Comparison of amorphous films and spray dried dispersions of itraconazole and HPMCAS

M. Honick[1], S. Sander[2], B. Cai[2], G. Hollenbeck[1], S. Hoag[1], J. Polli[1]
[1]University of Maryland, [2]U.S. Food and Drug Administration

Background: Compounds with poor water solubility, such as itraconazole (ITZ), present significant challenges to formulators. Converting the crystalline form of the drug into amorphous spray dried dispersions (SDDs) with a polymer carrier such as hypromellose acetate succinate (HPMCAS) is one strategy that can improve their solubility and bioavailability. However, spray drying is a time and resource-intensive process. Film-casting is a potentially time and resource-sparing method to screen drugs and polymers for SDDs, although its predictive value is not fully described. For this study, we compared the solid state characteristics and dissolution profiles of amorphous films and SDDs consisting of itraconazole and one of three grades of HPMCAS: L, M, and H. The objective of this study was to evaluate the usefulness of film casting as a tool with which to screen materials for spray drying feasibility.

Methods: Solutions containing 10% solids (HPMCAS and ITZ) in 2:1 (w/w) dichloromethane and methanol were prepared for both film casting and spray drying. Film casting was performed by pouring the solutions into round 121 mm diameter aluminum pans (50g/pan) and allowing the solvent to evaporate for 45 min. The pans were then transferred to a drying oven and dried at 40°C for over 12 hr. Spray drying was performed using a Buchi B-290 spray dryer in closed-loop mode. Solutions were pumped into the spray nozzle at a rate of 17 g/min. The inlet and outlet temperatures were 100 and 56°C, respectively. SDDs were then collected and stored at 40°C for 12 hours. Both films and SDDs were analyzed by polarized light microscopy (PLM), scanning electron microscopy (SEM), and differential scanning calorimetry (DSC). Dissolution testing was performed on capsules containing ground films and tablets containing SDDs. Tablets were prepared by blending SDDs with 30% silicified microcrystalline cellulose, 4% sodium starch glycolate, and 0.5% magnesium stearate by shaking. The blend was dry granulated under 8 MPa pressure using a Natoli NP-RD10A press. The slugs were then ground by trituration, and the powder collected after passing through a #100 (150 µm) mesh sieve. The powder was then compacted under 40 MPa to produce cylindrical tablets (1.27 cm diameter) containing 100 mg of ITZ and 763 mg total weight. Dissolution testing was performed with USP paddles at 100 RPM in 900 mL SIF (pH 6.8) without enzyme. Samples were collected at 10, 20, 30, 45, 60, and 90 minutes, passed through 0.45 µm syringe filter and analyzed by HPLC.

Results: Visual observation of films revealed greater opacity with increased drug load. Examination of films and SDDs under PLM confirmed the presence of crystallinity in films. SEM images of the SDDs revealed “shriveled raisin” morphology, while neat ITZ powder showed a crystalline morphology. DSC confirmed that increased drug load resulted in increased crystalline content in films. Greater crystalline content was observed in films containing HPMCAS-H compared to HPMCAS-L and HPMCAS-M (Figure 3). No crystallization was detected in any of the SDD samples. Storage at 40/75 for 28 days did not result in significant changes in the crystalline content of films and SDDs. The SDD-containing tablets achieved faster and more complete dissolution compared to the films. However, a dissolution rank order of HPMCAS-L> HPMCAS-M> HPMCAS-H was observed for both SDDs and films (Figure 4).

Conclusion: In general, SDDs outperformed films, both in terms of amorphous content and dissolution. The differences between films and SDDs were more pronounced at higher drug load (i.e. - 30% ITZ). However, film casting was successful in predicting the feasibility of producing ITZ:HPMCAS SDDs and in identifying the optimal polymer grade (HPMCAS-L).