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Formulation and Delivery - Chemical

Category: Poster Abstract

(T1230-04-19) Effect of Polymers and Drug Loadings on the Performance of Itraconazole Spray-Dried Dispersions (SDDs)

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Purpose: Amorphous solid dispersions (ASD) are a proven method of improving the solubility and bioavailability of poorly soluble drugs. Immediate-release tablets are frequently used as the final dosage form for ASDs. Thus, polymer and drug loading selection is critical for the manufacturability and bioavailability of ASD tablets. In this project, ASDs were prepared using the spray drying; ASD tablets were made using a

compaction simulator. The influence of polymer types and drug-polymer ratios on bulk powder properties, compaction behavior, and physical stability of ASDs were examined. Itraconazole (ITZ) was used as model drugs, and two polymers were used: hydroxypropyl methylcellulose acetate succinate (HPMCAS) and polyvinylpyrrolidone (PVP).

Methods: Materials - The model drug, ITZ, was purchased from Letco Medical. PVP was purchased from BASF Japan Ltd. HPMCAS L was purchased from Ashland. Spray drying solvents - dichloromethane and methanol (HPLC grade) were obtained from Sigma-Aldrich and Thermo Fisher. Spray-drying method: Dispersions were spray-dried using Buchi mini spray dryer B-290. ITZ was dissolved in the solvent, followed by the addition of the polymer. The drug loadings were 10, 30, and 50% (w/w) of the total solid content, see Table 1. Powder properties and compaction methods: Particle size distribution, surface area, bulk density, and true density of spray-dried dispersions were measured using USP paddle methods. Scanning Electron Microscopy (SEM) images were acquired using a Quanta 200 (FEI. Co; Hillsboro, OR) under the conditions specified in the images. The compaction properties were tested using the Styl'One compaction simulator at compression pressures ranging from 25 to 125 MPa at a 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 using an MT50 hardness tester immediately following tablet ejection. Tabletability, compressibility, and compactability were analyzed using the Analis™ software. Physical stability: Physical stability studies were conducted under 75% RH at 40 °C. The powder X-ray diffraction (XRD) was used to detect the potential crystallization of spray-dried dispersions.

Results: Powder characterization of ASDs: Each type of ASD has similar particle size distribution, bulk density, and true density (Table 1). It was observed that the surface area increased with decreasing the drug loadings for ITZ – HPMCAS solid dispersions. However, there is no change in surface area when increasing drug loading in ITZ dispersions with PVP. The itraconazole dispersions with PVP exhibit collapsed spheres for all three drug loadings (Figure 1). While ITZ – HPMCAS dispersion with 10% drug load have wrinkle surface, and ITZ – HPMCAS dispersions with 50% drug load are round spheres. This explains the differences in surface area. Compaction Study: We observed that ITZ solid dispersions with PVP have lower tabletability and higher compressibility than dispersions with HPMCAS (Figure 2). ASDs with PVP have larger ejection force and low elastic recovery due to the nature of PVP polymer. For ITZ – HPMCAS dispersions, the tabletability decreased with increasing the drug loading. However, in the ITZ dispersions in the presence of PVP, the drug load does not influence tabletability. The multivariate linear regression analysis confirms that the tabletability of ITZ – PVP dispersions does not change with increasing the drug load. We used partial least square analysis to reveal the correlation between polymer properties and tensile strength. The result indicates that particle surface area was the most significant factor attributed to the tensile strength of ASD tablets. The multivariate linear regression analysis shows that compared with solid dispersions containing HPMCAS, the ones with PVP have lower tabletability, compatibility, and elastic recovery, but higher compressibility. There is no significant influence of the

drug loading on compressibility, compatibility, and elastic recovery of ASDs ($p > 0.05$). Physical stability: The potential crystallization of ASDs was investigated by powder XRD. The results suggest that ITZ ASDs in the presence of HPMCAS were stable after 2-months for all drug loadings that were tested. However, for ITZ ASDs with PVP, the 30% and 50% drug loading samples crystallized after 2 weeks. The results suggest that PVP is not sufficient for enhancing amorphous itraconazole stability, which may be due to weak drug–polymer interactions.

Conclusion: The results indicated that the tabletability increased along with decreasing drug loadings for ITZ dispersions with HPMCAS, while the drug load does not influence the tabletability of ITZ-PVP ASDs. Multivariate analysis revealed that particle surface area was the most significant factor attributed to the tensile strength of ASD tablets. The results and inferences drawn from this project will provide valuable insights into ASD formulation selection for downstream tablet formulation development.

ITZ ASDs						
% of drug loading + Polymer type	Particle Size Distribution (μm)			Bulk density (g/cm^3)	Surface area (m^2/g)	True density (g/cm^3)
	d (10)	d (50)	d (90)			
10% HPMCAS	2.68	12.31	41.69	0.17	3.68	1.33
30% HPMCAS	2.56	13.12	37.93	0.16	1.35	1.35
50% HPMCAS	3.07	14.79	45.79	0.16	0.53	1.31
10% PVP	1.78	6.34	16.44	0.21	1.34	1.28
30% PVP	1.61	6.07	15.01	0.22	1.37	1.30
50% PVP	1.69	6.02	14.94	0.21	1.05	1.27

Table 1 Particle size distribution, bulk density, true density, and surface area of spray-dried dispersions with ITZ.

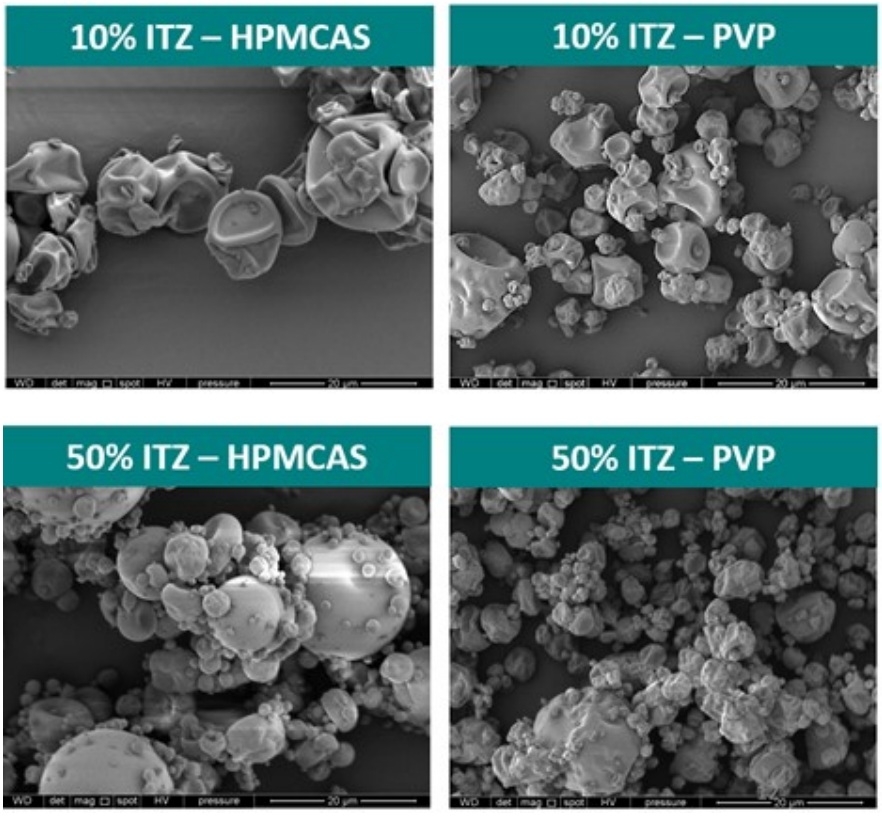

Figure 1: SEM images of ASD powders.

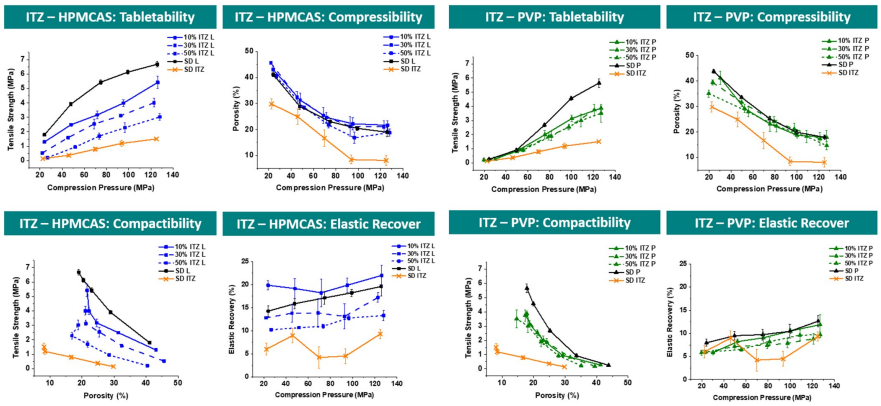

Figure 2: Compaction profiles of ASDs containing itraconazole with blue: HPMCAS and green: PVP K30 (and corresponding spray-dried polymers). n=5.