A Bayesian Population Compartmental Absorption and Transit Modeling Approach to Support Generic Drug Development and Regulation - Application to Bupropion

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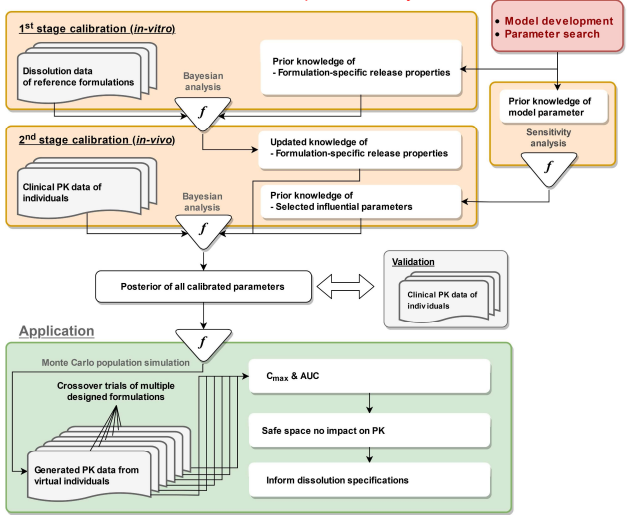
MOTIVATION

To support decision-making in drug development by:

1. Developing a compartmental absorption and transit model for bupropion hydrochloride in oral dosage forms including immediate release, sustained release and extended release formulations. The model integrates information on gut physiology, *in vitro* dissolution and systemic pharmacokinetics (PK).
2. Conducting a Bayesian calibration of the model, using *in vitro* dissolution data and clinical PK data.
3. Applying the calibrated model to define a dissolution "safe space" for bupropion hydrochloride.

WORKFLOW

1) We developed a physiologically-based absorption model based on the well-known compartmental absorption and transit (CAT) framework to describe absorption and disposition for oral dosage forms of bupropion hydrochloride including immediate release, sustained release and extended release formulations.
2) Informed parameter values from previous publications were used for the development of the CAT model.
3) Applied global sensitivity analysis to find the parameters that have a relatively high impact on plasma concentration, to focus parameter estimation and to improve computational efficiency (Hsieh et al., 2018).
4) Performed two-stage Bayesian model calibration (using *in vitro* and *in vivo* data from Connarn et al., 2017) to determine the posterior distribution of the model parameters (Smith et al., 2008).
5) Used clinical PK data (Connarn et al., 2017, secondary dataset for external validation) to validate the predictability of the calibrated model.

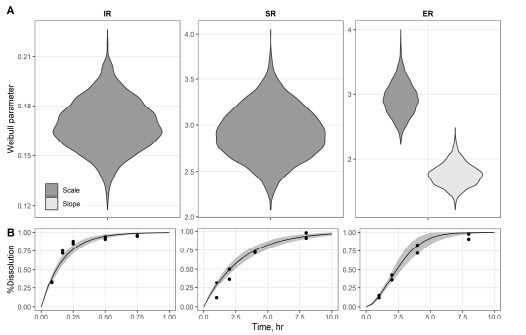


6) Conducted virtual bioequivalence (BE) trials with the calibrated model, varying the drug *in vitro* dissolution-related parameters.
7) We finally determined the "safe space" for *in vitro* dissolution profiles for bupropion hydrochloride; a space where BE is anticipated.

Model building and calculations were performed with GNU MCSim (Bois, 2009).

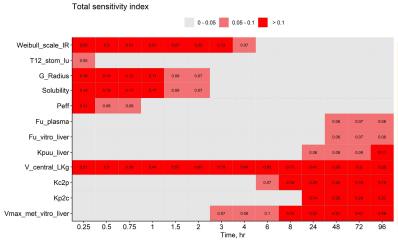
RESULTS

Predicted *in vitro* dissolution profiles



Bayesian-estimated *in vitro* dissolution of bupropion hydrochloride formulations. (**A**) Box-plot of the posterior sample of Weibull function parameters describing *in vitro* dissolution profiles.
(**B**) Posterior predicted *in vitro* dissolution profiles (mean, 5/95% prediction intervals) plotted against observed *in vitro* dissolution data.
IR: immediate release, SR: sustained release, ER: extended release from Connarn et al., 2017.

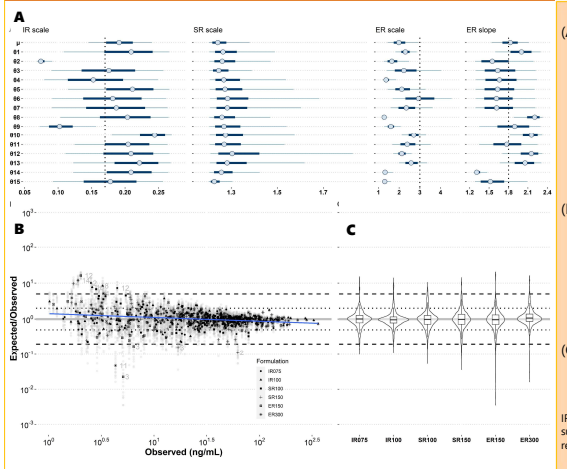
Identification of influential parameters on bupropion plasma concentration



Heatmap of the time-dependent sensitivity coefficient of the influential parameters in the physiologically based absorption model.

Weibull_scale_IR - Weibull scale coefficient; T12_stom_lu - Transit half-life in the stomach lumen; G_radius - galenic radius; Peff - effective permeability; Fu_plasma - fraction unbound in plasma; Fu_vitro_liver - fraction unbound in in-vitro metabolic assay in the liver; Kpuu_liver - liver partition coefficient; Vmax_met_vitro_liver - maximum liver metabolism rate in in-vitro assay; V_central_LKg - distribution volume of the central compartment; Kc2p - central to peripheral compartment transfer rate constant; Kp2c - peripheral to central compartment transfer rate constant; Kelim - elimination rate constant

Predicted *in vivo* dissolution profiles and model performance assessment

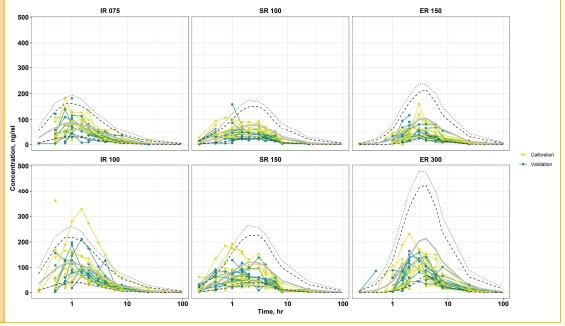


(A) Central (quantile-based) posterior interval estimates of drug-release related parameters (Weibull scale and slope) for calibrated subjects (θ1-15, μ population mean) from Markov Chain Monte Carlo draws. The thick and thin lines represent 50% and 90% interval, respectively.
(B) Posterior predictive check across formulations and doses. The dotted and dashed lines represent the predicted-to-observed ratio over a factor of 2 and 5, respectively. The blue line is a linear regression fitted curve.
(C) Comparative analysis of predictive accuracy and precision.

IR: immediate release/75 and 100 mg, SR: sustained release/100 and 150 mg, ER: extended release/150 and 300 mg (Connarn et al., 2017).

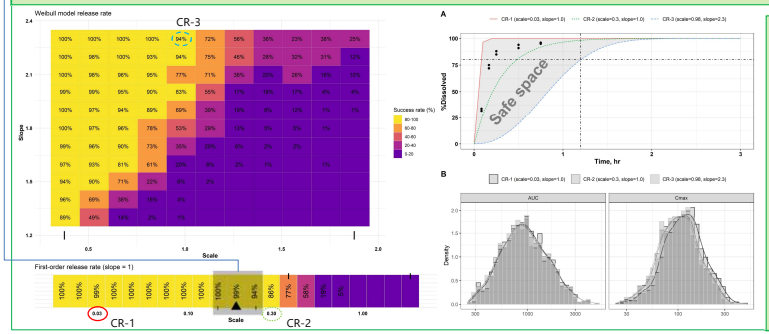
Simulated virtual trials for the given bupropion hydrochloride formulations. Simulations are compared with the observed PK profiles (Connarn et al., 2017). Model validation with experiment data and median prediction (grey line) from random sample-generated PK curve. The dotted and dashed lines delimit the 95% and 99% probability intervals, respectively.

IR: immediate release/75 and 100 mg, SR: sustained release/100 and 150 mg, ER: extended release/150 and 300 mg (Connarn et al., 2017).



Virtual BE assessment and safe space prediction

BE assessment of designed test formulations of bupropion hydrochloride with first-order and Weibull released patterns. The **black triangle and bars** represent the maximum a posterior and 90% credible interval of the immediate-release formulation. A successful trial was declared when both C_{max} and AUC fell within the 80-125% BE limits.



(A) In vitro dissolution "safe space" prediction. The dissolution profile of three hypothetical controlled release formulations, CR1, 2 and 3.
(B) The histogram of simulated AUC and C_{max} for 900 virtual subjects obtained for three hypothetical controlled release formulations, CR1, 2 and 3.

SUMMARY

- A Bayesian-based population modeling-workflow was developed and evaluated for various bupropion hydrochloride oral formulations.
- The workflow was used to integrate *in vitro* dissolution and clinical PK data to predict dissolution "safe space" for each formulation.
- The developed Bayesian workflow demonstrated its potential to integrate all available data and to support decision making in generic drug product development.

ACKNOWLEDGEMENTS

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