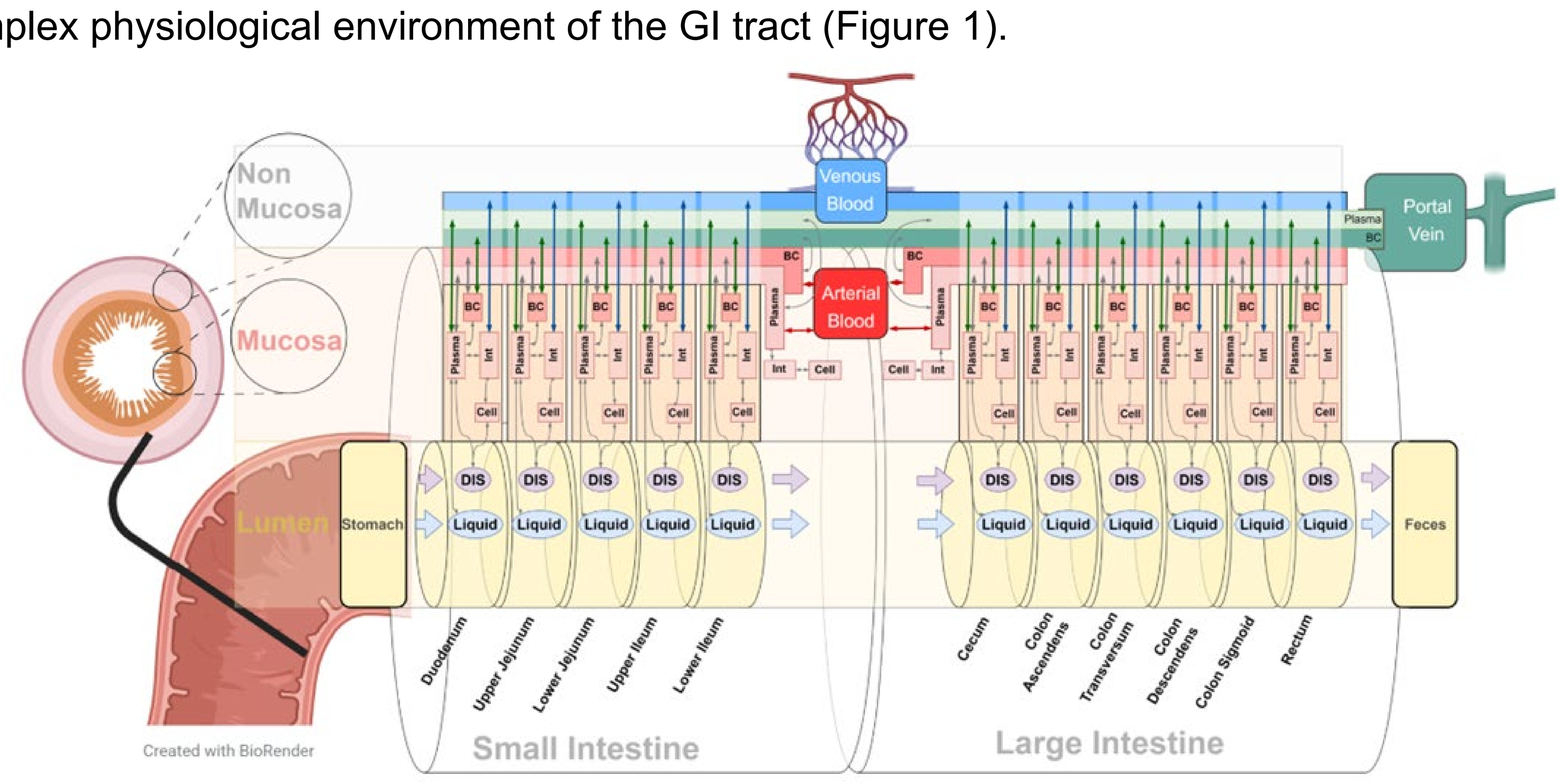

Figure 1: Graphical representation of the compartmental structure of PK-SIM® oral absorption model.

A review of the literature highlighted a variety of application scenarios as described in Figure 2, from understanding biopharmaceutical drug properties to developing IVIVC.

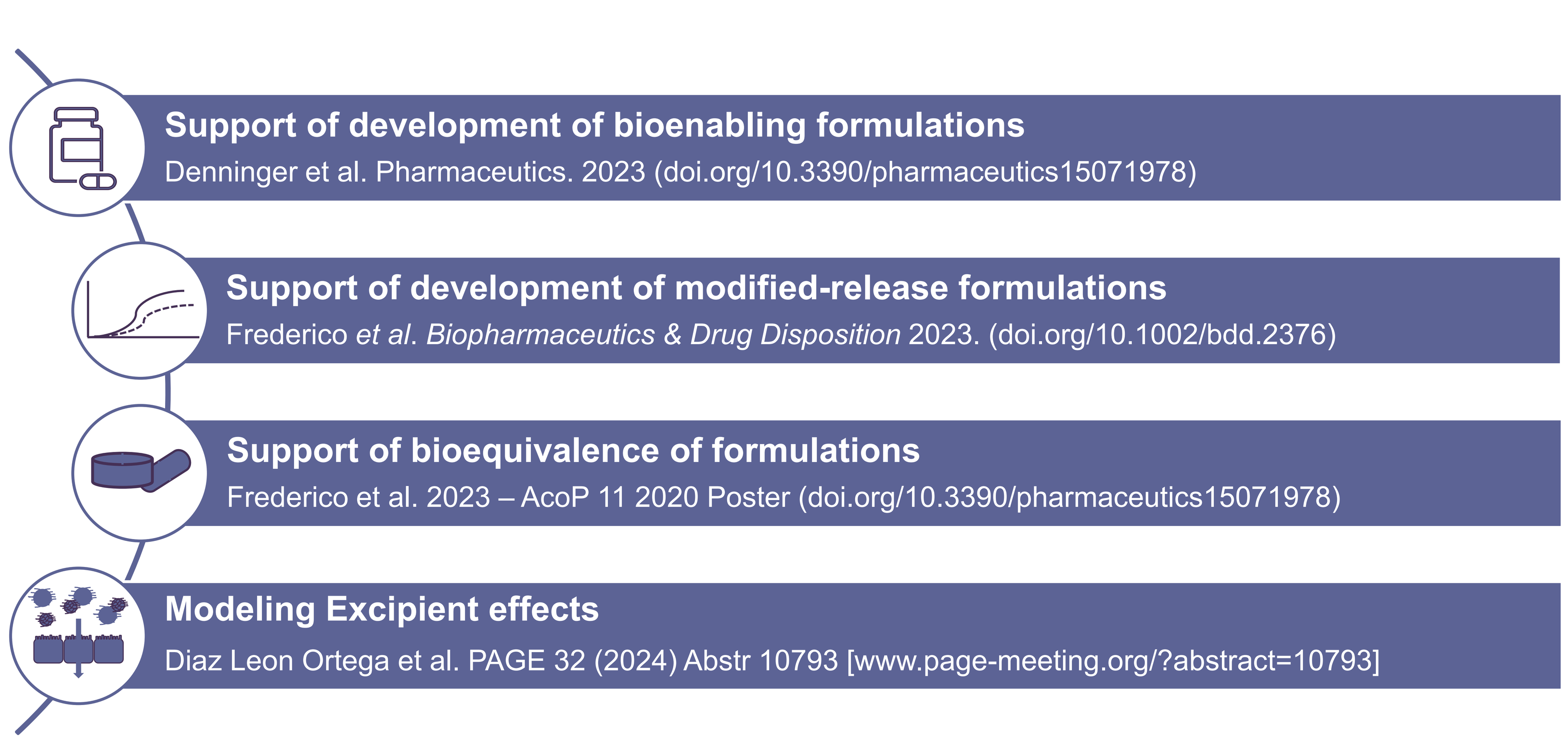

Figure 2: Examples of PK-Sim® PBBM applications.

Illustrative Example: development of an IVIVC for metoprolol

- One of the key areas of application of PBBM is IVIVC and its application for establishing a dissolution-safe space. A case study was developed for metoprolol to demonstrate a workflow for establishing a PBPK-based IVIVC with PK-Sim®.
- A correlation was developed from the simplest (linear) to the more complex (i.e., polynomial 1st /2nd and 3rd order) relationships in a step-wise approach. A 4th-order polynomial correlation was developed (Figure 3). The FDA guideline states that nonlinear correlations, while uncommon, may also be appropriate. Many IVIVC studies on controlled-release formulations exhibit nonlinear characteristics, despite the expectation that these formulations, governed by dissolution, would result in linear IVIVCs (4).
- It has been shown before that non-linear PK of metoprolol, CYP2D6 metabolism (existence of poor metabolizers and extensive metabolizers in the dataset), as well as other factors such as gastric emptying and relevance of dissolution methodology, can influence the establishment, and predictability of the IVIVC (4,5).

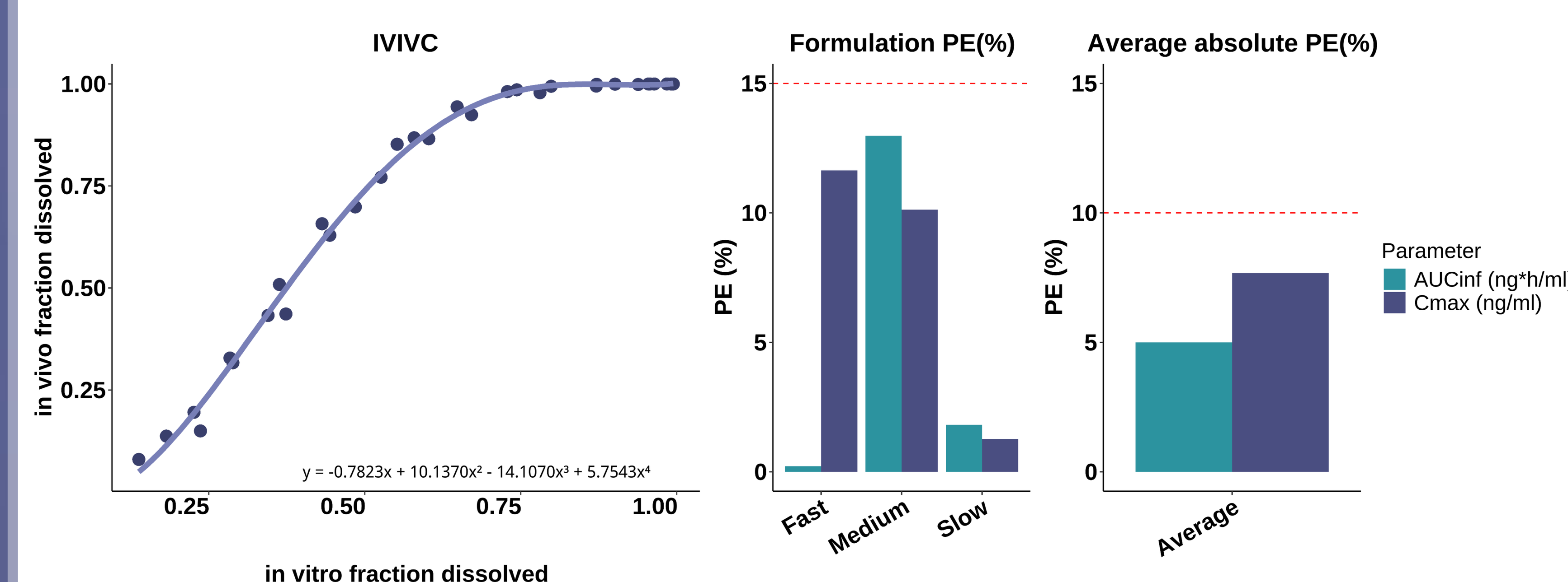

Figure 3: Summary of IVIVC Internal Predictability evaluation based on Percent Prediction Error (%PE) according to the limits established by FDA IVIVC guidance as dashed red lines.

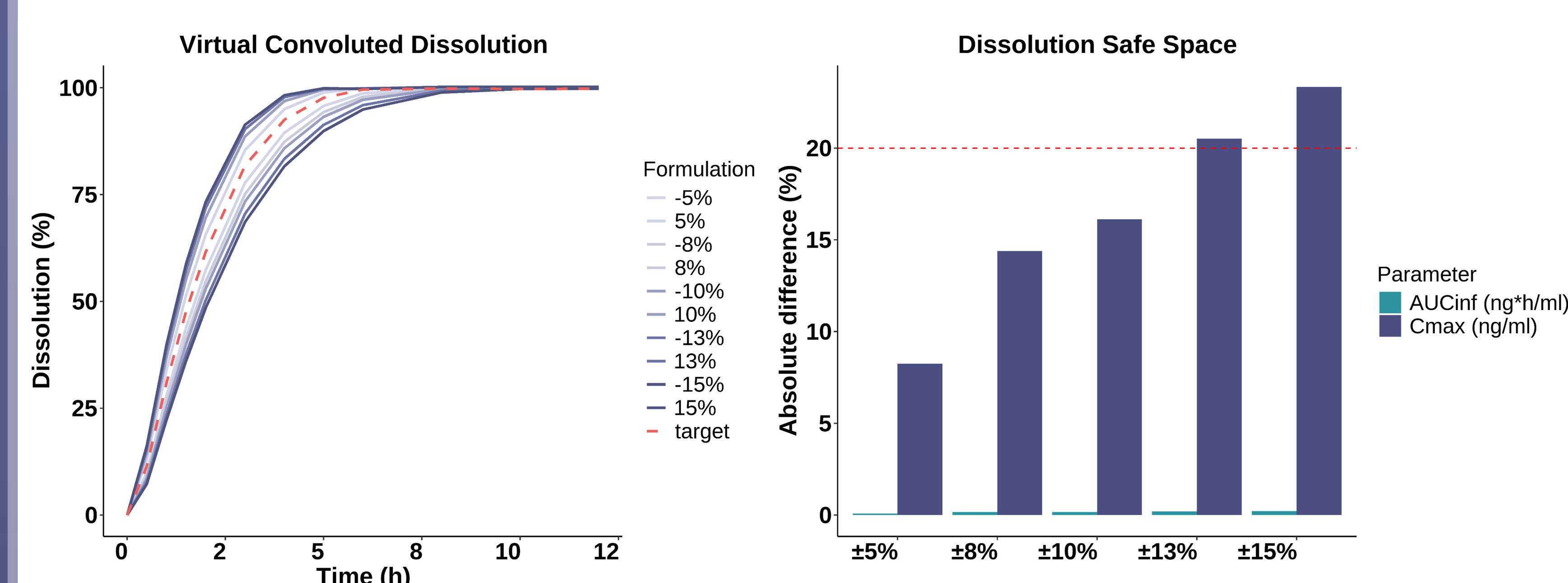

Figure 4: Establishment of a virtual dissolution safe space. On the left side the convoluted in vivo dissolution profiles are presented, and on the right side the dissolution safe space results according to the absolute error calculation between upper and lower

- PBPK-based IVIVC was then used to convolute virtual *in vitro* dissolution profiles around the target and converted to in vivo dissolution (Figure 4).
- The dissolution profiles were added to the PBPK model, and its PK profile and parameters were calculated for each virtual formulation.
- The absolute difference of Cmax and AUC between upper and lower virtual formulations was calculated. Based on this case study, a dissolution safe space was established around the target of ± 10%.

Conclusion

This work highlights the **potential of OSP suite software to support formulation development**. Integrated biopharmaceutical analysis with verified models containing population-specific and compound-specific data can **lead to patient-centric-drug development.**

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Modeling Scaling Coding

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