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

Bend Research Inc.
Innovators In Pharmaceutical And Health Science Technologies

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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, hydroscopic, etc.) are even more challenging to formulate.

This poster describes a general pulmonary-delivery platform based on engineered particles that overcomes 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 ^{13}C 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.

Acknowledgments

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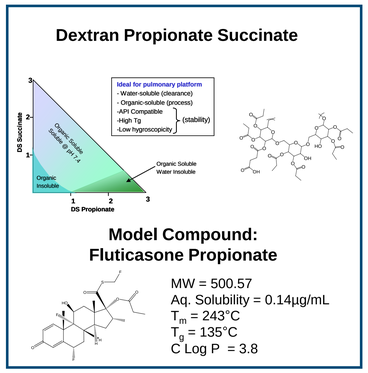
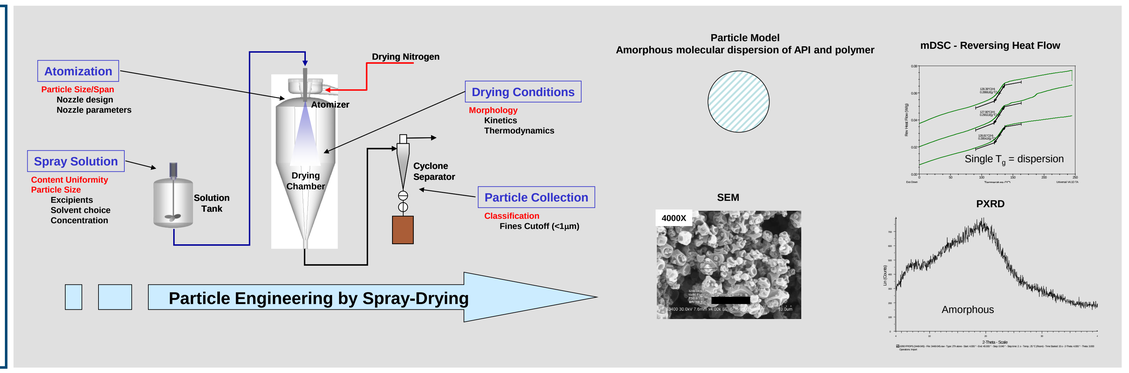
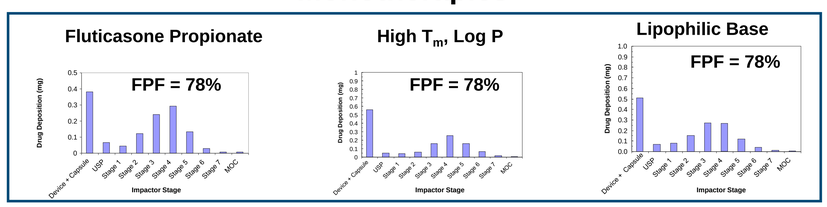
Results: Homogeneous Amorphous Molecular Dispersion



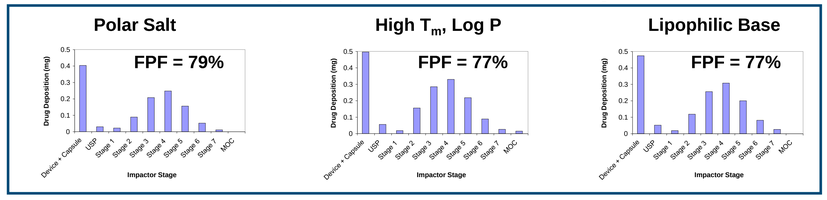


Results: *In Vitro* Aerosol Performance

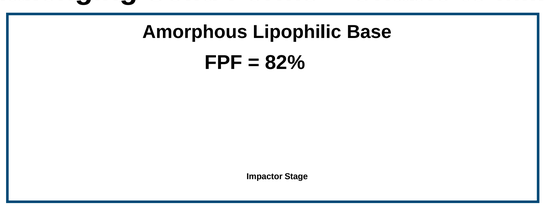
Monotherapies



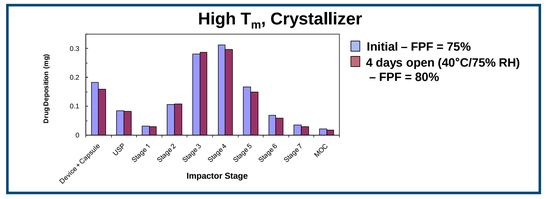
Triple-Combination Therapies



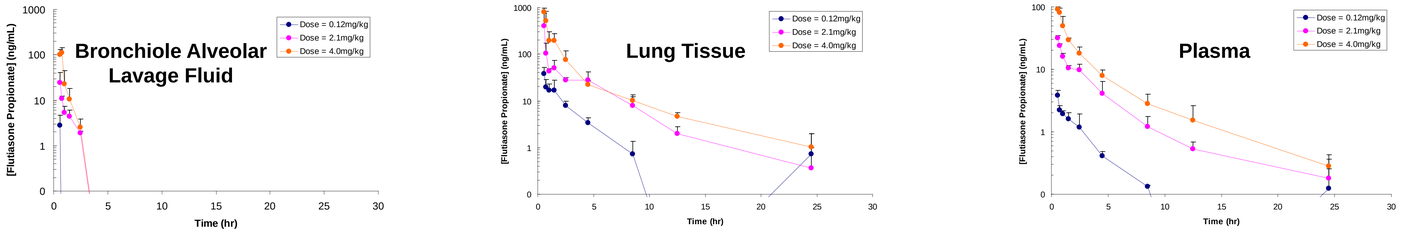
Challenging Solid Forms – Unable to Mill



Robust Physical Stability



Results: *In Vivo* Performance of Fluticasone Propionate Formulation



Formulation	Actual Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}12hr}$ (ng*hr/mL)
10%A Fluticasone Propionate:Dextran Propionate Succinate	0.12	3.9	0.58	6
10%A Fluticasone Propionate:Dextran Propionate Succinate	2.1	32	0.58	58
10%A Fluticasone Propionate:Dextran Propionate Succinate	4.0	96	0.58	139

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.