Tablet formulation of itraconazole and HPMCAS spray dried dispersions

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Background: Formulating spray dried dispersions (SDDs) into solid oral dosage forms presents numerous challenges. SDDs contain small particles and have very low bulk density making SDDs unsuitable for direct compression or direct filling of capsules. Dry granulation, by roller compaction or slugging, is generally necessary to densify the SDD. However, dry granulation has the potential to impact the compactibility of the material. These challenges are further compounded by the drug's poor solubility and propensity to precipitate from solution.

Objective: The aim of this study was to assess the effects of HPMCAS grade, drug load, slugging pressure, and compaction on the mechanical strength and dissolution of tablets.

Methods: A mixed-level fractional factorial design of experiments (DOE) was utilized where drug load was varied at 20 and 30%, slugging pressure was varied at 20 and 40 MPa, and polymer grades were HPMCAS-L, HPMCAS-M, or a 1:1 ratio of HPMCAS-L and HPMCAS-M. All formulations were then compacted into tablets with 70, 85, and 100 MPa of compaction pressures for a total of 24 runs. The overall process for all formulations was as follows: SDDs were blended with silicified microcrystalline cellulose (SMCC), magnesium stearate, and sodium starch glycolate (SSG) totaling 65.5% SDDs, 30% SMCC, 4% SSG, and 0.5% magnesium stearate. The blend was dry granulated by slugging using a STYL'One compaction simulator with flat round 11.28 mm diameter tooling. The slugs were then milled by trituration until able to pass through a #100 mesh sieve. The granules were then compacted into tablets with 70, 85, or 100 MPa of pressure using the STYL'One compaction simulator with oblong 0.4 x 0.75". Dissolution experiments were performed using paddles at 100 RPM, and USP SIF w/o enzyme (pH 6.8). Samples were collected at 10, 20, 30, 45, 60, 90 and 120 minutes, filtered through a 0.45 µm syringe filter and analyzed by UPLC-FLR. Tablet mechanical strength was measured using a Dr. Schleuniger Pharmatron MultiTest 50 tablet hardness tester (SOTAX, Aesch, Switzerland).

Results: Two factors generally contributed to dissolution profile performance: disintegration and solution thermodynamic factors. In general, thinner tablets (resulting from higher drug load), tablets containing HPMCAS-M, and tablets with lower tensile strength (resulting from higher slugging pressure and lower compaction pressure) disintegrated more rapidly. Once fully disintegrated, solution thermodynamics were the predominant factor determining dissolution profile. Tablets with HPMCAS-L reached the greatest extent of dissolution. The dissolution differences between polymer grade were more evident at 30% drug load, with tablets containing the HPMCAS-M more adversely impacted by higher percent drug load.

Conclusion: Formulation and process effects impacted dissolution profile via disintegration and solution thermodynamic effects.