Spray Freeze Dried Large Porous Particles for Nano Drug Delivery by Inhalation

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INTRODUCTION

Tuberculosis (TB) is a bacterial infection caused by *Mycobaterium tuberculosis*. TB has recently reemerged as a disease of interest for improved drug delivery, with a focus on leveraging the benefits of anti-tubercular drug nanoparticle formulation (1, 2). Drug nanoparticles can target infected cells and provide a large payload, but the optimal administration route remains uncertain (3). While oral formulations are most preferred, the passage of nanoparticles across the gastrointesintal tract is challenging. On the other hand, intravenous injection of nanosuspensions is invasive (4). Alternatively, dry powder aerosols have the stability of a solid dosage form and their delivery is noninvasive. Local drug targeting to the lungs also lowers the dose and systemic adverse effects. It is therefore desirable to produce inhalable powders comprised of a biocompatible matrix containing high loadings of drug nanoparticles. The present work provides a new understanding of the production of inhalable particles by ultrasonic spray freeze drying to enable precise control over particle density and aerodynamic properties.

METHODS

A series of highly porous mannitol, lysozyme, or bovine serum albumin (BSA) particles were produced by spray freeze drying aqueous solutions of the compounds using a CV-24 ultrasonic nozzle powered by a Vibra Cell 40 kHz ultrasonic generator (Sono-Tek Corp. Milton, NY, USA) at a liquid flow rate of 0.5 mL/min. The solute concentration of the solutions was varied from

10-50 mg/mL to obtain particles with the same geometric diameter but different porosity. The solutions were injected through the nozzle at 0.5 mL/min by a PHD 2000 syringe pump (Harvard Apparatus, Holliston, MA, USA). The atomized droplets fell by gravity over 3-10 cm and were collected in a container of liquid nitrogen. The frozen droplets were freeze dried at 25°C for 18 h (for mannitol) or first maintained at -25°C for 48 h and then at 20°C for 24 h (for BSA and lysozyme). The particle size distribution was determined by laser diffraction (Mastersizer 2000; Malvern, Worcestershire, UK). *In vitro* aerosol performance was measured by dispersing 2.5-5.0 mg of a powder from an Aerolizer® (Novartis, North Ryde, NSW, Australia) into a Next Generation Impactor (NGI) at 100 L/min.

Cholesterol nanoparticles (Sigma, St. Louis, MO, USA) stabilized by poly(ethylene glycol)-*block*-polylactide (PEG_{5k}-*b*-$PLA_{3.8k}$; Surmodics, Birmingham, AL, USA) were prepared by anti-solvent precipitation in a confined impinging jets mixer. The nanoparticles were sized by dynamic light scattering (ZetaSizer Nano ZS; Malvern Instruments, Worcestershire, UK). Cholesterol was employed as a model hydrophobic compound. A 1:1 mixture by weight of mannitol to nanoparticles at 20 mg/mL total solids concentration in deionized water was spray freeze dried as described above to obtain large porous particles loaded with cholesterol nanoparticles. The powder aerosol performance was determined by dispersion into the NGI.

RESULTS

Large porous particles were produced from spray freeze drying of all three compounds (Figure 1). The particle sizes of mannitol, BSA, and lysozyme powders were essentially independent of solute concentration when produced from the same ultrasonic nozzle. Both mannitol and lysozyme formulations showed a linear relationship between the fine particle fraction (FPF) (mass fraction of the loaded dose with aerodynamic diameter ≤ 5 μm) and the square root of solute concentration (C_s), which is proportional to the particle density (ρ), when geometric particle diameter is constant (d_g) (Figure 3). Due to cohesion, the FPF for BSA was < 10% and independent of C_s.

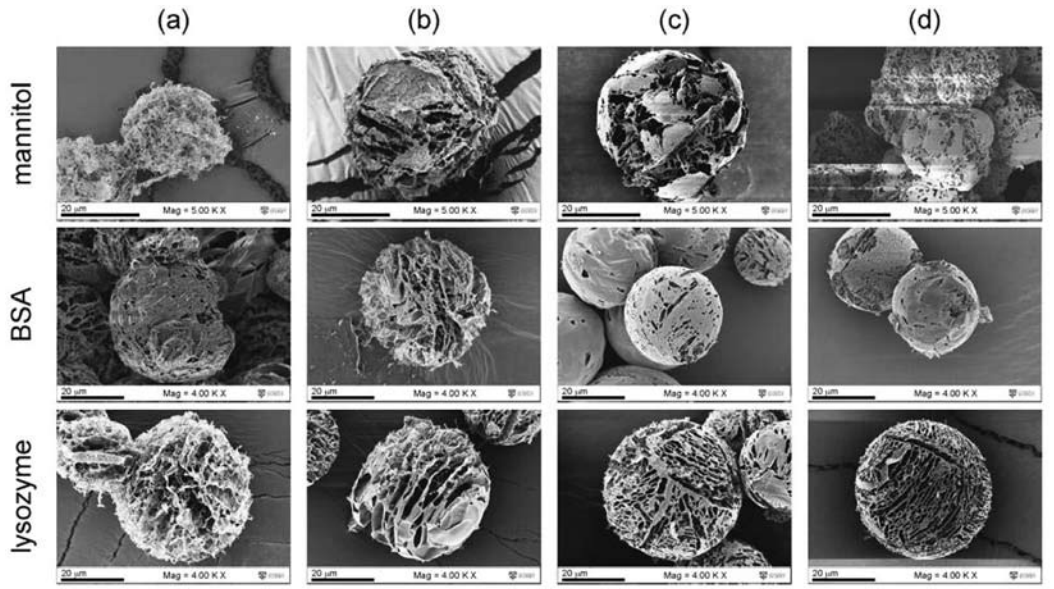

Figure 1. SEM images of large porous particles prepared from spray freeze drying aqueous solutions at (a) 10 mg/mL, (b) 20 mg/mL, (c) 40 mg/mL, and (d) 50 mg/mL.

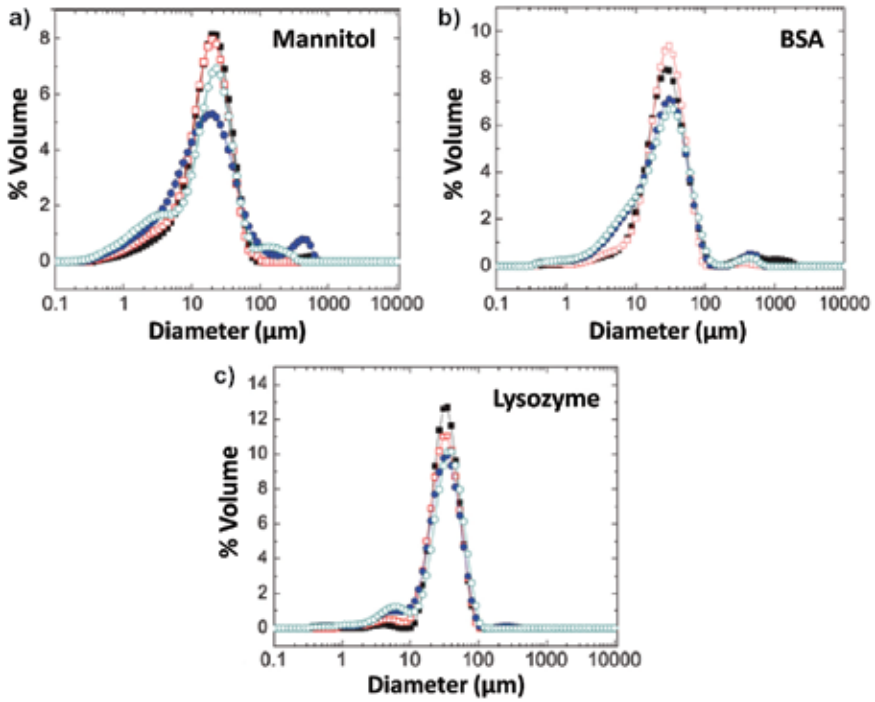

Figure 2. Volume-weighted size distributions for each particle formulation, prepared from aqueous solutions of a) mannitol, b) BSA, and c) lysozyme at 10 mg/mL (■), 20 mg/mL (□), 40 mg/mL (●), and 50 mg/mL (○).

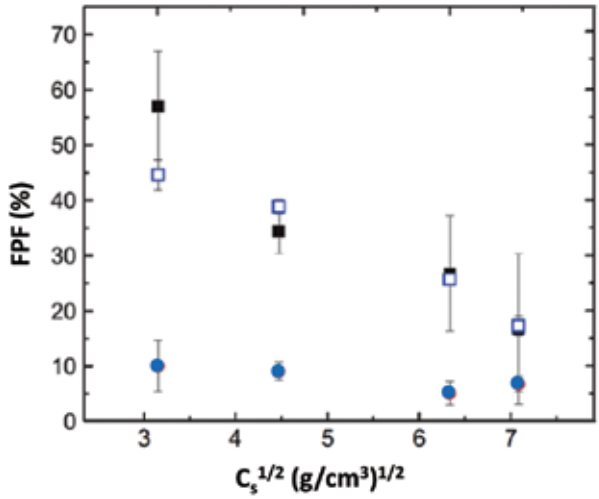

Figure 3. FPF of large porous (■) mannitol, (□) lysozyme, and (●) BSA plotted against the square root of aqueous solution concentration.

The intensity-weighted Z-average diameter of the cholesterol nanoparticles was 82 nm. Large porous mannitol particles with a 50% nanoparticle loading yielded a FPF of 63%.

CONCLUSIONS

Ultrasonic spray freeze drying enabled separate control over particle size and aerodynamic size (d_a). This allowed us to make the first experimental demonstration of the widely accepted relationship for spherical particles,

$$d_a = d_g\sqrt{\frac{\rho}{\rho_0}} \qquad \textit{Equation 1}$$

(ρ_0 = unit density), by varying the particle density rather than the geometric diameter. Large porous mannitol particles with a high nanoparticle loading (50% by mass) showed excellent aerosol performance. Thus, spray freeze drying may be a feasible technique for formulating powders to deliver drug nanoparticles into the lungs.

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