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Thermal and Compaction Behavior of Spray-Dried Itraconazole-HPMCAS Dispersions

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PURPOSE

Hydroxypropyl methylcellulose acetate succinate (HPMCAS), an anionic polymer, demonstrates wide applicability in drug delivery. It can be used as a carrier for amorphous spray-dried dispersions (SDDs) and thus enhance the solubility of BCS Class II compounds (e.g. Itraconazole (ITZ)). However, the grades of HPMCAS and drug loadings can play roles in formulating. The aim of this study was to assess the influence of the grades of HPMCAS and drug loadings on the thermal and compaction profile.

METHODS

- **Materials:** The model drug, ITZ, was purchased from Letco Medical. HPMCAS L and H grades were purchased from Ashland.
- **Preparation of SDDs:** ITZ and HPMCAS dispersions were spray dried using Buchi mini spray dryer B-290. HPMCAS (L or H) was dissolved in a 2:1 (w/w) mixture of dichloromethane and methanol. ITZ was then added to the solutions to constitute 10 and 30% (w/w) of the total solid content in the solution. The total solid concentrations in the final solutions were 10% (w/w). The solutions were pumped into the atomizer at a rate of 16 g/min. The inlet and outlet temperatures were maintained at 100 and 56°C, respectively. The atomizing gas was set to 40.
- **Thermo analysis:** The glass transition (Tg) of ITZ was analyzed using a Discovery DSC 2500 by heating to 200°C at 10°C/min under nitrogen purge (50 mL/min) and Tg was the midpoint of the transition. Decomposition temperatures (Td) of SDDs were obtained using TGA 5500 at a heating rate of 10 °C/min from 30 to 500 °C under a constant flow of nitrogen (25 mL/min).
- **Particle size distribution and true density:** Laser diffraction was utilized to measure the particle size by using a Master Sizer-2000 optical laser diffraction system. True densities of SDDs and spray-dried ITZ were measured using a helium pycnometer Accupyc 1330.
- **Compression methods:** The compaction properties were tested by using a Styl'One compaction simulator (Medelpharm, France). 25, 50, 75 and 100 MPa compression pressures were applied under 5 mm/sec compaction velocity. Five replicate tablets were made and tested for each compression pressure. After compression, each tablet was weighed and measured for thickness and breaking forces with the use of MT50 hardness tester immediately following ejection. Tabletability, compressibility, compactability, elastic recovery and Heckel analysis were analyzed using the Analis™ software.

RESULTS

According to the particle size distribution, the results show that the order of decreased d50 is: 30% L > 10% L > 30% H > 10% H. The true densities of 10% SDDs are smaller than the SDDs with 30% drug loading (Table 1).

Table 1: Particle size distribution and surface area of each SDD

Drug loading percentage / grade of HPMCAS	Particle size distribution (um)			True density (g/cm^3)	Tg (°C)	Td (°C)
	d(0.1)	d(0.5)	d(0.9)			
10% L	2.68	14.31	41.69	1.33	82.69	374.86
10% H	2.51	10.62	32.82	1.30	77.85	382.43
30% L	3.07	16.09	45.79	1.35	72.93	384.23
30% H	2.71	12.88	41.24	1.33	74.42	388.68
Spray dried ITZ	2.9	13.39	44.27	1.32	Melting T = 171.2	381.07

The DSC results indicate that the order of decreased Tg is: 10% L > 30% L > 10% H > 30% H, while the TGA shows that the order of decreased Td is just the opposite: 30% H > 30% L > 10% H > 10% L (Tablet 1). The DSC and TGA plots are shown in Figure 1.

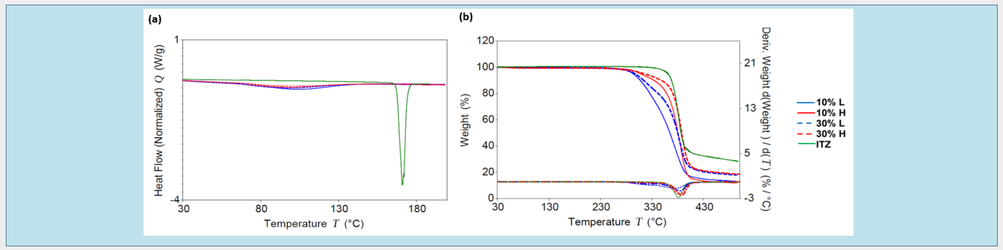

Figure 1: (a) DSC and (b) TGA plot of SDDs and spray-dried ITZ

In the compaction study, an increase in tensile strength of all the materials directly correlated with an increase in compression force. The order of increasing tensile strength formulations with an increase in compression force was 10% L > 10% H > 30% L > 30% H. According to the compressibility results, the compact porosity of four SDDs decreased with an increase in compression force. The compressibility profiles of SDDs appeared to have undergone volume reduction to a similar extent. The compactibility study shows that the compact tensile strength increased, and porosity decreased with an increase in compression force. It was observed that with the same drug loading, "L" SDDs exhibited better compactibility at low compression pressures than "H" SDDs. "L" SDDs also showed the higher elastic recovery compared with "H" SDDs. All SDDs showed similar trends in Heckel analysis (Figure 2).

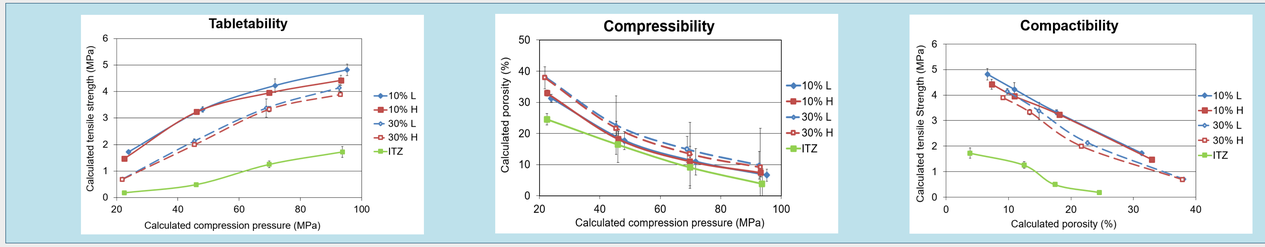

Figure 2: Compression profiles of SDDs and spray-dried ITZ: effect of compression force on (a) tabletability, (b) compressibility and (c) compactibility

CONCLUSIONS

- Thermal analysis results showed the SDDs with 10% of drug loading have slightly higher glass transition temperature but lower decomposition temperature.
- Compaction study has shown that with the same drug loading, "L" SDDs had higher Tg, lower Td and lower true density compared with "H" SDDs.
- Meanwhile, "L" SDDs showed slightly better tabletability at high compression pressure (75 and 100 MPa), higher compactibility at low compression pressure (25 and 50 MPa), and higher elastic recovery. These differences may due to the particle size differences and the interactions between API and different grades of HPMCAS.
- Each SDD exhibited similar compressibility and mean yield pressure. With the same grade of HPMCAS, the SDDs with 30% of drug loading showed lower tabletability, compactibility and elastic recovery which correlated to the natural property of ITZ.

REFERENCE

Roberts, M., et al., The effect of spray drying on the compaction properties of hypromellose acetate succinate. Drug Dev Ind Pharm, 2011. 37(3): p. 268-73.

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