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Impact of Ice Morphology on Design Space of Pharmaceutical Freeze-Drying

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ABSTRACT

It has been known that the sublimation kinetics of a freeze-drying product is affected by its internal ice crystal microstructures. This article demonstrates the impact of the ice morphologies of a frozen formulation in a vial on the design space for the primary drying of a pharmaceutical freeze-drying process. Cross-sectional images of frozen sucrose–bovine serum albumin aqueous solutions were optically observed and digital pictures were acquired. Binary images were obtained from the optical data to extract the geometrical parameters (i.e., ice crystal size and tortuosity) that relate to the mass-transfer resistance of water vapor during the primary drying step. A mathematical model was used to simulate the primary drying kinetics and provided the design space for the process. The simulation results predicted that the geometrical parameters of frozen solutions significantly affect the design space, with large and less tortuous ice morphologies resulting in wide design spaces and vice versa. The optimal applicable drying conditions are influenced by the ice morphologies. Therefore, owing to the spatial distributions of the geometrical parameters of a product, the boundary curves of the design space are variable and could be tuned by controlling the ice morphologies.

Introduction

Freeze-drying, also called lyophilization, has long been known as the best drying method for maintaining the biological activity of pharmaceuticals. Industrial freeze-drying for pharmaceuticals is usually a batch process, where vials filled with drug solution are placed on shelves in a drying chamber with controllable shelf temperature. The solution in the vials is cooled and frozen on the shelves, and the ice formed in the solution is sublimated in the subsequent primary drying step. The heat required for the ice sublimation is also supplied from the shelves; therefore, the shelf temperature is the most important factor for the freeze-drying operation as it determines the product temperature and, consequently, the sublimation rate. The sublimated water is transferred with a certain velocity toward a condensation device and trapped on it (i.e., cold trap). If the velocity of the water vapor from the product to the cold trap and the condensation rate of water at the trap surface are infinitely large, the chamber pressure is theoretically kept equal to the saturated water vapor pressure at the trap temperature. However, especially in industrial dryers, the chamber pressure is typically under the influence of the various water vapor mass-transfer resistances; consequently, it has a much higher value than the saturated water vapor pressure at the trap temperature. The chamber pressure is thus an important operating factor. The chamber pressure can be controlled by changing the temperature of the cold trap; however, this is not recognized as a practical technique because the applicable temperature range of the cold trap produces a narrow pressure range.

To maximize the sublimation rate (and thus minimize the drying time), it is necessary to deliver heat to the sublimation interface. The most practical approach to achieve this in a vial freeze-drying process is to increase the shelf temperature. However, the temperature of the sublimation interface must be maintained below the eutectic or glass-transition temperature to avoid the risk of collapsing, which can cause serious product shrinkage and/or incomplete drying. Therefore, a promising strategy for minimizing drying time is, first, to determine the temperature of the sublimation interface during operation and, subsequently, to estimate the shelf temperature limit at which the product does not collapse. The manometric temperature measurement is an industrial method used to measure the mean temperature of the sublimation interface during freeze-drying and operates without any contacting devices

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Notations

A	sublimation surface area (m^2)
d_p	mean pore diameter (m)
e_d	dried layer thickness at the bottom of the product (m)
D_A	effective diffusion coefficient in dried layer (m^2/s)
D_k	Knudsen diffusion coefficient (m^2/s)
ΔH	latent heat of sublimation (J/kg)
J_A	mass flux of water vapor (kg/m^2s)
i	number of fraction (-)
m	mass of ice fraction (kg)
n	total number of fraction (-)
K_V	heat transfer coefficient (W/m^2 K)
M_W	molecular weight of water (kg/mol)
P_c	pressure in drying chamber (Pa)
P_s	pressure at sublimation interface (Pa)
Q_s	heat consumption at sublimation interface (W)
R	ideal gas constant (J mol/K)
R_p	mass transfer coefficient (m/s)
t	time (s)
T_c	temperature of drying chamber (K)
T_d	temperature of dried layer (K)
T_{sh}	temperature of shelf (basket) (K)
T_s	temperature at sublimation interface (K)
W_0	initial water content in product (kg)
W	water content in product (kg)

Greek letters

ε	porosity (-)
λ_{dry}	thermal conductivity of dried layer (W/m K)
τ	tortuosity (-)

to the products.[1-5] Soft sensing, which is a virtual sensing technique, has been proposed as a promising approach to determine important processing parameters based on experimentally obtained data.[6] Based on these backgrounds, sophisticated techniques and methodologies were reported to help operators to monitor products and select better (i.e., fast and safe) drying conditions.[7,8]

The operating conditions can be selected in a design space. According to "Guidance for Industry: Q8(R2) Pharmaceutical Development,"[9] the design space is the relationship between the process inputs (i.e., material attributes and process parameters) and the critical quality attributes. The design space provides information about the result of a selected operation; for example, in the case of freeze-drying, a prediction of the total drying time (or risk of collapse) for a selected combination of shelf temperature and chamber pressure. It is useful for evaluating whether the current operating conditions are sufficiently safe and for selecting alternative operating conditions that may accelerate the sublimation rate.[10-14] Mathematical modeling that simulates the impact of processing parameters on the process attributes is a powerful tool. Procedures to build a design space for the freeze-drying process based on a simple mathematical model were proposed.[15-18] This model required several experimentally obtained mass and heat transfer coefficients, which enabled an easy simulation that produced realistic results. In the present study, we performed a simulation based on the mathematical model developed by the research group of Velardi and Barresi.[18]

The process attributes that affect design space are not only in primary drying but also in freezing step.[16,19,20] Pisano et al.[19] reported that the annealing step effectively enlarged the design space, and this was due to the change in ice microstructure. The microstructures of ice crystals formed in a frozen formulation strongly affect the primary drying rates.[21-24] It is well known that the ice nucleation process is a spontaneous and stochastic phenomenon generally related to material and processing parameters that are difficult to control without external devices. Owing to a number of studies, laboratory-scale freeze-dryer equipped with controlled nucleation system can be achieved, but it is still challenging to realize in commercial scale.[25] However, recent developments in industrial freeze-dryers have made it possible to control ice nucleation even for solutions in a number of vials.[26] One realistic approach is to use ice fog in an apparatus for nuclei.[27,28] Another approach is to induce ice nucleation by a rapid reduction of the chamber pressure.[29-31] These techniques are aimed at breaking the supercooling in a solution contained in a vial. After the ice crystals are nucleated, the process is almost the same as that used in conventional methods. An alternative freeze-drying system proposed by a Japanese machinery company used a tube-type chamber to freeze a solution by falling film flow cooling on the inner tubular wall, where pure water was frozen to first produce a thin layer and subsequently a thick frozen layer of product formulation.[32,33] This approach enables to avoid ice crystallization via supercooling state; thus, the ice formation process and/or resultant ice microstructures could largely differ from those obtained from conventional processes. These developments can achieve a highly optimized freeze-drying process for future freezing systems that ensures high-level product quality.

In this study, we are interested in investigating the impact of the ice microstructures of a frozen solution on the design space for freeze-drying. As reported by previous works, the ice microstructures could have an impact not only on the sublimation kinetics but also on the stability of the bioactive ingredients.[34-36] Furthermore, the kinetics of freezing also has an influence on the redistribution and stability of the ingredients.[36] It would be a promising but challenging approach to tune a design space for freeze-drying by optimizing the freezing processes. We are thus motivated in this study to build up a design space based on the geometrical parameters of the ice microstructures. A common method for calculating a design space uses empirical mass transfer coefficient that reflects ice microstructures. The coefficients, however, are simply estimated from the mass flux and the product temperature, so they are an indirect consequence of the ice microstructures.

In this study, cross-sectional images of frozen sucrose–bovine serum albumin (BSA) aqueous solutions were optically observed, digital pictures were acquired, and the geometrical parameters of the ice crystals were extracted. A simulation was conducted with a mathematical model that used the geometrical parameters to estimate the drying kinetics of the freeze-drying runs, and the design space was obtained from the simulations. The calculation performed using commercial spreadsheet software is also presented as an Appendix.

Experiments

Materials

Millipore-purified water was used for the sample preparation. BSA, sucrose, and rhodamine B were purchased from Sigma-Aldrich (Sigma Chemical Co., Japan). The glass vials (20-mL capacity,