

# Influence of Milling Process on Hot Melt Extruded Amorphous Solid Dispersion

M. Pimparade, X. Ye, P. Patel, M. Rane and A. Rajabi-Siahboomi

Colorcon, Inc. Harleysville, PA 19438, USA  
www.colorcon.com

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## Introduction

Hot melt extrusion (HME) technology is used to produce amorphous solid dispersions (ASD) of poorly soluble drugs to improve their solubility<sup>1</sup>. As part of the formulation and process development, these dispersions are milled before being subjected to downstream processing into tablets or capsule dosage forms. Therefore, the characteristics of milled extrudates, specifically shape and size, are critical for powder flow and compressibility, which can adversely affect the tableting process. It is generally perceived that milling of HPMCAS based extrudates is often a challenging step in the process development for ASD. The purpose of this study was to evaluate the critical conditions such as milling speed, screen mesh size and feed rate, on itraconazole and hypromellose acetyl succinate (HPMCAS) ASD produced by HME.

## Methods

Amorphous solid dispersions of itraconazole (ITR) and hypromellose acetyl succinate (HPMCAS 912G, DuPont) were prepared by HME using a twin-screw extruder (Pharma 11, Thermo Fisher), in 1:3 w/w ratio of drug: polymer. The HME process was carried out at 5 g/min feed rate, 100 rpm screw speed and 170°C target process temperature. The extrudates were air-cooled, pelletized and milled (using ZM 200, Retsch Mill) into powder. Milling was performed at high and low speed, screen mesh size and feed rate conditions as shown in Table 1. Milled extrudates were characterized using powder x-ray diffraction (XRPD; Equinox 100, Thermo Scientific), differential scanning calorimetry (DSC; Q200, TA Instruments), scanning electron microscopy (SEM; Phenom XL, Phenom World), particle size distribution (Mastersizer 2000, Malvern Instruments Ltd.), powder properties, and dissolution testing in 1000 ml phosphate buffer pH 6.8 using paddle apparatus (Agilent) at 75 rpm. Results were analyzed using Fusion Pro Software (S-Matrix Corporation).

Table 1. Milling Process Parameters

Trial #	Milling Speed (rpm)	Screen Mesh Size (microns)	Feed Rate (g/sec)	# of Mill Pass
Trial 1	18,000	350	3.0	Single
Trial 2	10,000	350	1.0	Single
Trial 3	10,000	350	3.0	Single
Trial 4	18,000	500	1.0	Single
Trial 5	10,000	500	1.0	Single
Trial 6	10,000	350	1.0	Single
Trial 7	18,000	500	3.0	Single
Trial 8	10,000	350	3.0	Single
Trial 9	10,000	500	1.0	Single
Trial 10	10,000	500	3.0	Single
Trial 11	18,000	350	1.0	Single

## Results

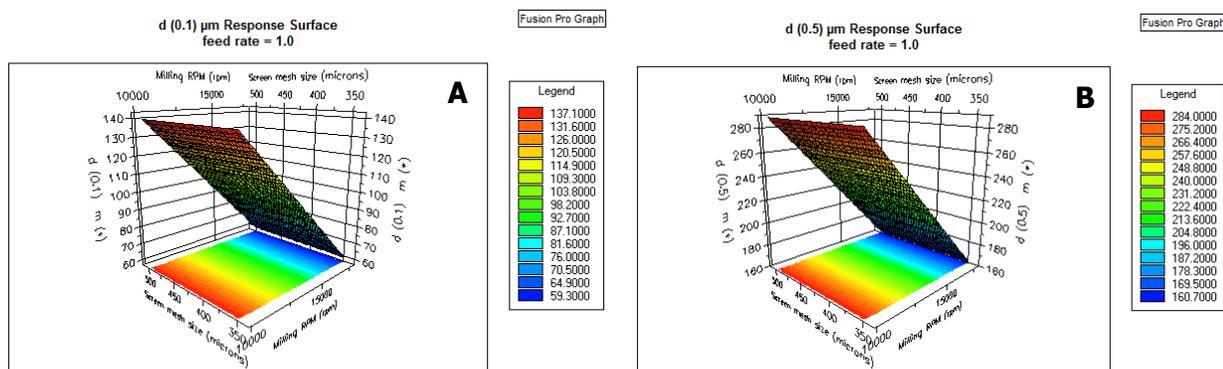
Based on a previous study, 1:3 (ITR: 912G) was selected as the model formulation to evaluate impact of milling conditions on extrudates.<sup>2</sup> During milling experiments (Table 2), the initial sieve temperature (before-milling) and final temperatures (after-milling) were recorded using infrared thermometer gun (MiniTemp FS, Raytek) to understand the influence of shear on localized temperature. The results

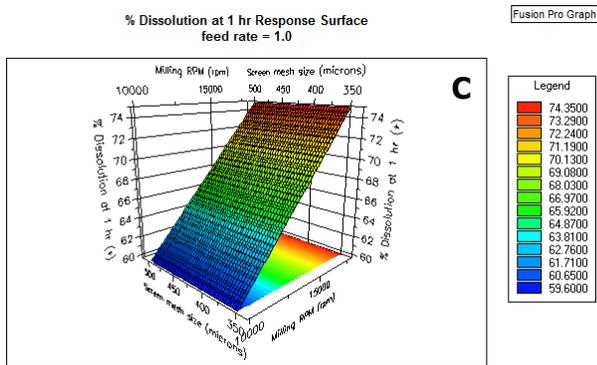
indicated that different milling conditions did not affect the temperature significantly and could be attributed to shorter residence time in the mill. Also, moisture content and density were not influenced by the milling conditions. Among all outputs, particle size and percentage dissolved were most sensitive to milling speed (Figures 1 A, B & C). However, sieve sizes did not significantly alter the powder characteristics (bulk and tapped densities, % compressibility) and percentage dissolved.

**Table 2. Milling Process Responses and Powder Evaluation**

Trial #	Time (s)	Start Temp (°C)	End Temp (°C)	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility (%)	Loss on Drying %	Particle Size		
								d(0.1) (µm)	d(0.5) (µm)	d(0.9) (µm)
Trial 1	40	22.0	45.0	0.50	0.69	28.0	2.19	51.18	172.32	334.53
Trial 2	101	23.8	60.0	0.52	0.69	25.0	2.36	140.17	291.60	516.56
Trial 3	35	23.6	55.0	0.53	0.73	27.7	1.96	142.10	296.23	524.14
Trial 4	36	23.4	44.0	0.49	0.69	29.4	2.12	56.93	151.66	312.47
Trial 5	105	24.0	47.0	0.52	0.69	25.0	2.67	116.57	282.04	531.46
Trial 6	69	20.8	22.8	0.57	0.70	19.1	1.93	145.69	269.67	452.71
Trial 7	93	23.0	45.0	0.49	0.65	25.5	2.54	66.46	167.68	336.01
Trial 8	36	23.8	44.8	0.54	0.67	19.6	3.05	149.26	304.86	531.68
Trial 9	103	21.0	25.0	0.55	0.69	19.6	1.84	183.15	341.04	574.67
Trial 10	33	23.6	44.0	0.53	0.71	25.5	1.93	102.37	233.24	431.93
Trial 11	104	23.2	38.0	0.52	0.69	25.0	2.85	62.79	151.29	294.24

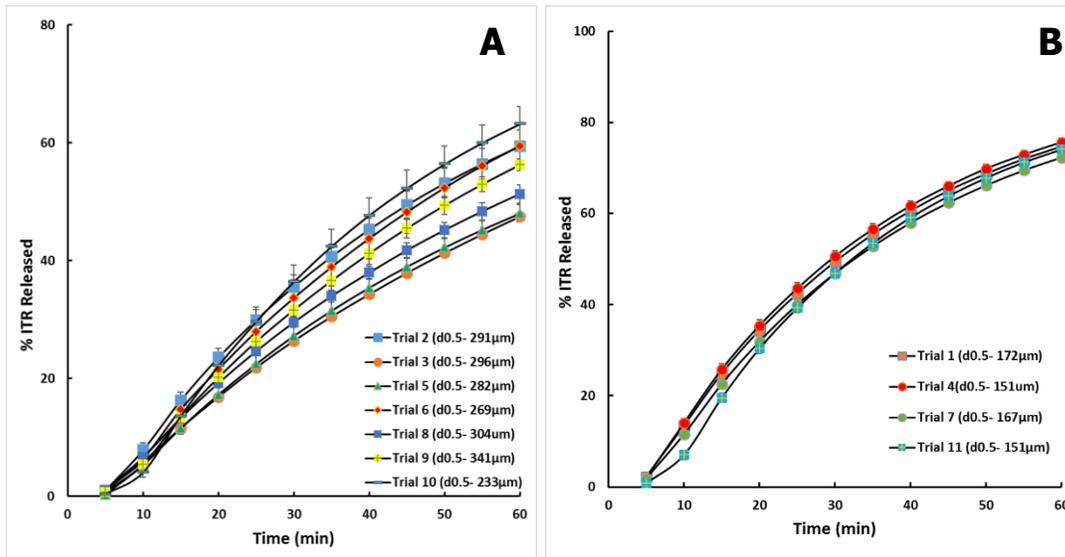
**Figure 1. Effect of Milling Conditions on (A) Particle Size d(0.1) (B) Particle Size d(0.5) (C) % Dissolved**





Trials with higher milling speed had a faster dissolution rate, attributed to smaller particle size (Figures 2A & B, Table 3). At higher speed (18,000 rpm) results for d(0.5) were 151-172 µm and at lower speed (10,000 rpm) the d(0.5) was 233-341 µm. These results demonstrated the direct correlation between the particle size and dissolution rate.

**Figure 2. Dissolution of Extrudates Milled at (A) 10,000 rpm (B) 18,000 rpm**

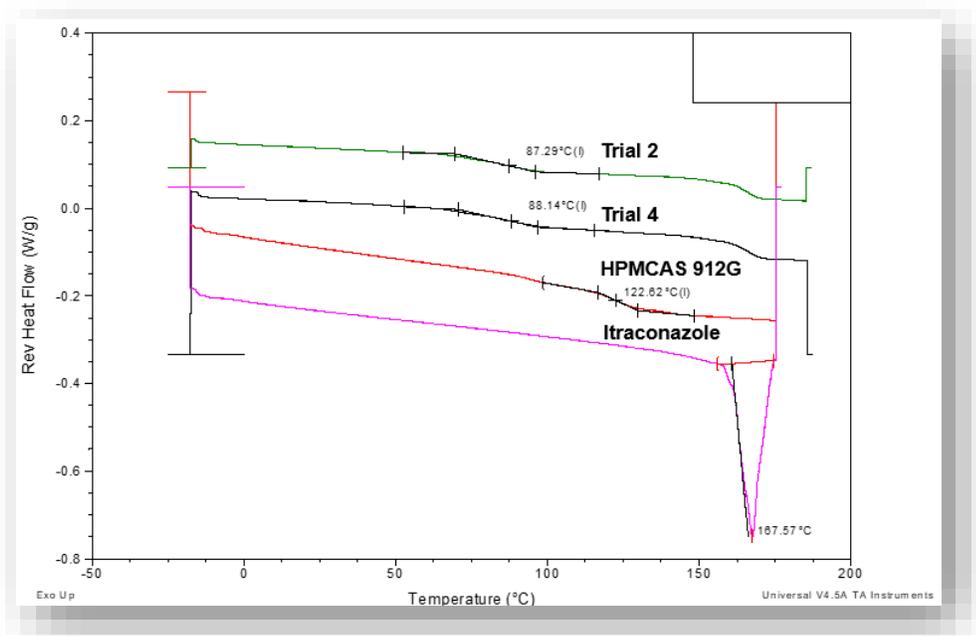


**Table 3. Percentage of Drug Dissolved for Extrudates Milled at 1 and 3 hours**

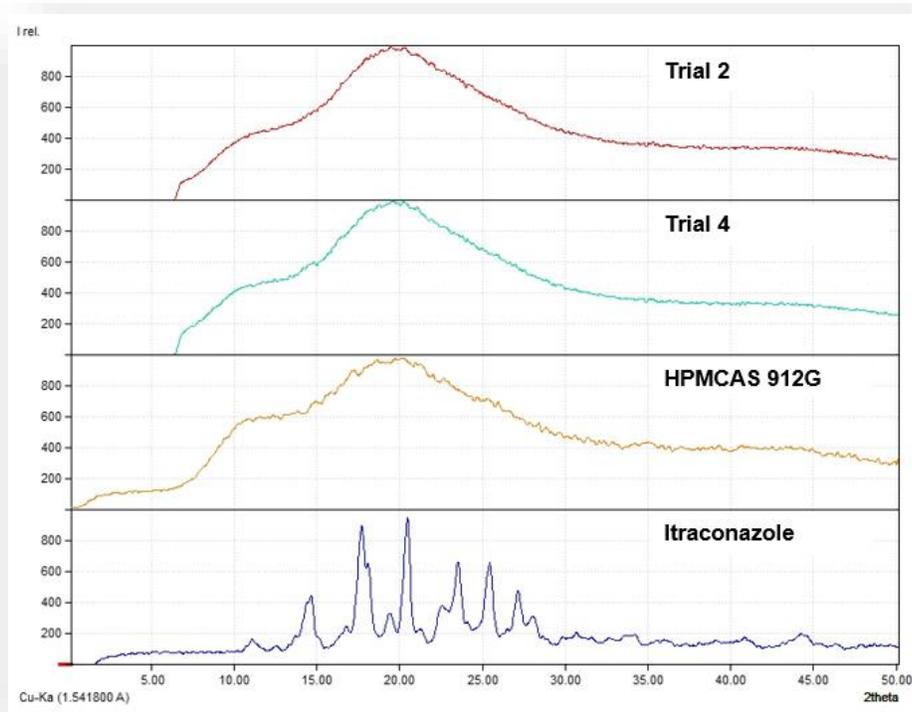
Trial #	% ITR dissolved @ 1hr	% ITR dissolved @ 3hr
Trial 1	74.68	90.73
Trial 2	59.44	87.02
Trial 3	47.49	83.94
Trial 4	75.67	91.36
Trial 5	48.02	11.36
Trial 6	59.50	90.80
Trial 7	72.30	90.81
Trial 8	51.31	83.65
Trial 9	56.26	89.31
Trial 10	63.20	87.71
Trial 11	74.08	89.78

DSC evaluation (Figure 3) on samples with the higher and lower milling speed confirmed the presence of ITR in an amorphous form. The localized elevated temperature during milling did not alter the glass transition temperature and physical state of ITR; demonstrating the robustness of HPMCAS based ASD at elevated temperature. In XRPD evaluation (Figure 4), milled extrudates showed a typical “amorphous halo”, with no ITR peaks and affirmed the ITR was in an amorphous form.

**Figure 3. DSC Thermograms of Milled Extrudates**

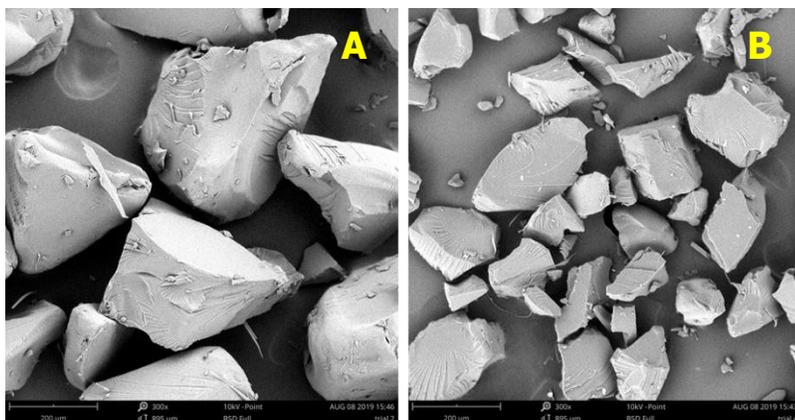


**Figure 4. XRPD of Milled Extrudates**



SEM images (Figures 5A & B) of trials 2 and 4 showed the clear differentiation in the particle fractures and sizes. At higher milling speed, the extrudates were at a very high velocity hitting the sieve, and due to this impact, the particle size was substantially reduced.

Figure 5. SEM of Extrudates Milled at (A) 10,000 rpm (B) 18,000 rpm



Trial 2

Trial 4

## Conclusions

This study demonstrated the impact of milling conditions on the properties of extrudates. The results showed that the milling speed was critical for particle size, distribution and dissolution rate. Solid state characterization results confirmed the presence of itraconazole in an amorphous form in HPMCAS 912G after the milling conditions.

## References

1. Repka, Michael A., et al. "Melt extrusion with poorly soluble drugs—an integrated review." International journal of pharmaceutics 535.1-2 (2018): 68-85.
2. Martin, L., Pimparade, M. et al. "Fundamental evaluation and characterization of itraconazole solid dispersions prepared by hot melt extrusion", CRS 2018.

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North America	Europe/Middle East/Africa	Latin America	India	China
<b>+1-215-699-7733</b>	<b>+44-(0)-1322-293000</b>	<b>+54-11-5556-7700</b>	<b>+91-832-6727373</b>	<b>+86-21-61982300</b>

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