Identify Biopredictive Dissolution for Predicting In Vivo Performance of a BCS II Drug Product Under Fed Conditions

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Introduction

Physiologically based pharmacokinetic (PBPK) absorption modeling is commonly used in predicting in vivo performance and can be used as an alternative bioequivalence (BE) approach. One of the challenges in PBPK modeling is to identify biopredictive dissolution conditions and demonstrate the bio-discriminating capability/sensitivity of the PBPK model. Drug X is a Biopharmaceutics Classification System (BCS) II drug. Drug X tablets contains amorphous solid dispersion (ASD) formulation. The applicant developed a PBPK model to waive the in vivo fed BE study for generic Drug X Tablets. Initially, reviewers found that the developed PBPK model was not sensitive with dissolution input from dissolution quality control (QC) method. The predicted in vivo performance under fed conditions remains the same with changes in dissolution profiles. Herein, this research incorporated dissolution data at different conditions into PBPK model and explored the possibility of using theoretical dissolution to evaluate the sensitivity of established PBPK model for detecting potential formulation differences. This research also conducted virtual BE using biopredictive and discriminating dissolution data and established dissolution safe space for Drug X tablets under fed conditions. The work establishes a good practice for demonstrating the credibility of a PBPK model for solid dispersion formulations, which can be used to support regulatory evaluations, including the possibility of waiving in vivo fed BE studies.

Methods

A series of theoretical dissolution profiles for test products were generated by manually varying the dissolution rates based on the submitted dissolution profiles in QC buffer, acetate buffer pH 4.5 and in phosphate buffer pH 6.8. Gastroplus® (Version 9.8.2, Simulations Plus, Inc. CA) was used to simulate in vivo PK of the varied dissolution profiles for test products using Z-factor approach under fed conditions. The in vivo PK of Reference Listed Drug (RLD) was also simulated by Gastroplus® using measured dissolution profiles. With the simulated PK generated, virtual BE was conducted and dissolution safe space was evaluated.

Figure 1: Z-factors from (3) dissolution media for test products with theoretical dissolution rates varying from -10% to 10%

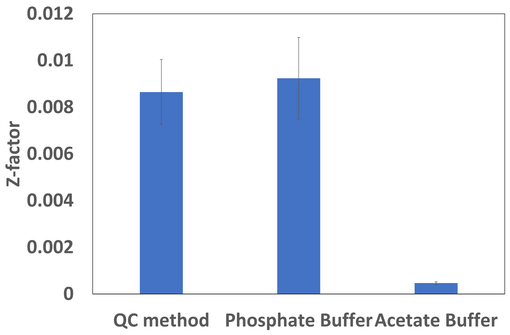

Figure 2: Parameter Sensitivity Analysis (PSA) Z-factors under fed conditions - Z-factors from (3) dissolution media with theoretical dissolution rates varying from -10% to 10%

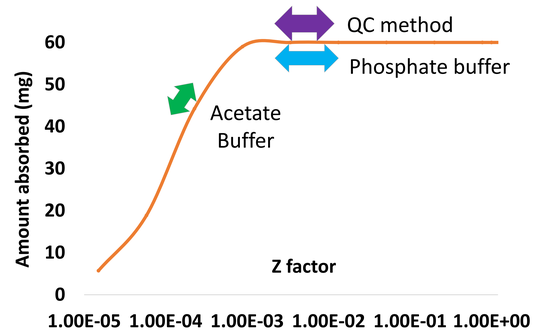

Figure 3: Z-factors for dissolution in acetate buffer with theoretical dissolution rates varying from -10% to 10% and assumed solubilities

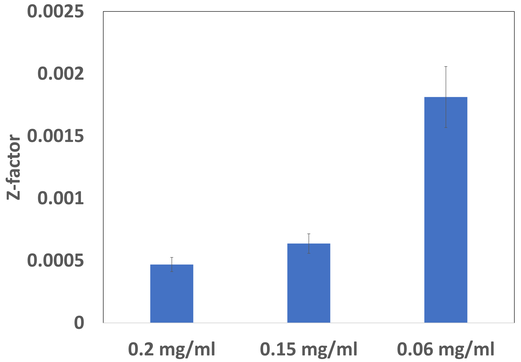

Figure 4: Established virtual design space (-55% to 10% dissolution rates) at 0.15 mg/ml solubility in acetate buffer

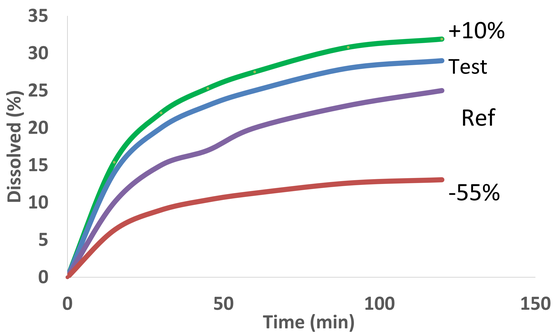

Table 1: Established Virtual Design Space (-55% to 10% dissolution rates) at 0.15 mg/ml solubility in acetate buffer

Acetate pH4.5 with varying dissolution rates	Cmax			T/R based on Z-factor profiles
	Test/ Reference	90% CI		
-60	79.37	75.01	83.98	0.79
-55	84.71	80.23	89.44	0.85
-40	98.22	93.30	103.62	0.99
0	116.7	111.03	122.62	1.18
10	119.5	113.16	125.45	1.21
20	121.7	115.95	127.79	1.22

Results

Different Z-factors were calculated with dissolution profiles from different dissolution media with theoretical dissolution rates varying from -10% to 10% (**Figure 1**). It was found that Z-factors have positive relationship with dissolution. In the current study, Parameter Sensitivity Analysis (PSA) from the developed PBPK modeling indicated that PK parameters were sensitive to Z-factor changes if Z-factor was low (e.g., Z-factor less than 1.00 x 10^{-3}). That is, PK parameters were more sensitive to changes in Z-factor in Acetate buffer pH 4.5 than Phosphate buffer pH 6.8 and QC method (**Figure 2**).

Further, a thorough investigation of the effect of solubility in the dissolution media (with assumed solubility: 0.06, 0.15, and 0.20 mg/mL) on Z-factor was conducted for dissolution in Acetate buffer at pH 4.5. It was found that Z-factors have negative relationship with solubility (**Figure 3**). It was shown that 0.2 mg/ml solubility was oversensitive in establishing dissolution space. 0.06 mg/ml solubility was not sensitive to establish reasonable dissolution safe space. While with 0.15 mg/mL solubility, the dissolution space was able to be established (**Figure 4, Table 1**).

Conclusions

In the current study, predicted in vivo PK parameters were affected by both solubilities and dissolution. For this case example with ASD formulation, it is a good practice to use measured solubilities and biopredictive dissolution as PBPK model inputs to establish dissolution safe space and support waiving in vivo fed BE study.

Disclaimer

References available upon request. This poster represents the views of the presenters only and should not be construed to represent FDA's views or policies.