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Optimization of secondary drying condition for desired residual water content in a lyophilized product using a novel simulation program for pharmaceutical lyophilization

Tatsuhiro Kodama [a,*], Masahito Takeuchi [a], Naoki Wakiyama [a], Katsuhide Terada [b]

[a] Formulation Technology Research Laboratories, Daiichi Sankyo Co., Ltd., 1-12-1 Shinomiya, Hiratsuka, Kanagawa 254-0014, Japan
[b] Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan

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ABSTRACT

The aim of this study was to optimize the shelf temperature and the drying time, mainly dependent on the residual water content of a lyophilized product using a novel simulation program for the secondary drying of lyophilization. The simulation program was developed based upon heat transfer formulas, two empirical formulas, and a modified Fick's second law. When a preliminary lyophilization run of secondary drying was carried out, the equilibrium product temperature at the end of secondary drying under various shelf temperatures was accurately predicted by the heat transfer formulas. The apparent diffusion coefficient of water, D_{eff}, and the apparent equilibrium residual water content, W_e, under the predicted equilibrium product temperature were estimated by two empirical formulas. These estimated D_{eff} and W_e allow the modified Fick's second law to predict the residual water content in the lyophilized product. Using the developed simulation program, it was verified that the secondary drying condition to achieve the desired residual water content in the lyophilized product was successfully predicted. Therefore, the simulation program can be used to effectively design the secondary drying condition of lyophilization cycles without a trial and error approach.

1. Introduction

Lyophilization is commonly employed in pharmaceutical industries to enhance the stability of drug products for parenteral injection. The lyophilization cycle is mainly divided into three stages: freezing, primary drying, and secondary drying. In the secondary drying stage, the residual water (unfrozen and bound water) in a lyophilized product is removed at a high shelf temperature until the desired residual water content is obtained. For many lyophilized products, the low residual water content in the lyophilized product, typically below 1%, is beneficial for good storage stability of API (Franks, 1992; Pikal and Shah, 1997). On the other hand, recent studies have demonstrated that some biological molecules show an optimum stability in intermediate moisture contents between 1% and 3% (Breen et al., 2001; Hsu et al., 1992; Sarciaux and Hageman, 1997; Schneid et al., 2011). Hence, enormous effort has been spent to optimize the desired residual water content in lyophilized products to ensure good stability by adjusting the shelf temperature and the drying time in secondary drying.

A number of reports about the mathematical model for primary drying has appeared by many authors (Ho and Roseman, 1979; Jennings, 1988; Kuu et al., 2006; Nail, 1980; Pikal et al., 1984). However, it is not yet clear whether the rate limiting step of water desorption in secondary drying is the diffusion in the solid matrix or the evaporation of water from the solid surface in secondary drying (Fissore et al., 2011; Pikal et al., 1990). On the other hand, it is known that the residual water content was calculated using the diffusion model based on the modified Fick's second law to fit the experimental data in the food industry (Cardoso Andrade et al., 2007; Gupta et al., 2011; Telis et al., 2004). It is thought that this modified Fick's second law is useful as an empirical model to predict the residual water contents in the lyophilized products during secondary drying. However, the study of a simulation program to predict the residual water contents in the lyophilized products dried at various conditions of the shelf temperature and the drying time in secondary drying has not been intensively focused on in the pharmaceutical field. In a previous study, our laboratories demonstrated that the simulation program could predict the product temperature profile during primary drying using the predictive model for dry layer resistance, providing an

* Corresponding author. Tel.: +81 463 31 6325; fax: +81 463 31 6478.
E-mail address: kodama.tatsuhiro.s8@daiichisankyo.co.jp (T. Kodama).

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optimized condition of shelf temperature and chamber pressure (Kodama et al., 2014). This simulation program is thought to be convenient for designing the lyophilization cycle, while the applicable prediction is limited to primary drying.

Therefore, this study focused on the development of the simulation program to predict the optimal condition of the shelf temperature and the drying time in secondary drying for the desired residual water content in the lyophilized product. The simulation program based on the heat transfer model, two empirical formulas, and the modified Fick's second law was developed, assuming that the diffusion of water is the rate-limiting in secondary drying.

2. Materials and methods

2.1. Mathematical model combined with heat transfer model and modified Fick's second law

The simulation program was developed to predict the residual water content in the lyophilized product during the secondary drying of lyophilization. The residual water content in the lyophilized product can be mathematically calculated, as follows. The heat transfer rate around the glass vial is comprised of three types of heat transfer rates, which are (1) the shelf heat transfer rate from the shelf to the bottom of the glass vial, Q_{sh}, (2) the conductive heat transfer rate from the tray frame to the side of the glass vial, Q_t, and (3) the radiative heat transfer rate from the chamber wall to the top and side of the glass vial, Q_r. The estimation of each heat transfer rate is shown in our previous study (Kodama et al., 2013). The total heat transfer rates for the "edge vial" and "center vial" are estimated in Eqs. (1) and (2), respectively. Edge vials are those placed on the peripheral positions of a shelf, and center vials are those placed on the center positions on a shelf.

$$Q_{\text{edge vial}} = Q_{sh} + Q_t + Q_r \quad (1)$$

$$Q_{\text{center vial}} = Q_{sh} + Q_r \quad (2)$$

In Eq. (1), the conductive heat transfer rate from the tray frame to the side of the glass vial, Q_t, is used for the edge vial, because only edge vials have direct contact with the stainless tray frame. The product temperature, T_b, of each edge and center vial during secondary drying can be estimated in Eq. (3), assuming that the heat transfer rate is spent for raising and maintaining the product temperature.

$$T_b = T_{bi} + \sum_{t=1}^{n} \left(Q \times \frac{\Delta t}{C} \right) \quad (3)$$

where, T_{bi} is the product temperature at the previous point of elapsed time. C is the heat capacity of the lyophilize product including the glass vial, rubber stopper, and lyophilized cake. The residual water content in lyophilized product is calculated according to the modified Fick's second law in Eq. (4).

$$W_t = W_e + (W_i - W_e) 8\pi 2e^{-D_{eff}} \times t\{1/(2\pi \times L)2\} \quad (4)$$

W_t is the residual water content in the lyophilized product dried at any time during secondary drying. W_e is the apparent equilibrium residual water content in the lyophilized product, dried for a sufficiently long time in secondary drying. W_i is the initial residual water content, which is determined by the residual water content in the lyophilized product after primary drying. D_{eff} is the apparent diffusion coefficient of water in the amorphous particle of the lyophilized cake. t is the elapsed time in secondary drying. L is the half thickness of the amorphous particle in the lyophilized cake, which can be calculated by the product density and the product specific surface area (Pikal et al., 1990). As shown in Section 3.1, the apparent diffusion coefficient of water, D_{eff}, and the apparent equilibrium residual water content in the lyophilized product, W_e, are calculated by two empirical formulas using the equilibrium product temperature, T_{be}, at the endpoint of secondary drying.

2.2. Lyophilization process

The lyophilization tests were performed using a laboratory scale lyophilizer (DFM-09A-S, ULVAC, Inc., shelf area: 0.3 m^2). Five mililiter of the aqueous solution containing 10 w/v% sucrose (purchased from Merck) or 5 w/v% lactose hydrate (purchased from Kanto Chemical Co., Inc.,) was filled into each φ20 mL vial (transparent
type 1 glass vial, Japan Glass Industry Co., Ltd., 320 vials), and the filled vials were partially stoppered with rubber stoppers (two leg 20 mm gray butyl rubber stoppers, Daikyo Seiko, Ltd.,). The fill depth of each solution was approximately 1 cm. The lyophilization was conducted as follows, (1) freezing the solution at −45 °C, (2) annealing at −5 °C, (3) re-freezing at −45 °C, (4) primary drying at −10 °C under 8 Pa, (5) secondary drying at the target shelf temperature under approximately 1 Pa (full vacuum). During lyophilization, the shelf temperature, the chamber pressure, and the product temperature at the bottom-center of the vials on the peripheral and center positions on a shelf were continuously recorded by thermocouples and a capacitance manometer (MKS, Baratron). As an example, the result of lyophilization of the 10 w/v% sucrose solution where the shelf temperature and the chamber pressure was set at −10 °C and 8 Pa for primary drying and 40 °C and no more than 1 Pa is presented in Fig. 1. The maximum product temperature, approximately −31.8 °C, of the edge vials was well controlled at no more than the collapse temperature of −31.5 °C, T_c (Kodama et al., 2014) in primary drying, and lyophilized products with an excellent appearance was obtained.

2.3. Preliminary lyophilization run

After the product temperature became unchanged at a temperature close to the shelf temperature of −10 °C in primary drying, the lyophilized products which were formed by an aqueous solution containing 10 w/v% sucrose or 5 w/v% lactose hydrate were continuously dried at the shelf temperature of −10 °C for 48 h. In this study, the additional drying process was expressed as a part of secondary drying. Then, the lyophilized products were

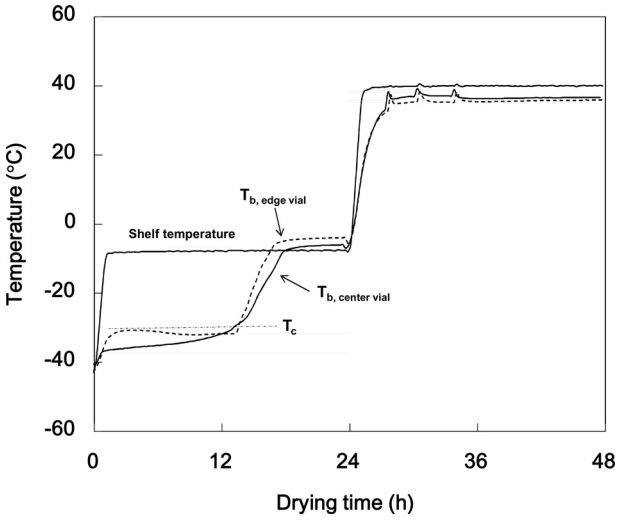

Fig. 1. Lyophilization profile of 10 w/v% sucrose solution. The shelf temperature and chamber pressure were set at −10 °C and 8 Pa for primary drying and 40 °C and full vacuum for secondary drying.