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Effects of temperature ramp rate during the primary drying process on the properties of amorphous-based lyophilized cake, Part 1: Cake characterization, collapse temperature and drying behavior

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ABSTRACT

In the lyophilization process for injectable pharmaceuticals, the shelf of the lyophilizer is heated to the target temperature at a constant ramp rate during the primary drying process. Although the shelf temperature (T_s) and chamber pressure (P_c) have mainly been investigated to optimize the primary drying process, the impact of the ramp rate on the lyophilized cake properties is poorly understood. We evaluated the relationship between the ramp rate and cake properties using a model formulation containing 10% trehalose as a bulking agent. Elegant lyophilized cakes were obtained when lyophilization was conducted at a fast ramp rate. In contrast, the lyophilized cakes collapsed at slow ramp rate cycles. To identify the cause of collapse, the impact of the ramp rate on the collapse temperature (T_c) was evaluated by light transmission freeze-dry microscopy. The T_c decreased with the decrease in the ramp rate. Lower T_c and higher resistance of the dried matrix in the low sublimation state were hypothesized as the cause of the collapse. Numerous lyophilization runs were executed at different T_s and ramp rates. We confirmed that an increased ramp rate led to successful lyophilization at a higher T_s and that the drying time was significantly reduced.

1. Introduction

Lyophilization has long been used to stabilize drug products in the pharmaceutical industry. In particular, lyophilization has been used in the development of injectable pharmaceuticals and has allowed for the stabilization of various materials, including small molecules, large molecules and nanoparticles. Furthermore, in recent formulation technology, lyophilization has been applied to orally disintegrating tablets, nasal formulations for vaccines and powders for pulmonary administration [16]. Thus, lyophilization is an essential technology in the pharmaceutical industry, and its use is expected to be expanded to various applications.

Lyophilization is generally known to be a time- and cost-consuming process. Thus, an optimization study has been conducted to minimize the process time. Lyophilization consists of three main processes: freezing, primary drying and secondary drying. In primary drying, ice crystals are sublimed from a frozen solution, and a great deal of time is required to reach the drying endpoint. Although the time required for primary drying can be shortened by the addition of heat to the vial, lyophilization may fail due to collapse or meltback when the product temperature (T_p) exceeds the critical temperature. Collapse or meltback during the primary drying process causes an increase in the residual moisture of the lyophilizate, potentially causing the product to become unstable. Several studies have reported that collapse during the lyophilization process has no significant impact on the stability of proteins [33,40]. However, formulation researchers and engineers generally recognize that collapse should be avoided because of the impact of collapse on product values, such as the elegance of the cake and the reconstitution time [4]. Thus, the primary drying process is the most important of the three processes, and product quality and manufacturing efficiency should be considered when determining the drying conditions.

The optimization of the lyophilization cycle has mainly focused on the primary drying process [20,32]. To avoid collapse or

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meltback, the T_p must be kept lower than the critical temperature (the collapse temperature or the eutectic point). However, maintaining a higher T_p is desirable to shorten the process time. Thus, T_s and P_c, which are related to the T_p, have been optimized in numerous trial experiments that have been performed to date [3,37]. It is also known that T_p and the sublimation rate during the primary drying process depend on the microstructure of the frozen product, and several studies have reported the impact of the freezing rate, annealing and ice nucleation kinetics [6,15,36]. Thus, the T_s, P_c and freezing conditions have been investigated with regard to the optimization of the primary drying process. Furthermore, the primary drying behavior can be theoretically predicted using a heat and mass transfer model, and simulation programs for cycle optimization have been proposed by a number of researchers [17,19,30]. For example, the T_p or the primary drying time is predicted as a function of the T_s and P_c, and the obtained values are plotted on a graph. The design space of the primary drying process can be determined based on the contour map that is prepared [17,19,26,28].

To promote ice sublimation, the T_s is increased to target temperature at a constant ramp rate in the beginning of the primary drying process. Although the above-mentioned process parameters have previously been the focus in efforts to optimize the primary drying process, the impact of the temperature ramp rate is poorly understood. In previous studies, a wide range of ramp rates have been applied to prepare lyophilizate samples (0.03 °C/min, [8]; 0.07 °C/min, [12]; 0.1 °C/min, [25]; 0.2 °C/min, [14]; 0.3–0.4 °C/min, [13]; 0.5 °C/min, [2]; 1.0 °C/min [9], and there is no common ramp rate that ensures a successful lyophilization process. In the mathematical model, other than T_s and P_c, both the heat transfer coefficient [1,5,10,11] and the resistance of the dry layer of the sublimed water vapor [18,21] have been reported to potentially affect T_p. However, the ramp rate is not an important parameter in the model equation, and the impact of the ramp rate on the drying behavior, such as the T_p and drying time, cannot be predicted theoretically. Thus, it will be of interest to learn whether the properties of the actual lyophilized cakes are changed by the ramp rate.

The aim of the present study was to investigate the impact of the ramp rate on the properties of lyophilized cakes and drying behavior. A sample solution containing 10% trehalose was used as a model formulation and was lyophilized at different ramp rates. The obtained lyophilized cakes were subjected to several evaluations, and the impact of the ramp rate on the properties of the cakes was investigated. Furthermore, the differences in the drying behaviors of the lyophilized cycles was discussed, focusing on the relationship between T_c obtained by light transmission freeze-dry microscopy (LT-FDM) and the recorded T_p data.

2. Materials and methods

2.1. Materials

All of the chemicals used in this study were obtained from the following commercial venders: D-(+)-trehalose dihydrate (Hayashibara, Okayama, Japan), l-arginine, l-arginine hydrochloride and citric acid monohydrate (EMD Millipore, Billerica, MA), Tween 80 (Croda, Edison, NJ), Hydranal® Coulomat AG (Sigma Aldrich, St. Louis, MO) and Hydranal® Coulomat CG (Sigma Aldrich).

All of the packaging materials used in this study were obtained from the following commercial venders: 5 mL type 1 glass vial (BB vial 23 × 43 VIST; outside diameter, 23 mm; inside diameter, 20 mm; Daiwa Special Glass, Osaka, Japan) and rubber stopper (20 mm gray butyl rubber stoppers, V10-F8, D713, RB2-40, Daikyo Seiko, Tokyo, Japan).

2.2. Sample preparation and lyophilization conditions

In the present study, D-(+)-trehalose dihydrate was used as a bulking agent because disaccharides are generally used in the lyophilized product and form fully amorphous cakes after lyophilization [22]. Among the commercially available protein formulations, disaccharide, amino acids and a small amount of surfactant are often formulated in a weak acidic solution [24,39]. Although the experiments were conducted using a placebo formulation, the sample was formulated to contain 10% D-(+)-trehalose dihydrate, 100 mM l-arginine, 0.01% Tween 80 at pH 5.5, and 10 mM citrate buffer as a model formulation. Then, 2.2 mL of the solution was filled in a vial after filtration using a 0.22-μm PVDF membrane (Merck Millipore, Tullagreen, Ireland), and each vial was partially stoppered with the rubber stopper. A total of 179 filled vials were loaded onto the shelf of a lyophilizer (S20NS, Nissan Edwards, Osaka, Japan) in a hexagonal arrangement, and thermocouples were placed at the center of the bottom of 1 representative vial in the center and 1 vial at the edge. The protocol of the lyophilization cycle was as follows. (1) Cooling was performed from the ambient temperature to −40 °C (0.67 °C/min). (2) The temperature was then held at −40 °C for 3 h, and (3) the P_c was reduced to the target value. (4) The shelf was then heated from −40 °C until the target T_s was reached (Table 1), and (5) the T_s and P_c were held until primary drying was achieved. (6) For secondary drying, T_s was changed to 25 °C for 6 h (Cycles 1–7, 0.07 °C/min; Cycle 8, 0.125 °C/min; Cycles 9–11, 0.01 °C/min; Cycles 12–14, −0.04 °C/min). and (7) T_s and P_c pressure were held for 48 h. During lyophilization, T_s, P_c and T_p were continuously recorded. The endpoint of the primary drying was determined by the drop point (offset point) of the Pirani pressure gauge signal.

2.3. Appearance

The lyophilized cake was carefully removed from the vial by breaking the bottleneck, and the appearance of the cake was evaluated. Furthermore, the lyophilized cake was split, and the appearance of the cross-section was observed using a digital microscope (VHX-5000, Keyence, Osaka, Japan).

2.4. Residual moisture

The amount of residual moisture was evaluated by coulometric Karl Fischer titration (CA-200, Mitsubishi Chemical Analytech, Kanagawa, Japan). Under low relative humidity, the lyophilized cake was uniformly crushed using a spatula, and the residual water in 50–150 mg of crushed powder was measured.

Table 1
Primary drying parameters used in the present study.

Cycle #	Ramp rate (°C/min)	Shelf temperature (°C)	Chamber pressure (Pa)
1	0.06	0	10
2	0.11	0	10
3	0.22	0	10
4	0.33	0	10
5	0.44	0	10
6	0.67	0	10
7	1.00	0	10
8	0.06	−20	10
9	0.06	20	10
10	0.44	20	10
11	1.00	20	10
12	0.06	40	10
13	0.44	40	10
14	1.00	40	10