# Crystallinity Risk Assessment in the Performance of Amorphous Solid Dispersions

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## Purpose

Recrystallization of an amorphous drug is one of the biggest risks on physical instability in amorphous solid dispersions (ASD); this may negatively affect solubility, dissolution and bioavailability. Purpose of this work was to assess the impact of level of crystallinity on the dissolution of amorphous solid dispersions using engineered ASD samples.

## Methods

ASDs of itraconazole (ITR) and hypromellose acetyl succinate (AFFINISOL™ HPMCAS 716G, International Flavors and Fragrances Inc., USA) in 1:3 ratio of drug:polymer, were prepared by hot melt extrusion (HME) using a twin-screw extruder (Pharma 11, Thermo Fisher, USA). The HME process was carried out at 3-7g/min feed rate, 100 rpm screw speed and 170°C target process temperature. The extrudates were air-cooled, pelletized and milled into powder using a 500 µm screen (ZM 200, Retsch, Germany).

Physical mixes (PM) of crystalline ITR and AFFINISOL™ 716G were prepared, also in 1:3 ratio of drug:polymer, through simple blending. Samples containing different levels of crystallinity were engineered by blending PM and ASD in different ratios (Table 1).

All samples were characterized using powder X-ray diffraction (XRD; Equinox 100, Thermo Scientific, USA), Fourier-transform infrared spectroscopy (FT-IR, Nicolet iS 10, Thermo Scientific, USA) and differential scanning calorimetry (DSC; Q200, TA Instruments, USA) at a heating rate of 10°C/min and modulating ± 2°C every 40 seconds. Scanning electron microscopy (SEM; Phenom XL, Phenom World, USA) was used to investigate the distribution of externally added crystalline ITR. Dissolution behavior of all the samples in 1000 mL of phosphate buffer pH 6.8 at 37°C, with USP apparatus II at 75 rpm, were evaluated. Aliquots were evaluated spectrophotometrically at 257 nm. Apparent solubility of samples was calculated from the absorbance values at 1 and 3 hours during dissolution testing.

**Table 1: Composition of Engineered Samples: Different Levels Physical Mixture Added to ASD**

| Ingredients | Sample A | Sample B | Sample C | Sample D | Sample E | Sample F |
|---|---|---|---|---|---|---|
| **Sample A (Physical Mix)** | 400 mg | ----- | 4 mg | 20 mg | 40 mg | 80 mg |
| **Sample B (Amorphous Solid Dispersion, ASD)** | ----- | 400 mg | 396 mg | 380 mg | 360 mg | 320 mg |
| **Total** | ***400 mg*** | ***400 mg*** | ***400 mg*** | ***400 mg*** | ***400 mg*** | ***400 mg*** |
| **Crystalline API in 100 mg Dose** | 100.00% | 0.00% | 1.00% | 5.00% | 10.00% | 20.00% |

## Results

Four characterization techniques were used to detect and quantitate % crystallinity in the samples. Figure 1 shows DSC thermograms for HPMCAS, ITR and ASD, as well as the engineered samples. Itraconazole gave a sharp melting point at ~ 168ºC during the first heating cycle. The physical mixture (PM) showed the melting point of ITR; this was also observed in 10% or higher crystallinity engineered samples. There was no thermal event (peaks) on DSC thermograms with lower amounts of crystalline API (5% w/w or lower) which may be attributed to the detection capability of DSC.

**Figure 1: DSC Thermogram of Component Materials and Engineered Samples**

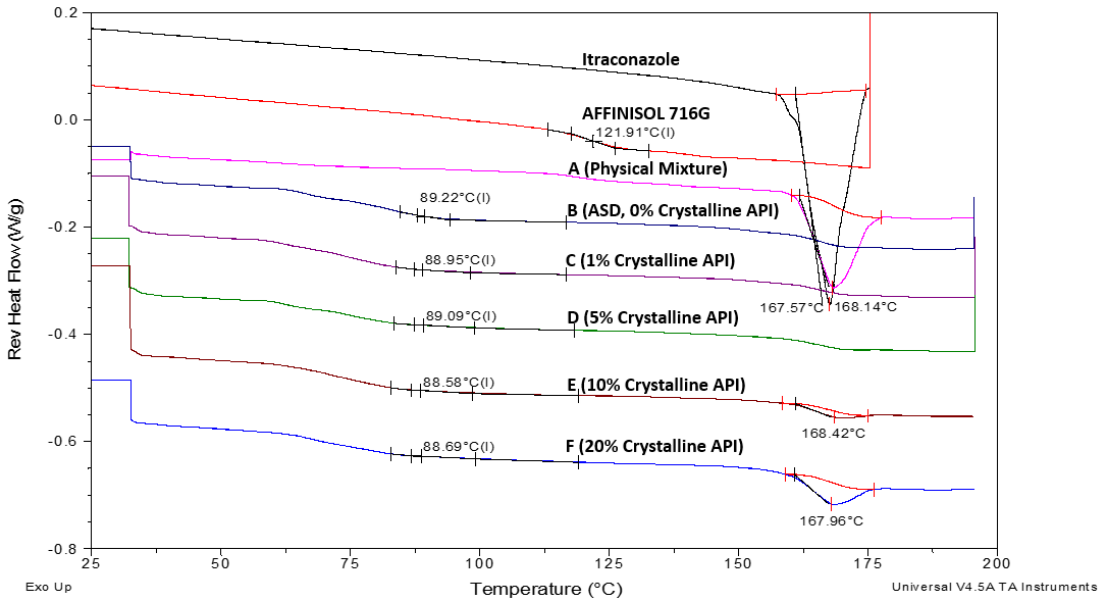
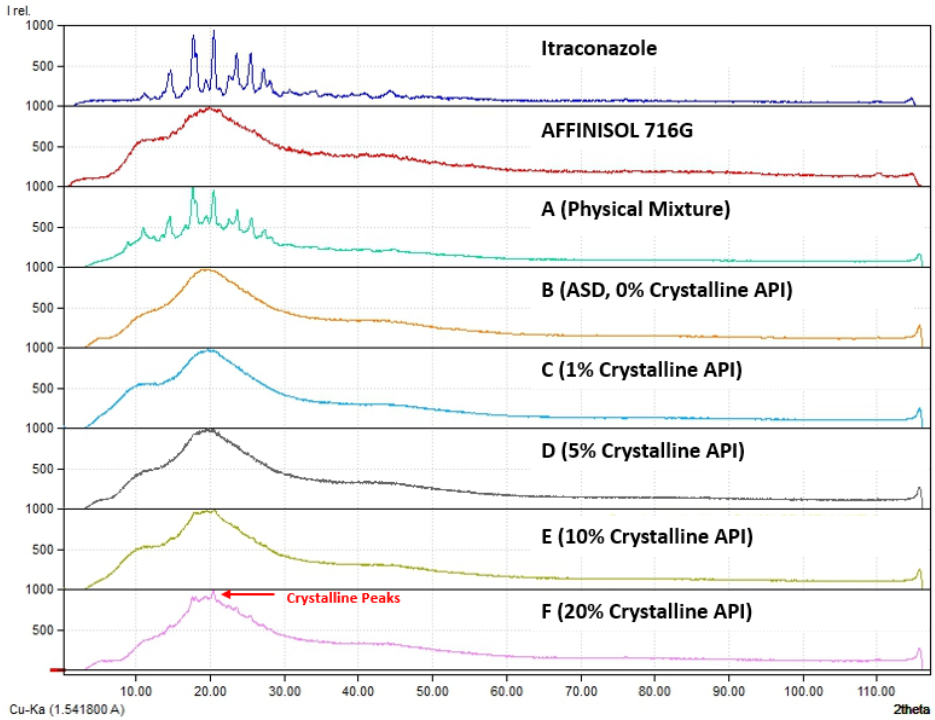



Figure 2 shows the X-ray diffractograms of pure polymer, ITR powder and engineered samples. ITR exhibited strong crystalline peaks, which is expected to be detected in the physical mixtures. The amorphous solid dispersion showed a *typical amorphous halo* which indicated the amorphous nature of the ASD sample. All samples, with the exception of 20% crystalline API, did not show crystallinity. Scan rate and collection time were varied to improve the sensitivity for XRD, but this technique was unable to detect crystalline API up to 10%. 20% sample showed some indication of crystallinity.

**Figure 2: X-ray Diffractograms of Component Materials and Engineered Samples**




FTIR spectra of crystalline ITR (Figure 3) showed a strong absorption peak at 1698 $cm^{-1}$ which ascribed to carbonyl stretching (C=O). The same characteristic peak was present in the physical mixture at a lower intensity, due to the dilution of crystalline itraconazole with the polymer. ASD did not display a characteristic carbonyl peak, which could be attributed to hydrogen bonding of amorphous ITR with AFFINISOL™ 716G.[2]

Engineered samples with 1% w/w crystalline ITR (sample C) did not show the carbonyl peak, which may be due to the lower limit of detection of this technique. Samples D, E and F, containing 5,10 and 20% w/w of crystalline API respectively, demonstrated characteristic carbonyl and notably, the intensity of peaks were increased to a corresponding concentration of the crystalline API.

**Figure 3: FTIR Spectras of Component Materials and Engineered Samples**

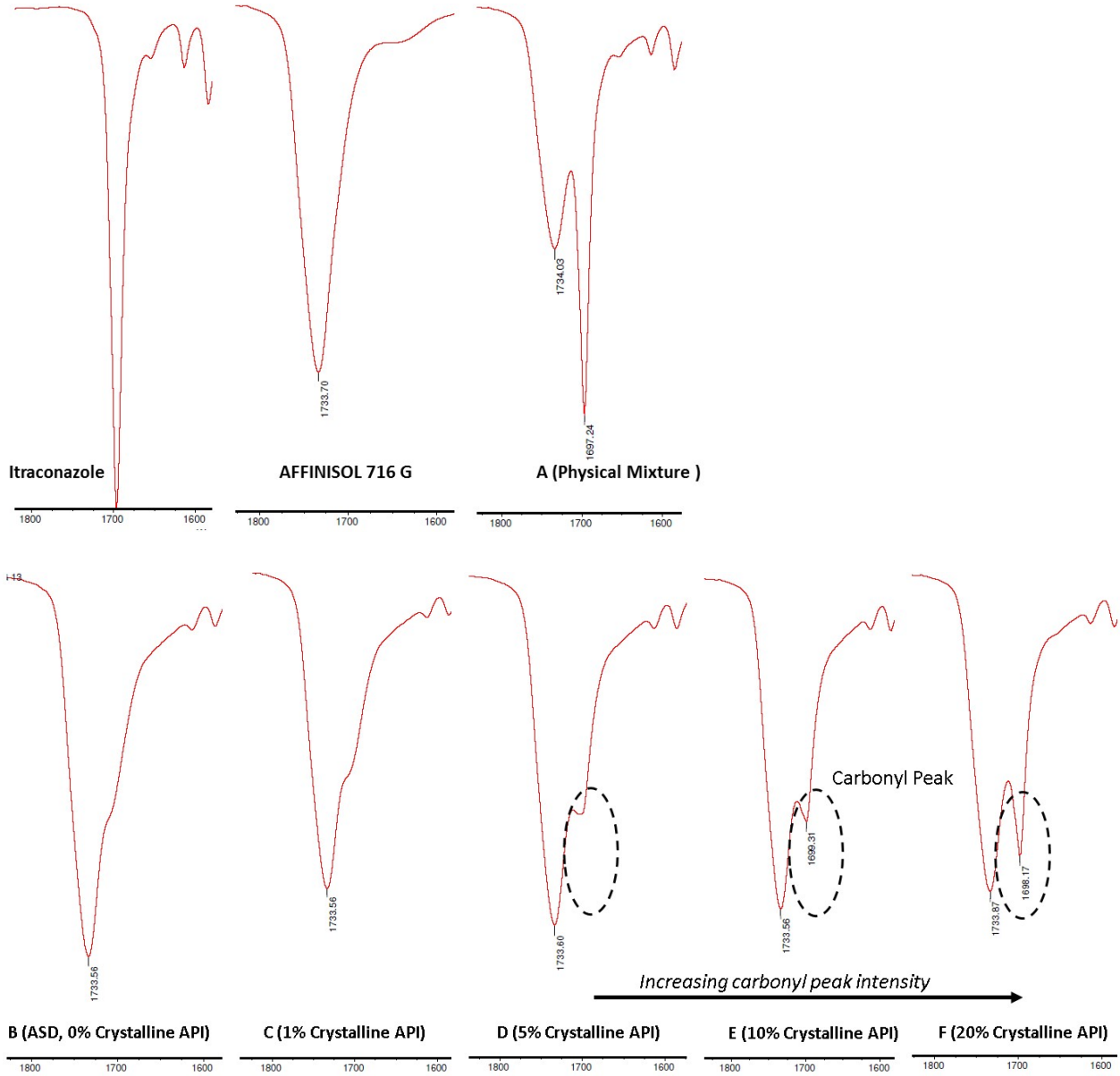
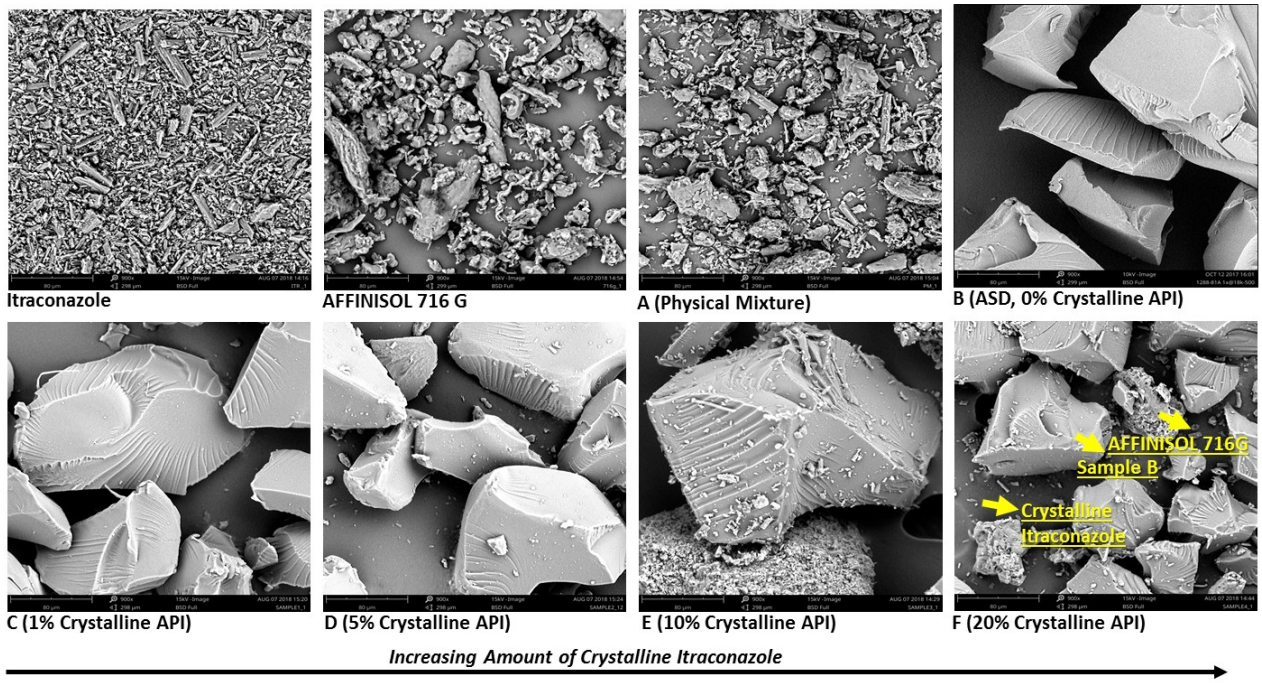



Figure 4 shows SEM images of pure polymer, ITR and processed or engineered samples. Prior to imaging, all samples were coated with gold sputter coater. ASD had irregularly shaped, jagged particles with visible fracture planes without any surface crystals.

Engineered samples showed a uniform distribution of milled extrudates, unprocessed polymer and crystalline ITR. The amount of crystalline API increased as the amount of physical mixture in the samples increased. SEM may be used as a visual tool to identify crystalline material in engineered samples.

**Figure 4: SEM Images of Component Materials and Engineered Samples**




Dissolution results demonstrated a reduction in dissolution rate for the first 30 minutes from engineered samples (Figure 5). Incorporation of 1%, 5%, 10% and 20% crystalline ITR in the engineered samples resulted in equivalent percentage reduction in drug dissolved. A similar trend was observed in the apparent solubility of engineered samples (Table 2). There was a minimal drop in solubility values from 1 to 3 hour. Based on the results, it was found that the presence of crystalline drug did not act as a nucleating agent for recrystallization of amorphous ITR.

**Figure 5: Dissolution Profiles of Component Materials and Engineered Samples**

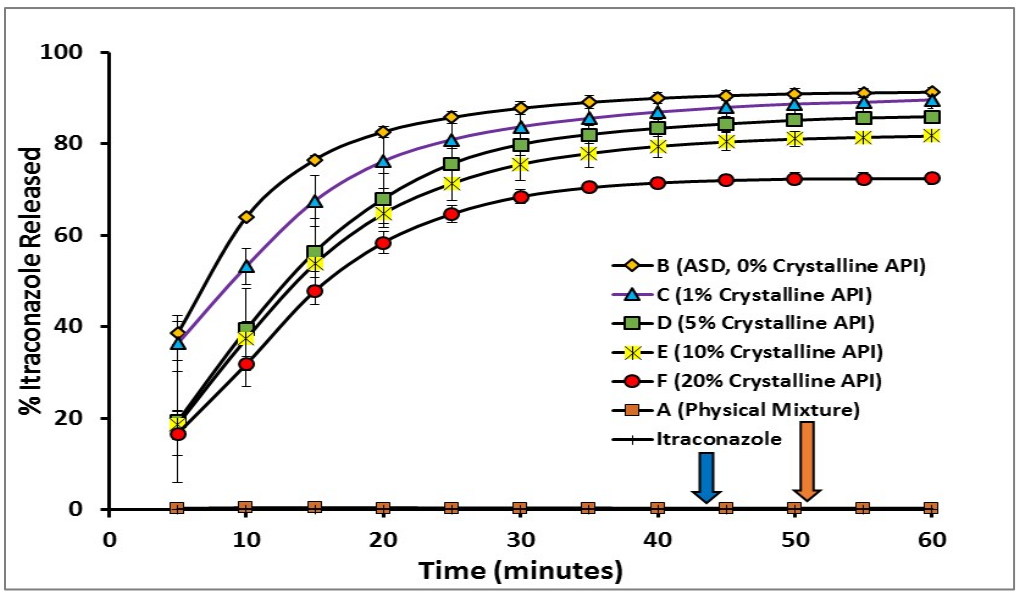


**Table 2: Apparent Solubility of Engineered Samples**

| Sample | Solubility @ 1h (µg/mL) | Solubility @ 3h (µg/mL) |
|---|---|---|
| ITR powder | Below Detection Limit | Below Detection Limit |
| A (Physical Mixture) | 0.26 | 0.24 |
| B (ASD, 0% Crystalline API) | 91.27 | 89.03 |
| C (1% Crystalline API) | 89.55 | 88.04 |
| D (5% Crystalline API) | 85.88 | 83.37 |
| E (10% Crystalline API) | 81.71 | 78.87 |
| F (20% Crystalline API) | 72.40 | 68.25 |

## Conclusions

Physical instability of amorphous solid dispersions presents a risk in the performance of ASD. Engineered samples containing various levels of crystalline API could help identify risks in the performance of amorphous dispersions, and thus help select appropriate analytical techniques for sample evaluation during formulation development. In the current study, various analytical techniques provided only qualitative information on the presence of crystallinity. However, the dissolution test provided quantifiable results on the presence of crystalline API. Addition of crystalline API to ASD (via engineered samples) did not affect the solubility of the dissolved drug in the media up to 3 hours. Additional tests such as saturation solubility could be used to further assess the risks of the presence of crystallinity in the performance of ASD.

## References


1. Martin, L., Pimparade, M. et al. Fundamental evaluation and characterization of itraconazole solid dispersions prepared by hot melt extrusion. CRS 2018.
2. DiNunzio, James C., et al. "Amorphous compositions using concentration enhancing polymers for improved bioavailability of itraconazole." Molecular Pharmaceutics 5.6 (2008): 968-980





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