Using Physiologically Based Absorption Modeling to assess the failing bioequivalence of ziprasidone capsules.

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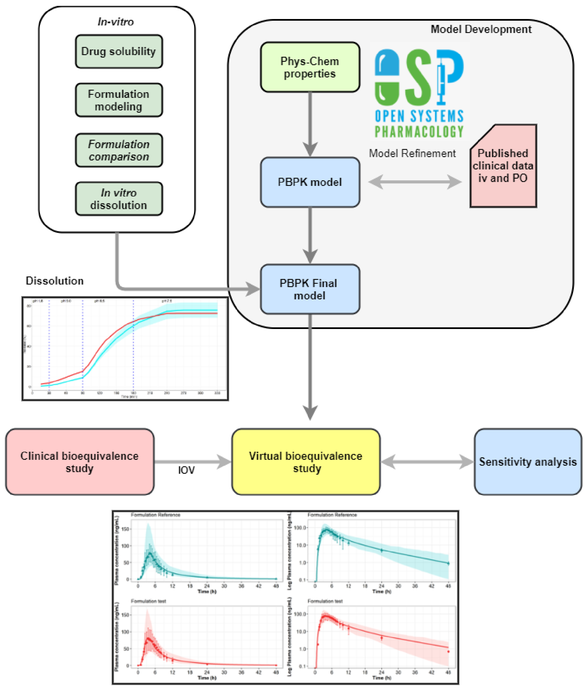
Objectives & Graphical Abstract

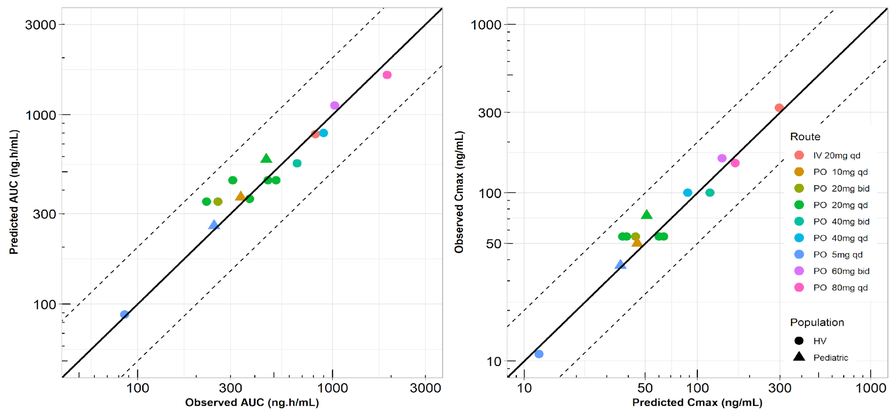
Physiologically-based pharmacokinetic (PBPK) modeling has been implemented successfully to support and inform (oral) drug product development and regulatory decision making[1]. Model informed drug development demands a link between *in-vitro in-silico,* and establish relevant clinical specifications, consequently, guarantee the quality of the drug product concerning safety and efficacy. The aim of this study was performing a VBE of two ziprasidone formulations, translating the *in vitro* dissolution test obtained under biorelevant conditions into an IVIVE PBPK model of ZIP[2] previously developed in PK-Sim/MoBi[3,4]. This work highlights the importance of linking translational absorption modeling with population PBPK to examine VBE.



Results

The MFE pharmacokinetic parameters of ZIP after ascending intravenous and oral doses in healthy adults are summarized in *Figure 1*. The simulated PK parameters for all dose tested were consistent with observed pharmacokinetics. MFE values for AUC ranged 0.7 to 1.3 and C_{max} 0.8 to 1. A model is considered robust when the MFE ranges within a 0.5 to 2.0-fold range for different doses and regimens.

Figure 1: Comparison between simulated and observed PK parameters from several studies in the literature for different populations. Solid lines represent line of unity; dashed lines represent 2-fold difference



The *in vitro* dissolution test was performed with USP apparatus 4, and the similarity factor between FR and FT was f_2=65.2, suggesting a similar dissolution performance between both formulations.

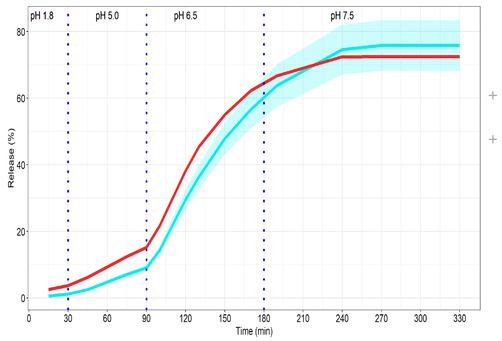


Figure 2: : In-vitro dissolution profiles of formulation reference (Geodon® -FR, blue line), formulation test (FT, red of 0.1 M of HCl solution pH 1.2 for 30 min; 60 min in FeSSIF pH 5.0; 100 min in FeSSIF pH 6.5 and 140 min in FeSSIF pH 7.5.line), safe zone (blue shadow) obtained in USP-4 Apparatus in the following conditions: 12 L/min

However we observed a faster release to FT between time 30-180min (*Figure 2*). pH fluctuations along the dissolution test revealed that the dissolution rate of FT increased more rapidly than reference capsules when changing the media pH from 1.2 up to 5.0. Both formulations were characterized with a Weibull function and integrated within the PBPK model and the simulated PK was compared with clinical observed data (*Figure 3*).

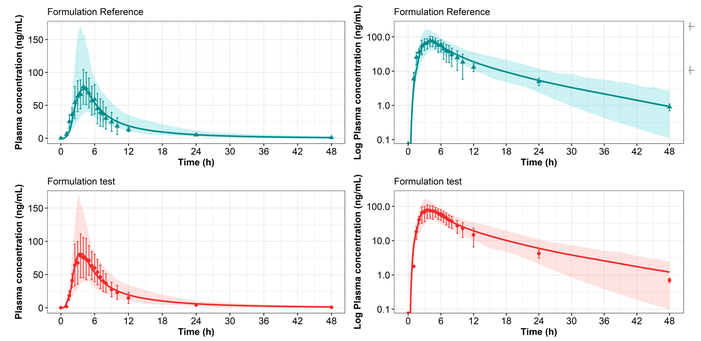
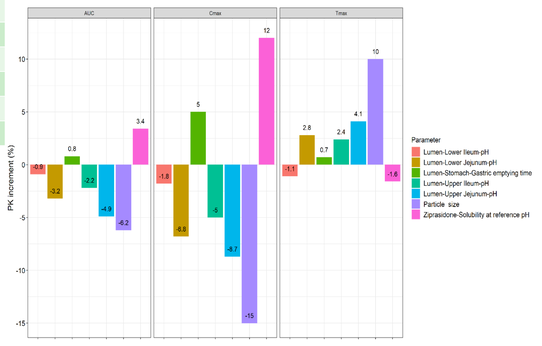


Figure 3 : Prediction and observed ziprasidone PK profiles for formulation test (●) and formulation reference- Geodon® (▲). The solid lines are the PK geometric mean predicted by ZIP-PBPK model and shades represent the 5th to 95th %ile

Table 1 : Confidence interval 90% for FT and FR

	FT/FR	Geometric mean	Confidence interval (90%)	Bioequivalence interval	CV %	Power test
BE	Ln (Cmax)	120.0	(112% - 128%)	(80% - 125%)	17.0	99.99%
	Ln (AUC0-t)	111.2	(105% - 117%)	(80% - 125%)	14.0	100.00%
	Ln (AUC0-∞)	111.7	(104% -115%)	(80% - 125%)	13.0	100.00%
VBE	Ln (Cmax)	119	(120% - 129%)	(80% - 125%)	19.0	99,99%
	Ln (AUC0-t)	109	(107% - 119%)	(80% - 125%)	16.0	99.99%
	Ln (AUC0-∞)	112	(102% -115%)	(80% - 125%)	17.0	99.99%

Figure 4: Sensitivity of AUC, C_{max} and t_{max} to most sensitive parameters in adults when incremented in of 10%.



The ZIP-PBPK model predicted well the PK studies of both formulation with MFE between 0.5 and 2.0. The ZIP absorption window is mainly located in the jejunum with fraction absorbed (fa) of 32 % to FR and 36 % to FT, and the total fa of 82% to FR and 86% to FT (*Figure 3*). The BE and VBE statistical analysis are illustrated on Table 1 shows that AUC 90% confidence interval (90% CI) were into the range of 80 to 125%, however, C_{max} 90% CI was 112 to 128% to BE and 120 to 129% for VBE, confirming the non-bioequivalence between FR and FT. A dissolution safe zone (SZ) was determined by global sensitivity analysis (*Figure 2*, blue shadow), and it shows the acceptable bias on the ZIP dissolution, formulation with release profile into this range would lead positive BE. The GSA shows that the most sensitive parameter to ZIP BE were: drug solubility, particle size, followed by jejunum local pH and gastric emptying (*Figure 4*).

Conclusions

The FT of ZIP is not BE in comparison to FR, the main cause is the higher apparent salt solubility and particle size. A dissolution safe zone can be used to support formulation development and reduce the risk on bioequivalence fail. Mechanism-based absorption PBPK modeling was efficient approach to access the bioequivalence of ziprasidone capsule. This work highlights the importance of linking translational absorption modeling with population PBPK to examine VBE.

References

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4 Open Systems Pharmacology Community (www.open-systems-pharmacology.org)