Novel PBBM Applications in OSPSuite v12: Modified-Release and Z-factor Metoprolol and Ibuprofen

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Introduction

The Z-factor approach (Takano et al., 2006) is a widely used dissolution-precipitation model in computational biopharmaceutics, not currently available in OSP software v12. Additionally, non-Immediate-Release (IR) formulations require modelling release kinetics to mechanistically predict pharmacokinetic (PK) performance. Hence, enabling robust formulation development of Modified-Release (MR) formulations in OSP requires introducing a new release and gastrointestinal (GI) transit framework. In this work, the base PK-Sim® platform was extended with new first-order release and Z-factor dissolution models in MoBi®. We showcase how the new framework can support the development of a PBBM for an IR or MR formulation, using the case-studies of IR ibuprofen and MR metoprolol.

Methods

The Z-factor approach was developed in MoBi®:

$$\dot{m}_{disso}^{(liq)} = \sum_{n=1}^{n=no.\,particle\,bins} Z_n \frac{m_{n,initial}^{(solid)}}{r_{n,intial}^2} r_n^2 [C_{sat} - C_{bulk}]$$

$$Z_n = \frac{Z'}{r_{n,initial}} \; where \; Z' = \frac{3D}{\rho h}$$

The dissolution model is mathematically identical to the current PK-Sim® 'Particle Dissolution Model' except it is expressed in terms of Z, a lumped parameter of PhysChem properties. In early-stage drug development this approach is efficient to explore uncertainty in the dissolution rate of any given particle size due to hydrodynamics, molecular diffusion and manufacturing precision with the modification of a single Z-factor.

The release and dissolution framework was developed in MoBi®:

$$\frac{d\dot{m}_j^{(solid)}}{dt} = \dot{m}_{j,release}^{(solid)} + \frac{m_{j-1}^{(solid)}}{\tau_{j-1}} - \frac{m_j^{(solid)}}{\tau_j} - \dot{m}_{disso}^{(liq)}$$

The mass balance describes the amount of solid drug particles in one intestinal compartment j, accounting for the rate of release from the solid drug product, intestinal transit rate according to a residence time τ, and rate of particle dissolution. In this implementation the drug product release kinetics were modelled as first-order with a gastric retention time. A PBPK model for ibuprofen and metoprolol were developed in PK-Sim® using *in vivo* oral solution data (Lockwood et al.,1983, Eddington et al., 1998). USP2 dissolution of IR Ibuprofen tablets, and Metoprolol slow/moderate/fast MR tablets were used to calibrate the dissolution kinetics (Z-factor) for both APIs, and the release kinetics for metoprolol (first-order release constant). The *in vivo* systemic circulation following administration of the oral solid formulations was then predicted to assess the accuracy of the developed PBPK models.

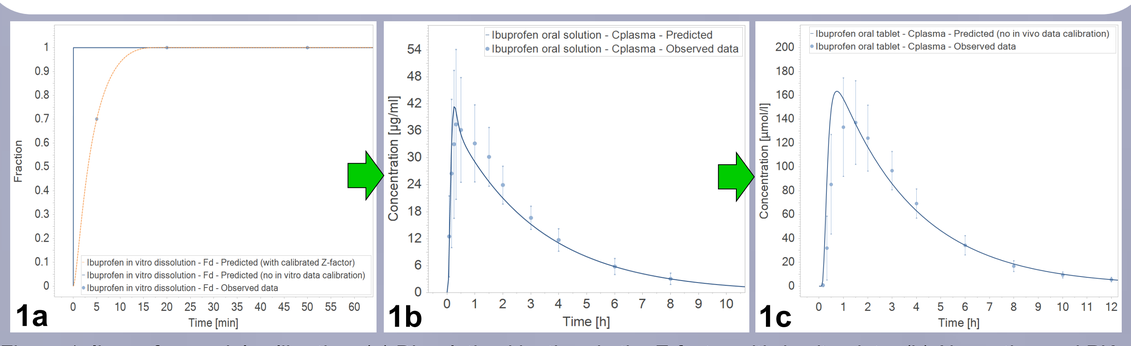

Figure 1. Ibuprofen model calibration. (a) Dissolution kinetics via the Z-factor with *in vitro* data. (b) Absorption and PK with *in vivo* oral solution data. (c) Prediction of oral tablet performance.

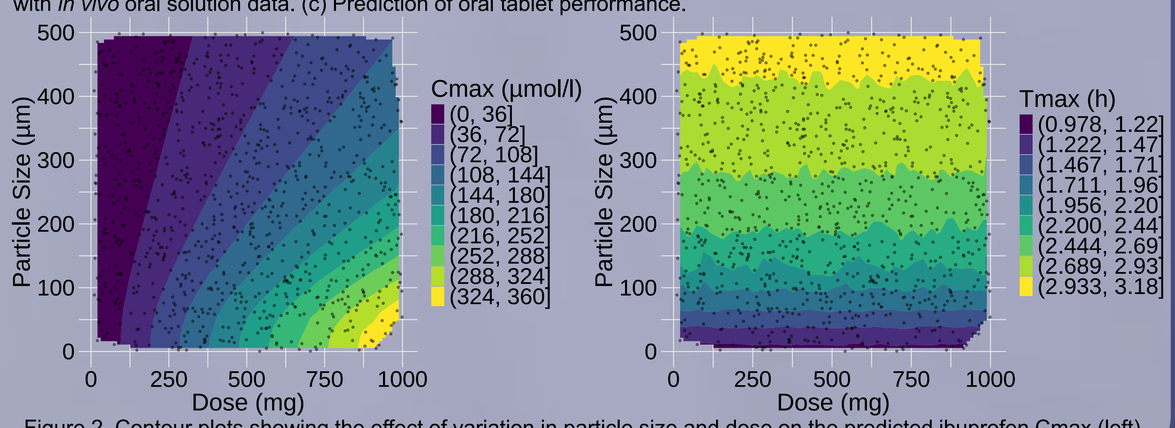

Figure 2. Contour plots showing the effect of variation in particle size and dose on the predicted ibuprofen Cmax (left) and Tmax (right). The dots represent the simulations of the uncertainty analysis.

Results

The Z-factor dissolution model was successfully used to predict the IR ibuprofen oral tablet performance (Figure 1). An uncertainty analysis was used to generate contour plots based on 1000 model realizations, considering random sampling from factor distributions of dose, particle size, Z factor. Plots for particle size are shown for illustration (Figure 2). Additionally, a GSA using OSP R (Najjar, A., 2024) was used to quantify the biopharmaceutics risk assessment by computing the Sobol' sensitivity analysis index (SI) of drug and physiological properties.

- A particle size increase from 10-100 µm would result in an ~20% Cmax reduction and an ~1 h Tmax delay (Figure 2) ;
- Dose-proportional absorption for small particles (<100 µm) and sub-proportional for larger particles (dissolution is rate-limiting) (Figure 2);
- Sobol' sensitivity indices (SI) produced in the GSA showed that Cmax was most sensitive to LogP (SI=0.8) and gastric emptying (GE) (SI=0.25), whilst Tmax was most sensitive to GE (1).

The biopharmaceutics risks of oral solid dose ibuprofen highlighted herein align with those identified in the literature (Tamilvanan S., 2006).

Including the first-order release kinetics in the development of the MR metoprolol PBPK model was necessary to produce a robust IVIVC (Figure 3). The application of first-order release and Z-factor dissolution produced a better fit of the calibration data (not shown here) and successfully predicted the *in vivo* PK of all three formulations. The accuracy of Cmax and Tmax predictions were greatly improved with the new model framework for release and dissolution; the mean Prediction Error (PE) was reduced from 41% and 27% of Cmax and Tmax respectively, to 3% and 14%. Metoprolol results highlight the importance of discriminating between release and dissolution during model-informed drug development workflows, particularly for MR formulations.

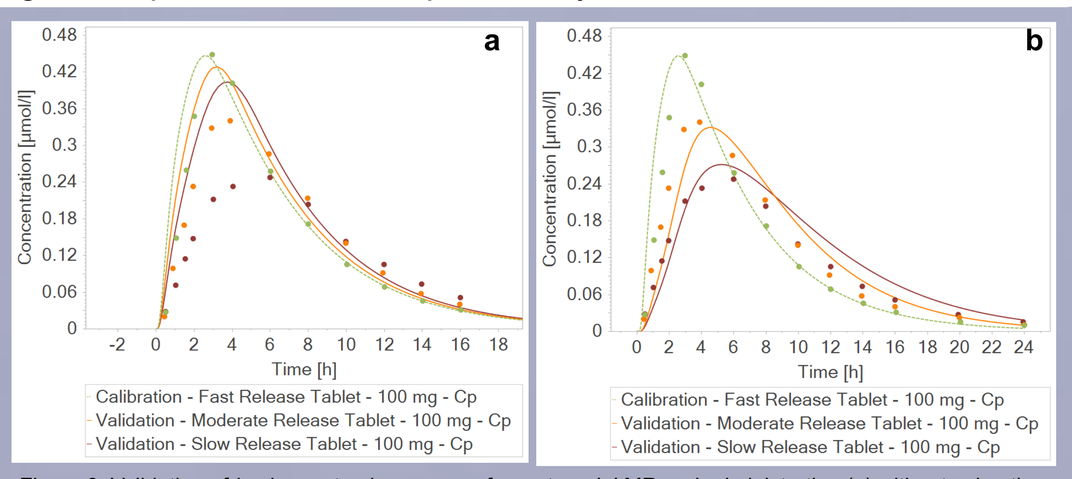

Figure 3. Validation of *in vivo* systemic exposure for metoprolol MR oral administration (a) without using the first-order release model and (b) using first-order release model

Conclusion

The new first-order release and Z-factor dissolution models in MoBi® successfully allowed efficient PBBM development for ibuprofen and metoprolol. In the case of MR metoprolol, the differentiation between release and dissolution kinetics during *in vitro* calibration enabled mechanistic prediction of their respective effects on GI drug distribution and absorption. The new model framework is currently limited to formulations exhibiting first-order release kinetics, but it could be extended (e.g., Weibull) and applied for any PBPK PK-Sim model.

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