Preparation and Characterization of Spray-Dried Powders of Voriconazole and Calcium Phosphate Nanoparticles for Pulmonary Administration

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Purpose
The objective of this study was to investigate the use of calcium phosphate nanoparticles as a novel excipient in spray-dried formulations of voriconazole with mannitol and/or leucine for pulmonary administration. In addition to characterization of the aerosol performance of the formulations, in vitro drug release was analyzed for comparison.

Methods
Nine batches of spray-dried powders were prepared using three levels of calcium phosphate nanoparticles, including 0.05, 0.1, and 0.2 mass ratio of nanoparticles to voriconazole. All of the powders were prepared with 50% drug loading, and either mannitol, leucine, or a 1:1 mixture of the two. The 1% (w/v) mixtures were prepared in 40:60 (v/v) ethanol:water and spray-dried using a Buchi mini-spray dryer model B-290 with 150°C inlet and 80°C outlet temperature. The solution feed rate was 3.5mL/min, aspirator at 100%, and air pressure at 7bar. The yield of the spray-drying process was determined by mass, as was fast screening impaction for aerosol performance including emitted dose, fine particle dose (≤5µm), and respirable fraction, with samples delivered using a Plastiape RS-01 medium resistance device at 60LPM. Particle size distribution was determined by laser diffraction using a dry cell with sample introduction using the same dry powder device and flow. In vitro drug release was determined using Franz cells with 25mm 0.45µm Tuffryn membranes and pH 7.4 PBS with 0.2% (w/v) Polysorbate80, maintained at 37°C. 180µL release samples were removed at 15, 30, 45, 60, 90, 120, and 180 minutes with media replacement, and diluted for HPLC assay. The membranes for in vitro drug release were loaded with ~1mg of powder using the second stage of a modified impactor, as emitted from the RS-01 dry powder inhaler. Solubility of the drug in the dissolution medium at 37°C was measured to verify sink conditions. Assay, potency, and purity analyses were performed using isocratic or gradient HPLC, respectively on C18 columns, with mobile phases consisting of 0.1% TFA (v/v) in water or acetonitrile, and a wavelength of 257nm.

Results
Yields for the nine powders were in the range of 51.4 – 73.4%. By fast screening, the emitted dose ranged from 64.6% (±7.2) to 86.9% (±1.7), while the respirable fraction (%loaded dose ≤5µm) was 22.6% (±2.7) to 23.2% (±1.1) for mannitol-only formulations and 44.1% (±4.2) to 54.4% (±3.5) for the other powders. Particle size distribution in a dry cell using inhaler introduction resulted in median volume diameters of 13.92µm (±0.70) to 16.03µm (±1.69) for mannitol-only formulations, 9.94µm (±0.44) to 11.69µm (±0.93) for leucine-only formulations, and 9.02µm (±0.83) to 9.82µm (±0.50) for the remaining powders. The percentage of volume <5µm was 10.8% (±1.5) to 12.3% (±2.1) for mannitol-only formulations, 19.6% (±1.6) to 23.8% (±1.5) for leucine-only formulations, and 23.0% (±1.2) to 25.3% (±3.8) for the other powders. No trends were noted for potency of the powders, which were between 42.4 and 48.4% versus 50% target. For in vitro release testing insufficient loading due to poor aerosolization was noted for the 0.05 and 0.1 calcium phosphate nanoparticle-mannitol powders and were therefore excluded. In contrast, the 0.2 nanoparticle-mannitol formulation had the fastest release observed at 559.9µg/cm2/hr0.5 (±53.7), while the 0.05 nanoparticle-leucine powder had the slowest release observed at 155.9µg/cm2/hr0.5 (±21.2). Release for the remaining powders indicated an increasing trend with increased nanoparticle ratios, particularly for the mixed leucine and mannitol powders, with release increasing from 272.9µg/cm2/hr0.5 (±25.3) at the 0.05 nanoparticle level to 443.1µg/cm2/hr0.5 (±83.4) at the 0.2 nanoparticle level. Voriconazole solubility in pH 7.4 PBS with 0.2% (w/v) Polysorbate 80 was measured as 911µg/mL, verifying sink conditions for up to ~1.5mg of voriconazole in 5mL of medium. Overall drug release was slowed by leucine, and enhanced by calcium phosphate nanoparticles.

Conclusion
The incorporation of calcium phosphate nanoparticles in spray-dried voriconazole formulations affected aerosol performance of the powders and in vitro release of the drug, as did the choice of excipients.