

Supplemental information for

**IN VITRO-IN VIVO CORRELATION OF AMORPHOUS SOLID DISPERSION ENABLED
ITRACONAZOLE TABLETS**

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Supplemental text related to In Vivo Clinical Study

Out of 23 study subjects who were screened to participate in the clinical study, five did not pass screening tests, and 17 subjects were randomized. Out of the 17 randomized subjects, two subjects were withdrawn from the study (i.e., subject was removed from the study by the research team due to COVID-19 restrictions), and three subjects dropped out (i.e., subject decided for themselves to not continue study). Details about the clinical study and the PK data analyzed can be found in the Supplemental Material.

Four subjects who completed the study received exactly one product prior to COVID-19 pandemic. Of these four subjects, Subject-002 exhibited rank order results that reflect a change in pharmacokinetic handling within the subject across dosing rounds (e.g., drug metabolism was inhibited in first round). Subject-002 PK profiles are shown in Figure S1. In particular, Subject-002 received Slow tablets in the first round (i.e., prior to COVID-19 pandemic). The other three products were administered 12 months or more after the first round. For this subject, Slow $AUC_{0-\infty}$ was 3101.2 ng*h/mL which was the highest AUC of any product administration in any subject. For this subject, oral solution, Fast, and Medium $AUC_{0-\infty}$ were 2169.6, 1484.9, and 2340.3 ng*h/mL, respectively, which were between 48-75% of the Slow $AUC_{0-\infty}$. Itraconazole metabolism is known to be inhibited by CYP3A4 inhibitors. Hence, it was concluded that a change in pharmacokinetic handling within Subject-002 occurred across dosing rounds, and Subject-002 was excluded from analysis.

Table S1 - Percentage of acetyl, succinoyl, methoxyl, and hydroxypropoxy functional groups in HPMCAS-L and -M grades. Fast tablet formulation employed HPMCAS-L; and Medium and Slow tablet formulations employed HPMCAS-M.

	Percentage of functional group			
HPMCAS Grade	Acetyl	Succinoyl	Methoxyl	Hydroxypropoxy
L	5-9%	14-18%	20-24%	5-9%
M	7-11%	10-14%	21-25%	5-9%

Table S2 - Dissolution conditions tested (n = 3-6 per condition). All dissolution conditions employed USP apparatus II (paddle) and 900 mL of phosphate buffer at 37 °C. Here, phosphate buffer with pH = 6.8 is the same as USP Simulated Intestinal Fluid (SIF) without enzymes. Dissolutions employed either a whole or a crushed tablet per vessel. Final dissolution conditions employed crushed tablet, pH 6.4, and 50 rpm.

Tablet	Form introduced to vessel	n	pH	Speed (rpm)
Fast	Tablet	6	6.8	100
		3	6.5	100
	Crushed tablet	3	6.4	100
		6		50
Medium	Tablet	6	6.8	100
		3	6.6	100
		3	6.5	100
		3	6.4	100
		3	6.3	100
		3	6.2	100
		3	6.0	100
	Crushed tablet	3	6.4	100
		6		50
Slow	Tablet	6	6.8	100
		3	6.5	100
	Crushed tablet	6	6.4	50

Table S3 - Demographics of 12 healthy participants who completed the IVIVC clinical study.

Characteristics	Number of Participants	Percentage of Participants
Age (years)		
< 30	8	67%
>30	4	33%
Sex		
Female	7	58%
Male	5	42%
Race		
White	7	58%
Black/African-American	3	25%
American Indian or Alaska Native	0	0%
Native Hawaiian or Other Pacific Islander	0	0%
Asian	2	17%
Other	0	0%
Ethnicity		
Hispanic/Latino/Latina	0	0%

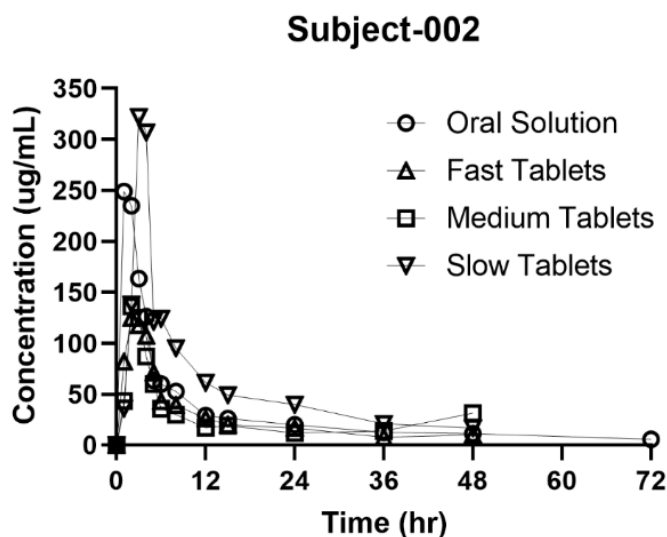


Figure S1 – Pharmacokinetic profiles of Subject-002. Subject-002 was excluded from PK analysis. Slow tablet provided the higher C_{max} and AUC, and was uniquely administered prior to COVID-19 pandemic shut down in this Subject while other products were administered over a year later.

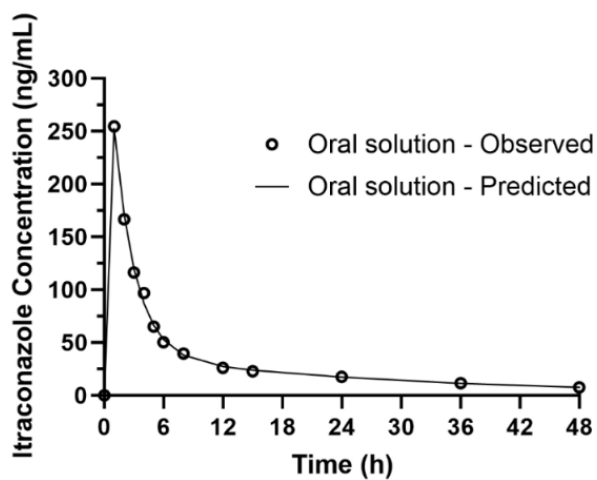


Figure S2 - Observed and fitted oral solution PK profile. Predicted PK profile employed a two-compartment model and no T_{lag} .

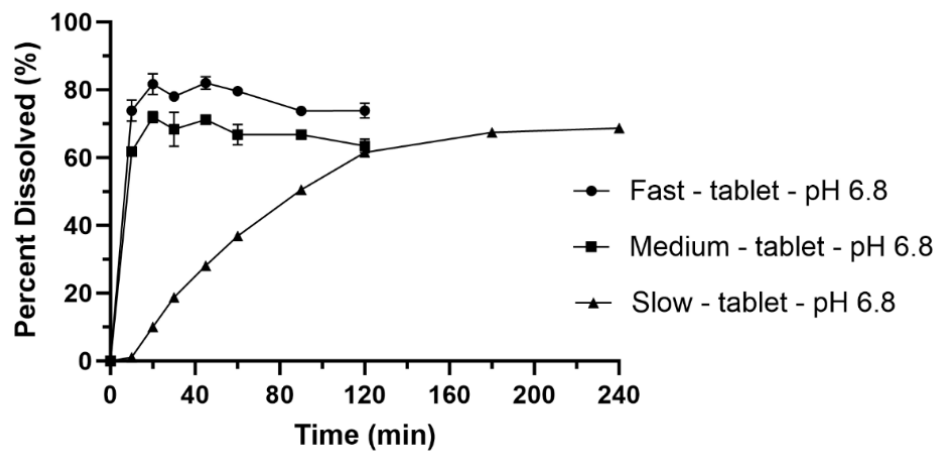


Figure S3 - Preliminary dissolution profile of itraconazole Fast, Medium, and Slow tablets in USP apparatus II (paddle), 100 rpm, and phosphate buffer (USP SIF pH 6.8) before clinical study.

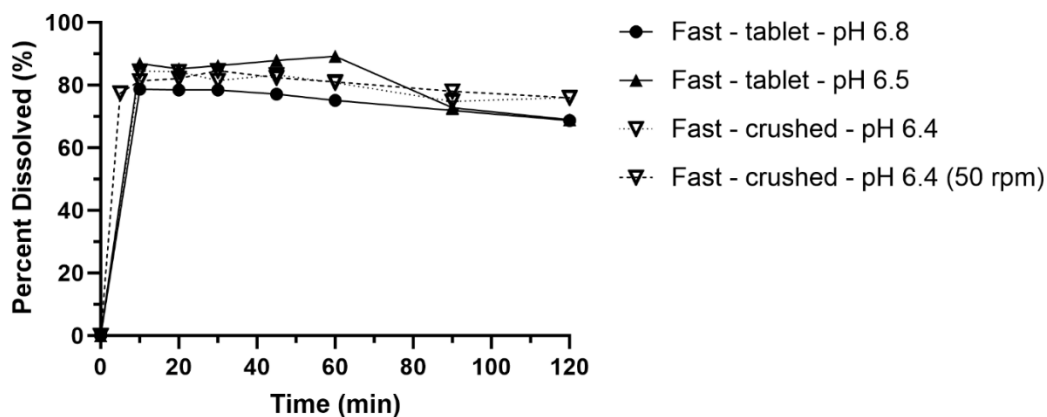


Figure S4 - Fast formulation dissolution profiles under several conditions. Form introduced to the vessel was either whole tablets (i.e., tablet) or crushed tablets (i.e., crushed). Phosphate buffer pH was 6.8, 6.5, or 6.4. Dissolution was performed using USP apparatus II (paddle) at either 100 or 50 rpm. When paddle speed is not noted, 100 rpm was used.

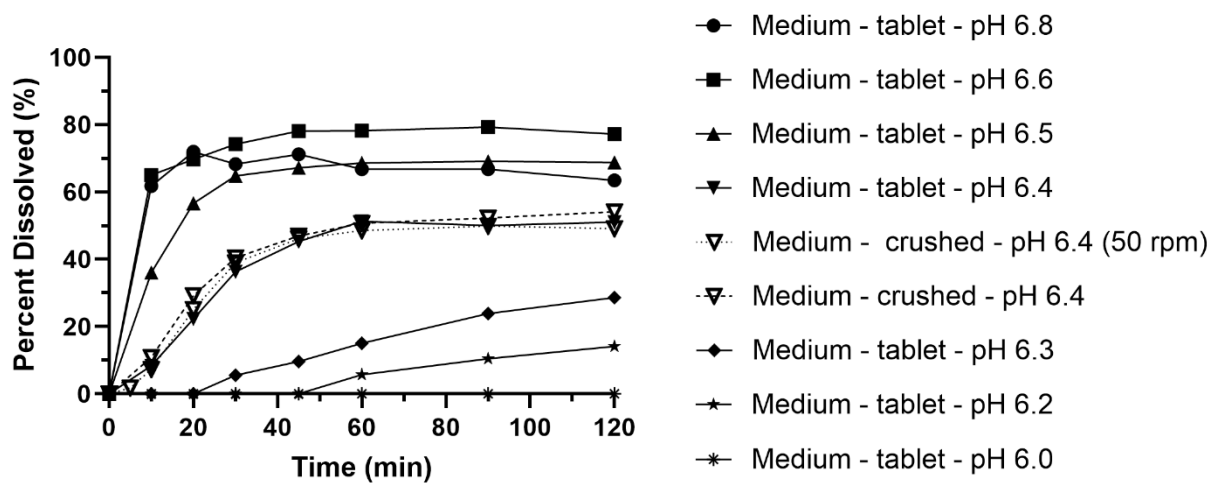


Figure S5 – Medium formulation dissolution profiles under several conditions. Form introduced to the vessel was either whole tablets (i.e., tablet) or crushed tablets (i.e., crushed). Phosphate buffer was 6.8, 6.6, 6.5, 6.4, 6.3, 6.2, or 6.0. Dissolution was performed using USP apparatus II (paddle) at either 100 or 50 rpm. When paddle speed is not noted, 100 rpm was used.

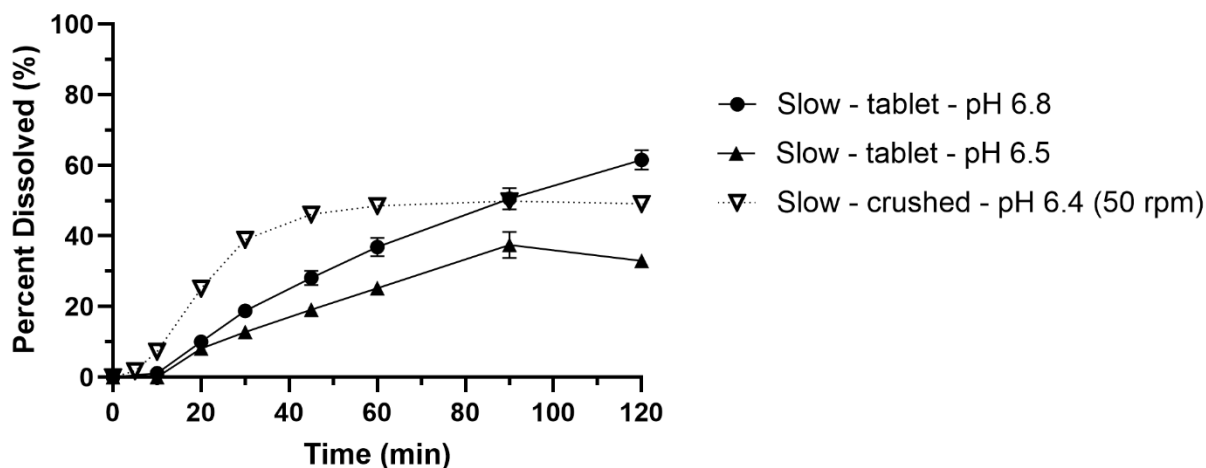


Figure S6 – Slow formulation dissolution profiles under several conditions. Form introduced to the vessel was either whole tablets (i.e., tablet) or crushed tablets (i.e., crushed). Phosphate buffer pH was 6.8, 6.5, or 6.4. Dissolution was performed using USP apparatus II (paddle) at either 100 or 50 rpm. When paddle speed is not noted, 100 rpm was used.

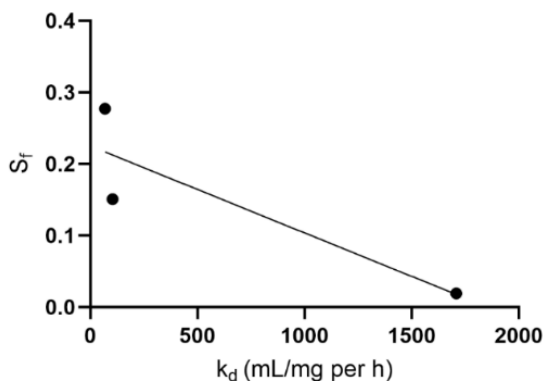


Figure S7 - Linear regression of fitted scaling factor (Fitted S_f) and dissolution rate constant (k_d) for Fast, Medium, and Slow tablets. Equation 11 resulted. Equation 11 was used to calculate final S_f . Table V lists Fitted S_f and Regression S_f . S_f is unitless and less than 1, reflecting the computational slowing of in vitro dissolution profile to fit in vivo PK profile.