Dissolution Method Development for Assessing Amorphous Solid Dispersions

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Purpose

The purpose of this study was to develop a discriminatory dissolution method to assess different formulations of itraconazole amorphous solid dispersions (ASD). Various dissolution conditions such as; media composition, volume and hydrodynamics were investigated.

Methods

ASDs of itraconazole (ITR) using hypromellose acetate succinate (AFFINISOL™ HPMCAS 716G, International Flavors and Fragrances Inc., USA) were produced by hot melt extrusion in 1:1, 1:2 and 1:3 ratios using a twin-screw extruder (Pharma 11, Thermo Fisher)[1]. The extrusion was carried out at 3-7 g/min feed rate, 100 rpm screw speed and target process temperature of 170°C. The extruded strands were air-cooled, pelletized and milled into a powder, then stored in double whirl packs at room temperature for evaluation within one week of processing.

Dissolution testing was carried out on ITR+HPMCAS 716G (1:3 ratio) ASD samples, in USP Type II (paddle) apparatus at 37°C, under variable conditions such as media composition (pH 1.2 to pH 6.8), presence of sodium lauryl sulphate (SLS) surfactant at concentrations of 0 to 2.0%w/w, media volume (500 and 1000 mL) and stirring speed (50, 75, 100 rpm) (Table 1). Formulations containing different drug to polymer ratio were subjected to selected dissolution methods to check the suitability to provide adequate discrimination.

Table 1: Dissolution Conditions Studied During Development of Discriminatory Dissolution Test for ASD

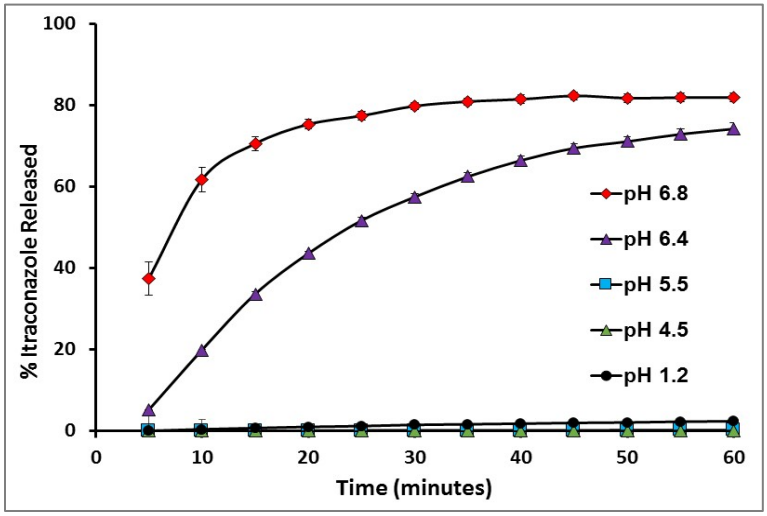
Condition	Media pH	Surfactant level (%)	Volume (mL)	Paddle Speed (rpm)	Dose of API (mg)
Effect of pH	pH 1.2^	----	500	75	25
	pH 4.5#	----	500	75	25
	pH 5.5*	----	500	75	25
	pH 6.0*	----	500	75	25
	pH 6.4*	----	500	75	25
Effect of surfactant (SLS)	pH 6.8*	0.10	500	75	25
	pH 6.8*	0.25	500	75	25
	pH 6.8*	0.50	500	75	25
	pH 6.8*	1.00	500	75	25
	pH 6.8*	1.50	500	75	25
Effect of media volume	pH 6.8*	----	500	75	100
	pH 6.8*	1.00	500	75	100
	pH 6.8*	----	1000	75	100
Effect of paddle speed	pH 6.8*	----	1000	50	100
	pH 6.8*	----	1000	75	100
	pH 6.8*	----	1000	100	100

Results

Effect of Media pH

Figure 1 shows the effect of media pH on drug release profiles using similar media volume (500 mL) and paddle stirring speed (75 rpm). Drug release (about 80%) only occurred in dissolution media with pH 6.4 and above. This behavior may be attributed to the enteric nature of HPMCAS polymer. Based on this data, all subsequent dissolution studies were conducted in phosphate buffer pH 6.8.

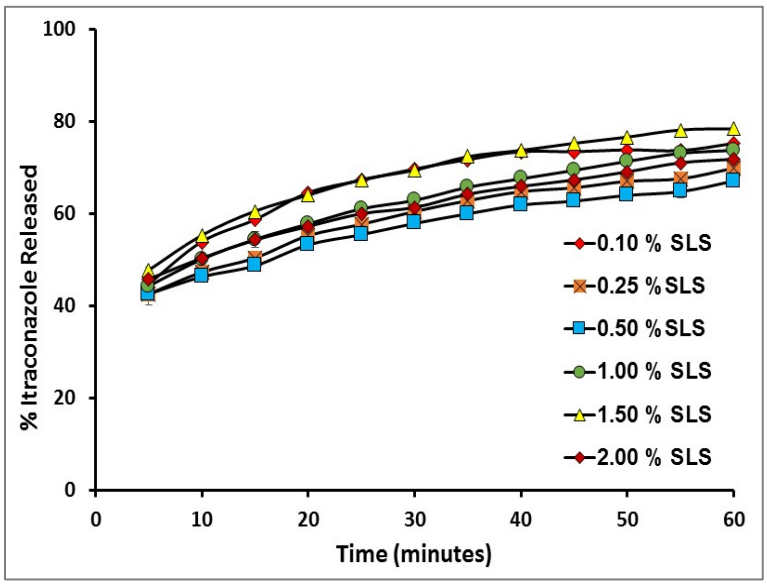
Figure 1: Effect of Media pH on ITR Release (25 mg dose) from ITR:HPMCAS ASD, 1:3 Ratio



Effect of Surfactant (SLS) Concentration

ITR + HPMCAS 716G dispersion was subjected to dissolution testing in sodium phosphate buffer pH 6.8 containing SLS, as surfactant, at various concentration (0.1 to 2.0%). Drug release in 0.1% SLS level was high initially, and then started to drop. All other concentrations showed an increase in drug release, up to 1 hour (Figure 2). None of the SLS concentrations achieved ≥ 80% drug release till 1 hour, with exception of media containing 1.5% SLS. Drug release in 1 to 2% SLS were similar at the end of 1.5 hour time point (data not shown).

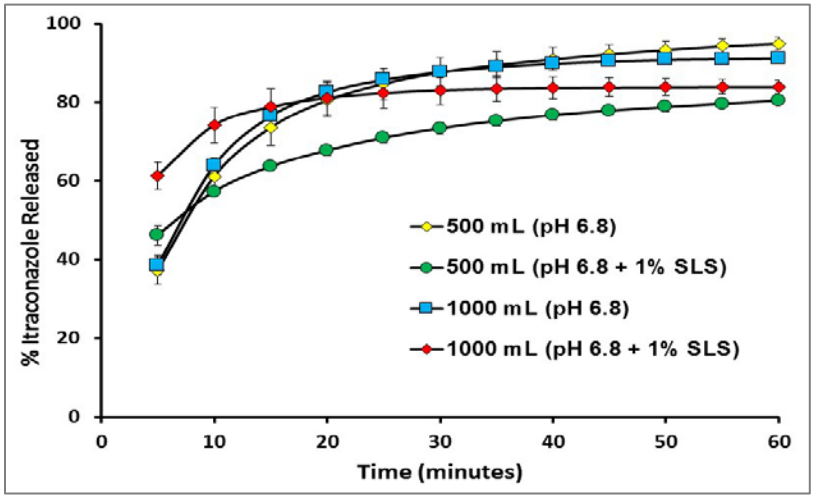
Figure 2: Effect of Surfactant (SLS) Concentration on ITR Release (25 mg dose) from ITR:HPMCAS ASD, 1:3 ratio



Effect of Media Volume

Figure 3 shows that drug release from itraconazole ASD (100 mg dose) in low (500 mL) or high volume (1000 mL) phosphate buffer pH 6.8 was similar. However, the presence of 1% SLS gave slightly different results in two media volumes.

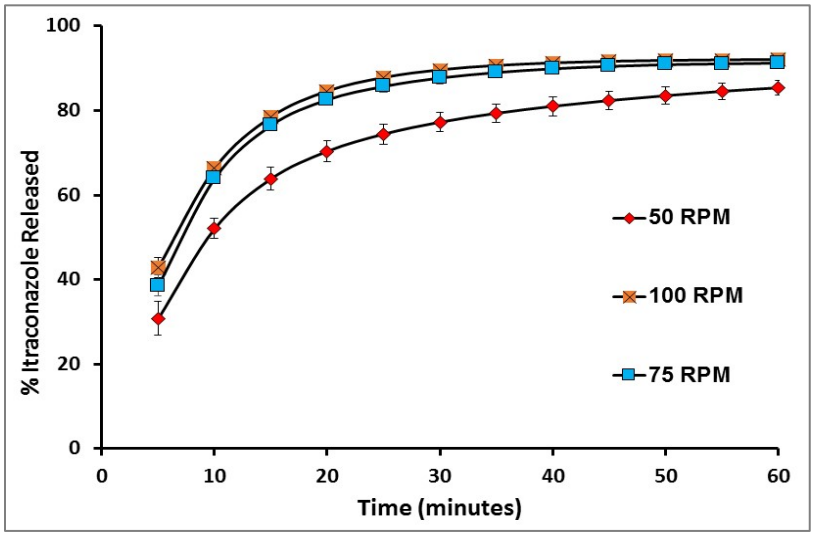
Figure 3: Effect of Media Volume on ITR Release from ASD (100 mg dose) in Phosphate Buffer pH 6.8



Effect of paddle speed

Initial dissolution testing was carried out at 75 rpm, based on findings from the literature review.[2] Further study was conducted at low (50 rpm) and high (100 rpm) paddle speed. As seen in Figure 4, dissolution was lower at 50 rpm, whereas, dissolution was comparable at 75 and 100 rpm paddle speeds. Higher paddle speed allowed ASD to be uniformly dispersed in the dissolution media within 2 minutes.

Figure 4: Effect of Paddle Speed on ITR Release from ASD

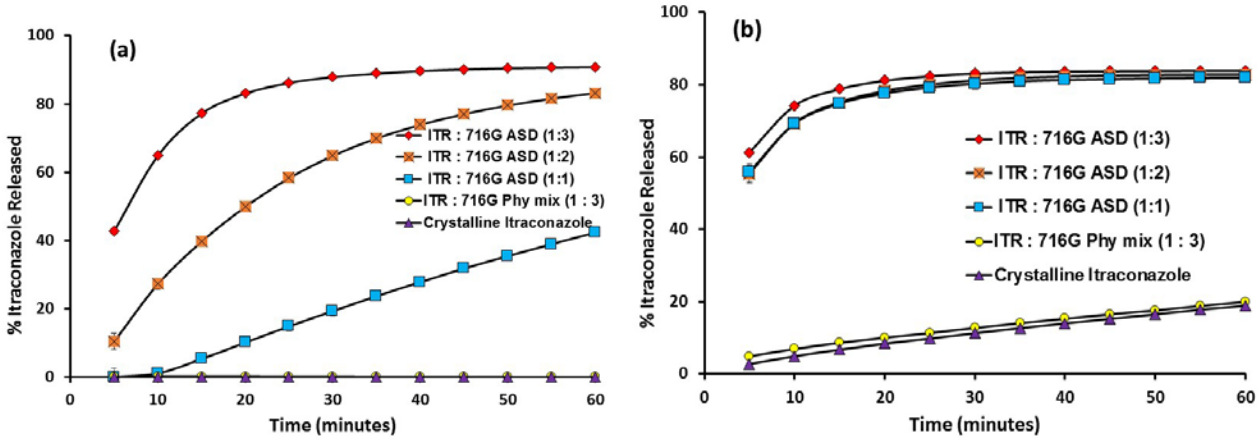


Determination of suitable dissolution method to provide discrimination between formulations

Based on the earlier results, formulations of ITR : HPMCAS solid dispersions at various drug : polymer ratio, were subjected to 1000 mL phosphate buffer pH 6.8, with or without 1% SLS, USP apparatus II (paddle) at 75 rpm and 37°C. Release profiles of ITR from the various ASD formulations showed adequate discrimination when subjected to phosphate pH 6.8 dissolution, as shown in Figure 5a. However, incorporation of 1% SLS in dissolution media failed to provide discrimination between various formulations. There was a definite improvement in the dissolution of

crystalline ITR, or its physical mixture with HPMCAS, in media containing 1% SLS. As reported previously, surfactants may interact with certain polymers during solubilization of API from amorphous solid dispersions, which may result in altered drug solubility, drug dissolution and drug absorption.[3-4]

Figure 5: ITR Release from ASDs with Different Drug:Polymer Ratio in (a) Phosphate Buffer pH 6.8 and (b) Phosphate Buffer pH 6.8 with 1% SLS.



Conclusions

Media composition was shown to have a major effect on dissolution of ITR from ASD containing HPMCAS. The dissolution method that provided discrimination amongst different formulations is 1000 mL phosphate buffer pH 6.8 in USP Type II (paddle) at 75 rpm. This method was selected for further formulation evaluation. Discriminating robust dissolution methods are critical during formulation screening and drug development.

References

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