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Assessing the Impact of Excipient and Food Intake on Bioequivalence Using PBPK and Virtual Bioequivalence Trial: A Case Example with Acyclovir Immediate Release Tablets

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PURPOSE

Physiologically based pharmacokinetic (PBPK) modeling is often used in lieu of dedicated drug-drug interaction (DDI) studies for new drug development. Currently, application of PBPK in generic drug development areas is being explored, in light of the increasing interest from generic industries and regulatory agencies. Using PBPK modeling to assess the impact of excipients on for supporting the possible biowaiver of non-Q1 (qualitatively) the same and Q2 bioequivalence (BE) (quantitatively) similar Biopharmaceutical Classification System (BCS) Class 3 generic products and to assess the impact of food on BE are some of the areas of interest in generic drug development. As a proof of concept, in this study, we have utilized an oral PBPK model of acyclovir immediate release (IR) tablet for assessing the impact of excipient and food intake on the BE of generic acyclovir IR tablet using virtual healthy subjects and virtual bioequivalence (VBE) trials.

OBJECTIVE(S)

Considering the potential of advanced mechanistic absorption models in the available commercial PBPK modeling platforms (e.g., GastroPlus™, Simcyp™, PK-Sim®), the objective of this study was to leverage the predictive capacity of PBPK model and advantages of virtual population simulation for assessing the impact of potential excipient-mediated intestinal permeability change and food intake on BE using acyclovir as a case example.

METHOD(S)

GastroPlus™ (version 9.8, Simulations Plus Inc., CA, USA) software with PKPlus™ module and Advanced Compartmental Absorption Transit (ACAT™) module were used for acyclovir PBPK model development. Once the disposition parameters were estimated using pharmacokinetic (PK) data of 2.5 mg/kg acyclovir IV infusion, oral PBPK model was developed using these parameters along with apparent intestinal permeability value (P_{app}) to predict the plasma profile of acyclovir 200 mg, 400 mg, and & 800 mg IR tablets under the fasted condition. To simulate food intake, GastroPlus™ fed physiology was used and plasma profile of acyclovir 800 mg IR tablet taken with food was predicted. The model was validated using pharmacokinetic data for oral 400 and 800 mg IR tablets under fasted and fed conditions. VBE studies were carried out under both fasted and fed conditions using virtual population simulations along with incorporation of in vitro dissolution data, obtained from FDA's approved abbreviated new drug application (ANDA) for test and reference (Zovirax®) tablet, into the PBPK model. To assess the impact of excipient-mediated intestinal permeability changes on the BE, the P_{app} value in the PBPK model used to simulate PK profiles of the test product was changed at different percent (test) compared to the P_{app} value used in the base PBPK model (reference). Additionally, similar to the fasted condition, the impact of P_{app} value changes were also assessed under the fed condition. Figure-1 depicts the PBPK model development, validation, and VBE steps for acyclovir IR tablet.

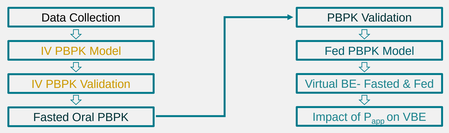

Figure-1: Flow chart of acyclovir PBPK model development, validation, and application.

RESULT(S)

- Validation results showed that acyclovir IV PBPK model captured the plasma profile for 5 mg/kg IV infusion with prediction error (PE) of less than 20% for C_{max}, $AUC_{(0\text{-}inf.)}$ and $AUC_{(0\text{-}t)}$. Validation of acyclovir oral PBPK model showed good predictive capability of the model (PE~20%), Table-1, where dissolution data generated under quality control condition (900 mL dissolution media of 0.1 N HCl; apparatus II; rotation speed 50 rpm) were used as model input. Population simulation was also conducted using the GastroPlus™ virtual population simulation platform and the 95% prediction probability of this population simulation was able to capture the observed acyclovir plasma profiles under fasted and fed conditions, Figure-2.

Table-2: PBPK Validation

Dose	PK	PE (%)
200 mg	C_{max}	-4.2
	AUC_{inf}	15
	$AUC_{(0\text{-}t)}$	12
400 mg	C_{max}	3.7
	AUC_{inf}	-21.3
	$AUC_{(0\text{-}t)}$	-6
800 mg	C_{max}	-15.8
	AUC_{inf}	-19.4
	$AUC_{(0\text{-}t)}$	-14.9

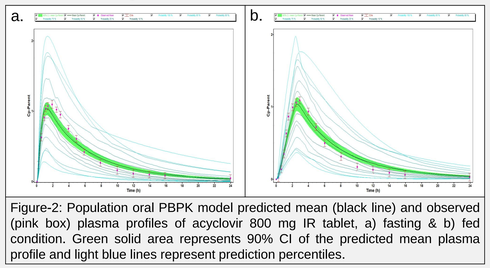

Figure-2: Population oral PBPK model predicted mean (black line) and observed (pink box) plasma profiles of acyclovir 800 mg IR tablet, a) fasting & b) fed condition. Green solid area represents 90% CI of the predicted mean plasma profile and light blue lines represent prediction percentiles.

- VBE of acyclovir 800 mg IR tablet conducted using acyclovir oral PBPK model and virtual population under fasted and fed conditions, Figure-3, Table-2.

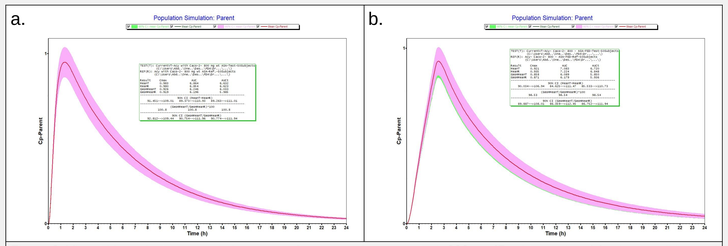

Figure-3: Virtual bioequivalence study between reference and test acyclovir 800 mg IR tablet under a) fasting condition and b) fed condition.

Table-2: VBE outcomes for acyclovir 800 mg IR tablets (fasted and fed condition)

BE Parameter	Test/ Ref.	90% CI of Ratio	VBE Outcome
VBE under fasted condition			
C_{max}	100.8	92.81-109.44	BE Pass
$AUC_{(0\text{-}inf)}$	100.8	90.75 -111.96	BE Pass
$AUC_{(0\text{-}t)}$	100.8	90.77 -111.94	BE Pass
VBE under fed condition			
C_{max}	98.53	89.89 -108.01	BE Pass
$AUC_{(0\text{-}inf)}$	98.54	86.36 - 112.45	BE Pass
$AUC_{(0\text{-}t)}$	98.54	86.75 -111.94	BE Pass

- Impact of excipient-mediated apparent intestinal permeability enhancement on the BE parameters (C_{max}, AUCs) of acyclovir indicated that the Test/Reference ratios for different % of P_{app} changes for test tablet were within 1.25 for up to 95% P_{app} change, Figure-4. However, this results show the effect on mean profiles only, no inter-subject variability were taken into account.

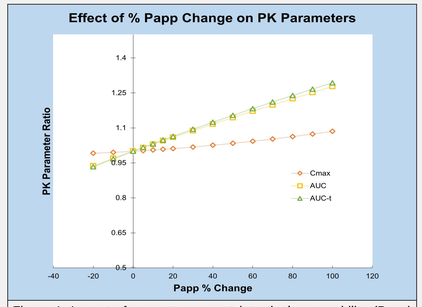

Figure-4: Impact of percent apparent intestinal permeability (Papp) changes on BE parameters under fasting condition.

- Impact of excipient-mediated percent apparent intestinal permeability (P_{app}) change on the VBE of acyclovir 400 mg & 800 mg IR tablets under fasted and fed conditions, Figure-5a & 5b.

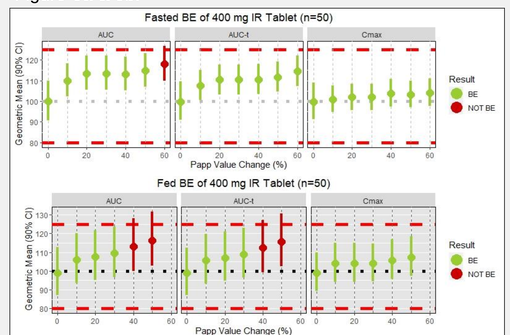

Figure-5a: Impact of percent P_{app} changes on VBE of acyclovir 400 mg IR tablet under fasted and fed condition. Figure-5a indicated, P_{app} changes of 60% and 40% for test tablet resulted in failed BE under fasted and fed condition, respectively.

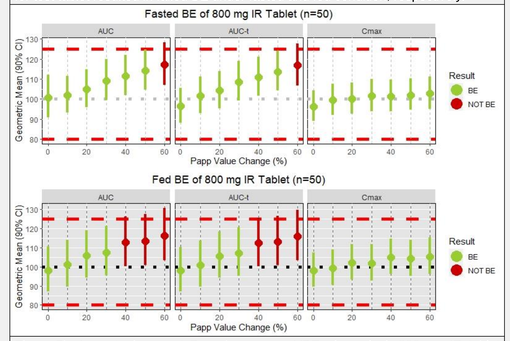

Figure-5b: Impact of percent P_{app} changes on VBE of acyclovir 800 mg IR tablet under fasted and fed condition. Figure-5b indicated, P_{app} changes of 60% and 40% for test tablet resulted in failed BE under fasted and fed condition, respectively.

CONCLUSION(S)

- In this study, an oral PBPK model for acyclovir IR tablet was developed and validated using clinical PK data collected from published literature and FDA's approved ANDA.
- Developed oral PBPK model predicted the plasma profile of acyclovir 800 mg IR table with adequate accuracy (PE<20%) under both fasted and fed conditions.
- VBE trials results for acyclovir 800 mg IR tablet using in-vitro dissolution data of test and reference tablets showed, that test and reference tablets were bioequivalent under fasted and fed conditions.
- Impact of excipient-mediated intestinal permeability changes were assessed using PBPK model and VBE trials. VBE results showed that, under the fasted condition, the test and reference were bioequivalent up to ~50% apparent intestinal permeability enhancement in test; however, under fed condition the test and reference are bioequivalent up to ~30% which could be partially due to the higher inter-subject variability under fed condition.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

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