Effect of Process Variables on Aerodynamic Properties of Voriconazole Formulations Produced by Thin Film Freezing for Dry Powder Inhalation

Nicole A. Beinborn and Robert O. Williams III
Pharmaceutics Division, College of Pharmacy, The University of Texas at Austin, 1 University Station A1920, Austin, TX 78712

Background

- Attention has begun to focus on pulmonary delivery of antifungal agents as inhalation is a frequent route of administration in the treatment of invasive pulmonary aspergillosis.
- Voriconazole is a second-generation, broad-spectrum, triazole antifungal agent primarily prescribed for the treatment of invasive pulmonary aspergillosis.
- Large porus particles have been shown to improve the fine particle fraction emitted from dry powder inhalers compared to micronized particles, thus increasing the amount of drug that deposits in the lungs.
- Physical properties of voriconazole: Molecular weight = 349.3 g/mol, Poorly soluble in water, Insoluble in chloroform.
- Pharmaceutical properties: Insoluble in water, Insoluble in chloroform.
- Objective: Focus on particle engineering to produce voriconazole formulations suitable for dry powder inhalation and to evaluate the effects of various process parameters on the aerodynamic properties of the resulting formulations.

Materials

Voriconazole (VRC)
Polyvinylpyrrolidone (PVP)
Grades: K12 and K30
Solvents: 1,4-dioxane
Water

Methods

- Thin Film Freezing (TFF) Process:
  - Dissolve API (VRC) in organic or non-ionic aqueous solvent systems (e.g., freeze solvent on dropletwise over rotating organic solvent surface to produce fine particles).
  - Collect in liquid nitrogen to solidify the material.
  - Remove by lyophilization yields highly porous, aerodynamic particles.

- Brunauer-Emmett-Teller Specific Surface Area (BET) Surface Area
  - Monosieve 21 BT adsorption apparatus was used to measure SSA by single point measurement at P/P0 = 0.04.
  - Samples were degassed for at least 2 h under nitrogen purge at 26 psi.

- Aerodynamic Particle Size Analysis
  - Handi Spray DPL Next Generation Pharmaceutical Impactor (NGI)
  - Powder filled into size 3 HPMC capsules
  - DPL actuation cycles 60/minute, flow rate of 4 L/min.
  - NGI collection plates coated with 1% w/v polyethylene glycol 400 in ethanol to prevent particle bounce, fracture, and entrapment.
  - NGI collection filters were dried in an oven at 60°C for 24 h under vacuum.

- Emitted Fine Particle (FFP) percentage of drug emitted from each formulation was calculated as a percentage of drug collected at each impactor stage.

Results

- Textural and aerodynamic properties of voriconazole particles are determined.
- SSA is measured using BET apparatus.
- Aerodynamic particle size is determined using DPL and NGI apparatuses.
- Fine particle fraction is calculated as a percentage of drug collected at each impactor stage.

Discussion

- This thin film freezing process uses a PVP solution in ethanol, acetonitrile, and water compositions to produce voriconazole particles with a primary particle size of approximately 100 nm.
- The SSA of the API and the API/PVP formulations were determined.
- The aerodynamic properties of voriconazole particles were measured.
- Overall, the data indicates that SSA may have the greatest influence on FFp as the formulations displaying the most aerodynamic properties (higher FFp and lower SSA) have the lowest SSA.

Conclusions

- Formulated particles with enhanced properties containing voriconazole were successfully produced by the TFF process.
- Formulation of voriconazole by TFF with or without PVP resulted in low density, lightest particles that could be bead-like in size and suitable for delivery by the dry powder inhaler. These particles display significant advantages over traditional voriconazole formulations.
- Composition, solvent, and pressure of dissolved solids in the liquid feed solution significantly affected the morphology and aerodynamic properties.

References

- Buchanan, C.M., N.L. Buchanan, K.J. Edgar, and M.G. Ramsey, Solubility and dissolution studies of amorphous

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