Effect of Additives on the Behavior of Amorphous Solid Dispersion

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Introduction

Hypromellose acetate succinate (HPMCAS) is frequently used for producing amorphous solid dispersions (ASDs) via spray drying. There is increased interest in its potential application for amorphous solid dispersions using hot-melt extrusion (HME) process; however, HPMCAS may not easily extrude due to the high torque generated during the extrusion process. The purpose of this study was to evaluate the effect of selected additives (organic acids, surfactants, and secondary polymers) to increase the extrudability of HPMCAS, as well as the chemical and physical behavior of final ASDs.

Methods

Three organic acids, three surfactants, and five secondary polymers were selected for this study (Table 1). ASD of itraconazole (ITR), HPMCAS and additives were prepared by HME using a twin-screw extruder (Pharma 11, ThermoFisher) at a temperature of 170°C, using a screw speed of 50 rpm, with a 2.0 mm strand die. The extrudates were air-cooled, pelletized, and milled (ZM 200, Retsch) into powder. Bulk density and tap density of milled extrudates were measured. Particle size distributions of the milled extrudates were determined using laser diffraction (Mastersizer 2000, Malvern Instruments Ltd). Loss on drying (LOD) was measured by infrared moisture analyzer (MA37-1, Sartorius) at 105°C, dried to a constant weight. Glass transition and thermal decomposition temperatures of the unprocessed polymers were determined using differential scanning calorimetry (DSC; Q200, TA Instruments) and thermogravimetric analysis (TGA; Q500, TA Instruments), respectively. FTIR spectra and XRD diffractogram were measured by FTIR spectrometer (NicoletTM iSTM10, ThermoFisher) and X-ray diffractometer (ARLTM EQUINOX 100, ThermoFisher). Images of all raw materials and milled extrudates were taken using scanning electron microscopy (SEM, Phenom XL, ThermoFisher). Dissolution tests were performed in 1000 ml phosphate buffer pH 6.8 using paddle apparatus at 75 rpm.

Table 1. Composition (%) of HME Blends

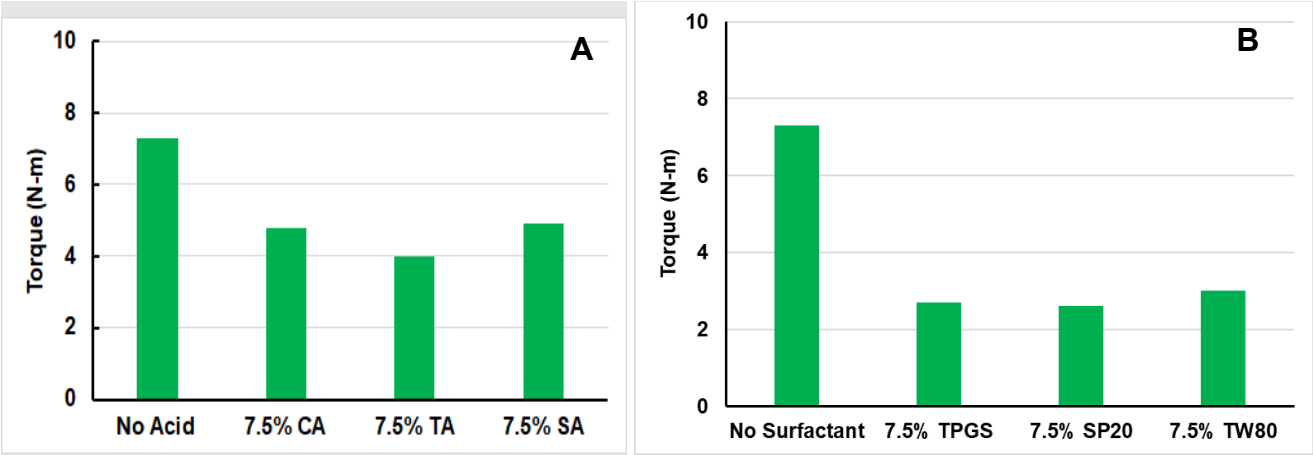
Ingredients	Only Primary Polymer (OP)	Secondary Polymer (SP)	Organic Acid (OA)	Surfactant (SF)
Itraconazole	25.00	25.00	25.00	25.00
Primary Polymer: HPMCAS 912G (medium substitution)	75.00	67.50	67.50	67.50
Organic Acid: **- Citric acid (CA)** **- Tartaric acid (TA)** **- Succinic acid (SA)**	-	-	7.50	-
Surfactant: **- Vitamin E TPGS** **- Span 20** **- Tween 80**	-	-	-	7.50
Secondary Polymer: **- HPMC (AFFINSOL, HPMC HME)** **- HPMCAS 716G (low substitution)** **- Soluplus**	-	7.50	-	-

- Kollidon VA 64 - Parteck MXP - PVA				
Total	100.00	100.00	100.00	100.00

Results

All formulations were extruded at 170ºC. The addition of organic acids and surfactants showed a substantial reduction of torque compared to ITR-HPMCAS only formulation (Figure 1. A & B). The effect of secondary polymers varied amongst the polymers used in this study (Figure 1. C). All physical mixtures showed a higher or similar amount of moisture compared to milled extrudates. Overall, the results could be attributed to the non-hygroscopic nature of HPMCAS. The average particle size of the extrudates containing organic acid was similar or lower compared to those of ITR-HPMCAS alone; the opposite was seen when a surfactant was included in the extrudates. No clear trends were observed when a secondary polymer was included in the blend. The higher particle size was due to the elasticity of extrudates; the lower particle size was attributed to brittle extrudates. Both DSC and XRD data confirmed the presence of amorphous ITR in milled extrudates (Figure 2, 3). FTIR was performed to evaluate the interactions between different components of formulations, and it showed the disappearance of the carbonyl peak at 1697 cm-1, which is attributed to hydrogen bonding between drug and polymer. Interestingly, the inclusion of additives did not change ITR transmittance compared to the formulation without organic acid (Figure 4). Figure 5 shows the dissolution profiles of different formulations; the only formulations with TA showed a lower drug release rate. All other formulations with additives showed a higher rate of drug release. However, the formulation without additives showed the highest extent of itraconazole release.

Figure 1. Torque Outputs: ITR + HPMCAS + Additives: (A) Organic Acids (B) Surfactants (C) Secondary Polymers



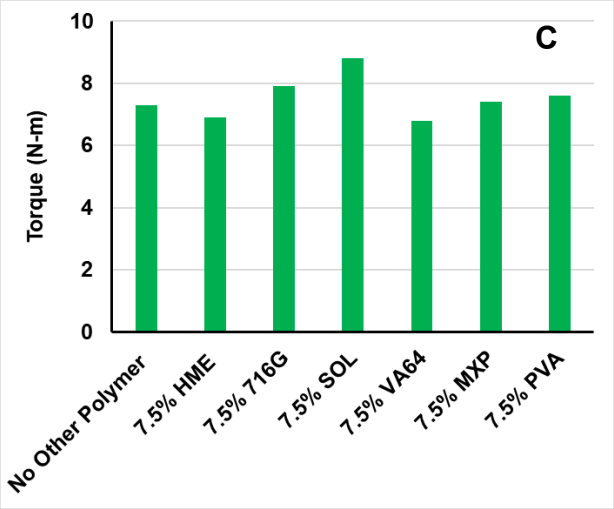

C
Torque (N-m)
10
8
6
4
2
0
No Other Polymer
7.5% HME
7.5% 716G
7.5% SOL
7.5% VA64
7.5% MXP
7.5% PVA

Figure 2. DSC Thermogram: ITR + HPMCAS + Additives: (A) Organic Acids (B) Surfactants (C) Secondary Polymers

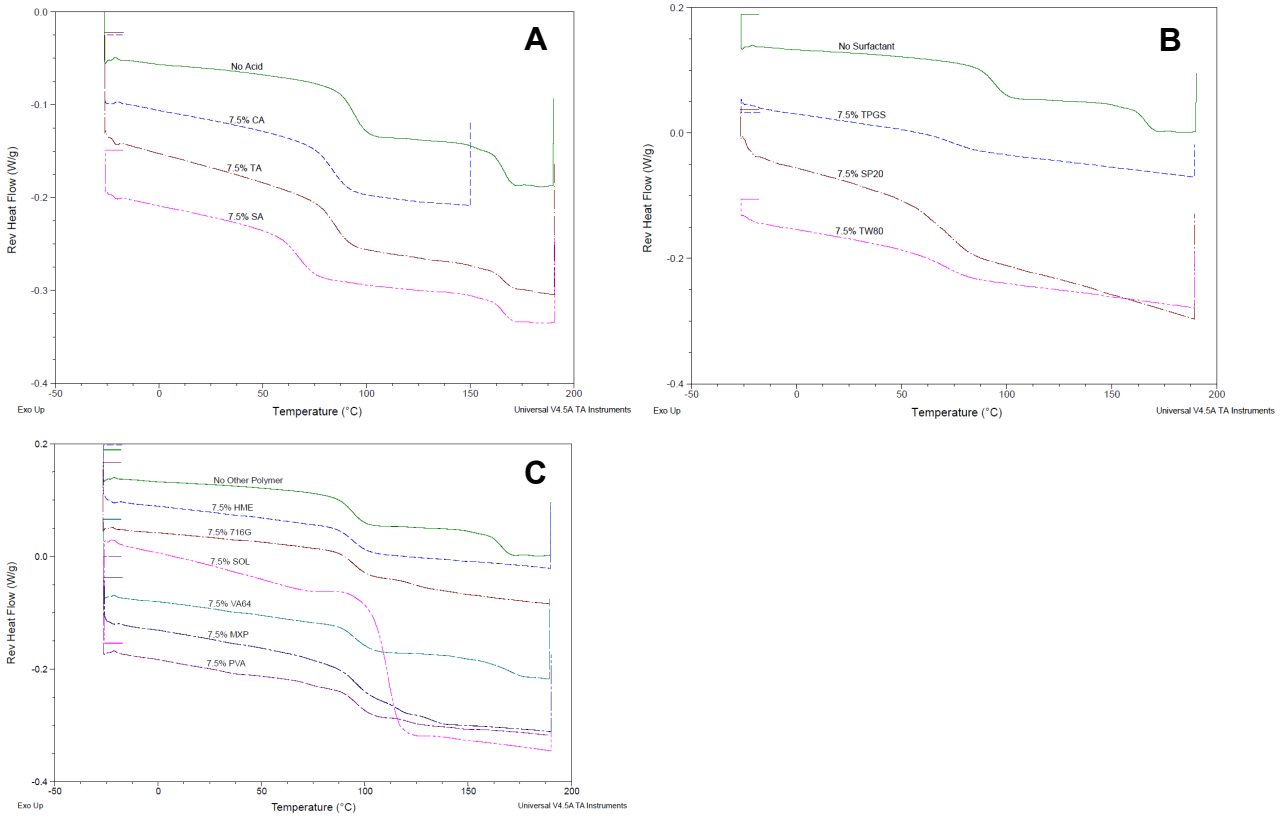
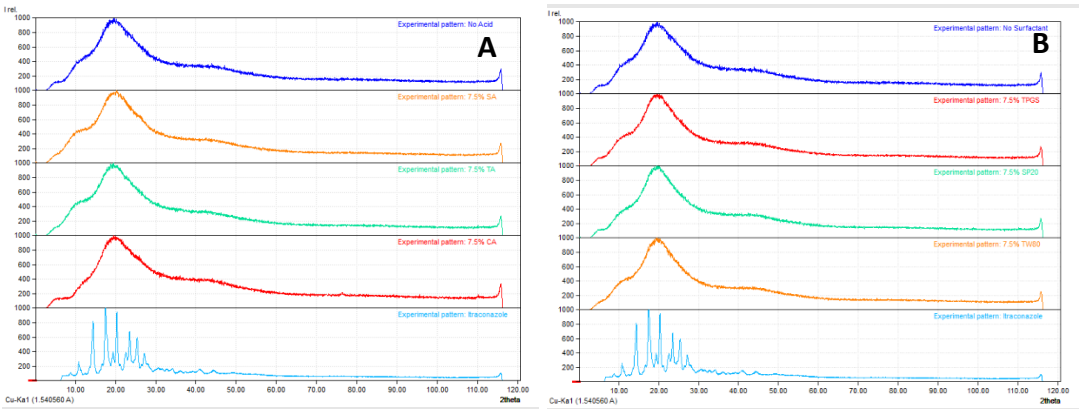


Figure 3. XRD Diffractogram: ITR + HPMCAS + Additives: (A) Organic Acids (B) Surfactants (C) Secondary Polymers



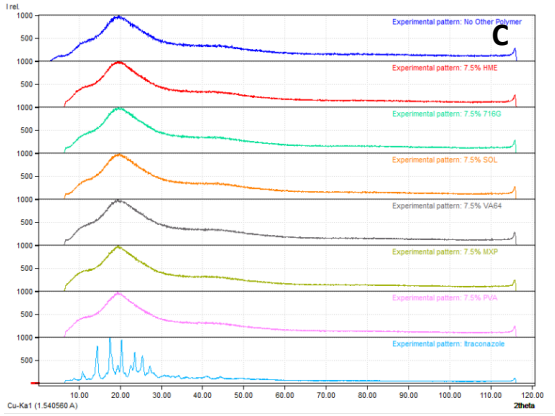


Figure 4. FTIR: ITR + HPMCAS + Additives: (A) Organic Acids (B) Surfactants (C) Secondary Polymers

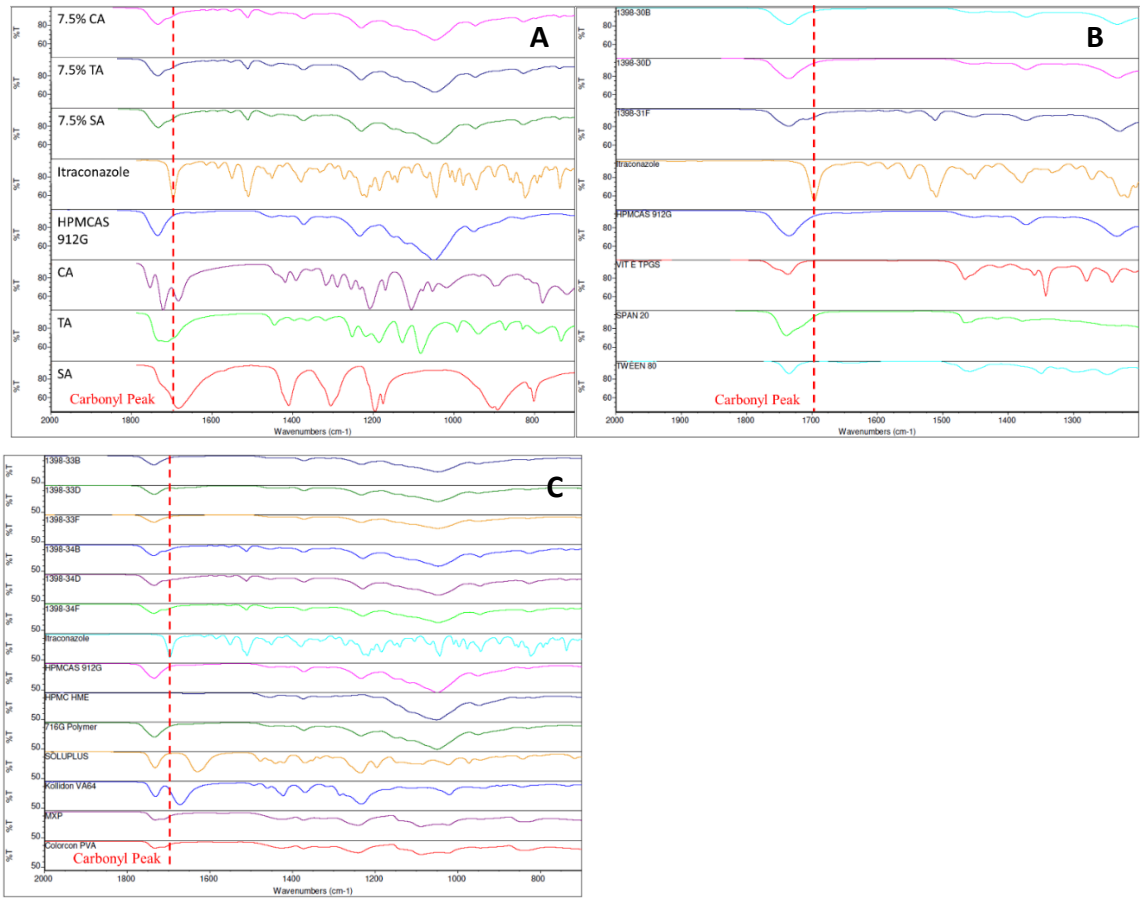
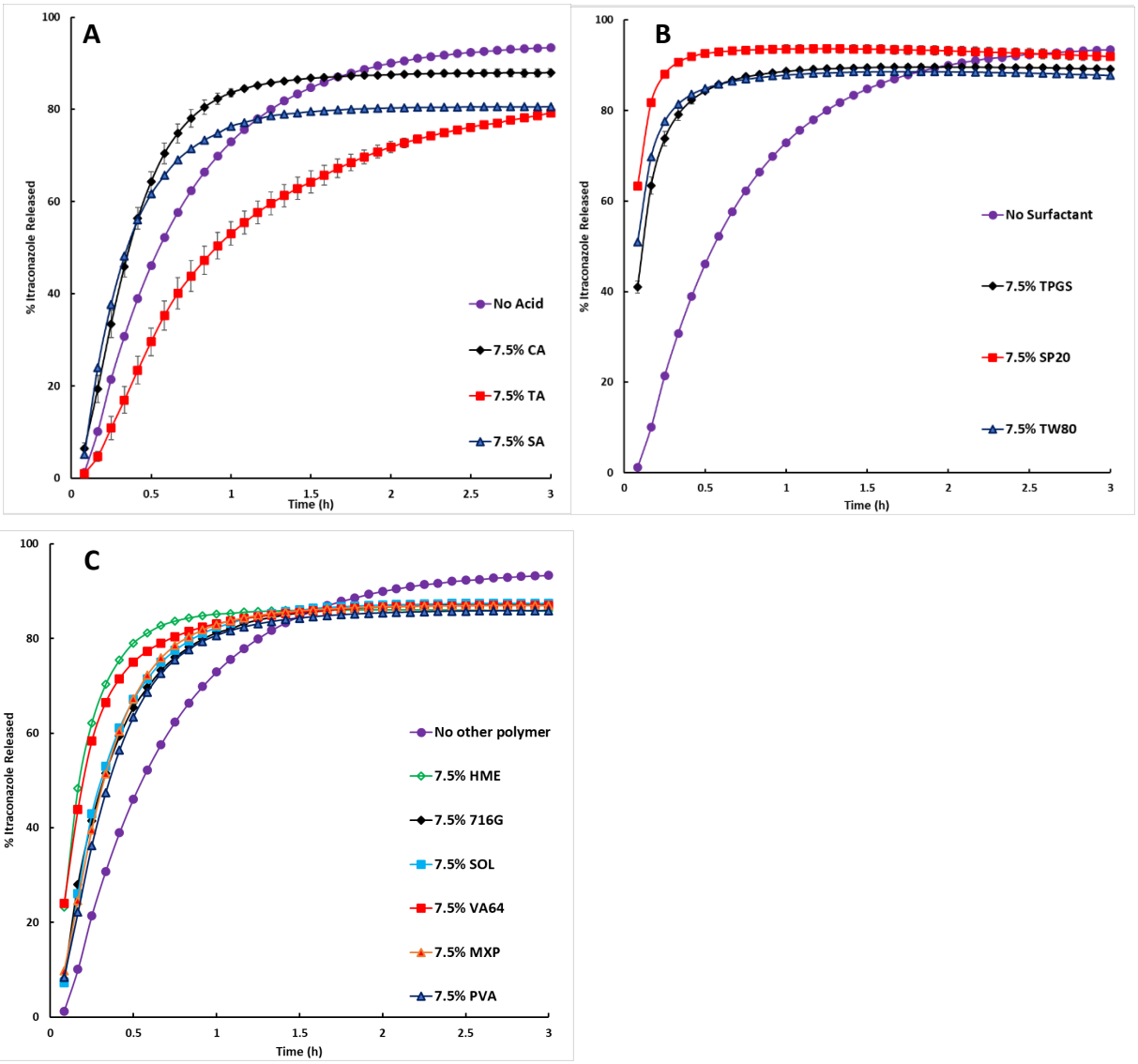


Figure 5. Dissolution Profile: ITR + HPMCAS + Additives: (A) Organic Acids (B) Surfactants (C) Secondary Polymers



Conclusions

This study demonstrated that the inclusion of different additives (organic acids, surfactants and secondary polymers) improved the extrudability of HPMCAS 912G with the API (itraconazole). Solid state characterization techniques confirmed the presence of itraconazole in an amorphous form. Inclusion of additives affected the elasticity of extrudates, which ultimately influenced their milling behavior. The presence of most additives to the formulations enhanced the rate of drug release, and this behavior could help to modulate the initial rate of drug release.

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