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The impact of supersaturation level for oral absorption of BCS class IIb drugs, dipyridamole and ketoconazole, using *in vivo* predictive dissolution system: Gastrointestinal Simulator (GIS)

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ABSTRACT

The development of formulations and the assessment of oral drug absorption for Biopharmaceutical Classification System (BCS) class IIb drugs is often a difficult issue due to the potential for supersaturation and precipitation in the gastrointestinal (GI) tract. The physiological environment in the GI tract largely influences *in vivo* drug dissolution rates of those drugs. Thus, those physiological factors should be incorporated into the *in vitro* system to better assess *in vivo* performance of BCS class IIb drugs. In order to predict oral bioperformance, an *in vitro* dissolution system with multiple compartments incorporating physiologically relevant factors would be expected to more accurately predict *in vivo* phenomena than a one-compartment dissolution system like USP Apparatus 2 because, for example, the pH change occurring in the human GI tract can be better replicated in a multi-compartmental platform. The Gastrointestinal Simulator (GIS) consists of three compartments, the gastric, duodenal and jejunal chambers, and is a practical *in vitro* dissolution apparatus to predict *in vivo* dissolution for oral dosage forms. This system can demonstrate supersaturation and precipitation and, therefore, has the potential to predict *in vivo* bioperformance of oral dosage forms where this phenomenon may occur. In this report, *in vitro* studies were performed with dipyridamole and ketoconazole to evaluate the precipitation rates and the relationship between the supersaturation levels and oral absorption of BCS class II weak base drugs. To evaluate the impact of observed supersaturation levels on oral absorption, a study utilizing the GIS in combination with mouse intestinal infusion was conducted. Supersaturation levels observed in the GIS enhanced dipyridamole and ketoconazole absorption in mouse, and a good correlation between their supersaturation levels and their concentration in plasma was observed. The GIS, therefore, appears to represent *in vivo* dissolution phenomena and demonstrate supersaturation and precipitation of dipyridamole and ketoconazole. We therefore conclude that the GIS has been shown to be a good biopredictive tool to predict *in vivo* bioperformance of BCS class IIb drugs that can be used to optimize oral formulations.

1. Introduction

The physicochemical properties of orally delivered drugs such as pKa, solubility, and crystalline phase are important factors for their dissolution and absorption. The physiological parameters like pH, buffer capacity, and the volume of the GI contents will also greatly affect the dissolution and absorption of oral dosage forms. The physiological pH in the gastrointestinal (GI) tract is extremely important to the solubility of weakly acidic and weakly basic oral medications due to their pH-dependent solubility. Their drug dissolution depends on the pH of the local environment at the different GI sites and, thus, they exhibit distinct dissolution profiles in the physiological pH range (Jambhekar and Breen, 2013; Tsume et al., 2014). For those reasons, appropriate *in vitro* dissolution methods should be chosen to reflect these considerations for the accurate prediction of *in vivo* dissolution and absorption of oral drug products.

Biopharmaceutical Classification System (BCS) class I and III drugs are highly soluble drugs within the physiological pH range and the oral absorption of those drugs would not likely be affected by their dissolution rates regardless of pH in the GI tract (Tsume and Amidon, 2010). However, for BCS class II and IV drugs categorized as poorly soluble drugs, the dissolution rate of those drugs has to be carefully determined in the pH of the GI tract in order to predict their oral absorption, especially for BCS class II drugs because of their high permeability. For

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weakly acidic and basic drugs, their solubility depends on the pH of the local GI environment. For instance, the elevation of pH above the pKa for weak acids increases the solubility. On the other hand, the reduction of the pH below the pKa for weak bases increases the solubility. Since pH exhibits a wide range in the GI tract, those drugs will demonstrate unique and different dissolution profiles in the GI tract. To capture the *in vivo* predictive performance of those drugs, the pH change of the GI tract has to be integrated into the *in vitro* dissolution system along with GI motility effects (hydrodynamics), luminal volume, buffer species and buffer capacity, which all influence drug dissolution and absorption (Fadda et al., 2010; Galia et al., 1998; Kalantzi et al., 2006a; Tsume et al., 2012; Vertzoni et al., 2004). Different *in vitro* dissolution systems have been developed and *in vitro* dissolution studies have been performed to capture *in vivo* phenomena of test drugs, especially for weak base drugs (Barker et al., 2014; Carino et al., 2006, 2010; Dickinson et al., 2012; Kostewicz et al., 2004; Koziolek et al., 2013a, 2013b; Mudie et al., 2012; Takeuchi et al., 2014; Tsume et al., 2015). Generally, the oral drug absorption of BCS class IIa drugs may be less problematic due to the longer residence time in the small intestine with favorable pH conditions facilitating dissolution and absorption; however, gastric emptying may still be important in determining oral drug absorption. On the other hand, for BCS class IIb drugs, they have the potential to supersaturate and precipitate when the drug moves from the stomach, a favorable pH environment, to the proximal small intestine, an unfavorable pH environment. The level and duration of supersaturation and the rate of precipitation are crucial factors influencing their oral bioavailability, especially for high permeable drugs like ketoconazole and dipyridamole (Cristofoletti et al., 2016; Kambayashi et al., 2016; Kostewicz et al., 2004; Matsui et al., 2015; Psachoulias et al., 2011). Weak base drugs, which have pH-dependent solubility, will dissolve in the stomach and supersaturate and then precipitate in the small intestine when dissolved drug solution moves from the stomach to the small intestine. Thus, gastric pH, the residence time in the stomach, the disintegration and dissolution rates, and the gastric emptying rate for weak base drugs may dramatically influence the level of supersaturation, the precipitation rate and, hence, the oral absorption of weak base drugs.

The primary aim of this study was to identify the impact of supersaturation level on the oral absorption of weak base drugs. Additionally, the precipitation rates of model drugs were calculated. In this study, ketoconazole and dipyridamole, BCS class IIb drugs, were used as model drugs and their supersaturation levels were created in our *in vitro* dissolution system, Gastrointestinal Simulator (GIS), which consists of three chambers ($GIS_{stomach}$, $GIS_{duodenum}$, and $GIS_{jejunum}$). We varied the drug dose in the $GIS_{stomach}$, utilizing a constant gastric half-emptying time of 8 min, and monitored the concentration of drug in all three GIS compartments. To evaluate the impact of supersaturation levels on oral absorption, the supersaturated drug solutions that were formed in the $GIS_{duodenum}$ were infused into the mouse jejunum and drug concentration in mouse plasma was determined by LC-MS and the relationship between *in vitro* supersaturation level and oral absorption was investigated.

2. Materials and methods

2.1. Materials

Ketoconazole tablets and dipyridamole tablets were obtained from Taro Pharmaceuticals U.S.A., Inc. (Hawthorne, NY) and from Zydus Pharmaceuticals (Pennington, NJ), respectively, through University of Michigan Hospital. Ketoconazole, dipyridamole, amlodipine besylate, hydrochloric acid, sodium phosphate dibasic, and sodium chloride were obtained from Sigma-Aldrich Chemical Co. (St. Louis, MO). Trifluoroacetic acid, formic acid, methanol and acetonitrile were obtained from Fisher Scientific Inc. (Pittsburgh, PA). All chemicals were of analytical grade or HPLC grade.

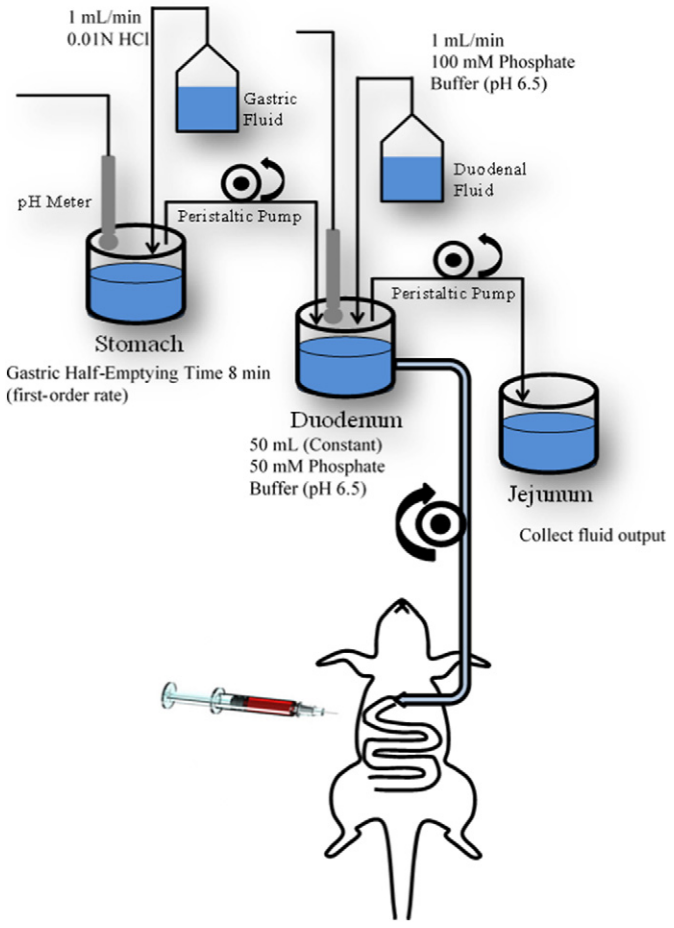

Fig. 1. The diagram of Gastrointestinal Simulator (GIS) and mouse infusion.

2.2. Dipyridamole and ketoconazole supersaturation study in the Gastrointestinal Simulator (GIS)

The GIS dissolution diagram is shown in Fig. 1 and its function and theory has been previously described (Matsui et al., 2015, 2016; Takeuchi et al., 2014; Tsume et al., 2015). The gastric chamber ($GIS_{stomach}$) was filled with 300 mL (50 mL of 0.01 N HCl as the gastric fluid and 250 mL of water as the dose volume). The duodenal chamber ($GIS_{duodenum}$) was filled with 50 mL of 50 mM sodium phosphate buffer (pH 6.5) and the volume was maintained the constant. The jejunal chamber ($GIS_{jejunum}$) simply collected the fluid output from the $GIS_{duodenum}$.

Table 1
Chemical/physiological/pharmacological parameters of dipyridamole and ketoconazole for GastroPlus™ simulation.

		Dipyridamole		Ketoconazole		
MW		504.6			531.4	
Dose	mg	25	50	100	200	400
Dose number		17[A]	35[A]	160[A]	321[A]	643[A]
Dose volume	mL	250[a]			250[a]	
Solubility (pH 7.8 or 8)	mg/mL	5.8×10^{-3}[b]			2.5×10^{-3}[f]	
logP		2.7[c]			4.3[g]	
pKa		6.2[c]			2.9/6.5[h]	
Human Peff	$\times 10^{-4}$ cm^2/s	3.0[d]			1.37[B]	
Body weight	kg	70			70	
Vc	L/kg	2.0[e]			0.7[i]	
CL	L/h/kg	0.12[e]			0.38[j]	

Vc: volume of Central Compartment, [A] Calculated by GastroPlus™9.0, [B] Calculated by ADMET predictor, a(Oberle et al., 1990), b (Mitra and Fadda, 2014), c (Kalantzi et al., 2006b), d (Sugano, 2010), e (Mahony et al., 1982), f(Vertzoni et al., 2010), g(Peeters et al., 2008), h(Mannisto et al., 1982), i(Baxter et al., 1986), j(Huang et al., 1986).