Introduction
The goal of this work was to determine the feasibility of formulating and testing a spray-dried combination powder using pharmaceutical compounds typically used to treat asthma and chronic obstructive pulmonary disease (COPD). Specifically, we describe the manufacturing approach and in vitro test for a spray-dried ipratropium bromide/albuterol sulfate dry-powder inhalation formulation that contained dextran as an excipient.

A combination powder fit for pulmonary delivery via inhalation was developed and spray-dried on a small-scale custom Bend Research spray dryer. Solid-state characteristics were evaluated using scanning electron microscopy (SEM), next-generation impact (NGI), modified differential scanning calorimetry (mDSC), and powder X-ray diffraction (PXRD) analysis. Humidity stress studies were performed to determine the glass-transition temperature ($T_g$) of the formulation after water uptake.

In vitro solid-state characterization revealed that the spray-dried combination ipratropium bromide/albuterol sulfate powder was amorphous with a single $T_g$. The size of the powder particles was in the range needed for delivery throughout the lung airways.

Using aerosol and solid-state characterization analytical tools, we confirmed the feasibility of a spray-dried powder fit for inhalation and lung delivery using two compounds typically used to treat asthma and COPD.

Methods

Spray-Drying
Spray-drying was performed using a custom Bend Research laboratory-scale dryer (BD-30). An aqueous based spray solution was prepared with ipratropium bromide/albuterol sulfate (Ipratropium 10% and Albuterol 16.6% by weight) at a solids loading of 52.5% (w/v) respectively, and at a solution concentration of 5 wt%. The spray-dried powder was a homogenous amorphous powder with a single glass-transition event at 45°C, indicating good physical stability.

Solid-State Characterization

Scanning Electron Microscopy (SEM): Dry powders were imaged by SEM using a Hitachi S-3000N instrument operating at 30 kV. Images were captured with Hitachi PC software.

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Thermal Characterization

The morphology of the spray-dried powder was wrinkled, which is characteristic of spray-dried dextran particles due to the drying of dextran as water is rapidly removed from the particles during drying. The morphology of the particles depends heavily on excipient type and compound loading in the particles.

Particle Sizing

NGI studies confirmed that the mass median aerodynamic diameter (MMAD) of the powder particles was suitable for lung delivery through inhalation.

Results and Discussion

The work presented here demonstrates the feasibility of manufacturing a combination therapy suitable for pulmonary delivery using spray-drying. In this study, spray-drying was used to manufacture an inhalable dry powder. The dry powder was characterized to determine if the solid-state physical characteristics of the manufactured powder were amenable to drug delivery through inhalation. The formulation contained Dextran 10, which has a $T_g$ of approximately 180°C when dry.

Powder Morphology

The morphology of the spray-dried powder was wrinkled, which is characteristic of spray-dried dextran particles due to the drying of dextran as water is rapidly removed from the particles during drying. The morphology of the particles depends heavily on excipient type and compound loading in the particles.

Conclusions

The feasibility of manufacturing a spray-dried combination ipratropium bromide/albuterol sulfate powder suitable for pulmonary delivery was demonstrated in this study. Dextran, being unprecedented for lung delivery, would require safety studies to be used for in vivo studies. Based on the physical and aerosol characteristics of the powder, spray-drying is a rational method of creating particles with the potential to be used in inhalation delivery to treat asthma and COPD. Additional work includes a physical and chemical stability assessment.

Spray-Drying

The work presented here demonstrates the feasibility of manufacturing a combination therapy suitable for pulmonary delivery using spray-drying. Spray-drying is an attractive approach for the preparation of formulations containing small molecule compounds because it is a thoroughly characterized, well-established unit operation; tunable; and bulk-sparing, requiring only minimal quantities of active pharmaceutical ingredient (API) to demonstrate feasibility.

References

Bend Research Inc., 64550 Research Road, Bend, OR 97701 USA
Phone: 1-800-706-8655
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