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Atmospheric Spray Freeze-Drying: Numerical Modeling and Comparison With Experimental Measurements

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ABSTRACT

Atmospheric spray freeze-drying (ASFD) represents a novel approach to dry thermosensitive solutions via sublimation. Tests conducted with a second-generation ASFD equipment, developed for pharmaceutical applications, have focused initially on producing a light, fine, high-grade powder consistently and reliably. To better understand the heat and mass transfer physics and drying dynamics taking place within the ASFD chamber, 3 analytical models describing the key processes are developed and validated. First, by coupling the dynamics and heat transfer of single droplets sprayed into the chamber, the velocity, temperature, and phase change evolutions of these droplets are estimated for actual operational conditions. This model reveals that, under typical operational conditions, the sprayed droplets require less than 100 ms to freeze. Second, because understanding the heat transfer throughout the entire freeze-drying process is so important, a theoretical model is proposed to predict the time evolution of the chamber gas temperature. Finally, a drying model, calibrated with hygrometer measurements, is used to estimate the total time required to achieve a predefined final moisture content. Results from these models are compared with experimental data.

Introduction

Lyophilization, commonly known as freeze-drying, has become the standard technique for drying compounds that are unstable as aqueous solutions. Biomolecular drugs and high-quality dried foods are common examples of freeze-dried products. The material to be lyophilized is first frozen so that its water content can be removed by sublimation. During the lyophilization process, vapor pressure and temperature conditions are maintained below the triple point of water, which can be best accomplished in a vacuum chamber. The vacuum environment, however, leads to reduced rates of heat and mass transfer, resulting in drying times on the order of days.[1-4] Consequently, conventional freeze-drying is an energy-intensive technique characterized by slow drying rates. To overcome the vacuum system constraints, alternative freeze-drying techniques performed at atmospheric pressure have been proposed. One can cite the tunnel freeze-drying, fluidized bed freeze-drying, and spray freeze-drying approaches.[5-7]

Atmospheric spray freeze-drying (ASFD) has been introduced in early 1990s as a fast-drying rate technology for thermosensitive biotechnologically derived materials.[8,9] In contrast with lyophilization, the entire ASFD process takes place at positive gauge pressures, and drying occurs mainly by convection rather than diffusion. An aqueous solution is first atomized downward into a concurrent flow of a cold dry inert gas (Fig. 1). The droplets are rapidly frozen and collected on a filter at the bottom of the chamber. As a result, a layer of frozen powder with a uniform thickness builds up on the filter. The drying process is carried out by the forced convection of the dry gas throughout the frozen material until the desired moisture content is achieved. Instead of a cake, ASFD results in a fine, light powder that does not require milling. ASFD production can be advanced immediately by filling vials, capsules, tablets, or containers for bulk storage.

There are other advantages that ASFD may confer in the manufacturing of pharmaceutical products. For example, the fast freezing may minimize the dendritic ice crystallization and, consequently, the changes in solute concentration and pH. Fast freezing should also minimize the time for phase separation, leading to a more homogeneous dispersion of the solutes throughout the frozen droplets. Furthermore, as compared to classic spray drying, there appears to be less thermal and mechanical stresses with ASFD.[10] Although the challenges of scale-up

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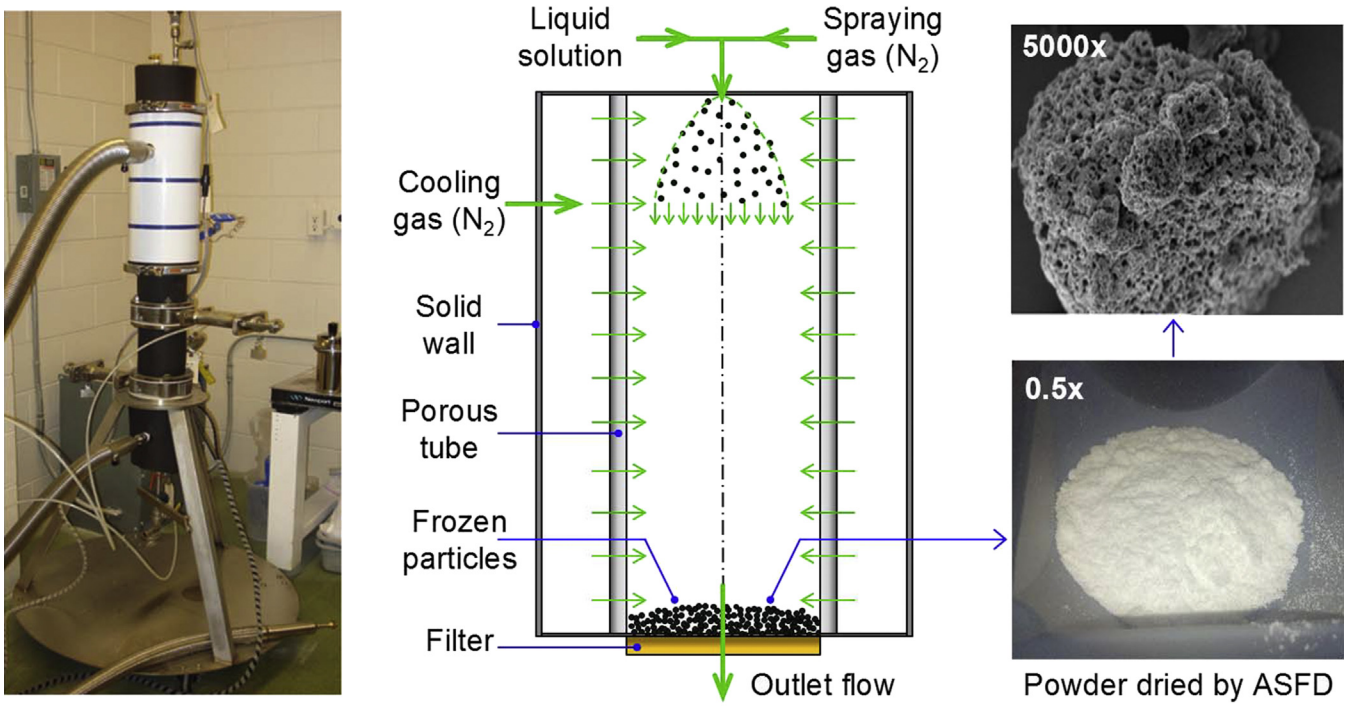

Figure 1. Atmospheric spray freeze-drying equipment. (Left) Photograph of equipment. (Right) Schematic of chamber with spray and drying gas inlets.

are now being addressed with ASFD, changes in the nozzle characteristics and spray conditions indicate that ASFD is quite flexible allowing particle properties, such as size, surface area, and density to be varied. This customization of product and process can be valuable to reduce protein denaturation, protein aggregation, and loss of potency. More comprehensive discussions on the state-of-art of spray freezing-drying techniques and their pharmaceutical applications can be found in recent reviews.[11,12]

ASFD Setup and Operating Conditions

The main component of an ASFD equipment is the cylindrical chamber where both spraying and drying occur. A photograph of the equipment setup investigated in this work and its schematic diagram is presented in Figure 1. The present chamber is comprised of 2 concentric tubes, a porous filter at the bottom, and a nozzle at the top of the chamber. The cooling gas is injected into the annular region between the 2 tubes. The porous inner tube helps to produce uniform temperature, pressure, and gas flow distributions within the core of the chamber. This gas flow also prevents spray droplets from adhering to the inner side of the porous tube. Moreover, as showed in next sections, the porous tube increases the heat capacity of the system.

Three models are proposed to describe the ASFD physical processes and to identify the key parameters that govern the present second-generation equipment: droplet freezing, heat transfer within the chamber, and powder drying. First, the velocity, temperature, and phase change evolutions of single droplets sprayed into the chamber are estimated for typical operational conditions. Second, because understanding heat transfer throughout the freeze-drying process is so important, a theoretical model is proposed to predict the time evolution of the chamber gas temperature. Finally, a drying model, calibrated with hygrometer measurements, is used to estimate the total time required to achieve a predefined final moisture content. In these modeling efforts, the thermophysical properties of the cooling gas, spraying solution, and frozen particles are taken as those of molecular nitrogen (N_2), water, and ice, respectively.

The model results are validated with actual data from multiple drying runs of bovine serum albumin (BSA). The typical corresponding run conditions are listed in Table 1. These 3 models represent the initial effort at developing a robust modeling framework for ASFD equipment. Ideally, calibration of the parameters with experimental data will allow the application of these models for different active pharmaceutical ingredients. Such models can help in the design of future large-scale production equipment.

Droplet Freezing and Transport Model

The droplet model describes the evolution of the velocity, temperature, and phase change (freezing) on spraying of an individual droplet into the ASFD cold chamber. The changes in a single droplet can then be extrapolated to estimate the structure of the entire spray cone in a typical ASFD cycle. In particular, the rate of freezing and the phase of the droplets by the time they reach the filter at the bottom of the chamber can be calculated. This task can be accomplished by combining the motion and energy equations for a freezing droplet.

Table 1
Typical ASFD Running Conditions

Parameter	Value
Initial BSA concentration in the solution	10%-20%
Sprayed volume	50-100 mL
Average droplet diameter (d_d)	<85 μm
Cooling gas flow rate	5-100 scfm
Cooling gas inlet temperature (T_2)	150-280 K
Chamber gas pressure	4-8 psig
Final powder moisture content (Δ_f)	≅1% (total mass basis)
Total drying/cycle time (t_f)	4-5 h