Exploration of Predictive Bioequivalence: Comparison of Methods to Incorporate *in vitro* Dissolution Data, Using Surface pH instead of Bulk pH, in Pharmacokinetic Modeling of BCS Class II Acidic Drugs

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Abstract

BCS Class II acidic drugs have low solubility at gastric pH but behave like BCS Class I drugs at intestinal pH. "Exploration of Predictive Bioequivalence: Comparison of Methods to Incorporate in vitro Dissolution Data, Using Surface pH instead of Bulk pH, in Pharmacokinetic Modeling of BCS Class II Acidic Drugs" aims to determine the best *in vitro* dissolution input approach for predicting pharmacokinetic AUC and Cmax values, and to establish boundaries for a "bioequivalence safe-space" range of dissolution rates for BCS Class IIa drugs, potentially making them eligible for biowaiver considerations. An in-silico model using GastroPlus™ software and pharmacokinetic inputs from an internal FDA database was built. Four methods—traditional z-factor, refined z-factor, theoretical product particle size distribution (P-PSD), and Weibull function with a "CR: Dispersed" formulation—were used to incorporate dissolution data for two different products of the same drug substance. Results showed that the refined z-factor method was the most accurate in predicting Cmax and discriminating between the two products, while all methods consistently provided good estimations of AUCi. None of the strategies consistently predicted Tmax, likely due to high variability in gastric emptying time and absorption patterns. Further research is needed to determine whether these findings can be generalized to establish bioequivalence and expand BCS-based biowaivers for all BCS Class IIa immediate release drug products.

Introduction

The Biopharmaceutics Classification System (BCS) classifies drugs according to permeability, solubility, and dissolution. Currently, Class I (high solubility and permeability) and Class III (high solubility, low permeability) immediate release drug products are eligible for waiver of *in vivo* bioequivalence studies (biowaivers) as per guidelines described in ICH M9. BCS Class II drug substances are highly permeable but have low solubility. BCS Class II acidic (IIa) drugs, more specifically, behave like BCS Class I drugs at intestinal pH (6.5-7.0) in the gastrointestinal tract, despite having low solubility at acidic (gastric) pH values. Using a single drug substance as a starting point, the purpose of this project is to determine the best *in vitro* dissolution input approach for predicting pharmacokinetic area under the curve (AUC) and maximum concentration (Cmax) values and use this to establish boundaries for a "safe-space" range of dissolution rates that render a BCS Class IIa drug bioequivalent and thus potentially eligible for biowaiver considerations.

Table 1. Average dissolution profile of products 1 and 2. (Dissolution conditions: USP Type II apparatus, pH 5.6 phosphate buffer, 50rpm, 900mL, 37±0.5°C)

Time, min	% Release (Averaged)	
	Product 1	Product 2
10	45	19
20	70	37
30	82	60
45	93	71
60	96	79

Methods

An in-silico model was built using GastroPlus™ simulation software with pharmacokinetic inputs determined in a population study conducted using Phoenix—which incorporated data from an internal FDA database. Available dissolution data for two different products of the same drug substance in pH 5.6 phosphate buffer (USP apparatus II, 900mL, 50 rpm, 37°C) were incorporated into the model using 4 different methods—traditional z-factor, refined z-factor, theoretical product particle size distribution (P-PSD), and Weibull function with a "CR: Dispersed" formulation using the Advanced Compartmental and Transit (ACAT) absorption model and two-compartment pharmacokinetic model. The gastrointestinal tract (GI) pH of each segment of gut physiology in GastroPlus™ was adjusted to the surface pH according to the buffer concentration associated with the *in vivo* dissolution conditions. The percent error of Tmax, Cmax, AUC0-infinity (AUCi), and AUC0-t (AUCt) of each method was calculated and compared with the reported values to determine the most predictive method.

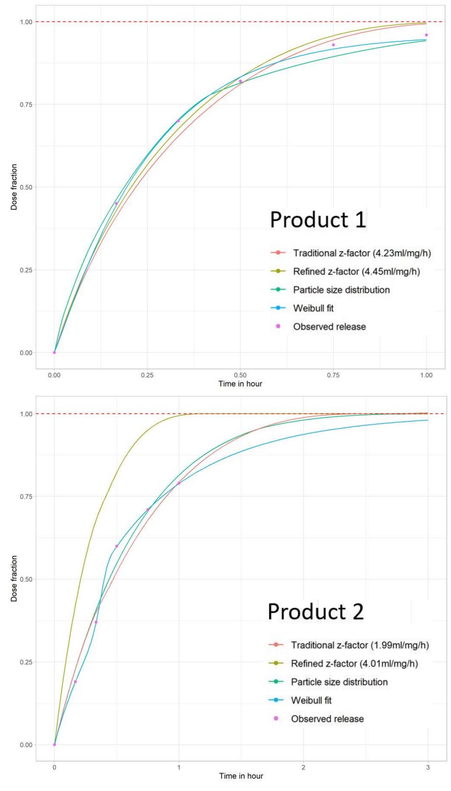

Figure 1. Comparison of *in vitro* dissolution and predicted *in vivo* dissolution profiles.

Results and Discussion

All methods were able to consistently provide good estimations of AUCi, while none of the strategies yielded consistent approximations of the time of maximum concentration (Tmax). The refined z-factor method accounted for the possible disintegration process from the dissolution profile of Product 2 and was able to accurately predict the Cmax and discriminate between the two products. The traditional z-factor consistently predicted the Cmax for both products although with slight discrepancy. Using the "CR: Dispersed" formulation with a Weibull fit on the dissolution profile resulted in a close prediction of Cmax for Product 1, but underpredicted this value for Product 2. Due to Product 2's incomplete dissolution profile, the dissolution was extended using the Weibull function until it reached completion at about 3 hours. The theoretical P-PSD approach underpredicted Cmax for both products, and only performed better than the Weibull function approach.

Table 2. Summary of reported and predicted Tmax, Cmax, AUCi, AUCt using baseline, Weibull function (Weibull), product particle size distribution (P-PSD), traditional z-factor (Traditional Z), and refined z-factor (Refined Z) methods.

	Method	Tmax, h (%PE)	Cmax, ug/mL (%PE)	AUCi, ug*h/mL (%PE)	AUCt, ug*h/mL (%PE)
Product 1					
	Reported	1.75 (-)	20.2 (-)	78.7 (-)	75.6 (-)
	Baseline	1.84 (5)	19.4 (-4)	77 (-2.2)	75.4 (-0.3)
	Weibull	1.16 (-33)	20.1 (-0.5)	77 (-2.2)	75.7 (0.1)
	P-PSD	1.72 (-1.7)	18.6 (-7.9)	77 (-2.2)	75.5 (-0.1)
	Traditional Z	1.6 (-8.6)	20.2 (0)	77 (-2.2)	75.5 (-0.1)
	Refined Z	1.56 (-10.9)	20.3 (0.5)	77 (-2.2)	75.5 (-0.1)
Product 2					
	Reported	1.5 (-)	19 (-)	72.2 (-)	67.9 (-)
	Baseline	1.12 (-25.3)	21.7 (14.2)	77.1 (6.8)	75.7 (11.5)
	Weibull	1.48 (-1.3)	17.2 (-9.5)	77 (6.6)	75.4 (11)
	P-PSD	2.2 (46.7)	17.6 (-7.4)	77 (6.6)	75.2 (10.8)
	Traditional Z	2 (33.3)	18.4 (-3.2)	77 (6.6)	75.3 (10.9)
	Refined Z	1.88 (25.3)	19 (0)	77 (6.6)	75.4 (11)

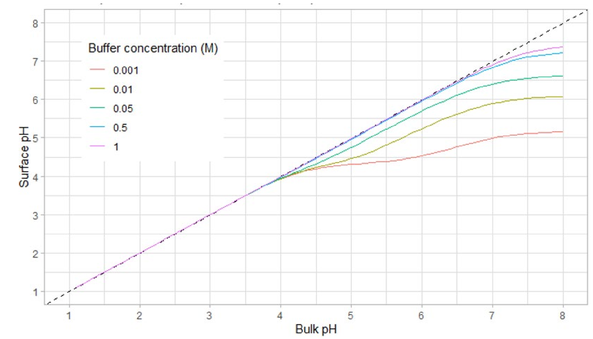

Figure 2. Surface pH vs Bulk pH at different phosphate buffer concentrations.

Conclusion

Using pH 5.6 dissolution medium could discriminate between different formulations of this drug. Incorporating dissolution data using refined z-factor demonstrated the best discriminating power while maintaining acceptable accuracy when predicting Cmax and AUC. When compared to other approaches, the Weibull approach with "CR: Dispersed" formulation underestimated Cmax when the initial dissolution rate is slow. This underprediction is likely due to the slow release in the initial phase of dissolution of Product 2 and suggests a possible disintegration process for this product. Due to the overall rapid disintegration of Product 1, the traditional z-factor method performed slightly better when predicting Cmax than the refined approach. It was, however, less accurate than the refined z-factor method when predicting Cmax for Product 2. Moreover, the z-factor method may have limited applicability because it has a maximum limit for prediction of Cmax—any dissolution rate after a certain point does not lead to further increases in Cmax, which results in a plateau of the dissolution graph. Overall, all modeling strategies have strengths and weaknesses. It is likely that none of the strategies were able to consistently predict Tmax due to high variability in gastric emptying time and absorption patterns. Further research is ongoing to determine whether these findings are drug specific or can be generalized to determine bioequivalence and present a case for the expansion of BCS-based biowaivers for all BCS Class IIa drug products.

References:
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