

Evaluation of a pH-Gradient Biphasic Dissolution Test for Predicting In Vivo Performance of Weakly Basic Drugs

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ABSTRACT

The present study aimed to confirm the biorelevance of the pH-gradient biphasic dissolution model for three ketoconazole (KTZ) formulations with different excipients and establish an in vivo-in vitro correlation (IVIVC). Experiments were performed with a pH-gradient biphasic dissolution model for drug absorption, consisting of a sequential pH-gradient in the aqueous phase and octanol phase, representing the stomach, duodenum, jejunum and ileum compartments, and small intestinal membrane, respectively. Conventional single phase in vitro dissolution tests with and without pH-shift lacked discrimination. The pH-gradient biphasic dissolution test showed discriminatory power for the three KTZ formulations, with the same ranking of drug release in vitro and in vivo. A good IVIVC was established between in vitro release data in octanol and in vivo data in rats, demonstrating the in vivo biorelevance of the pH-gradient biphasic dissolution model. This study presents a promising approach for predicting in vivo performance of weak bases containing formulations in early drug development.

KEYWORDS: pH-gradient biphasic dissolution test, in vitro-in vivo correlation, weakly basic drugs, biorelevance, oral bioavailability, dissolution

INTRODUCTION

Oral absorption of weakly basic drugs is a dynamic complex process mainly influenced by physicochemical properties of the drug and physiological conditions in the gastrointestinal (GI) tract, especially for dynamic pH conditions. The pH values in the fasted stomach usually in the range of 1.5–2.0, with a transit time of 0.5–2 h (1, 2). Average pH values in the fasted upper small intestine are 5.0–7.5, including pH 5.0–6.5 in the duodenum, pH 6.0–7.0 in the jejunum, and pH 6.5–7.5 in the ileum (3, 4). Transit time in the small intestine is often considered to be approximately 4 h (5). Weakly basic drugs can quickly dissolve at gastric pH, but not at intestinal pH following a supersaturation-precipitation process in the small intestine, which shows limited absorption. Conventional in vitro dissolution tests lack biorelevancy with in vivo dissolution (6, 7). Many attempts have been made to overcome the limitations and better predict bioperformance of oral products by creating different biorelevant dissolution methods (8–11).

The biphasic dissolution test has exhibited improved in vivo prediction by incorporating an absorptive sink. In this technique, the drug first dissolves in the aqueous phase to simulate dissolution at gastric pH, then the dissolved drug immediately partitions in the organic phase to mimic drug absorption through the intestinal membrane. This biphasic dissolution model enables the evaluation of various formulation factors such as particle size, drug loading, wettability, polymorphic forms, and drug precipitation (12–19).

In our previous report, a pH-gradient biphasic dissolution system was developed through an orthogonal test design with three factors and three strengths of ketoconazole (KTZ) to simulate pH conditions in the stomach, duodenum, and jejunum and ileum in the aqueous phase and to mimic an intestinal absorptive sink in the octanol phase (20). The aim of the current study was to confirm the biorelevance of the pH-gradient biphasic dissolution model for three KTZ formulations

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with different excipients compared to conventional dissolution tests. Subsequently, an animal study with rats was also performed to evaluate the relationship of the in vitro and in vitro dissolution profiles.

METHODS

KTZ was purchased from Wuhan Dahua Weiye Medicine Chemical Co., Ltd. (Wuhan, China). Lactose monohydrate was donated by PinTech Pharmaceutical Co., Ltd. (Shanghai, China). β -cyclodextrin (β -CD), microcrystalline cellulose (MCC), 1-octanol, hydrochloric acid (HCl), sodium dihydrogen phosphate dihydrate, sodium hydroxide (NaOH), tribasic sodium phosphate, and sodium chloride were obtained from Sichuan Kelun Pharmaceutical Co., Ltd. (Chengdu, China). Hard gelatin capsules (size 0) were donated by Suzhou Capsugel Ltd. (Suzhou, China). All other reagents used were of analytical grade.

Preparation of KTZ Formulations

Three formulations were prepared by mixing 100-mg KTZ with lactose, β -CD, and MCC at a weight ratio of 1:1. Powder blends were filled in size 0 hard gelatin capsules.

Conventional USP Single-pH Dissolution Test

The compendial dissolution test was performed in 900 mL 0.1 N HCl at 50 rpm and 37 °C in a USP apparatus 2 (paddle) (RCZ-8, Shanghai Huanghai Drug Inspection Instrument Co., Ltd, Shanghai, China) ($n = 3$). Samples were collected at predetermined time intervals and measured using a UV-spectrophotometer (T6, Beijing Puxi General Instrument Co. Ltd, Beijing, China) at 224 nm.

Conventional USP pH-Shift Dissolution Test

To evaluate the effect of pH change, drug release was assessed according to the *USP* general chapter <711> enteric dissolution test (method A) in USP apparatus 2. The KTZ formulations were first tested in 750 mL of 0.1 N HCl for 2 h followed by a pH adjustment to 6.8 ± 0.05 by adding 250 mL of 0.2 M tribasic sodium phosphate ($n = 3$). Samples were withdrawn at predetermined time points and used for UV spectrophotometry.

pH-gradient Biphasic Dissolution Test

Based on our previous study, the developed pH-gradient biphasic dissolution test (Fig. 1) was used to assess three KTZ formulations (20). Briefly, each formulation containing 100 mg KTZ with a sinker was added into 250 mL of gastric buffer (pH 2.0) for 30 min, then the aqueous medium was adjusted to pH 5.5 to mimic the duodenum by adding 5 M NaOH and 100 mL of pre-saturated 1-octanol as the upper organic phase to simulate the intestinal membrane ($n = 3$). Subsequently, the aqueous phase was readjusted to pH 6.5 to mimic the jejunum for 2 h, then the final pH was increased to

6.8 for 1 h. The rotating speed was set to 30 rpm. The temperature was maintained at 37 °C. Samples were withdrawn manually from both the aqueous and organic phases at predetermined time points and replaced with the same volume of fresh media. The aqueous samples were passed through a 0.45- μ m Durapore membrane filter, and the organic samples were centrifuged at 12,000 rpm for 20 min (TG-16, Gongyi Yuhua Instrument Co. Ltd, Gongyi, China). Drug concentrations in aqueous and organic phases were determined by UV spectrometry at 224 nm.

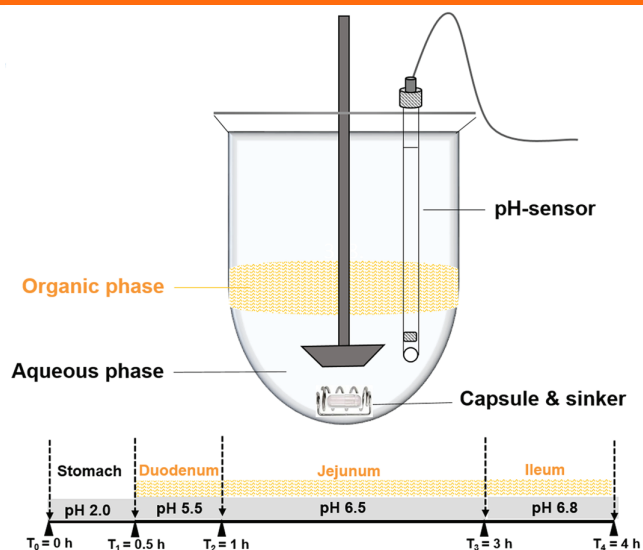


Figure 1. Schematic diagram of a pH-gradient biphasic dissolution system. Reprinted from (20).

In Vivo Studies

Animal studies were approved by the local ethical committee at the Third Military Medical University, Chongqing, and performed in accordance with guidelines of experimental animal care. Female Sprague-Dawley rats weighing 200–250 g were fasted for 12 h before drug administration. Each KTZ formulation was dispersed in deionized water prior to dosing and administered by oral gavage at a dose of 45 mg/kg ($n = 5$). Blood samples were collected from retro orbital choroid plexus under mild anesthesia at 0, 1, 2, 3, 4, 6, 8, 12, and 24 h after dosing and placed into heparin pretreated tubes. The blood samples were centrifuged at 3500 rpm for 10 min, and plasma was stored at –20 °C until further analysis.

Plasma concentration of KTZ was determined by high-performance liquid chromatography (HPLC) analysis. Samples were analyzed using the Agilent HPLC system (1260 Infinity, Agilent, Germany) equipped with an Ultimate XB-C18 column (250 $\times$ 4.6 mm, 5 μ m, 120 Å) maintained at 25 °C. The mobile phase was a mixture of acetonitrile and 0.02 M phosphate buffer at pH 6.8 (65:35,

v/v) at the flow rate of 1.0 mL/min, and the UV detector was set to 254 nm (21, 22).

Pharmacokinetic Analysis

The pharmacokinetic (PK) parameters, including area under the plasma concentration time curve from 0 to 24 h ($AUC_{0-24\text{ h}}$), the time to reach maximum plasma concentration (T_{max}), and the peak plasma concentration of drug (C_{max}) after administration of KTZ formulations in rats were determined using a non-compartmental model analysis by a freely available add-in program for Microsoft Excel, PK Solver (23).

Statistical Analysis

All data were expressed as mean $\pm$ standard deviation (SD). The results were compared by one-way analysis of variance (ANOVA), and $p < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Conventional USP Single-pH Dissolution Test

As shown in Figure 2, all three KTZ formulations had similar dissolution profiles in the single-pH dissolution test, and they dissolved more than 80% at 10 min. The compendial dissolution test lacked discrimination between these KTZ formulations due to fast drug dissolution.

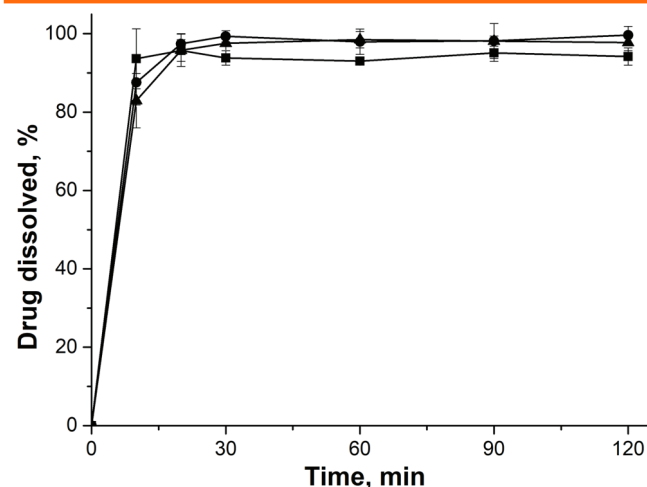


Figure 2. Dissolution profiles (mean $\pm$ SD; $n = 3$) of three ketoconazole (KTZ) formulations under sink conditions (900 mL 0.1 N HCl): (●) KTZ-lactose, (■) KTZ- β -CD, and (▲) KTZ-MCC.

Conventional USP pH-Shift Dissolution Test

KTZ is classified as a weakly basic Bipharmaceutical Classification System (BCS) class II drug with a diphasic pK_a (2.94 and 6.51) and a log P value of 3.73, so drug solubility in a pH-dependent manner is reported as 20.3 mg/mL in simulated gastric fluid (pH 1.2) and 6 μ g/mL in simulated intestinal fluid (pH 6.8), respectively (24). Thereby, a pH-shift dissolution test was used to assess the influence of pH change throughout the GI tract. All three KTZ

formulations showed similar dissolution profiles in 0.1 N HCl for the first 2 h. However, drug concentration of KTZ decreased after the pH change, which was attributed to fast precipitation due to much lower solubility at neutral pH (Fig. 3). Unexpectedly, drug concentration at pH 6.8 was almost constant over time. The dissolved excipients in the phosphate buffer would facilitate dissolution of precipitated KTZ, leading to a concentration plateau, or the interactions between KTZ and lactose, β -CD, or MCC might occur via hydrogen bonding to delay crystallization (25, 26).

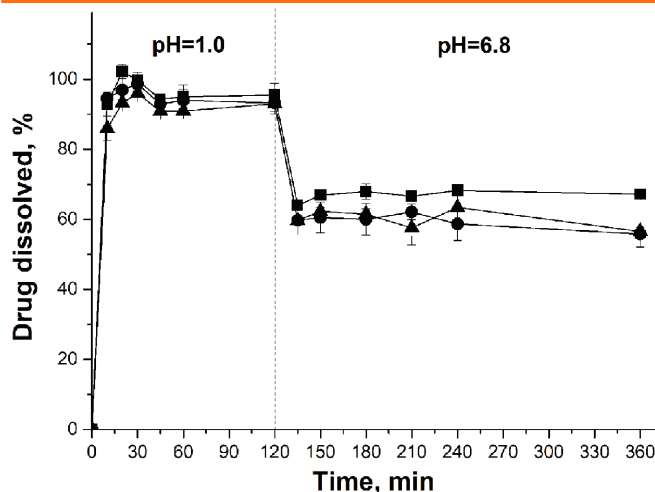


Figure 3. Dissolution profiles (mean $\pm$ SD; $n = 3$) of three ketoconazole (KTZ) formulations under pH-gradient conditions (750 mL 0.1 N HCl for 2 h followed by a pH adjustment to 6.8 ± 0.05 with addition of 250 mL 0.2 M tribasic sodium phosphate solution) (dashed vertical line represents the pH change): (●) KTZ-lactose, (■) KTZ- β -CD, and (▲) KTZ-MCC.

pH-Gradient Biphasic Dissolution Test

Each formulation (containing 100 mg drug) maintained sink conditions ($< 20\%$ of drug solubility ($C_s = 5.6$ mg/mL) in 100 mL octanol (20). All KTZ formulations dissolved fast and reached 100% release in the gastric buffer at pH 2.0 (Fig. 4A). After pH change, drug concentrations significantly decreased to a plateau in the aqueous phase due to immediate precipitation and partitioning into the organic phase of drug. In contrast, the corresponding dissolution profiles in the organic phase differed, with a ranking of KTZ-lactose $>$ KTZ- β -CD $>$ KTZ-MCC (Fig. 4B). Thus, these KTZ formulations were well-discriminated in the organic phase of the pH-gradient biphasic dissolution test. KTZ-lactose showed the highest dissolution profile in the organic phase, which could be the result of maintaining the most free drug in the aqueous phase and quickly partitioning into the organic phase. The hydrogen bonds forming between KTZ and lactose could retard recrystallization, or the formation of smaller dispersed drug particles redissolve by de-agglomeration due to

the hydrophilicity of fine lactose (25, 27). Although β -CD had good solubilization for KTZ and displayed a slightly higher drug concentration in the aqueous phase, drug concentration in the organic phase was lower compared to KTZ-lactose. This was because solubilized drugs that form cyclodextrin complexation may have limited permeability due to the decreased free fraction of the drug available for membrane permeation (28, 29).

Other studies have reported inconsistent results between in vitro dissolution and in vivo absorption (30, 31). Compared with lactose and β -CD, MCC as a hydrophobic carrier would be expected to perform inferiorly (32). Another reason could be immobilizing of KTZ molecules on the MCC surface by hydrogen bonding and facilitating heterogeneous nucleation owing to MCC having a heterosurface (33). Given the continuous concentration gradient between two phases, the differences of dissolution and precipitation kinetics in the aqueous phase could be magnified by the presence of an organic phase (15).

In Vivo Study

To evaluate in vivo PK performance of the three KTZ formulations, a non-crossover study in rats was conducted. The PK parameters are summarized in Table 1. Significant differences were found between the $C_{\max}$ and AUC_{0-24h} values of the three KTZ formulations ($p < 0.05$). The same rank order of drug release observed in the pH-gradient biphasic dissolution test (KTZ-lactose > KTZ- β -CD > KTZ-MCC) was consistent with the $C_{\max}$ and AUC values of KTZ-MCC, KTZ- β -CD, and KTZ-lactose.

Table 1. Pharmacokinetic Parameters for Three Ketoconazole (KTZ) Formulations in Rats After Oral Administration (45 mg/kg)

Formulation	$C_{\max}$ ($\mu\text{g/mL}$)	AUC_{0-24h} ($\mu\text{g h/mL}$)	$T_{\max}$ (h)
KTZ-MCC	1.52 ± 0.22^a	12.61 ± 1.78^a	2.60 ± 0.89
KTZ- β -CD	$3.19 \pm 0.46^{a,b}$	$19.62 \pm 3.11^{a,b}$	1.80 ± 0.34
KTZ-lactose	3.50 ± 0.41^b	27.97 ± 4.41^b	2.80 ± 0.45

Values are expressed as mean $\pm$ SD, $n = 5$.

^a $p < 0.05$ vs. KTZ-lactose; ^b $p < 0.05$ vs. KTZ-MCC

In Vitro-in Vivo Correlation

A level C in vitro-in vivo correlation (IVIVC) was tested using the percentage of KTZ dissolved in both aqueous and organic phases in the biphasic test at 3 h vs. an in vivo parameter (AUC or $C_{\max}$). No meaningful IVIVC was obtained in the aqueous phase at 3 h and AUC_{0-24h} or $C_{\max}$ (Figs. 5A and 5B); however, good linear relationships were obtained in the organic phase at 3 h and the in vivo $C_{\max}$ ($R^2 = 0.96$) and AUC_{0-24h} ($R^2 = 0.92$) (Figs. 5C and 5D). This pH-gradient biphasic dissolution system thus reflected both in vitro and in vivo dissolution kinetics of the three KTZ formulations with different excipients, and the release profiles from the organic phase could serve as an indicator for in vivo drug performance.

CONCLUSIONS

Compendial dissolution tests lacked discrimination and in vivo prediction for three KTZ formulations, including the conventional pH-shift dissolution test. Conversely, the pH-gradient biphasic dissolution system showed discriminatory power for the KTZ formulations with different excipients. A good IVIVC was obtained between in vitro dissolution in the organic phase and in vivo

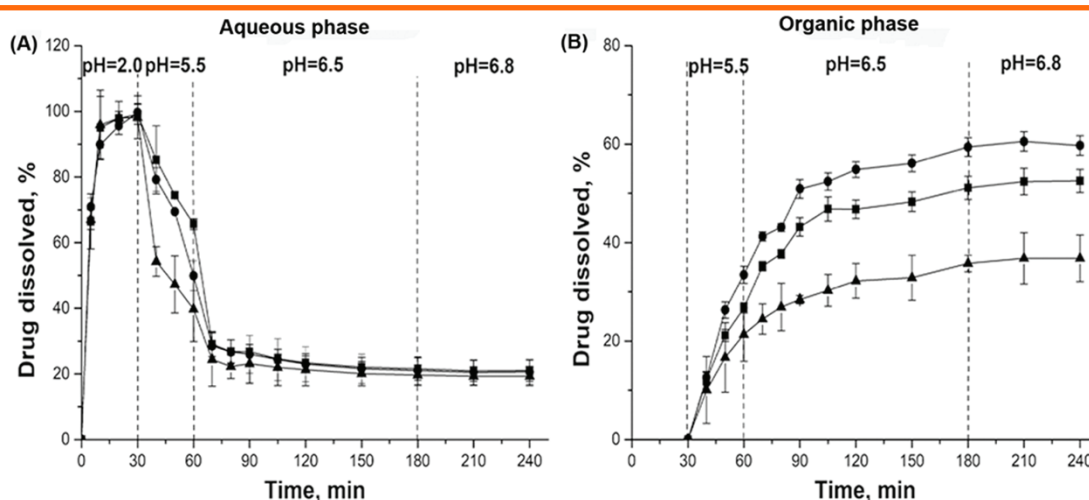


Figure 4. Dissolution profiles (mean $\pm$ SD; $n = 3$) of three ketoconazole (KTZ) formulations determined from the (A) aqueous and (B) organic phases in the pH-gradient biphasic dissolution test (gastric buffer pH 2.0 for 30 min followed by a pH adjustment to 5.5 ± 0.05 for 30 min, 6.5 ± 0.05 for 2 h, and 6.8 ± 0.05 for 1 h, respectively) (dashed vertical lines represent the pH changes): (●) KTZ-lactose, (■) KTZ- β -CD, and (▲) KTZ-MCC.

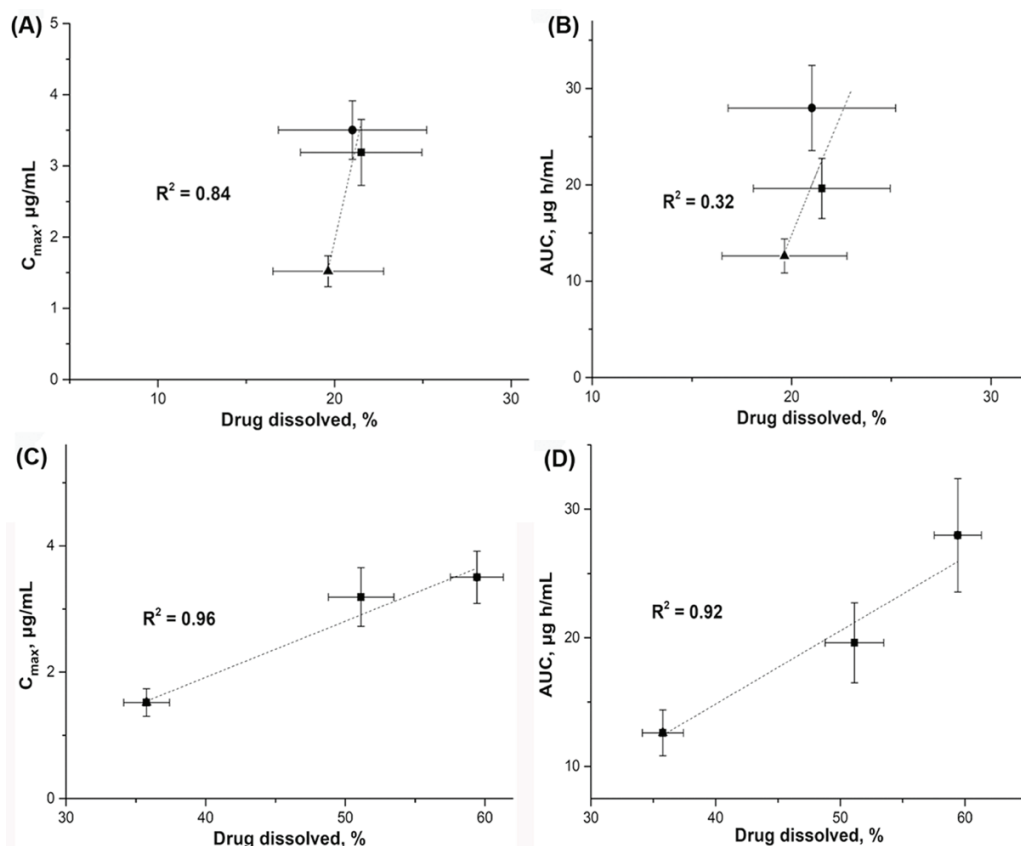


Figure 5. Relationships of in vitro dissolution (mean $\pm$ SD) of three ketoconazole (KTZ) formulations with different excipients in the aqueous and organic phases of the biphasic test at 3 h plotted against in vivo C_{max} (A and C), or AUC (B and D) values: (●) KTZ-lactose, (■) KTZ- β -CD, and (▲) KTZ-MCC ($n = 3$ for in vitro studies; $n = 5$ for in vivo rat studies).

performance in rats. The pH-gradient biphasic model has great potential for weakly basic BCS class II drugs in the early development of formulations.

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DISCLOSURES

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The authors have no conflicts of interest to disclose.

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