DESIGNING STABLE AND HIGH PERFORMANCE RESPIRABLE PARTICLES OF PHARMACEUTICALS

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INTRODUCTION

The use of spray drying to prepare dry powders for inhalation of small molecules, such as antibiotics and asthma therapeutics, peptide drugs like salmon calcitonin (sCT), or proteins like insulin, has gained popularity in recent years. The main aim of this study is to produce powders that do not require the use of a carrier, which may represent an advantage when large amounts of powder need to be delivered in a single aerosol dose. However, fast drying promotes the formation of amorphous material that is often intrinsically cohesive and thermodynamically unstable (1). The objective of the present study is to design non-cohesive spray dried particles with small, aerodynamic diameters that are physically and chemically stable, to be efficiently delivered as a dry powder aerosol. We describe the one-step preparation of dry powders of biopharmaceuticals suitable for inhalation using trileucine (2). We also delineate the main physicochemical factors that determine the particle formation process during drying.

METHODS

Dry powders for inhalation of antibiotics (netilmicin and gentamicin), asthma therapeutics (albuterol formulated with raffinose), and a therapeutic peptide (sCT formulated with raffinose), were obtained by spray drying an aqueous solution both with and without trileucine in a Büchi 190 spray dryer. Surface tension of the solutions prior to spray drying was measured using the Wilhelmy plate method using a Krüss model K-12 tensiometer. Surface energy of the albuterol/raffinose/trileucine powders was calculated from acetone and octane adsorption isotherms at 25°C, which were gravimetrically determined in a dynamic vapor sorption balance (DVS). Scanning electron microscopy (SEM) was used to qualitatively assess particle morphology. Powder surface composition was determined by X-ray photoelectron spectroscopy (XPS). The powders’ aerosol
performance were characterized by their in vitro emitted dose (ED) and their fine particle mass (FPM) less than 3.3 µm, determined by using a Nektar Pulmonary Delivery System (PDS Device) and an Andersen Cascade Impactor (ACI), respectively, under controlled ambient conditions (21°C and 40% RH) at a flow rate of 27 LPM. The chemical stability of sCT in the spray dried powders was monitored by RP-HPLC. A Vydac C18 column was eluted with acetonitrile gradient (0.1% TFA) at a flow rate of 1 mL/min (40°C). Column effluent was monitored at 210 nm. Salmon calcitonin aggregation was monitored by size exclusion chromatography (SEC). A TosoHaas TSK-Gel G2000SWXL column was eluted with 0.25 M Na₂SO₄ at a flow rate of 0.7 mL/min (25°C). Column effluent was monitored at 210 nm.

**RESULTS AND DISCUSSION**

Typical spray-dried particles of gentamicin and raffinose are shown in Figure 1A and B, respectively. Addition of as little as 2% wt trileucine dramatically alters the morphology of the spray-dried gentamicin particles, Figure 1C. Similarly, addition of 5% wt of sCT alters the morphology of spray-dried raffinose, producing corrugated particles, Figure 1D. Powders containing only antibiotic or raffinose used as bulking agent (neat or with 2% wt albuterol), presented low ED and large FPM <3.3 µm when compared to those prepared with trileucine. For example, with the addition of as little as 2% wt trileucine to gentamicin, the ED improved from 35% to more than 75% and the FPM <3.3 µm increased from 28% to 48%. Addition of 25% wt of the trileucine to gentamicin produced powders with an ED > 90%. Similarly, ED of raffinose powders containing 5% wt sCT is improved from 48 to 85% upon the addition of 60% wt trileucine. Results from the surface analysis of the spray-dried particles by XPS show that trileucine surface concentration increases three- to ten-fold with respect to the nominal bulk concentration. For all the molecules tested, the increase in the surface concentration correlates with the depression surface tension of the solution before spray drying. For example, addition of 0.6% wt trileucine decreased the surface tension of water from 72 to 42 mN×m⁻¹ at 25°C. The surface energy of spray-dried powders containing a constant amount of albuterol (2% wt), 5, 20, and 60% wt trileucine and 93, 78, and 38% wt raffinose, respectively, was calculated from the gravimetrically determined acetone and octane adsorption isotherms at 25°C. A significant reduction on the surface energy is observed as the amount of trileucine is increased (254, 192, 173 J×m⁻²).

Besides governing the surface properties, there are additional benefits of using trileucine to protect peptides during drying and in the dry state. Improved chemical and aggregation stability of sCT is observed in high humidity environments with the addition of trileucine (Figure 2). Significant degradation (nearly 80% with respect to initial concentration) and decrease in monomer content (nearly 70% monomer loss) was observed when a spray-dried powder of neat sCT was stored at 25°C and 75%RH for seven days. The initial sCT concentration and monomer content was virtually unchanged for a spray-dried powder of sCT formulated with 60% wt trileucine. This is in striking contrast with spray-dried powders of sCT formulated with mannitol, a stabilizer, which are unstable exposed to humidity regardless of the concentration of mannitol (3).
CONCLUSIONS

The addition of small amounts of trileucine to the formulation produces dry powders for inhalation with superior FPM and ED of small molecule drugs and a peptide hormone. We have found a relationship between water solubility and morphology of spray-dried powders from aqueous solutions.
Water-soluble molecules tend to produce spherical particles and less soluble molecules produce corrugated particles. Trileucine containing particles are corrugated with significantly improved aerosol performance. However, corrugation is not the overriding factor for improving aerosol performance, which seems to be also driven by the non-cohesive nature of trileucine in the solid state. Finally, salmon calcitonin aggregation and chemical degradation (deamidation and hydrolysis) can be controlled by the addition of trileucine in the formulation.

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REFERENCES

