PBPK Modeling to Predict the Effect of Gastric pH on Bioequivalence of Dabigatran Etexilate Capsules

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INTRODUCTION

- In generic drug development, physiologically based pharmacokinetic (PBPK) modeling and simulation has played an important role in the design of clinical bioequivalence studies and provided risk assessment to support the review of Abbreviated New Drug Applications (ANDAs).
- A noteworthy application of PBPK modeling in generic drug development is to predict the impact of gastric pH changes after co-administration of acid-reducing agents (ARAs) on the bioequivalence of weak base drug products.
- Dabigatran Etexilate (DABE) is a weak base drug which demonstrates pH-dependent solubility and DABE products also shows pH-dependent dissolution characteristics that may be formulation-dependent (1).
- Therefore, there is a potential of having different "drug-drug interaction (DDI)" or pH impact on absorption due to formulation differences when the generic drug product or reference listed drug (RLD) product is co-administered with PPI.

PURPOSE

- Purpose of this study was to use an PBPK absorption model of DABE capsules and virtual bioequivalence (VBE) simulations to assess the impact of gastric pH change on the BE of generic DABE capsules.
- This work will also support the future implementation of ICH M13A to help assess the potential impact of ARAs on BE outcome and determine if an additional in vivo BE study is needed for weak base drugs under the condition with elevated gastric pH.

METHODS

- Simcyp™ simulator (version 22; Certara, Sheffield, UK) was used to develop the PBPK model for DABE capsules (Figure-1). The disposition model of DABE capsules was modified based on previously developed DABE PBPK models (2-5). DABE is a prodrug, and the active metabolites are free Dabigatran (DAB) and Dabigatran-glucuronide (DAB-G) conjugate. Therefore, disposition models for DAB (as primary metabolite) and DAB-G (as secondary metabolite) were also developed. The absorption model of DABE capsules was developed using the Advanced Dissolution, Absorption, and Metabolism (ADAM) module.
- The dissolution data of DABE capsules in quality control (QC) media at pH 2 and plasma profiles of free DAB and total DAB (total DAB = free DAB + DAB-G) following oral administration of 150 mg DABE capsule under fasted condition were used to estimate the absorption parameters.
- The developed PBPK model was further validated using pharmacokinetic (PK) data after dosing 75 mg, 200 mg, and 600 mg DABE capsules (data obtained from clinical pharmacology review for DABE capsules (6)).
- Administration of PPI (pantoprazole) is known to increase the gastric pH up-to 5.0 (7). Therefore, in case of the co-administration of PPI under fasted condition, the available dissolution profiles in QC media with elevated pHs (e.g., 4.5 and 6.8) were used as model inputs and the PBPK model was used to predict the PK following administration of 150 mg DABE capsule.
- Since all the available QC dissolution profiles (at pH 4.5 and 6.8) resulted in underprediction of the PK profile, a hypothetical bio-predictive dissolution profile was generated to achieve a better model prediction of the PK data for 150 mg DABE capsule. To generate the hypothetical dissolution profile, QC dissolution profile at pH 4.5 was used and scaled up at each time point to get an overall higher dissolution values.

METHODS (CONT.)

- When applying this model to predict the PK profiles of RLD and generic products in Indian population, model parameters (e.g., clearance and regional permeability values) were adjusted based on published report of population PK differences of DABE between Indian and Caucasian populations (8-10). This modified model was validated using data from multiple generic products (150 mg). The hypothetical bio-predictive dissolution profiles were generated for both RLD and generic products in a similar way and used as model inputs for VBE simulations.

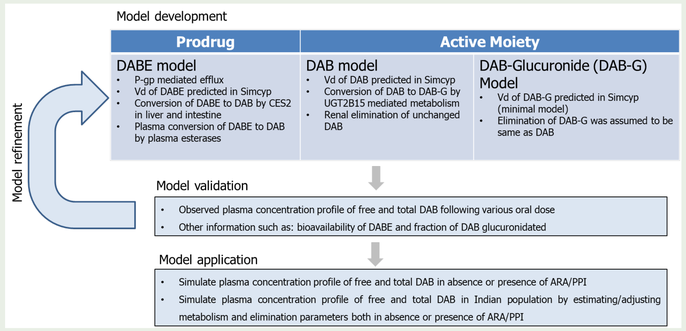
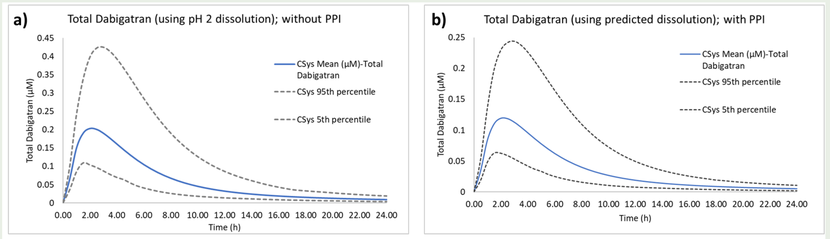


Figure-1: General workflow for development, validation, and application of the PBPK model for DABE

RESULTS

- Development and validation of DABE PBPK absorption model in Caucasian population showed good predictive capability (PE ~ 20%) under fasted condition, where dissolution data generated under quality control (QC) condition (pH 2) were used as model input (Figure-2a).
- In case of fasted condition with coadministration of PPI (pantoprazole), the available dissolution profiles in QC media with elevated pHs (e.g., 4.5 and 6.8) failed to provide a satisfactory prediction (PE > 50% and PE > 200% at pHs 4.5 and 6.8 respectively) when used as model input. Therefore, a hypothetical bio-predictive dissolution profile was generated and used as model input. As such, the PBPK model demonstrated a good predictive performance (PE < 20%) (Figure-2b).



	C_{max}	AUC_t	AUC_{inf}
% Prediction Error (PE)	1.0	7.17	7.75

	C_{max}	AUC_t	AUC_{inf}
% Prediction Error (PE)	3.42	17.60	19.04

Figure-2: Predicted profile of total Dabigatran following 150 mg capsule under a) Fasted condition without PPI and b) Fasted condition with co-administration of PPI (pantoprazole) in Caucasian population. The bottom tables shows the % PE accordingly.

- Furthermore, this PBPK model also demonstrated good predictive capability (PE < 20%) for Indian population after adjusting the clearance and regional absorption parameters based on the published reports.
- Lastly, using the hypothetical bio-predictive dissolution profiles as model inputs, VBE of DABE 150 mg capsule was conducted under fasted conditions with concomitant administration of PPI (pantoprazole) in Indian healthy subjects. Those VBE simulations demonstrated BE between generic and RLD products (Figure-3).

RESULTS (CONT.)

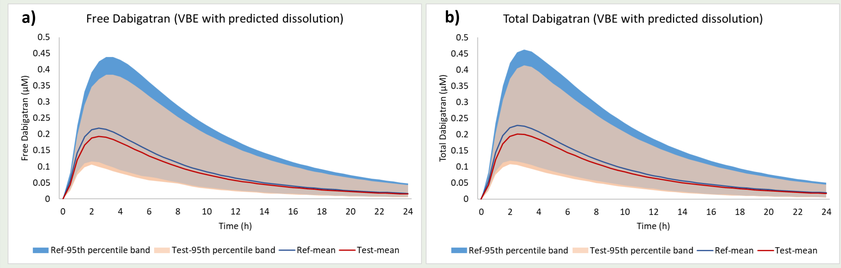


Figure-3: Virtual bioequivalence study between reference (RLD) and test DABE 150 mg capsule under fasted condition with PPI (pantoprazole) coadministration; a) free dabigatran simulation and b) total dabigatran (free DAB + DAB-G conjugate) simulation

CONCLUSION

- In this research work, a PBPK model for DABE capsule was developed and validated. Using the hypothetically generated bio-predictive dissolution profiles (to mimic elevated pH conditions) as model inputs, the model was able to predict the PK profiles when the DABE capsule was co-administered with PPI.
- Furthermore, virtual BE simulations predicted BE between generic and RLD when both products were co-administered with PPI, suggesting low risk of non-BE for this specific generic product, thus an in vivo BE study with PPI coadministration may not be needed.
- Our work showed the utility of PBPK modeling as an alternative for BE assessment.
- Since hypothetically generated bio-predictive dissolution data were used in the model, further experimental bio-predictive dissolution data might be needed to refine and validate this model for predicting the effect of ARAs on BE.

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