

Integration of a Novel First-Order Release Z-Factor Dissolution Model with Global Sensitivity Analysis to Guide Formulation Development using Physiologically-Based Biopharmaceutics in OSPSuite v12



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Introduction

The Z-factor approach [1] is a widely used dissolution model in Physiologically Based Biopharmaceutics Models (PBBM) and represents an efficient approach to link the dissolution kinetics of Immediate-Release (IR) formulations to pharmacokinetic (PK) performance. Although complex formulations that supersaturate or are highly polydisperse may require more complex dissolution-precipitation frameworks, the Z factor model can be efficiently applied in simpler cases, such as IR Ibuprofen, which is detailed in this work.

For solid drug product formulations, disintegration into solid particles precedes dissolution in the gastrointestinal (GI) fluids. Modeling the disintegration step with a release function as a separate phenomenon from dissolution is imperative to establish a mechanistic relationship between drug product properties, physiological variability, and drug product performance. Inherently, bio-predictive *in vitro* methods must be used to validate the release and dissolution models *a priori* to *in vivo* prediction.

Overall, the current PBBM capabilities of the Open Systems Pharmacology (OSP) software were extended with the Z-factor dissolution model, and a first-order release and gastrointestinal transit model, to better predict the impact that properties of oral solid formulations have on drug PK. The base PK-SIM® platform was extended with PBBM workflows in MoBi® to assess formulation-release kinetics and integrated with an Uncertainty Analysis (UA) and Global Sensitivity Analysis (GSA) using the 'ospsuite' R library [2]. This work enables modeling disintegration-limited formulations, paving the way to more mechanistic predictions for Modified-Release (MR) formulations in the open-source community.

Objectives

1. Development of an extended MoBi® Z-factor dissolution model
2. Development of an extended MoBi® release model and associated GI transit
3. Deploying the new framework with an Ibuprofen case-study
4. Integration with GSA to perform a biopharmaceutics risk assessment

Methods

The Z-factor dissolution model and first-order release framework were developed in MoBi® v12 using the 'modularization' feature. The new modules can be readily applied as 'extensions' for future solid dosage form administrations. The newly calculated release rate is defined by gastric retention time, a release constant, and dispersive transit of the tablet.

A PBPK model was developed for Ibuprofen (weakly acidic, pKa 4.5, poorly water-soluble, highly permeable with a logP of 4), with PK-SIM® v12 based on published physicochemical and PK properties [3], [4]. *In vivo* data from the administration of an oral solution were used to calibrate the distribution and elimination kinetics in the model [5].

The performance of the standard particle dissolution model and Z-factor dissolution for predicting Ibuprofen dissolution kinetics was assessed. Biorelevant dissolution in simulated intestinal fluids of IR ibuprofen tablets (Stride Pharma Science Ltd) [3] was used to calibrate the molecular diffusivity or the Z-factor for Ibuprofen in the respective dissolution model. Then, the *in vivo* performance following administration of an IR Ibuprofen tablet (Motrin®) was assessed, assuming a constant Z-factor between the two studies due to a lack of dissolution data for the Motrin® tablets.

The 'ospsuite' R library was used to conduct an UA and generate contour plots based on 1000 model realizations, considering random sampling from factor distributions of dose, particle size, Z factor, and first-order release rate constant. Additionally, a GSA using the 'ospsuite.globalsensitivity' R library was used to quantify the biopharmaceutics risk assessment by computing the Sobol' sensitivity analysis index (SI) of these factors, along with other drug substance and physiological properties of interest (logP, intestinal permeability, gastric emptying time, and gastrointestinal pH).

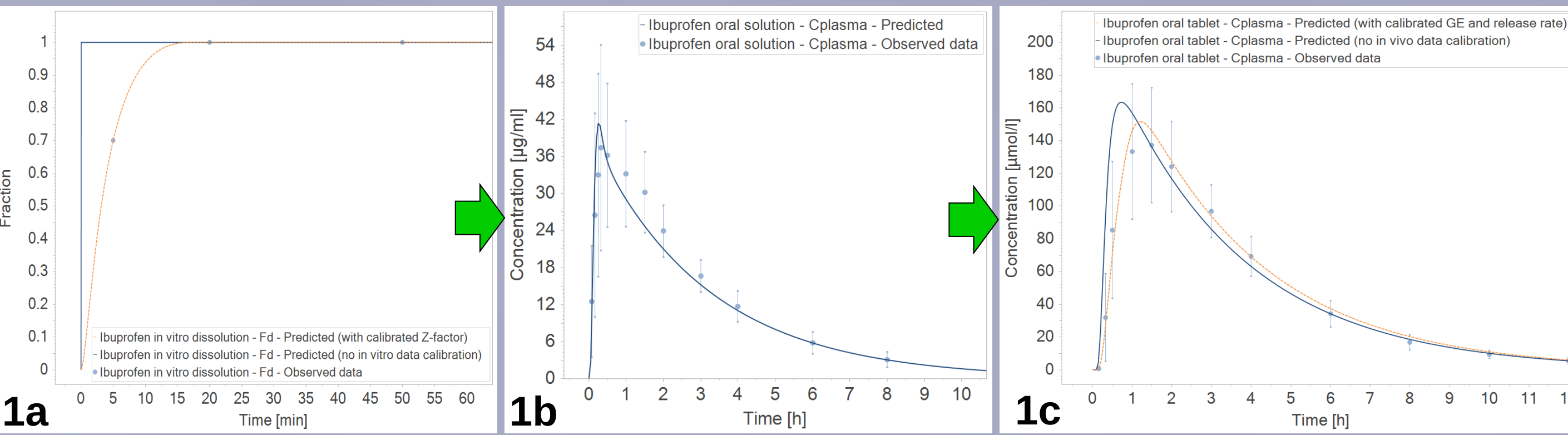


Figure 1. Ibuprofen model calibration. (a) Dissolution kinetics via the Z-factor with *in vitro* data. (b) Absorption and PK with *in vivo* oral solution data. (c) Prediction of oral tablet performance and subsequent fitting of the release kinetics.

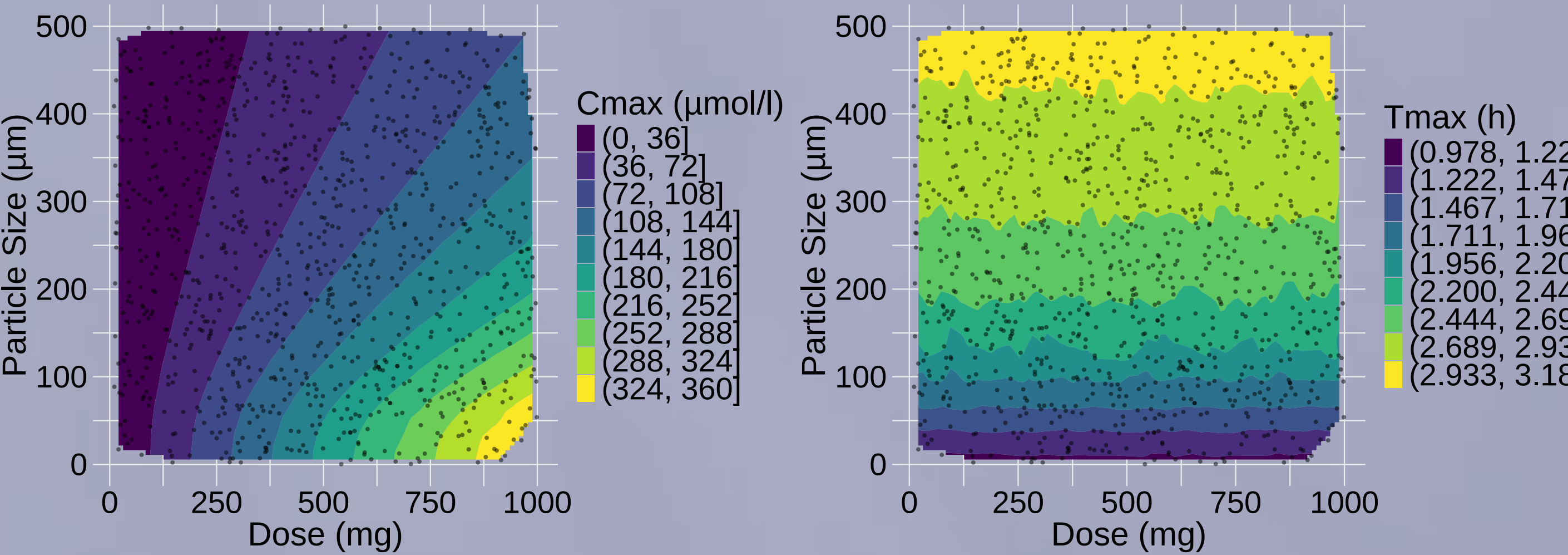


Figure 2. Contour plots showing the effect of variation in particle size and dose on the predicted ibuprofen Cmax (left) and Tmax (right). The dots represent the simulations of the UA.

Results

- In vitro* dissolution data and *in vivo* oral solution data were successfully used to fit Ibuprofen's dissolution, absorption, distribution, and elimination kinetics; the model then well-predicted Ibuprofen oral tablet performance *in vivo*, although the prediction could be further improved by considering optimization of the release model (Figure 1).
- The estimated molecular diffusivity of Ibuprofen for the IR tablet (Stride) using the PK-SIM® particle dissolution model was 116 μm²/s, compared to that calculated from molecular weight is 661 μm²/s [6]. This discrepancy may arise from experimental issues such as poor wetting, or lack of other mechanisms such as the particle surface, excipient effects, or bile micellization.
- The Z-factor model was applied for the same purpose, wherein Z was reduced from 397 l/min/kg to 189 l/min/kg. The IR tablet (Motrin®) Cmax was not significantly overpredicted (1.14-fold). However, Tmax was underpredicted (0.75 vs 1.5 hours), indicating slower tablet release and gastric retention, which was predicted by an estimated release rate constant = 0.05 min⁻¹ and gastric retention = 37 min.
- UA demonstrates that at the therapeutic dose of 400 mg:
 - 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);
 - Slower release rate leads to reduced Cmax, delayed Tmax, and increased sensitivity to particle size (Figure 3);
 - Sobol' sensitivity indices (SI) produced in the GSA (Figure 4) 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 [7].

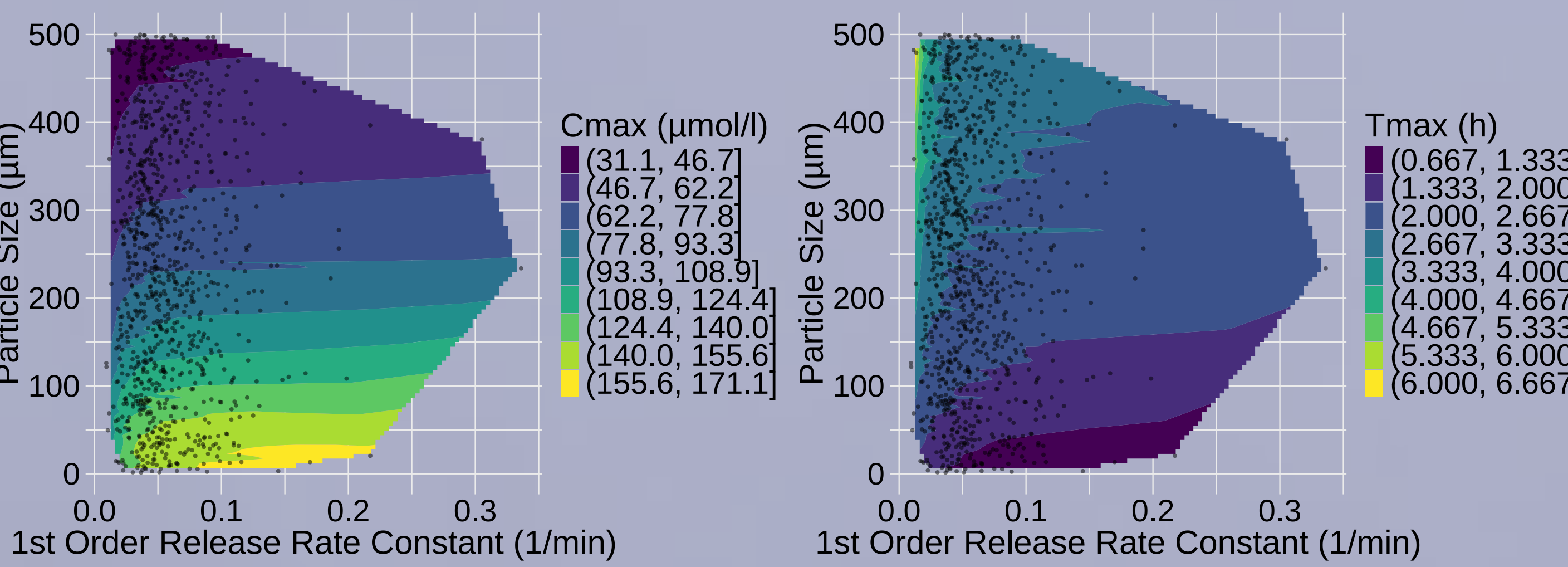


Figure 3. Contour plots showing the effect of variation in the first-order release rate constant and particle size on the predicted ibuprofen Cmax (left) and Tmax (right). The dots represent the simulations of the UA.

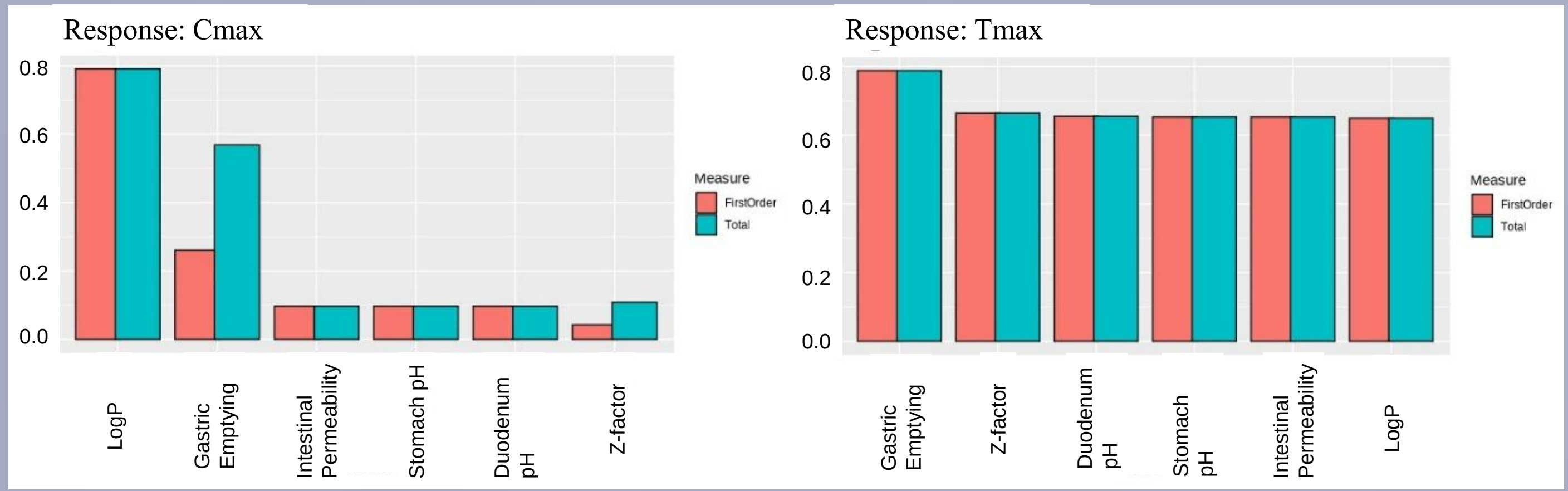


Figure 4. Sobol' sensitivity indices (first order and total order) of C_{max} (left) and T_{max} (right) in a GSA exploring the effect of physiological variability on ibuprofen exposure following fasted oral solid dose administration

Conclusion

The release and Z-factor MoBi® extensions were successfully applied to characterize Ibuprofen's release and dissolution and predict *in vivo* performance using *in vitro* data. UA and GSA were effectively applied to perform a biopharmaceutics risk assessment and identify the rate-limiting steps of solid dose ibuprofen during oral absorption. The developed approach is also suitable for further application to different formulation modalities (e.g., MR) and their combinations with drug classes. In future work, the applicability of the release framework for developing mechanistic simulations of MR formulations should be investigated.

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