Platform Formulation Development Using a Novel Pulmonary Excipient and In Vivo Evaluation of a Model Formulation of Fluticasone Propionate

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Introduction

It is challenging to formulate carrier-based dry powders of even optimal active pharmaceutical ingredient (API) forms for pulmonary delivery that:

• deliver a high fraction dose to the lung reproducibly, and
• control content uniformity and deliver dose well, especially in combination therapies.

API forms with poor properties (i.e., amorphous, hydrosopic, etc.) are even more challenging to formulate.

This poster describes a general pulmonary-delivery platform based on engineered particles that overcome these challenges and, due to its broad applicability, makes it possible to rapidly develop formulations and then advance pulmonary dry-powder formulations. This broadly applicable platform is based on:

• dextran propionate succinate, a novel polymeric excipient; and
• a spray-drying process that produces particles of the desired size and morphology.

The work described in this poster has two goals:
1. demonstrate consistent aerosol performance in vitro for multiple formulations with multiple APIs and
2. demonstrate in vivo feasibility using a model 10% Active (A) fluticasone propionate:dextran propionate succinate engineered-particle formulation.

Materials and Methods

• Preparation and Characterization of Dextran Propionate Succinate. Dextran propionate succinate was prepared by derivatization of a Dextran 10 backbone (Pharmacosmos A/S) with propionate and succinate groups through ester bond linkages. The degree of substitution was verified using 1H nuclear magnetic resonance (NMR) spectroscopy (Varian, 600 MHz).

• Spray-Drying Process. The engineered-particle formulations were prepared by completely dissolving the active(s) and dextran propionate succinate in a common organic solvent. The solution was spray-dried using a custom spray dryer (similar to a Niro Mobile Minor) in which the dryer geometry and cyclone collector were optimized for generation and collection of respirable particles. Residual solvent was removed by vacuum desiccation.

• In Vitro Analysis. Aerodynamic particle-size distribution was determined with a Next Generation Impactor (MSP Corp.) via chemical analysis of active in the spray-dried formulation (60 L/min, no pre-separator). Aerosols for in vitro testing were generated using the monodose inhaler. The particle size and fine particle fraction (FPF < 4.6 µm) were determined. Replicates were generally n = 2 or 3, as the quantity of formulation allowed.

• In Vivo Analysis. The pharmacokinetics of the spray-dried fluticasone propionate formulation was evaluated in a Sprague Dawley rodent model. Aerosols were generated with a powder dispersion generator with a rotating brush (Palas GmbH RBG 1000) into a flow-past rodent exposure system, delivering fluticasone propionate doses of 0.2, 2.0, and 4.0 mg/kg. Twenty-seven animals were exposed to each targeted dose. Aerosol concentration at the breathing zone was determined by filter-sample collection. The particle-size distribution was determined in the exposure chamber by an aerodynamic particle sizer (TSI Model 3321 APS) at the breathing zone of the exposure system.

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Results: Homogeneous Amorphous Molecular Dispersion

Results: In Vitro Aerosol Performance

Monotherapies

- Fluticasone Propionate
- Lipophilic Base

Challenging Solid Forms – Unable to Mill

- Amorphous Lipophilic Base

FPF = 78%

Results: In Vivo Performance of Fluticasone Propionate Formulation

FPF = 77%

Lung Tissue Plasma

Conclusions

Individual compounds and combinations of compounds that have a wide range of physical and chemical properties were successfully formulated as spray-dried powders using dextran propionate succinate. The resulting amorphous powders consistently demonstrated high FPF values in vitro and showed excellent content uniformity and resistance to agglomeration when exposed to humidity in in vitro impaction experiments. In vivo tests demonstrated the feasibility of delivering a model engineered-particle formulation of fluticasone propionate to the lungs in a rodent model.