Virtual Bioequivalence Outcome May Depend on Dissolution Inputs in Physiologically Based Pharmacokinetic Modelling: Investigating Potential Impact of Gut Physiology on Dissolution of Two Tyrosine Kinase Inhibitors

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Virtual Bioequivalence (VBE) Outcome May Depend on Choice of Dissolution Inputs in Physiologically Based Pharmacokinetic Modelling

Background & Objective

Physiologically based pharmacokinetic (PBPK) models can be used to conduct virtual bioequivalence (VBE) studies. There are different ways to input dissolution parameters in PBPK models. Depending on the dissolution inputs in PBPK model it may or may not be possible to incorporate the impact of gut physiological parameters on drugs dissolution and absorption [1]. For example, it is simpler to directly enter in vitro biopredictive dissolution profiles into PBPK, nevertheless this means the dissolution in the gastrointestinal tract is already established and the individuals' gut physiology are not going to affect the dissolution processes of the administrated drugs (see Figure 1). Majority of small molecule tyrosine kinase inhibitors (TKI) are weakly basic with significant pH-dependent solubility [2]. Therefore, physiological parameters such as stomach and small intestine pH and transit time may affect the bioavailability of these drugs. ***Using virtual bioequivalence (VBE) simulations, this work assesses the potential impact of two different dissolution inputs in PBPK models.***

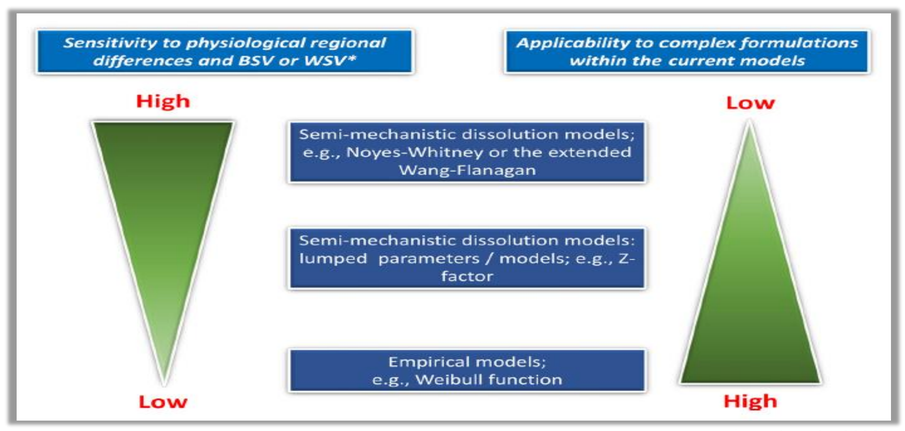
Methods

Ibrutinib and Crizotinib PBPK models from the Simcyp Simulator V23 (Certara UK) are used for this study. The Advanced Dissolution Absorption and Metabolism (ADAM) model is selected for both drugs. Further, the Diffusion Layer (DLM) model (the reference model) that can handle within and between subject variability is also used. Then two new PBPK models (the test model) for each of these drugs were developed where the dissolution profiles are determined and entered instead of using the DLM model (see Figure 2). The dissolution profiles were manually fitted to the give very close dissolution profiles, Cmax and AUC values when a population representative subject is simulated. Next, the Virtual Bioequivalence (VBE) module was used to evaluate the bioequivalence of these two inputs for each of these two drugs.

Methods, Count.

A crossover BE study of 2 treatments (T1: reference and T2: test), two periods and 2 sequences (2T2P2S) of T1T2/T2T1 was simulated. For each VBE simulation 10 replicates of 12 subjects from the healthy volunteer population in the age range of 20-50 years and 50% females were simulated. The duration of simulation for Ibrutinib and Crizotinib was 48 and 144 hours respectively. To simulate an ideal situation inter-occasion variability was not considered, meaning the same physiological values used in both sequences.

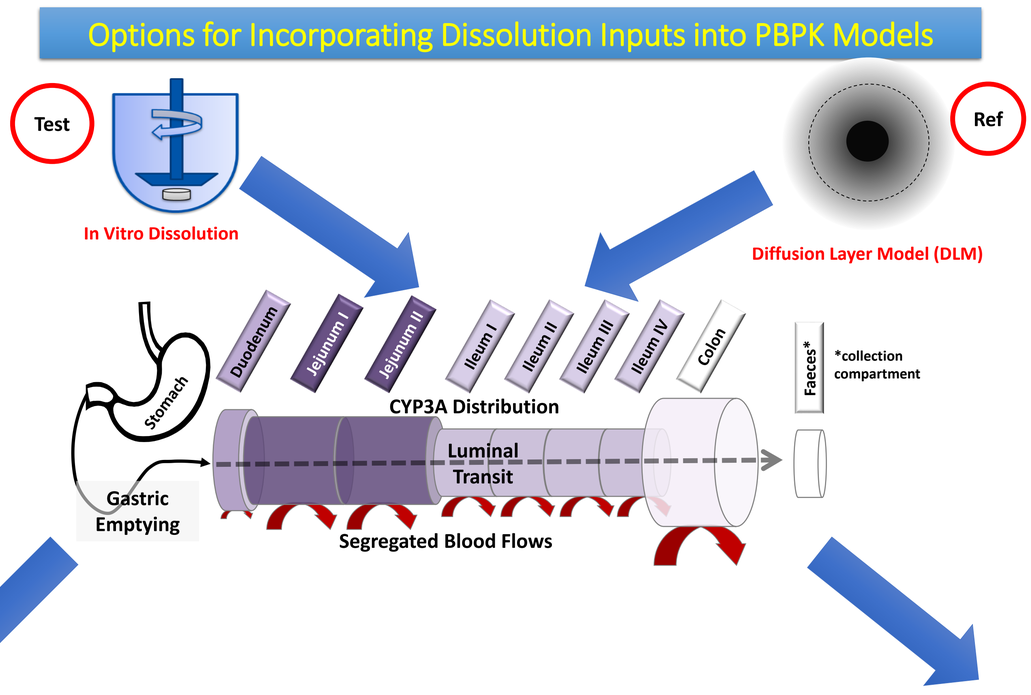
Choice of models can be based on what is fit (sufficient) for purpose

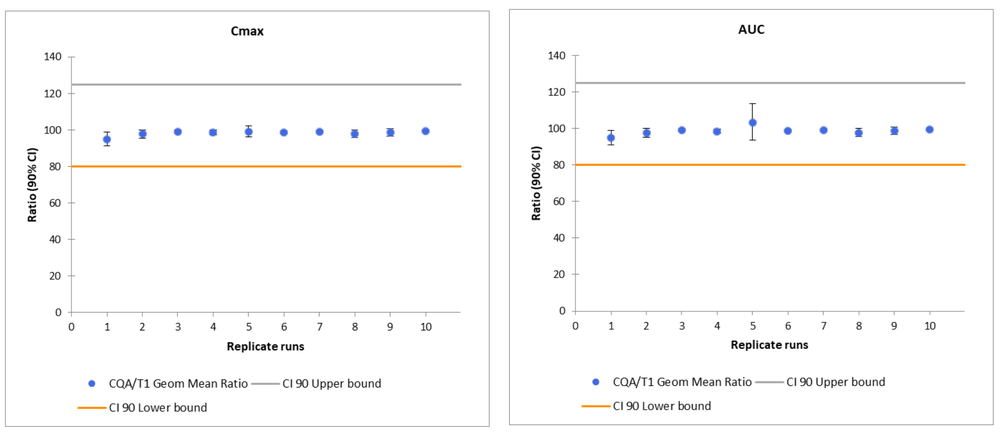


BSV = Between Subject Variability
WSV = Within Subject Variability

(Jamei et al., 2020)

Figure 1 – Choice of mechanistic vs empirical models affect how much of physiological variability can be reproduced in the simulation.





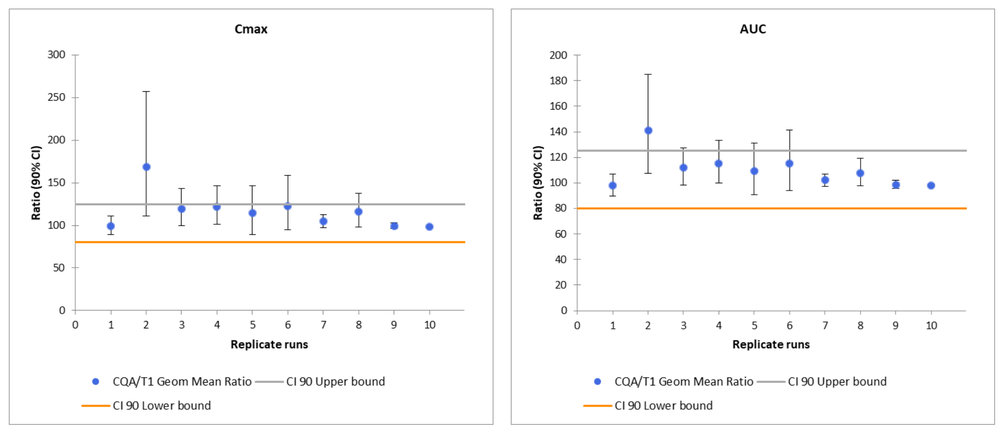


Figure 2 –The dissolution input options (Test vs Reference) in PBPK model where the impact of model input is investigated using VBE for two model drugs.

Results

The Tmax, Cmax and AUC values for Ibrutinib (using the DLM model as input) for population representative were 1.44 (h), 0.035 (mg/L) and 0.275 (mg/L.h) and the same PK parameters for the Ibrutinib (biopredictive dissolution profiles as input) were 1.44 (h), 0.035 (mg/L) and 0.274 (mg/L.h). The VBE simulation results for Ibrutinib showed that for Cmax only 4 out of 10 replicates were BE while for AUC and AUCinf 5 out of 10 replicates were within the BE ranges. The rest of replicates were undecided meaning they were not bioequivalent [2]. The Tmax, Cmax and AUC values for Crizotinib (using the DLM model as input) for population representative were 2.16 (h), 0.112 (mg/L) and 2.26 (mg/L.h) and the same PK parameters for the Crizotinib (biopredictive dissolution profiles as input) were 2.16 (h), 0.112 (mg/L) and 2.26 (mg/L.h). The VBE simulation results for Crizotinib showed that for the three PK parameters i.e. Cmax, AUC and AUCinf all 10 replicates were well within the BE ranges.

Conclusions

Virtual BE simulations were used to investigate the potential impact of dissolution inputs on the simulation outcomes. Six out of 10 replicates for Ibrutinib failed the BE test when dissolution profile was used instead of the diffusion layer model. However, for Crizotinb the choice of dissolution inputs for the PBPK model didn't significantly alter the simulation outcome. This demonstrates that the outcome of the VBE studies may depend on the PBPK model inputs, specifically for cases where the drug dissolution is sensitive to the gastrointestinal pH, transit time or other physiological parameters.

References:

[1] Jamei et al., (2020) European Journal of Pharmaceutics and Biopharmaceutics 155:55-68.

[2] Williams et al., (2018) Mol. Pharmaceutics 15:5678-5696.

[3] Bego et al., (2022) American Association of Pharmaceutical Scientists Journal 24:21.