Fundamental Evaluation and Characterization of Itraconazole Solid Dispersions Prepared by Hot Melt Extrusion

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Introduction

Hypromellose acetate succinate (HPMCAS) is a versatile polymer which has been used mainly for enteric coating of solid dose formulations. Recent attention has focused on the use of HPMCAS for solubility enhancement of poorly soluble drugs, with solid dispersions produced by spray drying or hot melt extrusion (HME). As a solvent-free process, HME is an attractive method of manufacturing amorphous solid dispersions (ASD) if the drug properties are amenable to processing in conditions of elevated temperature and shear stress. The purpose of this work was to evaluate and characterize ASDs comprising itraconazole (ITR) and HPMCAS produced via an HME process.

Methods

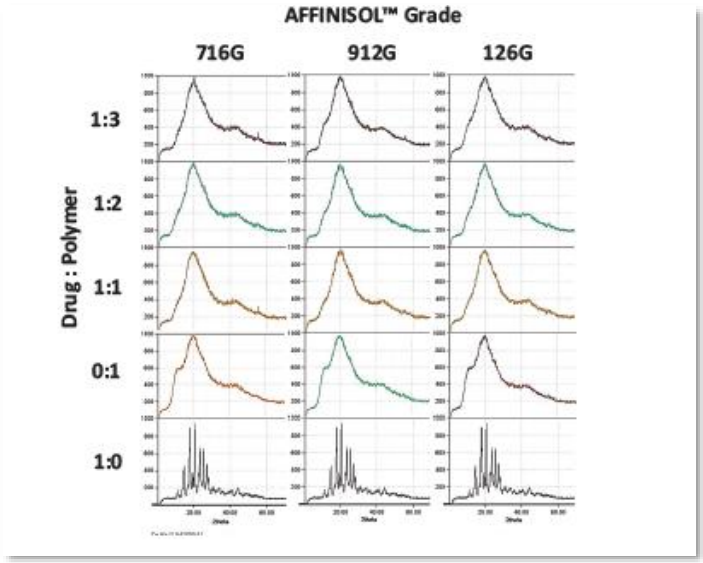
Formulations of ITR and three grades of HPMCAS (AFFINISOL™ 716G, 912G and 126G, Dow Chemical Company, USA) were produced by dry blending the two components at drug-to-polymer ratios of 1:3, 1:2, and 1:1 (25%, 33.3%, or 50% w/w concentrations). The resulting nine formulations were processed in a lab scale twin-screw hot melt extruder (Pharma 11, Thermo Scientific, USA) at 170°C, with a screw speed of 100 rpm and throughput of 3-7 g/min through a 2.0 mm strand die. According to manufacturer recommendations for general HME applications, the extruder screw elements were configured with two kneading sections and three conveying sections. Extruded strands were air-cooled and pelletized to approximate lengths of 2 mm, then reduced to powders using a centrifugal mill (ZM200, Retsch, Germany) with a 500 µm sieve and 12-tooth rotor at 18,000 rpm. Particle size distributions of the milled extrudates were determined using laser diffraction (Mastersizer 2000, Malvern Instruments Ltd, UK). Powdered formulations were subjected to accelerated stability conditions for four weeks at 40°C/75% RH (open dish). Thermal analysis of the powders was conducted using differential scanning calorimetry (DSC; Q200, TA Instruments, USA) at a heating rate of 10°C/min and modulating ± 2°C every 40 seconds. Drug crystallinity was investigated using X-ray powder diffraction (XRPD; Equinox 100, Thermo Scientific, USA). Scanning electron microscopy (SEM; Phenom XL, Phenom World, USA) was used to investigate the presence of surface recrystallization of the drug after stability storage. Dissolution testing was conducted using powder samples containing 100 mg of the drug in 1000 mL phosphate buffer pH 6.8 using USP apparatus II at 75 rpm.

Results

Pelletized extrudates were readily milled into powders. The drug load of the formulations strongly influenced the particle size distribution by modifying the brittleness and milling behaviour of the extrudates. The D50 values of 75, 120 and 160 microns were achieved for drug-to-polymer ratios of 1:1, 1:2 and 1:3, respectively.

Evaluation of the milled extrudates by XRPD and DSC confirmed ITR in the HME formulations was in an amorphous rather than crystalline phase. The X-ray diffractograms for all formulations had only the typical “amorphous halo” with none of the crystalline peaks observed for the ITR raw material (Figure 1). This indicated that the drug crystals converted into amorphous solid dispersions through HME with AFFINISOL™.

Figure 1. X-ray Diffractograms of ITR ASD vs. Component Materials



Furthermore, DSC results showed the absence of a crystalline melting peak for all formulations, as compared to the unmodified drug (Figure 2a and b). The DSC scans and the ASD samples showed single glass transition temperatures, indicating the amorphous API was homogeneously dispersed into the polymer. Glass transition temperature (Tg) of the ASDs decreased as ITR concentration increased, a consequence of the plasticizing effect of the drug on all three grades of HPMCAS. The shift in the drug-to-polymer ratio also contributed to lower Tg by increasing concentration of amorphous ITR and lowering polymer content.

Figure 2a. DSC Thermograms of Raw Materials: Crystalline ITR and HPMCAS

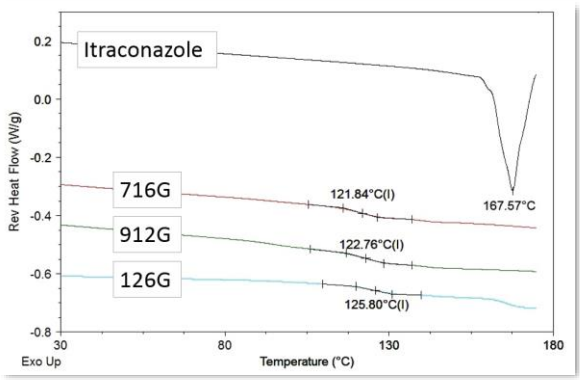
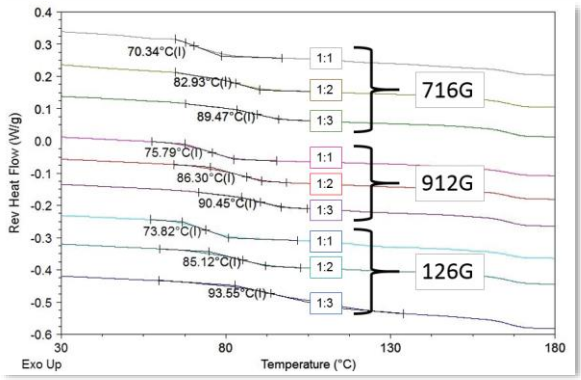


Figure 2b. DSC Thermograms of ITR ASD



ASD dissolution testing showed significant improvements in the rate and extent of ITR dissolution for formulations comprising HPMCAS grades 716G and 912G compared to the crystalline API or unprocessed physical mixtures. For example, ITR formulations comprising HPMCAS 716G released up to 90% of the dose after 45 min, while the comparable physical mixture released only 0.3% (Figure 3). As drug load increased, rate and extent of the release (solubility) decreased for all formulations (Table 1). Release rates at all drug-to-polymer ratios were faster for ASD based on HPMCAS 17G and slower for those based on HPMCAS 126G, which is likely due to the differing solubility of each polymer grade in this dissolution medium (pH 6.8). HPMCAS 126G provided negligible release at all formulation ratios due to its low solubility in media below pH 7.0.

Open-dish storage of the ASD formulations at 40°C/75% RH had moderate to negligible impacts on drug assay, total free acid content (Table 1) and solubility depending on HPMCAS grade and formulation ratio. The results for total free acid content were consistent with previous observations for pure polymers, indicating the minimal impact of HME on the polymer.[1] Release profiles (post-storage) of the 716G and 912G formulations with 1:3 drug-to-polymer ratio were slower in the early time points but still achieved a comparable extent of release (solubility) compared to the non-aged samples. Release profiles (post storage) from HPMCAS 716G and 912G formulations at higher drug loads (1:2, 1:1) resulted in similar profiles ($f_2 > 50$) to the initial results. SEM imagine of the particle surfaces at 900x magnification after stability storage showed no evidence of surface recrystallization of the drug for the lower drug loads (1:3, 1:2) and although some small artefacts were observed on the surfaces of the 1:1 particles, no extensive recrystallization was observed upon subsequent re-evaluation using XRPD or DSC (reappearance of pattern or melting peaks, respectively).

Table 1. Accelerated Stability Data for ITR ASD

Polymer Grade	API:Polymer Ratio	Initial			1 month (40°C/75% RH open dish)		
		Assay (%)	Free Acid Content (%)	Solubility @ 3 h (µg/mL)*	Assay (%)	Free Acid Content (%)	Solubility @ 3 h (µg/mL)*
716G	1:1	101.8	0.059	71.4	99.2	0.040	66.9
716G	1:2	103.5	0.113	87.8	100.9	0.080	82.9
716G	1:3	103.1	0.140	88.9	99.9	0.078	86.6
912G	1:1	101.1	0.060	41.2	99.9	0.049	40.1
912G	1:2	103.9	0.117	79.3	103.5	0.071	79.9
912G	1:3	106.0	0.131	91.0	103.8	0.098	91.3
126G	1:1	100.2	0.000	0.2	103.3	0.029	0.1
126G	1:2	102.0	0.053	0.4	99.5	0.046	0.5
126G	1:3	100.0	0.089	0.8	98.2	0.036	0.7

Figure 3. Dissolution of 716G ASD Formulations (100mg dose) vs. Physical Mixture Crystalline ITR

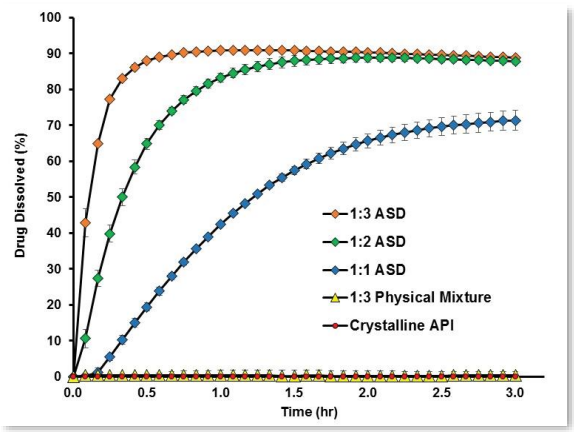
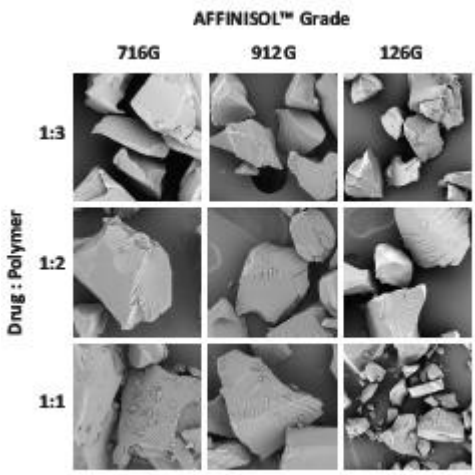


Figure 4. Particle Surface Appearance



Conclusions

HME processing enabled the production of itraconazole amorphous solid dispersions comprising AFFINSOL™ HPMCAS with a range of drug loading and significantly increased solubility over unprocessed physical mixtures. By varying the formulation composition in terms of drug load and HOMCAS grade, a wide range of product performance was achieved with respect to dissolution profiles and solubility enhancement while maintaining the drug in its amorphous form for 1 month under accelerated stability conditions.

References

1. Martin L., Mehta R., Rane M., Cunningham C. And Rajabi-Siahboomi A. Determination of processing window for hot melt extrusion and milling of hypromellose acetate succinate by assessing thermal degradation. AAPS 2017

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