Establishment of Virtual Bioequivalence Using Population-Based PBPK Modelling: Application to the Setting of Dissolution Limits

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ABSTRACT

In vitro-in vivo correlation (IVIVC) is a biopharmaceutical tool widely used in formulation development and quality control of extended release (ER) formulations. A validated IVIVC can be used to set dissolution limits and as a surrogate for an *in vivo* study[1]. Recent advances in physiologically-based pharmacokinetic (PBPK) modelling have enabled the translation of *in vitro* dissolution data to the prediction of *in vivo* performance of drug product for a patient "population"[2]. Such models can be used to predict the population variability of the PK of the formulated API & therefore enable the assessment of the likelihood of product bioequivalence (BE) via virtual trials[3]. Unlike IVIVC, which is usually limited to the modelling of "mean data", such virtual trials can permit population variability to be taken into account and enable the setting of dissolution limits that may ensure greater likelihood of exhibiting BE.

Population PBPK can be used to guide formulation design space specification and aid in the identification of suitable enabling formulations in BA/BE studies, potentially reducing the cost/time of product development cycles. This study demonstrates how a PBPK modelling approach can be used to 1) specify the upper (UL) and lower limits (LL) of dissolution for Tramadol ER formulations[4] and, 2) build a formulation design space based upon Weibull parameters.

METHODS

A PBPK Model- Constructed using Relevant Drug Physchem and Disposition Parameters in Simcyp® V14.1

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Model Validation- by Utilising Clinical Study Dataset of Different Dosage Forms, Formulations, Dosage Regimen, Drug-Food & Drug-Drug Interaction Conditions

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Biorelevance- of the *in vitro* Dissolution Method Established Using Mechanistic IVIVC Model and Validated Internally as well as Externally

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Virtual Population- Plasma Concentration time Profiles Predicted Using *In Vitro* Dissolution Parameters in Validated Simcyp® PBPK model

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Inter- Occasion Variability added into the PK Parameters- C_{max} and AUC

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Virtual Bioequivalence - Established using the Certara Phoenix® BE module

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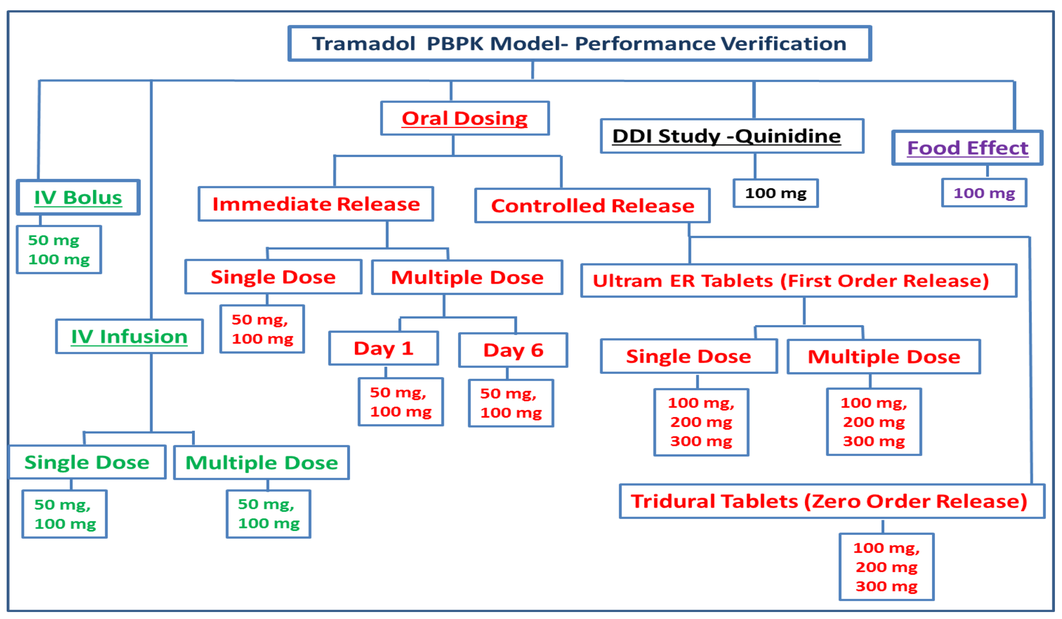
Model Exploration- 1. Setting Dissolution Limit Specifications
2. Construction of Safe Space Design

Fig.1. General Stepwise Workflow

A PBPK model was developed for Tramadol and its predictive performance verified against observed PK profiles of intra-venous (IV) bolus, IV infusion, oral immediate release (IR) formulations and also at different doses and dosing regimens (single and multiple dose) reported in the literature (Fig. 2).



A PB-IVIVC was developed and validated internally (and externally) for ER products of Tramadol[5]. PK profiles for 16 healthy Caucasian male subjects were predicted after single dose administration of target and test samples of an ER formulation using an estimated *in vitro* dissolution profile characterised with a Weibull function.

Inter-occasion (IO) variability obtained from a cross-over replicate clinical study was *added* to the PBPK-estimated *between-subject* (BS) variability of the key PK parameters C_{max} and *AUC* (Fig.3).

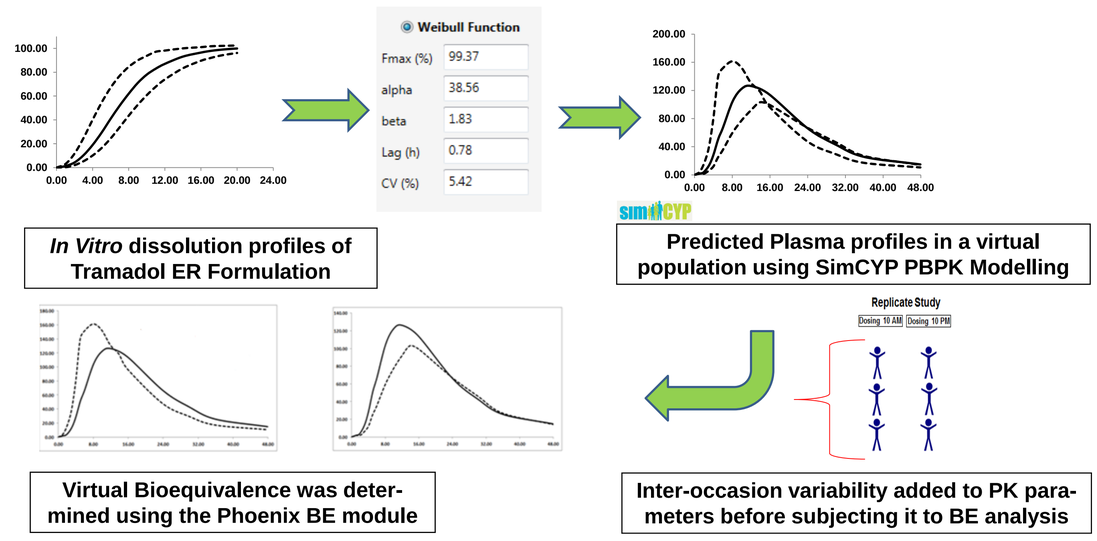


Fig.3. Virtual Trial Design using PBPK Modelling.

A virtual BE assessment (90% CI) was performed for the Target *vs*. Test profiles using the Phoenix® BE module. The range of optimal Weibull shape parameters *α* and *β* was established to define the safe formulation space that is BE to the bio-batch/Target formulation.

RESULTS

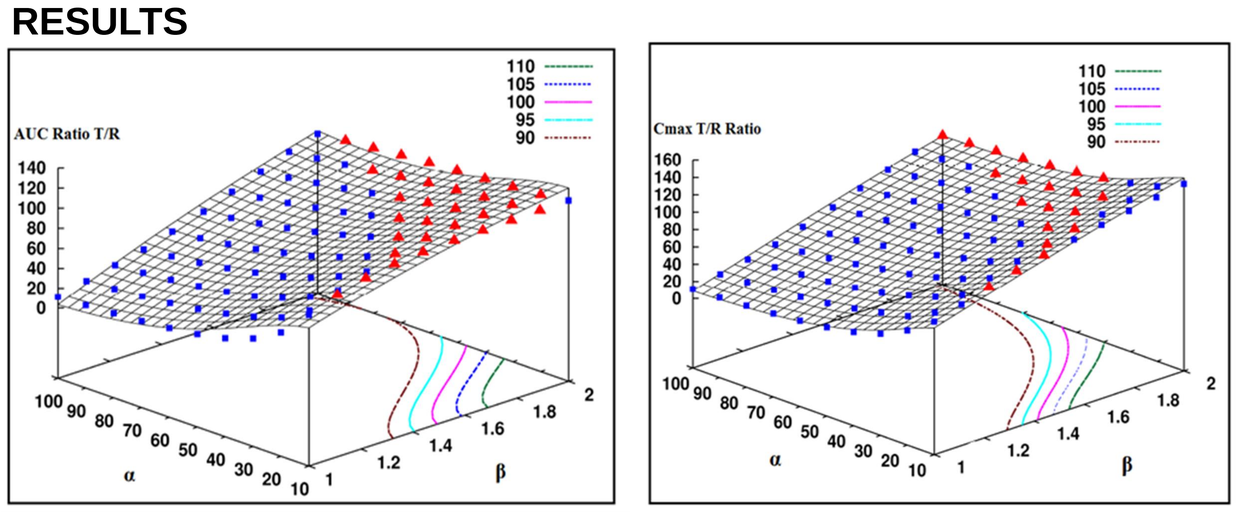


Fig.4. *α* and *β* Weibull parameters in formulation dissolution space building (Contour lines at the bottom refer to the compliant Weibull Parameter Combinations).

The optimum values of the *α* and *β* Weibull parameters were estimated on the basis of the virtual trials ensuring BE (C_{max} and *AUC* within 80 - 125% of the Target formulation) and then transformed into dissolution profiles (Fig. 5). Upper (UL) and Lower (LL) limits of dissolution were demarcated allowing wider specifications compared to a classical IVIVC approach.

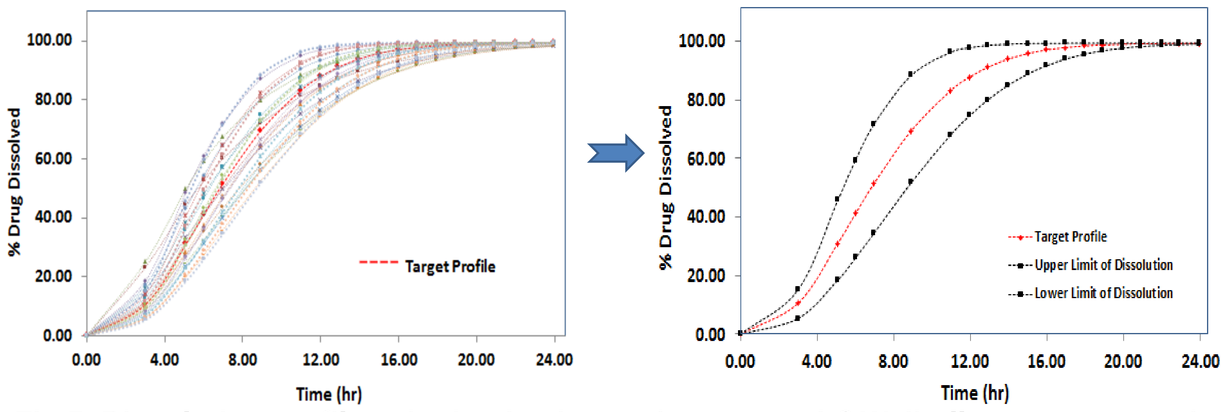


Fig.5. Dissolution profiles obtained using optimum *α* and *β* Weibull parameters and used to define UL and LL dissolution specifications.

CONCLUSION

Generally dissolution limits are linked to either a maximal difference of 20% in the IVIVC predicted C_{max} and AUC or the dissolution limits are fixed at ±10% of the target dissolution profile in the absence of a valid IVIVC model[1]. Validated PBPK models can be used to run virtual BE trials with potential application to dissolution specification settings, defining formulation design space, informing QbD, alcohol dose dumping and beyond. Further validation of the proposed approach with a range of drugs & formulations is needed to increase confidence in and spread awareness of this novel approach.

REFERENCES

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