Title: Food effect prediction of high permeability/low solubility compound, formulated as an amorphous solid dispersion (ASD) using an Open Systems Pharmacology (OSP) PBBM approach

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Introduction: Model-Informed Drug Development (MIDD) approaches are increasingly encouraged by regulatory agencies and adopted across the pharmaceutical industry to streamline development. A key MIDD pillar is Physiologically Based Biopharmaceutics Modeling (PBBM), which utilizes mechanistic models to translate in vitro-derived biopharmaceutical properties into predicted in vivo PK within a PBPK framework.

In this work, we present a PBBM workflow used to guide the clinical development of Drug X, a poorly soluble, highly permeable compound. Despite being formulated as an amorphous solid dispersion (ASD) to mitigate solubility limitations, Drug X exhibited non-linear absorption kinetics in fasted-state clinical trials. To characterize this behavior, a PBBM was developed by integrating systemic distribution and metabolism with in vitro-informed biopharmaceutical properties. Key model inputs included drug-specific (solubility/permeability) and formulation-specific attributes (mechanistic dissolution kinetics).

Objectives: The PBBM was utilized to:

- prospectively evaluate the impact of food on the pharmacokinetics of Drug X and to optimize the design of food-effect clinical trials
- and to simulate the exposure profiles of twice-daily (BID) versus once-daily (QD) dosing regimens in the fasted state.

Methods: The PBBM was developed using the Open Systems Pharmacology (OSP) framework recently published (1,2). In vitro experiments informed biopharmaceutical properties of the drug and formulation.

- Aqueous solubility and bile salt-mediated solubilization were characterized using the OSP solubility toolbox (4). This toolbox facilitates mechanistic parameterization of drug solubility by integrating in vitro measurements in various media to account for the impact of pH and bile salt concentrations on gastrointestinal solubility.
- Dissolution kinetics were informed using the MoBi®-based dissolution module (4), using in vitro dissolution experiments in the United States Pharmacopeia 2 (USP 2) paddle apparatus.

- Intestinal permeability was informed by applying an in house developed human P_{eff}-Caco2 P_{app} correlation tailored for PK-Sim® integration.

A PBPK model was developed in PK-Sim® where distribution and metabolism parameters were informed and qualified using subsets of the fasted state clinical data.

Results: Non-linear absorption observed in the fasted state clinical study was successfully captured by the PBBM. Fold deviations (observed/predicted) for PK parameters C_{max}, AUC_{Tlast} and $AUC_{\tau,ss}$ were all between 0.62 and 1.41, indicating adequate predictions. Fasted state 150 mg BID dosing was predicted to increase Drug X $AUC_{\tau,ss}$ by 23% over 300 mg QD dosing, by reducing the fraction of the dose that precipitates upon gastrointestinal transfer. An increase in exposure was predicted when the drug is co-administrated with food, and therefore recommendations were made for the fed state clinical study design (i.e., wash-out period, dose selection, and sampling times).

Conclusion: The developed OSP-PBBM successfully characterized Drug X ASD's non-linear absorption in fasted state. It provided a prospective food effect prediction, offering mechanistic insights into altered absorption and allowing for a preliminary assessment in patients. Furthermore, the evaluation of BID vs. QD dosing regimens demonstrated the benefits of dose fractionation in the fasted state. This MIDD approach was instrumental in optimizing the clinical food effect study design, potentially minimizing trial burden and supporting efficient drug development.

References:

(1) Vrenken P et al. Eur J Pharm Sci. (2025a) 212, 107164.

(2) Vrenken P et al. Eur J Pharm Sci. (2025b) 212, 107189.

(3) https://github.com/Open-Systems-Pharmacology/Oral-PBBM-Workflow/tree/main/OSP-Solubility-Toolbox

(4) https://github.com/Open-Systems-Pharmacology/Oral-PBBM-Workflow/tree/main/In-Vitro-Dissolution-Model