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Assessment of the Impact of Drug Dissolution on Pharmacokinetics of Diltiazem Extended Release Drug Products Using Physiologically Based Pharmacokinetic Analysis

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PURPOSE

Diltiazem is a calcium ion cellular influx inhibitor indicated for the treatment of angina and hypertension. There are multiple extended release (ER) oral dosage forms of diltiazem hydrochloride (HCl) with different formulations available in the U.S. market. It is well recognized that the drug release of the ER products can significantly impact the drug absorption and pharmacokinetic (PK) performance hence affecting the efficacy and safety[1]. Although in vitro dissolution test is required for ER product batch release, it is often used for quality control purpose and may not readily reflect the in vivo performance of a drug product unless an in vitro in vivo relationship/correlation (IVIVR/C) is available. For diltiazem HCl ER capsules, there are a total of 20 dissolution tests listed in the USP monograph (USP42-NL37)[2]

Physiologically based pharmacokinetic (PBPK) analysis is a modeling approach which integrates anatomical and physiological parameters of the gastrointestinal (GI) tract as well as the physicochemical properties of a drug product to predict the drug's in vivo performance. This modeling approach has been increasingly used as a biopharmaceutics tool to evaluate the impact of drug product quality attributes, e.g., in vitro dissolution, on in vivo performance[3]. This study focuses on the evaluation of the biopredictive capability of the dissolution methods and the impact of drug release on PK performance using PBPK modeling and simulation.

OBJECTIVES

- **To test the in vitro dissolution performance of selected diltiazem HCl ER capsule products marketed in the United States including both brand and generic products**
- **To assess the biopredictive capability of the in vitro dissolution test methods for diltiazem HCl ER capsules using PBPK modeling**

METHODS

In vitro dissolution tests were conducted on 2 brand products and 5 generic drug products per dissolution test listed in the USP monograph as indicated in the product label. These diltiazem HCl ER products were also tested under the same dissolution testing method using USP apparatus 2 (100 rpm) with phosphate buffer at pH 6.8 for comparison of all these drug products. Additionally, in vitro drug dissolution of selected drug products under various conditions (e.g., in multimedia (pH 1.2, 6.8 and 7.2) using USP apparatus 1 and 2 methods) was also studied.

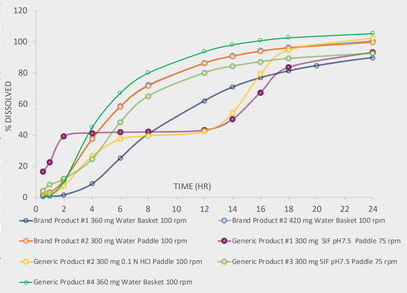
The PBPK model was developed using GastroPlus Version 9.7 (Simulation Plus). The physicochemical parameters of the drug substance (e.g., solubility, permeability and protein binding) were obtained from published studies. The plasma concentration-time profiles of diltiazem in healthy humans from the administration of intravenous (IV), oral solution and ER formulations were used to develop and verify the model. Using the verified model, the in vivo dissolution profile was deconvolved from the plasma concentration-time profile of ER drug products. The in vitro dissolution profiles from the study of marketed drug products using different dissolution methods/media were compared to the deconvolved in vivo dissolution profiles. The selection of in vitro dissolution test method was discussed, taking into consideration formulation characteristics. Using the in vitro dissolution profiles from the most relevant method, the PK profiles in healthy humans under fasted conditions were simulated.

RESULTS

In vitro dissolution test results:

The brand and generic diltiazem HCl ER capsule products tested in this study all met the USP monograph dissolution specifications at L1. The test condition in the label varies among tested products. Brand products #1 and #2 showed different in vitro dissolution under the same condition (Water, 900 ml, Basket 100 rpm). In general, the in vitro dissolution of both Brand Products #1 and #2 is independent of testing conditions (data not shown). Two generic products (#1 and #2) showed different dissolution profiles from the brand products and released the drug in two phases fitting a double Weibull function. The drug release from Generic Product #2 was dependent on the pH of the medium (data not shown).

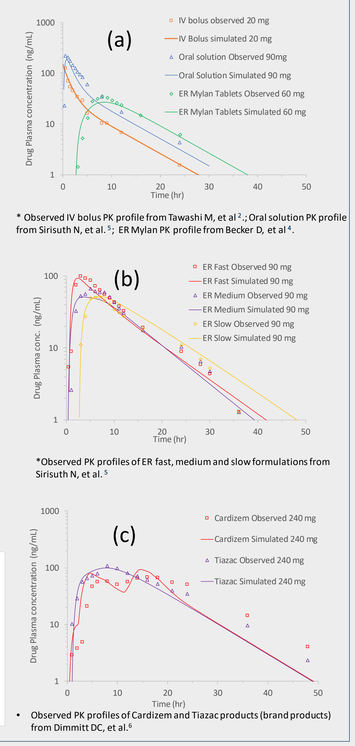
Figure 1: In vitro dissolution profiles of brand and generic drug products of diltiazem HCl ER capsules



PBPK model development and verification:

The mechanistic absorption model (ACAT) was combined with a 2-compartment model and a fixed first-pass effect (58%) was developed based on the PK data from IV data (20 mg) and oral solution (90 mg) digitally extracted from the paper of Tawashi M, et al. [3], Becker D. et al.[4] and Sirisuth N. et al.[5] The drug physico-chemical parameters and PK parameters are listed in Table 1. The model was further verified with published PK data from various ER formulations with different doses (see Figure 2). For ER formulation products, in vitro dissolution profiles collected in the corresponding paper were used as input after Weibull function fitting for predicting systemic exposure.

Figure 2: Simulated and observed PK profiles for model development and verification



* Observed IV bolus PK profile from Tawashi M, et al [3].; Oral solution PK profile from Sirisuth N, et al. [5]; ER Mylan PK profile from Becker D, et al [4].

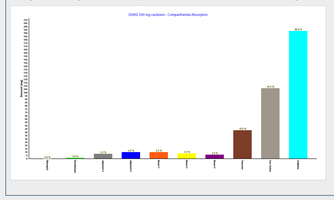
Table 1: input Model Parameters

Drug physico-chemical parameters		Drug PK parameters	
Log P	2.79	Fup(%)	16.665
Solubility (mg/mL)	465@pH7.2	FPE	58%
		CL (L/h/kg)	0.72
Diffusion Coefficient ($Cm^2/s*10^5$)	0.62	Vc (L/kg)	1.93
Peff ($cm/s \times 10^4$)	9.14	K_{12} (1/h)	0.265
pKa	8.33	K_{21} (1/h)	0.257

*Compartment PK parameters were obtained from IV bolus PK
FPE (First pass effect in %) optimized based on oral solution data

*Observed PK profiles of ER fast, medium and slow formulations from Sirisuth N, et al. [5]

Figure 3: Regional Absorption of Brand Product #1 240 mg

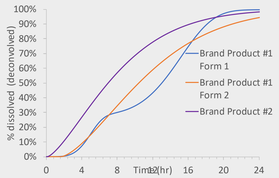


- Observed PK profiles of Cardizem and Tiazac products (brand products) from Dimmitt DC, et al.[6]

In vivo dissolution profiles deconvoluted from the PK profiles of Brand Products

The in vivo release profiles in the GI tract was deconvolved from the PK profiles of the brand products (fasted study in healthy volunteers) based on the verified PBPK model (see Figures 7). It is worth noting that Brand Product #1 had major formulation changes (from Form 1 to Form 2) after the approval of the drug product. The two formulations of this product showed different release profiles. Brand Product #2 was found not bioequivalent to the Brand Product #1, but the differences in the PK profiles would not affect the efficacy of the drug product.

Figure 4: Deconvoluted in vivo dissolution profiles in the GI tract for the brand products based on PBPK model



*The deconvoluted in vivo dissolution profiles were generated based on the observed PK profiles of Brand Product #1 360 mg formulations (available at Drug@FDA) and the PK profiles for the Brand Product #2 240 mg in Dimmitt D et al.[6]

Comparison of in vitro vs. in vivo dissolution profiles

Figure 5: The in vitro dissolution profiles of generic products (refer to Brand Product #1 as the reference listed drug, RLD) vs the in vivo dissolution profiles of Brand Product #1

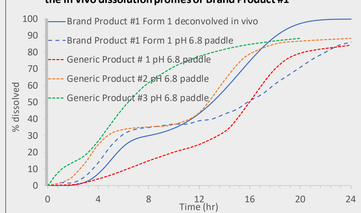


Figure 6: The in vitro dissolution profiles of generic product (refer to Brand Product #2 as the RLD) vs the in vivo dissolution profiles of Brand Product #2

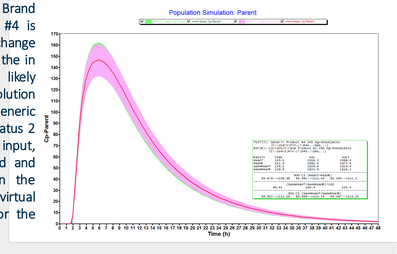
Biopredictive dissolution testing

The PBPK model can guide the development of biopredictive in vitro dissolution method. The in vivo dissolution profiles of the brand products deconvolved from the PK profiles can be used as a reference to develop an in vitro dissolution method. By exploring different in vitro test conditions, the in vitro dissolution tests which can reproduce the similar in vitro dissolution as the in vivo might be selected for further method optimization. In addition, the in vitro dissolution method selection should also take into account the formulation, the release mechanism and the discriminating ability of the method. The biopredictive performance of the selected in vitro dissolution method should be confirmed by the in vivo studies, e.g., in vivo bioequivalence (BE) or IVIVC/R studies.

Figure 7: The in vitro dissolution profiles of generic product (refer to Brand Product #2 as the RLD) vs the in vivo dissolution profiles of Brand Product #2

Virtual BE trials to assess Bioequivalence

As the in vitro dissolution of Brand Product #2 and Generic Product #4 is condition independent (e.g., no change with media pH or rotation speed), the in vitro dissolution profiles are very likely similar as in vivo. Using the dissolution profiles of both brand and generic products obtained from USP apparatus 2 100 rpm in phosphate buffer 6.8 as input, virtual BE studies were conducted and showed bioequivalence between the brand and generic products in virtual healthy human subjects (n=40) for the 300 mg strength.



RESULTS(CONT'D)

IVIVC development for Brand Product #2 240 mg

IVIVC development was explored for Brand Product #2, 240 mg. In general, a linear relationship was found between the in vitro and the in vivo release. For the products showing double Weibull function of in vitro dissolution, the IVIVC development is challenging and needs a good selection of the in vitro dissolution method to well represent the in vivo release.

Figure 8. Fraction of in vivo release vs. time

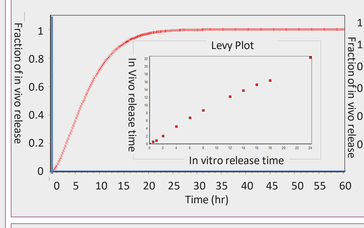
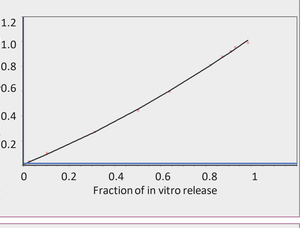


Figure 9: Fraction of in vivo release vs. Fraction of in vitro release



CONCLUSIONS

- In vitro dissolution tests for diltiazem HCl extended release capsules are formulation-/product-specific.
- The generic ER products may not use the same dissolution test used for the RLD. The in vitro tests listed in FDA dissolution methods database can be used as a starting point for generic product development.
- The selection of the in vitro dissolution test for quality control of the drug product should consider the release mechanism of the formulation, the discriminating ability, and biopredictive ability of the method.
- Exploration of the clinical relevance of in vitro dissolution test in pharmaceutical development would be valuable for guiding formulation and process development as well as assessing quality risk and setting patient-focused quality specifications.
- A verified PBPK model can be effectively used to support formulation and process development, design space establishment, and clinically relevant product specifications.

REFERENCES

1. *M. Li, S. Sander, J. Duan, et al. Scientific and regulatory considerations in solid oral modified release drug product development AAPS J, 2016;18 (6):1406-1417*
2. *United States Pharmacopeia and National Formulary* (USP 42-NF 37). Rockville, MD: United States Pharmacopeial Convention; 2019. https://online.uspnf.com/uspnf/document/GUID-1056B178-7964-4327-8482-3307E192BBBB_7_en-US?highlight=diltiazem. Accessed May 18, 2019.
3. Tawashi M, Marc-Aurèle J, Bichet D, Spénard J, Larivière L, Plante D, *et al.* Pharmacokinetics of intravenous diltiazem and five of its metabolites in patients with chronic renal failure and in healthy volunteers. *Biopharm Drug Dispos* [Internet]. 1991;12(2):105–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2031991
4. Becker D, Zhang J, Heimbach T, Penland RC, Wanke C, Shimizu J, Kulmatycki K. 2014. Novel orally swallowable IntelliCap® device to quantify regional drug absorption in human GI tract using diltiazem as model drug. *AAPS Pharm Sci Tech* DOI: 10.1208/s12249-014-0172-1
5. Sirisuth N, Augsburger LL, Eddington ND. Development and validation of a non-linear IVIVC model for a diltiazem extended release formulation *Biopharm Drug Dispos.* 2002 Jan;23(1):1-8.
6. Dimmitt D, Bhargava VO, Arumugham T, *et al:* Relative bioavailability of cardizem CD and tiazac controlled-release diltiazem dosage forms after single and multiple dosing in healthy volunteers. *Am J Ther* 1998; **5**: 173–179.

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