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Research Paper

Freeze-Drying Process Design by Manometric Temperature Measurement: Design of a Smart Freeze-Dryer

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Purpose. To develop a procedure based on manometric temperature measurement (MTM) and an "expert system" for good practices in freeze drying that will allow development of an optimized freeze-drying process during a single laboratory freeze-drying experiment.
Methods. Freeze drying was performed with a FTS Dura-Stop/Dura-Top freeze dryer with the manometric temperature measurement software installed. Five percent solutions of glycine, sucrose, or mannitol with 2 ml to 4 ml fill in 5 ml vials were used, with all vials loaded on one shelf. Details of freezing, optimization of chamber pressure, target product temperature, and some aspects of secondary drying are determined by the expert system algorithms. MTM measurements were used to select the optimum shelf temperature, to determine drying end points, and to evaluate residual moisture content in real-time. MTM measurements were made at 1 hour or half-hour intervals during primary drying and secondary drying, with a data collection frequency of 4 points per second. The improved MTM equations were fit to pressure-time data generated by the MTM procedure using Microcal Origin software to obtain product temperature and dry layer resistance. Using heat and mass transfer theory, the MTM results were used to evaluate mass and heat transfer rates and to estimate the shelf temperature required to maintain the target product temperature.
Results. MTM product dry layer resistance is accurate until about two-thirds of total primary drying time is over, and the MTM product temperature is normally accurate almost to the end of primary drying provided that effective thermal shielding is used in the freeze-drying process. The primary drying times can be accurately estimated from mass transfer rates calculated very early in the run, and we find the target product temperature can be achieved and maintained with only a few adjustments of shelf temperature. The freeze-dryer overload conditions can be estimated by calculation of heat/mass flow at the target product temperature. It was found that the MTM results serve as an excellent indicator of the end point of primary drying. Further, we find that the rate of water desorption during secondary drying may be accurately measured by a variation of the basic MTM procedure. Thus, both the end point of secondary drying and real-time residual moisture may be obtained during secondary drying.
Conclusions. Manometric temperature measurement and the expert system for good practices in freeze drying does allow development of an optimized freeze-drying process during a single laboratory freeze-drying experiment.

KEY WORDS: end point of primary drying; freeze-dryer overload; freeze-drying process design/optimization; heat and mass transfer; manometric temperature measurement; process analytical technology for freeze drying; radiation effect; residual moisture content.

INTRODUCTION

Lyophilization is widely used to manufacture labile drugs such as enzymes and therapeutic proteins (1). Because the product temperature during primary drying depends on many factors, such as chamber pressure, shelf temperature, heat transfer coefficient of the container, resistance of the dried cake to water vapor flow, and so forth, it is difficult to optimize the freeze-drying process for a given pharmaceutical formulation. Because primary drying normally consumes the largest fraction of the freeze-drying cycle time, optimization of this portion of the process has significant economic impact (2). With high product temperature (T_p), the sublimation rate is high and the primary drying time is short. However, the product temperature (T_p) must be below collapse temperature during freeze drying (usually several degree lower than T_c) to avoid collapse of the freeze-dried cake (2,3). The product temperature normally increases during primary drying as the product dry layer resistance increases with freeze-drying time, which makes the freeze-drying process design even more difficult. Even with highly skilled development scientists, optimization of primary drying can require a number of

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time-consuming experimental studies. However, many formulations are freeze dried at conditions that are not optimized. Nonoptimized freeze-drying processes may enormously increase the process time and compromise product quality and/or produce regulatory concerns. Efforts have been made to facilitate the freeze-drying process optimization, such as computer modeling to predict the optimum freeze-drying conditions. However, computer modeling requires input data that still need to be collected from many real freeze-drying experiments. Also, the success of freeze-drying process design by computer simulation depends on the accuracy of the input data used and model chosen, and confirmation of accuracy, which requires a number of laboratory experiments (4,5). It would be an enormous advantage if process development scientists could optimize the freeze-drying procedure during a single laboratory freeze-drying experiment.

Manometric temperature measurement (MTM) is a procedure to measure the product temperature during primary drying by quickly isolating the freeze-drying chamber from the condenser and analyzing the pressure rise during this period. This analysis yields product temperature and the mass transfer resistance of the dried product (6). In principle, the shelf temperature required to achieve a given target product temperature can be calculated from product temperature and dried layer resistance by steady state heat and mass transfer theory. Thus, at least in principle, the freeze dryer itself can optimize the freeze-drying process during a single experiment.

In this project, a procedure to optimize the freeze-drying process is developed by combination of feedback information from manometric temperature measurement (MTM) during lyophilization, an "expert system" for good freeze-drying practices and steady state heat/mass transfer theory. The optimized process includes optimizing the following: freezing conditions, chamber pressure, target product temperature, the shelf temperature required to achieve the target product temperature during primary drying, and the secondary drying conditions. In addition, the end point of primary drying is determined from MTM data. An end point method based on manometric temperature measurement (MTM) has the advantage of being representative of the batch as a whole and does not require the use of probes placed in product vials. Further, the MTM procedure may be modified to determine the water desorption rate during secondary drying, which may be used effectively to indicate the end point of secondary drying as well as optimize secondary drying.

The algorithm providing parameters to initialize the calculations, the algorithm required to calculate the shelf temperature needed to attain the desired product temperature during primary drying, and the methodology to determine the end point of primary drying and to estimate the water desorption rate during secondary drying were developed and tested against experimental data. Success was judged by the ability of the "smart freeze-dryer" to perform in the following ways: 1) adjusting the shelf temperature automatically and quickly to attain the correct product temperature; 2) accurately determining the end point of primary drying; and 3) determining the residual moisture content during secondary drying in real-time.

Using the smart freeze-dryer system, even relatively inexperienced development scientists will be able to optimize the freeze-drying process with only a single freeze-drying experiment, given only the product collapse (or eutectic) temperature. In addition, the procedure will provide data on mass and heat transfer coefficients for the product and container that can be used to better characterize the freeze-drying system.

MATERIALS AND METHODS

Materials

Sucrose, glycine, and mannitol were purchased from Sigma (St. Louis, MO, USA) and used without further purification. All the reagents were analytical grade. All the vials used for freeze drying were 5 ml serum tubing vials from Fisher, with a inside cross-sectional area of 2.91 cm^2 and outside cross-sectional area of 3.64 cm^2.

Freeze Drying

Freeze drying was performed with a FTS Dura-Stop/Dura-Top freeze dryer (Kinetics, FTS) with the manometric temperature measurement (MTM) software installed. Solutions were prepared by weight volume ratio (w/v). A given number of vials (normally 150 unless stated otherwise) were used for all freeze-drying runs. The fill volumes were either 2 or 4 ml as required. Sample vials were loaded on the middle shelf of the freeze dryer. Thermal or radiation shields were used for all experiments including empty (dummy) vials around sample vials to decrease radiative heat transfer from the freeze-dryer chamber wall and the door, and aluminum foil attached at the inside of the chamber door to reduce radiation from the door (7–9).

Manometric Temperature Measurement

The MTM measurement was made at 1 hour or one-half hour intervals during primary drying, and pressure data were collected at the rate of 4 points per second during the MTM measurement. Typically, the data were collected for 25 s by closing the valve connecting the freeze-drying chamber and condenser and recording the chamber pressure as function of time. The MTM equation (Eq. 1) describes the behavior of vapor pressure rise in freeze-drying chamber (P, Torr) as a function of valve closure time during MTM (t, seconds) (7).

$$P(t) = P_{ice} - (P_{ice} - P_0)\exp\left[-\left(\frac{3.461NAp T_s}{V(\hat{R}_p + \hat{R}_s)}\right)t\right] + 0.0465P_{ice}\Delta T\left[1 - 0.811\exp\left(-\frac{0.114}{L_{ice}}t\right)\right] + Xt \quad (1)$$

where P_{ice} is vapor pressure of ice (Torr) at the sublimation interface, determined by a fit of Eq. (1) to the pressure rise data; P_0 is the chamber pressure (set, Torr); N is the total number of filled vials (known); A_p is the inner cross-sectional area of vials (known, cm^2); T_s is the shelf temperature (set, K); V is the freeze-drying chamber volume (known, L); $\hat{R}_p + \hat{R}_s$ is the total area normalized product and stopper resistance, determined by the fit; L_{ice} is ice thickness (calculated, cm); ΔT is the temperature difference between ice sublimation interface and bottom of the vials (fixed, or evaluated from Eq. 2); and X is a constant (Torr/second), determined from the fit.

The value of ΔT may be related to other parameters using steady-state heat and mass transfer by Eq. (2). A simultaneous fit of both Eqs (1) and (2) to the data yields improved MTM results compared to using a fixed value of ΔT (8,10).

$$\Delta T = \frac{[24.7L_{ice}(P_0 - P_c)/(R_p + R_s) - 0.0102L_{ice}(T_s - T_p)]}{1 - 0.0102L_{ice}} \quad (2)$$

where T_p is the product temperature at the ice sublimation interface (K), which is related to vapor pressure of ice at the sublimation interface by Eq. (3) (5,11), and P_c is the pressure in the freeze-drying chamber (Torr).

$$\ln(P_{ice}) = \frac{-6144.96}{T_p} + 24.01849 \quad (3)$$

The MTM Eqs. (1) and (2) were fit to MTM raw data, which is the chamber pressure as a function of time, by nonlinear regression analysis using a software package (Microcal Origin). The regression analysis yielded both the vapor pressure of ice (P_{ice}), from which product temperature (T_p) was obtained by solving Eq. (3), and total resistance of stoppers and product dry layer ($\hat{R}_p + \hat{R}_s$) (6,12). The resistance of the stopper $\hat{R}_s$ does not vary at constant pressure and is usually negligibly low (10).

Calculation of Mass and Heat Flow by MTM Results

Ice sublimation rate (mass flow) was calculated by Eq. (4) using MTM data (10,13).

$$\frac{dm}{dt} = A_p \frac{P_{ice} - P_c}{\hat{R}_{ps}} \quad (4)$$

where dm/dt is the ice sublimation rate (g/hour per vial); A_p is internal cross-sectional area of vials (cm^2); P_{ice} is vapor pressure of ice (Torr) at the temperature of sublimation surface, which is determined by the MTM data fit; and $\hat{R}_{ps}$ is the sum of area normalized dry layer and stopper resistance, which is determined by the MTM data fit (cm^2 Torr-hour/g). The heat flow, dQ/dt, was calculated from MTM mass flow, dm/dt (Eq. 5):

$$\frac{dQ}{dt} = \Delta H_s \frac{dm}{dt} \quad (5)$$

where ΔH_s is the heat of ice sublimation (cal/g).

Calculation of Shelf Temperature Required to Achieve Target Product Temperature

During primary drying, the freeze-dryer shelf serves as the heat source for ice sublimation. The heat transfer from shelf to samples is expressed by Eq. (6).

$$\frac{dQ}{dt} = A_v K_v (T_s - T_b) \quad (6)$$

where dQ/dt is heat transfer rate (cal/hour per vial); A_v is the vial cross-sectional area (cm^2); T_s is the shelf temperature (K), T_b is the temperature of the vial bottom (K); and K_v is the heat transfer coefficient of the vials (10). Because MTM measures the product temperature at the ice sublimation interface, the temperature at vial bottom needs to be calculated. For this purpose, we assume that all the heat consumed by ice sublimation is provided by the freeze-dryer shelf, which gives the simple relationship (Eq. 7).

$$T_b = \frac{(dQ/dt)l}{A_v K_I} + T_p \quad (7)$$

where l is ice thickness, which is taken as the fill depth of solution at the begining of primary drying divided by ice density; K_I is the thermal conductivity of ice; and T_p is the product temperature as determined by MTM. This is not completely accurate as even for a vial in the interior of an array, there is radiation heat transfer from the top. However, Eq. (7) is a good approximation.

The thickness of the frozen layer during primary drying is calculated from the cumulative amount of ice sublimed. The mass of ice sublimed, m (t), is calculated by numerical integration of dm/dt over the primary drying time, t and the ice thickness remaining is calculated by Eq. (8) (9,13).

$$l(t) = \frac{m_0 - m(t)}{\rho_i A_p \varepsilon} \quad (8)$$

where l(t) is the ice thickness at time t (cm); m_0 is the initial mass of water in the vial (g/vial); m(t) is the mass of ice sublimed at time t (g/vial); ρ_i is density of ice (g/cm^3); and ε is the volume fraction of ice, which is about 0.97 for 5% glycine, sucrose, or mannitol.

Next, the shelf temperature (T_s) required to achieve the target product temperature is estimated by combination of Eqs. (6 and 7).

$$T_s = T_p + \frac{1}{A_v}\frac{dQ}{dt}\left(\frac{1}{K_v} + \frac{l}{K_I}\right) \quad (9)$$

where T_p is the target product temperature, which is always above the "current" product temperature at the beginning of primary drying; dQ/dt is the calculated heat flow at the target product temperature; and K_v is the vial heat transfer coefficient. If the assumption of steady state is valid in primary drying, the heat flow (dQ/dt) in Eq. (9) at the target product temperature can be calculated by Eqs. (4 and 5), where P_{ice} is calculated for a known target product temperature, P_c is known, and $\hat{R}_{ps}$ is obtained from the most recent MTM.

It should be emphasized that the use of Eq. (9) assumes steady state, which is not entirely valid early in primary drying. Methodology used to overcome this limitation is discussed later.

The Residual Moisture Content in Secondary Drying

The pressure rise data were collected periodically (typically every hour) by closing the valve connecting the freeze-drying chamber and condenser, and the pressure rise rate (dP/dt) was calculated. The amount of water desorption was estimated by using the ideal gas law, where the rate of water desorption, dw/dt, is given by Eq. (10) and the loss in water during the ith measurement period, Δw_i, is given by Eq. (11).

$$\frac{dw}{dt} = \frac{M \cdot V}{R \cdot T}\frac{dP}{dt} \quad (10)$$

$$\Delta w_i = \frac{dw}{dt}\Delta t_i \quad (11)$$

where P is the partial pressure of water in the freeze-dryer chamber, V is the volume of the chamber, M is the molecular weight of water, R is the gas constant, T is the temperature of the water vapor, w is the mass of water, and Δt_i is the time interval between the *i*th and *i* – 1th MTM measurements (usually 1 hour). The total amount of water removed between a reference time (i.e., the start of secondary drying) and any given time of interest is simply the summation of all Δw_i values between the reference time, t_R, and the time of interest, t (Eq. 12).

$$\Delta w = w(t_R) - w(t) = \sum_i \Delta w_i \quad (12)$$

Product Temperatures Measured by Thermocouples

Copper-constantan thermocouples (28 gauge) were used to determine the product temperature during freeze drying. The thermocouple product temperatures were measured in vials at different locations during freeze drying including edge vials (front and side vials) and interior vials. The thermocouple junctions were placed in the middle of the vials touching the bottom.

RESULTS AND DISCUSSIONS

The Operation of the Smart Freeze-Dryer: Overview

A schematic providing an overview of the operation of the smart freeze dryer is shown in Fig. 1. The smart freeze-dryer has "built in" expert system algorithms, which control all stages of freeze drying (14). For freezing, the expert system chooses the freezing cycle using input information (e.g., collapse temperature (T_c), fill depth, nature of the product, (i.e., small molecule or protein), crystalline or amorphous based formulation, and so forth. In primary drying, the expert system uses feedback information from MTM, including current product temperature (or vapor pressure of ice) and dry layer resistance, selects the target product temperature, calculates the optimum chamber pressure for primary drying, predicts primary drying time at the target product temperature, calculates the optimum shelf temperature to achieve the target product temperature, and determines the end point of primary drying. The expert system also evaluates the potential for freeze-dryer overloading by calculation of heat/mass flow at the target product temperature. In secondary drying, the expert system chooses a suitable shelf temperature ramping rate from input information, calculates the water desorption rate using pressure rise information, and calculates residual moisture content vs. secondary drying time by combination of the calculated water loss and one experimental moisture content measurement made at the end of primary drying, and determines the shelf temperature vs. time profile required to reach the target residual moisture content. Details of the algorithms are provided in the following text and in the Appendix.

Reliability of Manometric Temperature Measurement: Impact of Drying Heterogeneity

Freeze-drying experiments were conducted for 5% sucrose (amorphous product) and 5% glycine (crystalline product). Sucrose (5%) samples were freeze dried at a shelf temperature of –30°C and 60 mTorr, and 5% glycine was freeze dried at a shelf temperature of –20°C and a chamber pressure of 80 mTorr. The thermocouples were placed in vials at different locations from front and side to middle rows. The numbers shown inside the squares in Fig. 2 indicate the specific thermocouple locations. The thermocouples from back vials behaved the same as from side vials, and their locations were not shown. The primary drying time for a given row is taken as the time when the thermocouple product temperature in that row showed the sharp increase in temperature to approach the shelf temperature, indicating end of ice sublimation in that vial. The total primary drying time was deter-

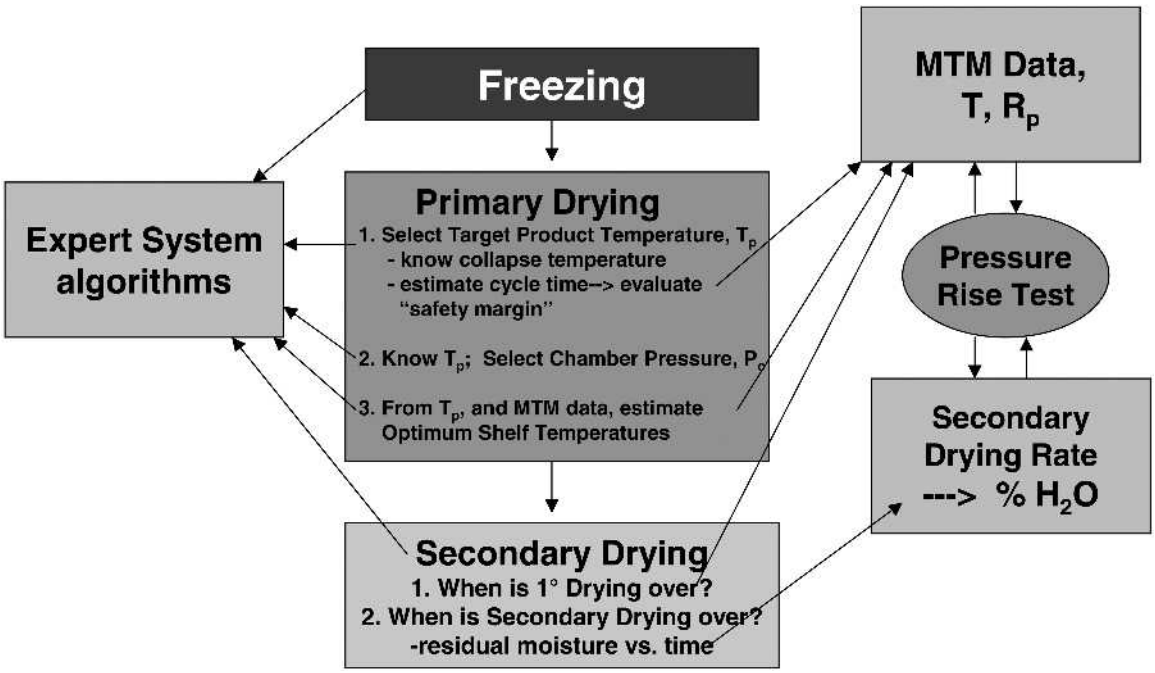

Fig. 1. A schematic summarizing the smart freeze dryer operation.

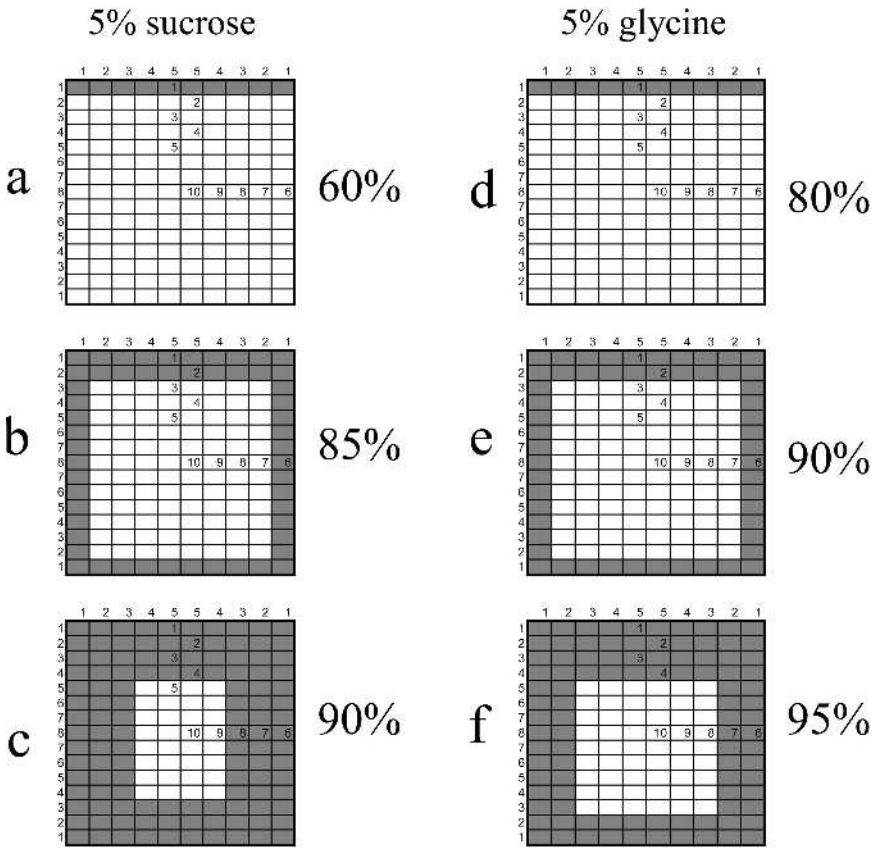

Fig. 2. The propagation of "dry vials" during primary drying. The MTM resistance is no longer accurate once the first row completes primary drying, and the MTM product temperature is no longer valid whenever enough vials "dry" so that the ice sublimation area is less than 150 cm^2. The shaded squares represent vials finished with primary drying (dry vials), and the open squares represent vials still in primary drying (ice vials). The percentages in the figure indicate the extent of primary drying. (a), (b), (c), 5% sucrose; and (d), (e), (f), 5% glycine. In (c), only about 90 cm^2 and in (f) only about 150 cm^2 of ice sublimation area remain.

mined by both a dew point sensor and thermocouple temperature response of vials in the center of the array. The dew point sensor, also called moisture analyzer, can detect the relative humidity or partial pressure of water change in the freeze-drying chamber as primary drying of the batch ends. The dew point sensor shows a much lower dew point at the end of primary drying than during primary drying since the vapor composition changes from essentially 100% water vapor to nearly 0% water vapor at the end of primary drying. The total primary drying time determined by the dew point sensor represents the longest primary drying time for the vials in the freeze dryer, which is always the primary drying time for the vials in the center of the shelf. The shaded squares represent dry vials and the open squares represent vials still in primary drying (ice vials). Freeze drying of 5% sucrose is presented in Fig. 2 a, b, and c. We found that, at 60% of the total primary drying time, the front row finished with primary drying (Fig. 2a). All the side vials, back vials and the vials in the second row from the front finished their primary drying at 85% of the total primary drying time (Fig. 2b), and most vials near the middle of the array finished their primary drying at about 90% of the total primary time (Fig. 2c). At the time represented by Fig. 2c, only about 32 vials were still in the primary drying stage, which means an active ice sublimation area of about 90 cm^2. Similarly, the freeze drying of 5% glycine is shown in Fig. 2 d, e, and f. Here, the vials in the front row finished primary drying at about 80% of total primary drying time (Fig. 2d). The vials in first two front rows and first row from side and back dried at about 90% of the total primary drying time. At 95% of total primary drying time, there were still 54 ice vials left near the middle. The ice sublimation area at this stage was about 150 cm^2.

For MTM data fitting, the number of vials still containing ice (N) must not decrease too much during the process or a systematic error in the resistance parameter, $\hat{R}_p + \hat{R}_s$, will result (8). As some vials finish primary drying before the end of primary drying for the batch, the ice sublimation area calculated at the start is no longer accurate, and the value of $\hat{R}_p + \hat{R}_s$ will be systematically high. That is, the actual value of N is smaller than the value assumed in the calculation (i.e., initial value), which results a high value of $\hat{R}_p + \hat{R}_s$. In practice, we find the fitted MTM $\hat{R}_p + \hat{R}_s$ is no longer accurate after about 60% of total primary drying time for 5% sucrose and at about 80% of total primary time for 5% glycine. The problem is more severe when primary drying is conducted at low shelf temperature, low chamber pressure, and for a low dry layer resistance product, such as 5% sucrose (8,9). As a good general rule, the MTM determined resistance is valid until about 2/3 of total primary drying time has expired.

Accurate MTM product temperature measurement re-

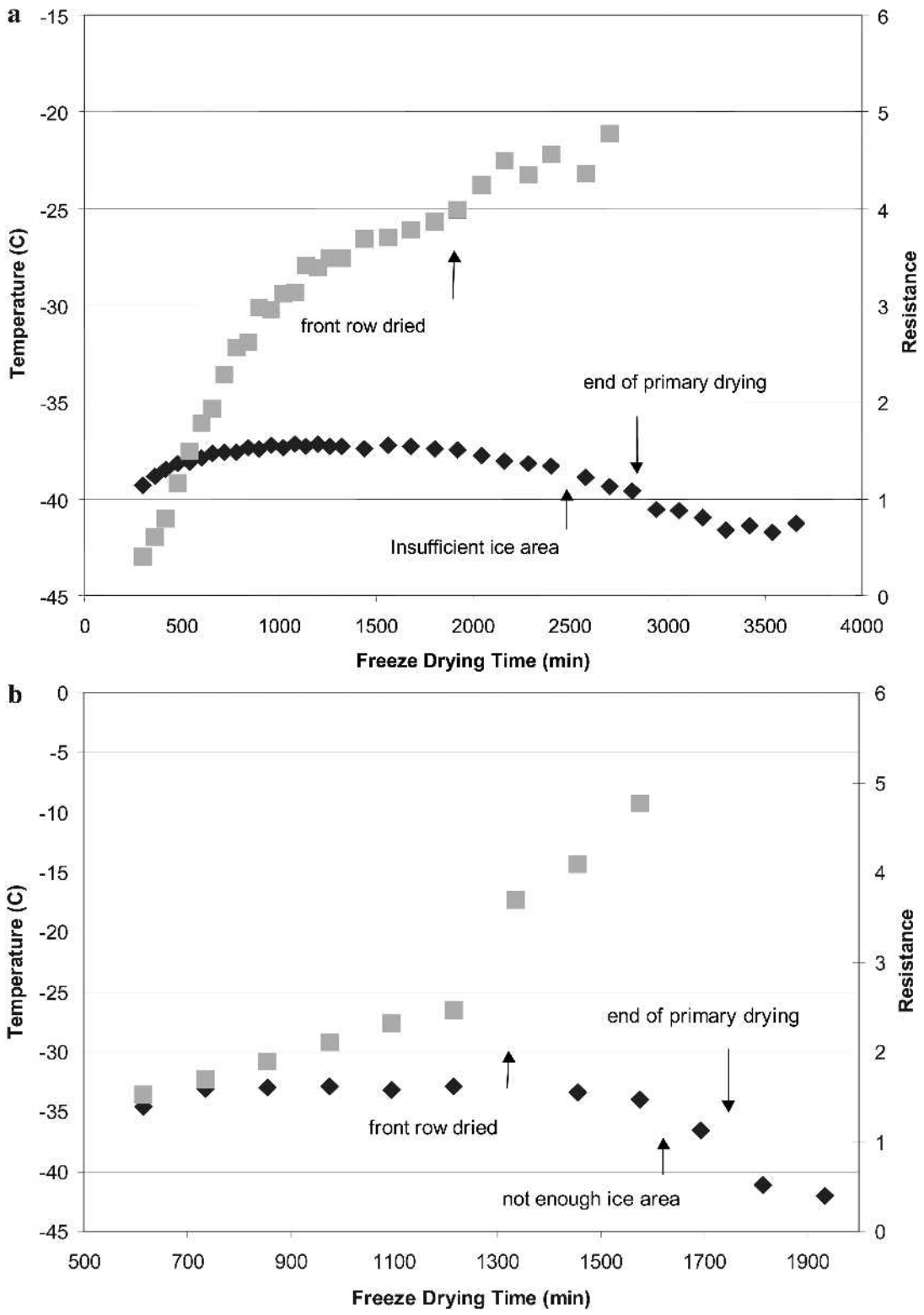

Fig. 3. The MTM product temperature and dry layer resistance for freeze drying of 5% sucrose (a) and glycine (b). The filled squares represent dry resistance and the filled diamonds represent MTM product temperature. The end of primary drying is evaluated by the moisture sensor response.

quires sufficient ice sublimation area to ensure nearly complete chamber pressure rise within the valve closure time (7). For typical freeze-drying runs in a laboratory freeze-dryer (chamber volume 50 L), this requirement means the ice sublimation area needs to be more than about 150 cm^2 or about 50 serum vials (5 ml). This requirement is violated after about 88% of the total primary drying time for 5% sucrose and after 95% of the total primary drying time for 5% glycine. There-

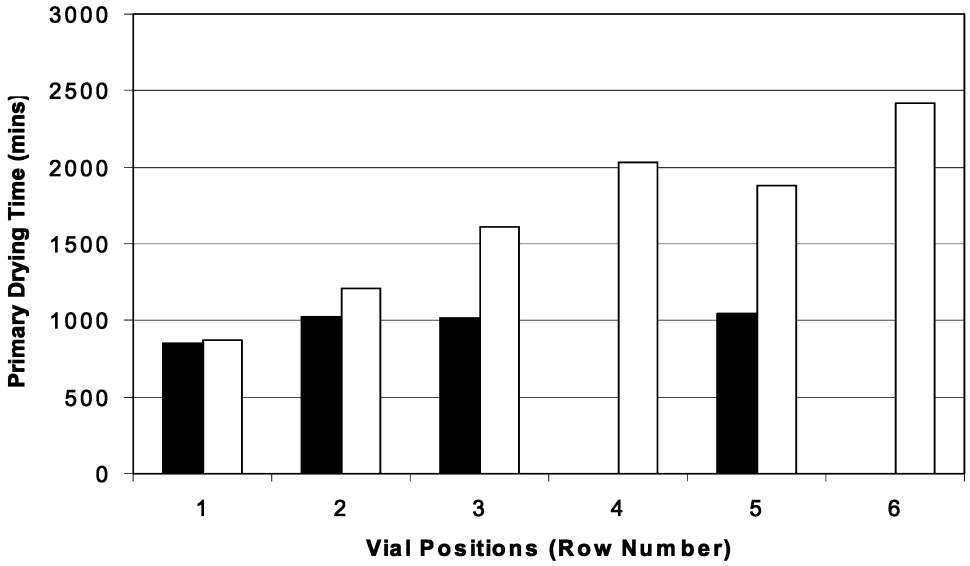

Fig. 4. The effect of vial position on the primary drying times: the edge vial propagation effect. The open bars represent normal vial array, and the filled bars represent product vials separated by empty vials.

fore, the MTM product temperature is reliable almost throughout all of primary drying for typical freeze-drying experiments. The fitted MTM resistance ($\hat{R}_p + \hat{R}_s$) and T_p are presented in Fig. 3a for 5% sucrose and Fig. 3b for 5% glycine. As expected, the MTM $\hat{R}_p + \hat{R}_s$ showed a moderate but sharp increase when the first row vials dried for both freeze drying of 5% sucrose and glycine (Fig. 3 a and b), but the T_p values were accurate (compared with thermocouple results) until much later in the process.

We observe (Fig. 2) that the front row vials finish their primary drying the earliest. The pattern of dry vials moves from outside to inside with the center vials drying last. This phenomenon is likely caused by ice sublimation rate differences between vials at different locations and/or "propagation of edge vials," which changes the next row of interior vials into edge vials whenever the dry vials become their neighbors. The interior vials are defined as the vials surrounded by six other vials containing frozen product. Our data indicate that the ice sublimation rate is essentially the same for all the interior vials during early stages of primary drying (data not shown). Hence, the primary drying time heterogeneity among the interior vials is not caused by differences due to location in the interior array. Rather, edge vial propagation by drying seems to be responsible for the observations. That is, as neighbors dry, the dried products warm to approximately shelf temperature and now transmit heat via radiation to vials still containing ice. A special experiment with freeze drying of 5% glycine was performed to verify this tentative conclusion. Here, all the sample vials were separated by empty vials, so no edge vial propagation would occur during primary drying. The results were compared with corresponding results using the same freeze-drying conditions except that the vials were arranged close-packed as normal. For this special experiment, or "isolated vial" experiment, the primary drying times for all interior vials were essentially the same and were shorter than those of the corresponding close-packed vial array (Fig. 4). For the close-packed array, the front vials finished their primary drying earlier than the interior vials, as expected (Fig. 2c). The shorter primary drying time for separated vials is the result of "edge vials effect," or atypical radiation heat transfer. The edge vials effect denotes the consistent observation that edge vials have high heat and mass transfer rate than the interior vials during primary drying, a result of extra heat transfer to the edge vials from the chamber wall or chamber door which have higher temperature than the sample vials (10). In the array of separated vials, all the vials in the experiment approximate edge vials giving faster primary drying than when the vials are arranged normally in a close-packed array. Therefore, the primary drying time difference between interior vials at different locations of normally close-packed array is caused by the edge vials propagation. That is, the second row vials are turned into edge vials whenever the first row finishes primary drying, thereby increasing their sublimation rate.

Optimum Chamber Pressure and Target Product Temperature During Primary Drying: Optimum Safety Margin

The "Optimum" Chamber Pressure

The chamber pressure should be much lower than the vapor pressure of ice at the target product temperature but yet high enough to minimize heat transfer heterogeneity in freeze drying (14). As a suitable compromise, the chamber pressure is initially set equal to the value of P_c calculated by Eq. (13), using the initial target product temperature ($t_{pinitial}$, °C), which is arbitrarily taken as 3°C below the collapse temperature (T_c) or –15°C, whichever is lower. The initial shelf temperature is then set equal to the initial target product temperature to ensure the product temperature is below the target product temperature (14). A final adjustment in P_c is made once MTM data are available to allow the final target product temperature to be calculated (Eq. 13).

$$P_c = 0.29 \cdot 10^{(0.0191 - t_{pinitial})} \tag{13}$$

Calculating the Target Product Temperature

The target product temperature must always be a safe margin below the collapse temperature. However, the safety

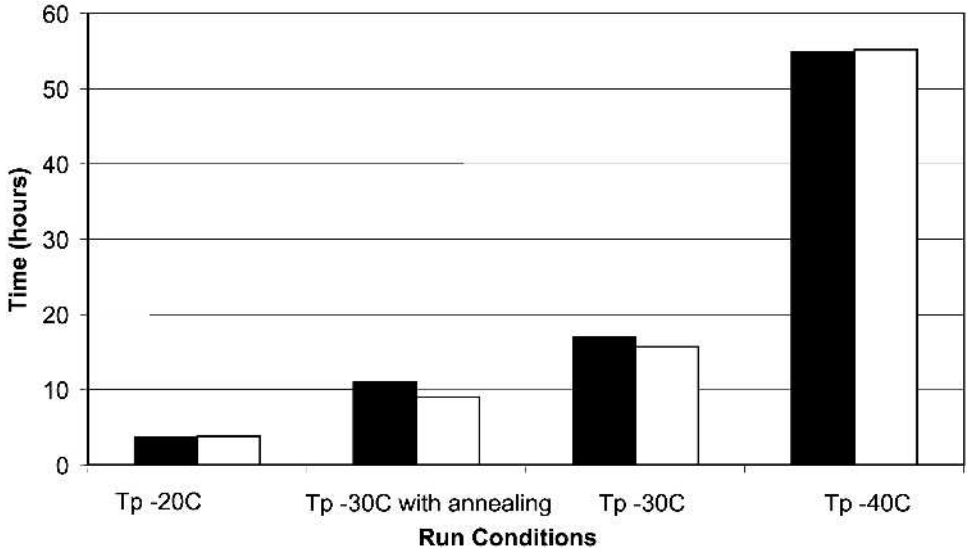

Fig. 5. Prediction of primary drying times by first MTM data for 5% glycine at different product temperatures. The filled bars represent experimental data, and the open bars represent predicted results. The target product temperatures from left to right are –20°C, –30°C, and –40°C, respectively.

margin should not be too large or the process becomes too long. If the primary drying time is estimated to be long (>50 h), the optimum safety margin should be small (i.e., ~2°C). Conversely, a large safety margin (i.e., 5°C) will be used when the primary drying time is expected to be short (<8 h). For the purpose of setting the safety margin, we estimate primary time at the target product temperature using mass transfer rates estimated by early MTM data at low shelf temperature (i.e., $T_s = T_{pinitial}$). To check the accuracy of such estimates of primary drying time, experiments were performed to estimate the primary drying times for different target product temperatures (–20°C, –30°C, and –40°C) and with different materials (glycine and sucrose). The measured thermocouple product temperatures in these experiments were –34°C, –37°C, and –43°C, respectively, when the MTM data were collected. The primary drying times were then predicted by using the MTM data. The results showed good agreement between this estimate of primary drying time and the actual value determined by allowing the process to run to completion (Fig. 5).

The target product temperature is then calculated from the appropriate safety margin and collapse temperature of the formulation (refer to Appendix for detail). The target product temperature is constrained to be no higher than –15°C to avoid mass and heat transfer overload of the freeze dryer. Freeze-dryer overload occurs whenever the heat/mass transfer rate is so high that control of chamber pressure and/or condensor temperature control is lost. The overload problem will be discussed further below. Note that the target product temperature could be slightly different for different formulations with the same collapse temperature (T_c) if their primary drying times are different. Long primary drying times are usually associated with low collapse temperatures. A 5°C difference in target product temperaure means about a factor of two difference in primary drying time. A factor of two is significant for a long primary drying time, but for a short primary drying time of 8 h or less, a factor of two time savings is not of great importance. Thus, large safety margins are used when the cycle is projected to be short.

Freeze-Dryer Overloading Problem

Overloading might occur if freeze drying is performed at high sublimation rate. The overloading could be mass flow overloading and/or heat flow overloading. The former is normally caused by small dimensions for the connection between the freeze-dryer chamber and condensor, and the later is caused by limited heat removal capacity of the refrigeration system. The freeze-dryer overloading problem can be avoided if freeze drying is performed at a low target product temperature, thus low heat/mass flow. However, freeze drying at low target product temperature requires long freeze-drying time. The optimum target product temperature should be one or two degrees below the product temperature at which the freeze-dryer overload occurs. Thereby, in order to estimate the target product temperature, one needs to know the product temperature at which the freeze-dryer overloads ($T_{p\ overloading}$).

The value of $T_{p\ overloading}$ is calculated using Eq. (9) by setting the target heat flow (dQ/dt) equal to the freeze-dryer overload heat flow. If the "normal" calculated target product temperaure is higher than the overloading product temperature, then the value of "$T_{p\ overloading} - 1$" is taken as target product temperature.

Optimizing the Shelf Temperature to Achieve Target Product Temperature

Different approaches to achieving the target product temperature by shelf temperature adjustment were explored (Fig. 6). In steady state, the heat flow may be calculated by Eqs. (4) and (5), in which the P_{ice} is the vapor pressure of ice at the target product temperature. However, heat and mass transfer are not necessarily at steady state early in primary drying, and we find the use of Eq. (9) provides accurate estimates of the proper shelf temperature only at very low target product temperature (i.e., –40°C). The calculated shelf temperatures are much higher than the correct shelf temperatures when higher target product temperatures (–20°C or

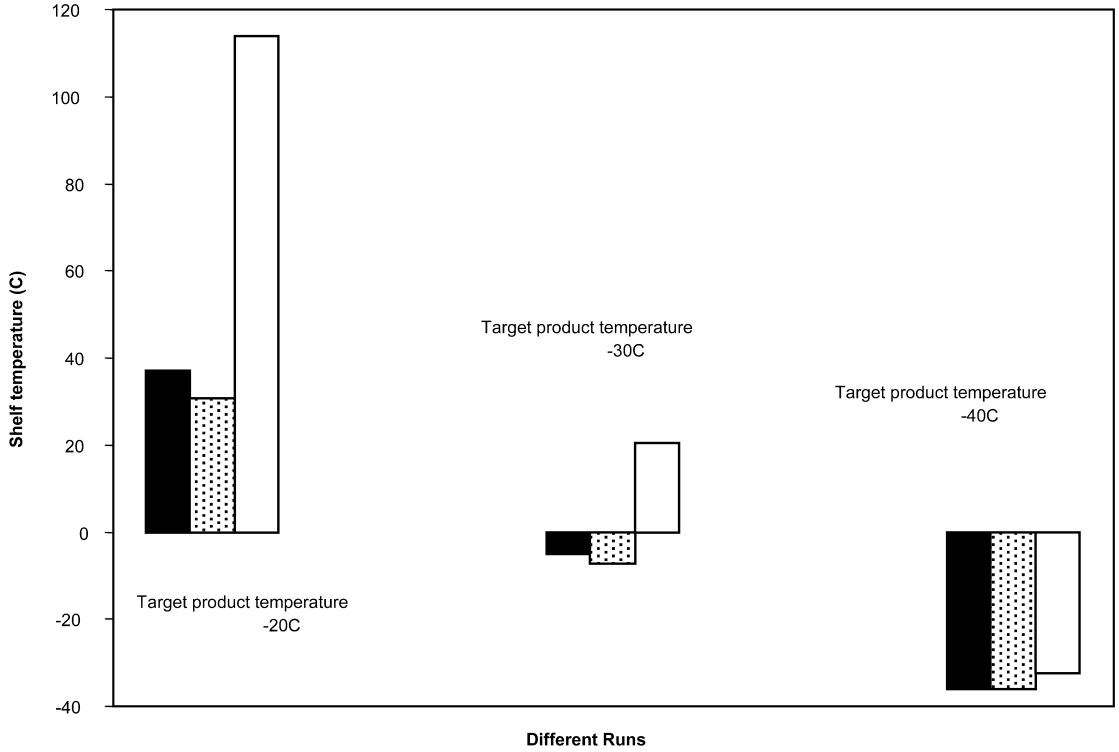

Fig. 6. Optimal shelf temperatures calculated by the steady state method and method B compared with experimental results. Optimal shelf temperature is the shelf temperature that produces a product temperature within 1°C of the target. The filled bars represent correct results, the dot-filled bars represent method B results, and the open bars represent shelf temperature calculated from steady state. Experiments are for freeze-drying 5% glycine.

–30°C) are needed, likely because we are not in steady state and the product resistance is rapidly changing with time (Fig. 6). We therefore explored a number of empirical algorithms that have the effect of moderating the increase in shelf temperature early in the primary drying process. One method that works well we denote "method B" (MB). Here, the calculation uses a heat flow that corresponds to a temperature equal to one-half of the sum of MTM temperature and target product temperature minus one degree. That is, the heat flow is calculated from equations 3-5 with T_p (Eq. 3) given by $T_p(MB) = (T_{MTM} + T_{p\ target} - 1)/2$. Heat flow values at different target product temperatures were predicted by method B and compared with the actual heat flow values calculated from MTM data when the products were freeze dried at the target product temperatures (Table I). The predicted heat flow values for different materials, using method-B values of T_p, are in satisfactory agreement with the actual heat flow values at the target product temperatures evaluated from MTM data. Therefore, method B is a useful method for predicting the heat flow using only MTM data obtained at the very early stages of primary drying.

Table I. The Comparison of Measured Heat Flow (HF) and Predicted HF by the First MTM Data

Formulation	Target T_p (°C)	Actual T_p (°C)	Measured HF cal/hour per vial	Pred HF cal/hour per vial
5% glycine	–20	–34	513	474
5% glycine	–30	–39	191	201
5% mannitol	–30	–38	107	102
5% sucrose	–36	–42	144	155
5% sucrose	–36	–43	134	148

Measured HF is actual heat flow by MTM data for freeze drying conducted at the target product temperature. Pred HF is the predicted heat flow from MTM data, using Eqs. (3)–(5) with T_p (Eq. 3) given by method B.

Figures 6, 7a, b, and c show the results calculated by Eq. (9) using the heat flow estimated from method B. Figure 6 shows that the predicted shelf temperatures using method B are in good agreement with the actual shelf temperatures required to achieve the target product temperatures during freeze drying of 5% glycine at different target product temperatures (Fig. 6). These results show that method B works well at both low (–40°C) and high target product temperatures (–20°C). In Fig. 7a, mannitol (5%) was freeze dried at a target product temperature of –30°C. The chamber pressure was 80 mTorr (as calculated by Eq. 14), and the initial shelf temperature was set to –30°C at the beginning of primary drying. The shelf temperature required to achieve the target product temperature was calculated by the method B using the MTM data from the first hour of primary drying at a shelf temperature of –30°C. Note that the method B procedure was able to achieve the target product temperature by only a few adjustments at the early stage of primary drying, and no further shelf temperature adjustments were required to maintain the target product temperature. Calculated shelf temperatures were similarly tested for different products (5% glycine and sucrose) at different target product temperatures (–30°C, –35°C, and –36°C). In Fig. 7b, sucrose (5%) was freeze dried

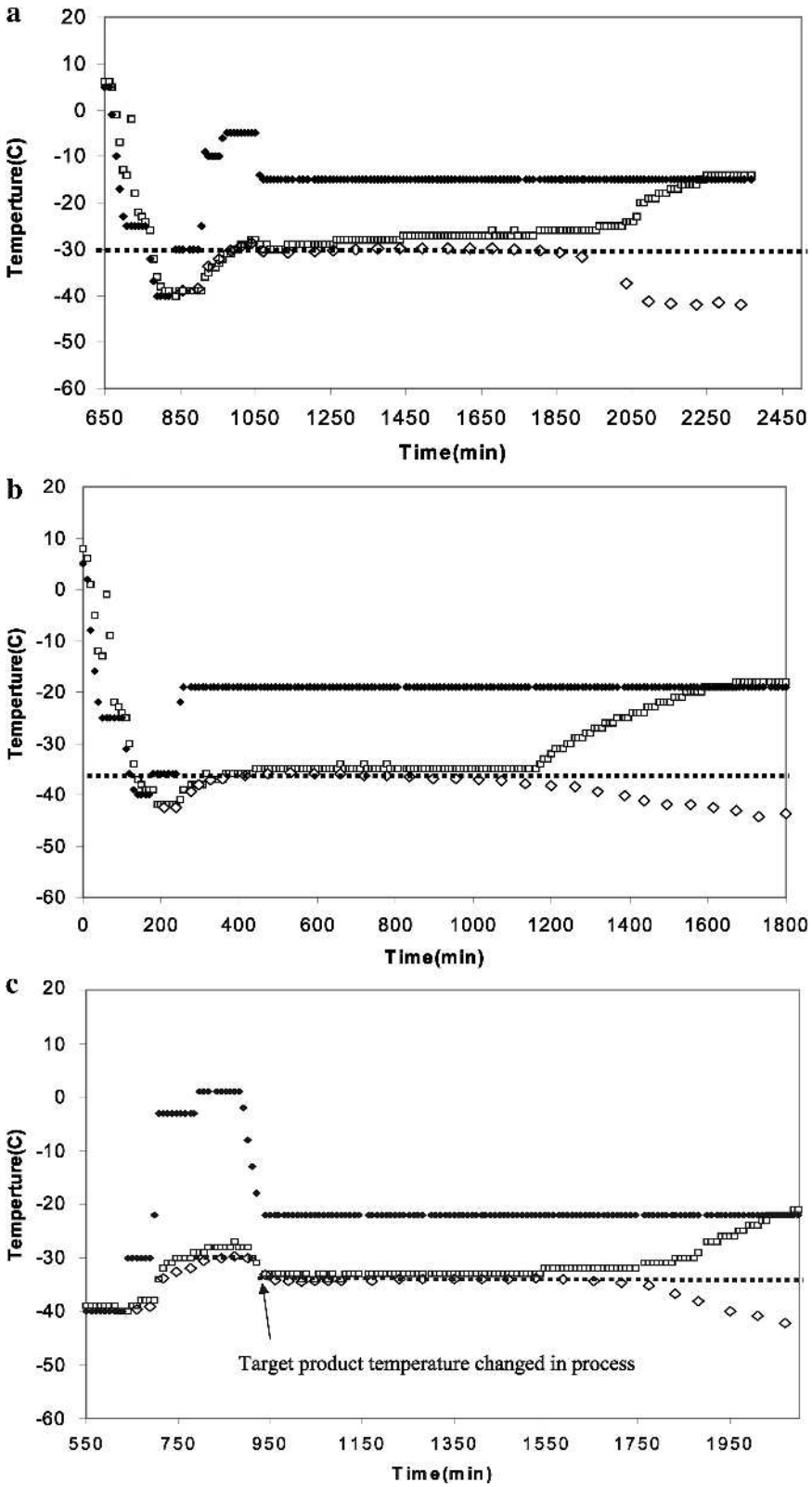

Fig. 7. Shelf temperature optimization by method B. The dashed line represents the target product temperature; filled diamonds represent shelf temperature; opened diamonds represent MTM temperature; opened squares represent thermocouple measured temperature (at bottom). (a) Freeze drying of 5% mannitol. The target product temperature –30°C, calculated P_c 80 mTorr. (b) Freeze drying of 5% sucrose. The target product temperature –36°C, calculated P_c 60 mTorr. (c) Freeze drying of 5% glycine. The target product temperature –30°C then changed to –35°C, P_c 80 mTorr at 900 min.

Table II. Primary Drying End-Point Determined by MTM: Comparison of P_{ice} (Eq. 1) with P_c at the End of Primary Drying

Formulation	T_p (°C)	P_c (mTorr)	P_{ice} (mTorr)	ΔP_{max} (mTorr)
5% mannitol	–30	79	81	124
5% glycine	–30	82	84	164
5% sucrose	–36	65	69	87

T_p is product temperature, P_c is chamber pressure at the beginning of valve closure, P_{ice} is MTM fitted vapor pressure of ice (Eq. 1), and ΔP_{max} is the total chamber pressure rise during the period of valve closure.

at a target product temperature of –36°C. The chamber pressure was 60 mTorr (as calculated by Eq. 13), and the initial shelf temperature was set to –36°C at the beginning of primary drying. The shelf temperature required to achieve the target product temperature was calculated by the method B using the MTM data from the first hour of primary drying at shelf temperature of –36°C. The method B procedure was able to achieve the target product temperature by only one adjustment early in primary drying and no further shelf temperature adjustments were required. Method B can even be used to predict the shelf temperature required to achieve a new target product temperature if the target product temperature is changed during primary drying. Figure 7c shows the results of freeze drying 5% glycine at target product temperatures of –30°C and –35°C during the same run. The first target product temperature (–30°C) was successfully achieved by one shelf temperature adjustment and followed by another successful shelf temperature adjustment to achieve the second target product temperature (–35°C) and the product temperature (–35°C) was maintained without further adjustment.

The shelf temperature is adjusted during primary drying if the product temperature deviates from the target product temperature by more than a predetermined amount (normally ±1°C), provided the primary drying is not more than two-thirds finished. No further adjustment in shelf temperature is needed if primary drying is more than two-thirds finished as determined by MTM results because further adjustment is really not necessary (9) and, second, the MTM data tend to become inaccurate after about two-thirds of primary drying is over.

The End Point of Primary Drying by MTM

The difference between initial chamber pressure and the P_{ice} parameter can be used as an indicator of the end point of primary drying.

Different materials at 5% solids, sucrose (amorphous product), glycine, and mannitol (crystalline products) were freeze dried at different product temperatures and chamber pressures. We find that after the end of primary drying the vapor pressure of ice determined by a fit of MTM data to Eqs. (1) and (2) were close to the initial value of chamber pressure (i.e., before the valve was closed), even though the chamber pressure at the end of the MTM data collection period would be far higher than the initial chamber pressure. At the end of primary drying, the difference between the parameter, P_{ice} (Eq. 1) and the initial pressure, P_c, was within 5 mTorr although the total chamber pressure increases during the MTM test were 124, 164, and 87 mTorr for mannitol, glycine and sucrose, respectively (Table II).

Sucrose and glycine (5%) were used in a test of the sensitivity of MTM to determine the end point of primary drying. In the glycine and sucrose runs, 5% of the vials (8 vials) were double filled (4 ml). All the double filled vials are placed together in the center of the array. Thus, when all the vials of 2 ml fill were dried, the 4ml vials were still in primary drying. The end points of primary drying for the samples with higher fill volume were determined by thermocouple and/or dew point sensor responses. Figure 8 shows one example of freeze-drying vials of 5% glycine with 2 ml fill volume except for 5% of the vials (8 vials) with a 4 ml fill volume. In Fig. 8, all vials under primary drying means no dry vial exists, interior vials under primary drying means all the front, side and back vials are dried, and 5% vials in primary drying means all the 2 ml

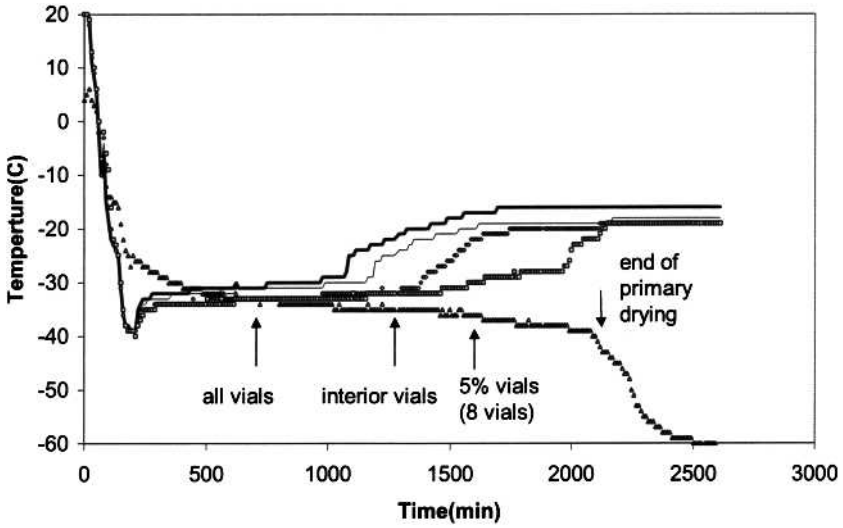

Fig. 8. The assignment of different freeze-drying stages by thermocouple response and dew-point sensor. The thick line represents thermocouple temperature (T_{TC}) for front vials, the thin line T_{TC} for side vials, the open diamonds T_{TC} for center vials, the open squares T_{TC} for center vials of double fill, and the triangles are dew point values.

Table III. Primary Drying End-Point by MTM: Sensitivity of the Method

	Pressure difference when indicated vials are in primary drying			
Formulation	All vials	Center vials	5% vials (8 vials)	End of 1° drying
5% sucrose	79	81	51	1
5% glycine	113	122	90	2
			2% vials (3 vials)	
5% sucrose	82	74	46	1

Pressure difference is $P_{ice} - P_c$, with P_{ice} determined from MTM data fit to Eq. (1). Detection of ice in vials of a given class is via thermocouple response.

fill vials are dried and all the 4 ml fill vials are still in primary drying. The end point of primary drying is indicated by the dew point sensor response (i.e., sharp decrease) and occurs only when essentially all vials are dry and the partial pressure of water sharply decreases (15). The data (Table III) show that even when 95% of the total product finished primary drying, the 5% of product vials still containing ice gave a significant pressure difference between P_{ice} and P_c. For the 5% sucrose run, 2% of 4ml fill vials with ice remaining (3 vials in the freeze dryer) still gave more than a 45 mTorr vapor pressure difference (Table III). Thus, the data show that the MTM method is more than sensitive enough to measure the primary drying end point.

While the results presented in Tables II and III are strictly empirical, such success is predicable. The end point of primary drying is defined as the point when all ice sublimation in the freeze dryer is complete. At this point, no ice remains, and the MTM fitted ice vapor pressure (P_{ice}) should be the same as the chamber pressure (P_c) even though the chamber pressure does slowly increase during the valve closure because of water desorption from the sample. The pressure rise from water desorption would be linear with time as long as the residual moisture content is roughly constant during the MTM process. This linear pressure rise is included in the linear parameter "X" in the MTM equation (Eq. 1) and does not complicate the MTM procedure for determination of primary drying end point. The term X in the MTM equation also includes the air leak rate and the vapor pressure rise due to ice temperature increase during valve closure period. As would be the case for most freeze dryers, the leak rate of the

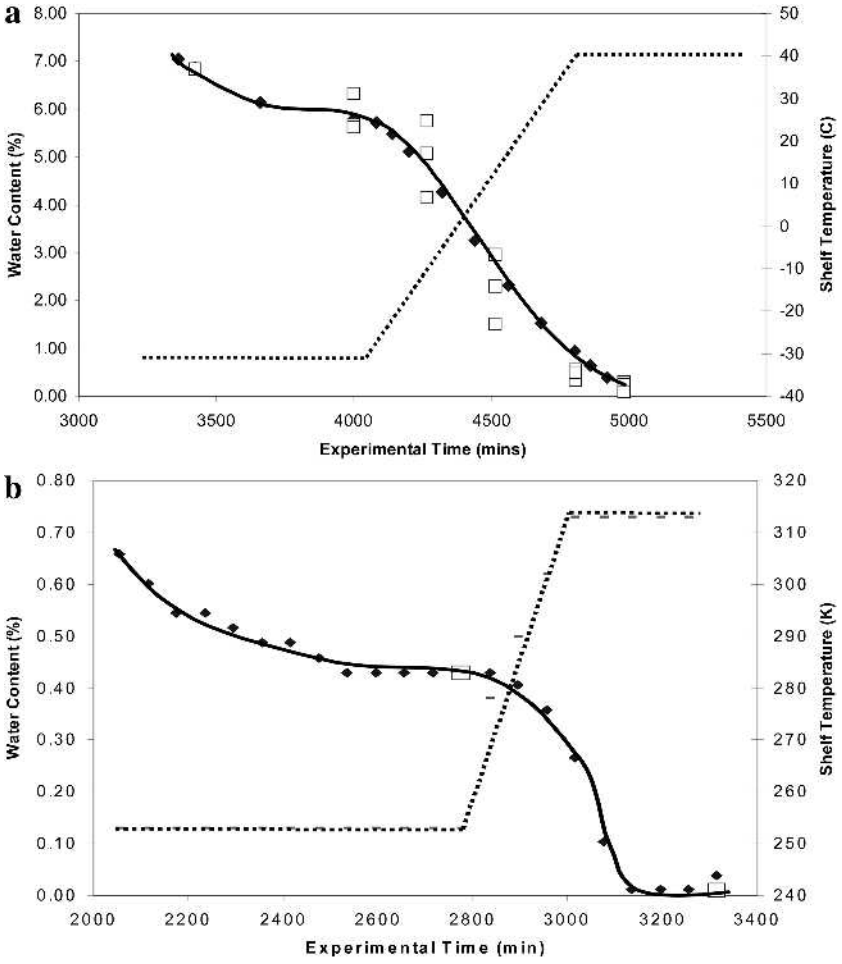

Fig. 9. Residual moisture content during the secondary drying by the pressure rise test (modified MTM method) for freeze drying of 5% sucrose (a) and glycine (b). The open symbols are moisture content directly measured by Karl Fischer and the filled symbols are calculated residual moisture content by modified MTM method. The dashed line is the shelf temperature during freeze drying.

freeze dryer we used is negligible (<1 mTorr/25 s), and when primary drying is over, the vapor pressure rise due to ice temperature increase is zero because there is no ice. Thus, the value of X found after primary drying is almost entirely a result of water desorption. These facts allow the value of P_{ice} compared to P_c to be a good indicator of the end of the primary drying. This method is a variation on the standard pressure rise test, but is much less arbitrary.

The End Point of Secondary Drying by Pressure Rise Method

A pressure rise method was investigated for its feasibility to optimize secondary drying and to estimate the end point of secondary drying. Sucrose (5%) was freeze dried at T_s = –30°C and P_c = 80 mT, and MTM data were collected both during and after the end of primary drying. At the end of primary drying, the fitted MTM vapor pressure, P_{ice}, is equal to chamber pressure, indicating absence of ice. However, the linear part of vapor pressure rise in equation 1 ($X \times t$) during MTM was still significant (ΔP_{max} in Table II). At this stage (no ice exists), the linear pressure rise is composed of two parts: a) air leaks into the freeze dryer, which are negligible for the freeze dryer used (data not shown), and b) the water desorption from the sucrose. Thus, the kinetics of water desorption can be estimated by Eq. (12), as noted earlier in the literature (16).

The assumption in use of Eq. (12) is that the rate of water loss is constant over the time interval between MTM measurements, but of course is allowed to change as the dP/dt changes from one MTM measurement period to another. By summing all Δw values during secondary drying (Eq. 12), one can evaluate the change in moisture content during secondary drying. Further with one independent experimental value for residual water content at a reference time, for example, at the end of primary drying, the real time actual moisture content vs. time curve can be calculated just from the MTM data.

Five percent sucrose (amorphous product) was freeze dried at T_s of –30°C and P_c of 80 mTorr (Fig. 9a). The water content by Karl Fisher (KF) and by the MTM kinetics estimation are in excellent agreement (here, the MTM water content at the end point of primary drying was directly measured by Karl Fischer titration). An experiment using 5% glycine (crystalline product) was performed at T_s of –20°C and P_c of 80 mTorr. Again, the residue moisture results from MTM method and KF are in excellent agreement (Fig. 9b), although here the number of directly measured water contents is limited. Thus, the data demonstrate that the MTM procedure can also be used to estimate residual moisture during secondary drying and define the end point of secondary drying. The real time moisture content can also be used to optimize the secondary drying process, as outlined in the appendix. Alternately, knowing the residual moisture content after the run, the residual moisture content history could be calculated as in Fig. 9.

The water content of the sample can be considered constant during the MTM procedure because the amount of water desorbed during the 25 s of MTM procedure (valve closure period) is small. Thus, the desorption rate during the valve closure period is constant, which means the pressure rise rate, dP/dt, is also a constant. This conclusion is supported by our observations (data not shown).

Limitations of the Procedure

There are obvious limitations in the "smart freeze-dryer" process optimization process discussed. Most important, we do not optimize for drug stability and the simple procedures are not designed for complex crystallization problems. We also observed that the MTM procedure only works well at the very early stage of primary drying when very high concentrations (>20%) of amorphous products are freeze dried (17). In this case, thermocouple temperature data need to be used in the middle and late stage of primary drying in place of the MTM temperature values. However, we note that the most critical shelf temperature calculations are performed at the very early stage of primary drying, where the MTM temperature and resistance are valid even in the case of high concentration of amorphous solutes.

CONCLUSIONS

Manometric temperature measurement and the expert system for good practices in freeze drying does allow development of an optimized freeze-drying process during a single laboratory freeze-drying experiment. The smart freeze-dryer concept does indeed work! It yields a nearly optimized freeze-drying cycle as long as difficult stability and crystallization problems are not present.

ACKNOWLEDGMENT

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Appendix: Smart Freeze Dryer Procedure and Algorithms

I. Start

Step 1) Load containers of interest filled with product of interest into freeze dryer.

Step 2) Input Data for MTM: N, number of vials; A_p, inner area of vials, cm2; L, fill depth, cm; W, fill weight, g; V, effective chamber volume, liter. Input Data for Smart Freeze Dryer or "SMFD": T_c, collapse temperature (obtained from freeze drying microscopy determination of collapse or glass transition temperature (T_g') or eutectic temperature) (°C); C: concentration of solids in solution (g/g).

Step 3) Input Data for SMFD: nature of Drug Product (protein or stable small molecule); physical form of drug product (amorphous or crystalline); type of bulking agent (none, crystalline, or amorphous); ρ, density of the solute (default 1.5)(g/cm^3); type of vials ("molded" or "tubing"); $Q_{overloading}$, overload heat flow for the freeze-dryer (from OQ/PQ data) (cal/hr).

II. Freezing Stage

- For formulation with crystalline products and/or crystalline bulking agents
  - Step 1) Cool shelf 1°C/min to 5°C, hold for 30 min;
  - Step 2) Cool shelf 1°C/min to −5°C, hold for 30 min;
  - Step 3) Cool shelf 1°C/min to −40°C;
  - Step 4) Heat shelf 1°C/min to −22°C, hold for 180 min;
  - Step 5) Cool shelf 1°C/min to T_c −5°C or −40°C, whichever is lower;
  - Step 6) Hold shelf temperature at the stage II, step 5 temperature for 60 min if the fill depth <1 cm; or hold shelf temperature at the stage II, step 5 temperature for 120 min if the fill depth >1 cm.
  - Step 7) Go to III. Primary drying stage—initial.
- For formulation without crystalline products or bulking agents (Amorphous Only)
  - Step 1) Cool shelf 1°C/min to 5°C, hold for 30 min;
  - Step 2) Cool shelf 1°C/min to −5°C, hold for 30 min;
  - Step 3) Cool shelf 1°C/min to T_g' −5°C or −40°C, whichever is lower;
  - Step 4) Hold temperature of shelf at the stage II, step 3 temperature for 60 min if the fill depth <1 cm; or hold temperature of shelf at the stage II, step 3 temperature for 120 min if the fill depth >1 cm.
  - Step 5) Go to III. Primary drying stage—initial.

III. Primary Drying Stage—Initial: Determination of Initial Shelf Temperature, $T_{s\ initial}$

Step 1) Calculate the estimated initial product temperature Tp(initial) and the "initial" chamber pressure, P_c, as described in the text (Eq. 13).

Step 2) Set the initial temperature of the shelf, T_s, to Tp(initial) calculated in stage III above, step 1; then, proceed to Section IV.

IV. Primary Drying Stage—Process Optimization, Data Fitting, and Control

After the shelf temperature has equilibrated to within 2°C of $T_{s\ initial}$ for 60 min, then start the MTM procedure (i.e., close the valve and take pressure vs. time reading at predetermined intervals, normally every ½ hr or every hour). Follow the procedure for calculating (final) target product temperature and shelf temperature settings to maintain target product temperature.

Step 1) Assign ice thickness as $L_{ice} = L/0.918$, where L is the liquid fill depth;

Step 2) Fit Eqs. (1) and (2) (to obtain P_{ice} and $(\hat{R}_p + \hat{R}_s)$) to MTM data;

Step 3) Calculate T_p (MTM) by Eq. (3);

Step 4) Calculate mass flow (dm/dt) by Eq. (4);

Step 5) Calculate nominal heat flow by **Method B** $(dQ/dt)_{MB}$. Here, we use Eqs. (3–5) with temperature T_p in Eq. (3) given by the mean of the present MTM temperature and the target temperature, minus 0.5°C: $T_p(MB) = (T + T_{p\ target})/2–0.5$. If $(dQ/dt)_{MB} \geq Q_{overloading}$, then $(dQ/dt)_{MB} = Q_{overloading}$, else $(dQ/dt)_{MB}$ is the value calculated from Eqs. (3–5);

Step 6) Calculate overload product temperature $T_{p\ overloading}$ by Eqs. (3–5). The maximum value of dm/dt is evaluated from Eq. (5) using Q_{ol} for dQ/dt, the maximum value of P_{ice} is evaluated from this maximum for dm/dt using Eq. (4), and the corresponding value of product temperature, $T_{p\ overloading}$ is calculated from Eq. (3) using this maximum value of P_{ice};

Step 7) Estimate the primary drying time,[1] $t_{primary}$ by the empirically determined approximation: $t_{primary} = 1.4*W*667/[(dQ/dt)_{MB}]$. Here, W is the total initial amount of water per vial, and the 667 is the heat of sublimation in calories per gram;

Step 8) Evaluate the safety margin from estimated primary drying time (step 7) and estimate T_p(target) product temperature,
- if $t_{primary} < 6$ hr; use 5°C safety margin (T_p(target) = T_c −5°C),
- if $t_{primary} > 48$ hr; use 2°C safety margin (T_p(target) = T_c −2°C,
- else use 3°C safety margin (T_p(target) = T_c −3°C),
- if T_p(target) ≥ T_p overloading, then T_p(target) = T_p overloading − 1

Step 9) Calculate "optimal" shelf temperature (T_s) using **Method 1**:

Method 1

- Calculate temperature of bottom ice [T_b by Eq. (7)];
- Calculate heat transfer coefficient of vials (K_v) by rearrangement of Eq. (6), using the current shelf temperature for T_s and using the current MTM data to evaluate dQ/dt from Eqs. (4) and (5);
- Calculate the new shelf temperature setting (T_s) using Eq. (9) with dQ/dt set equal to $(dQ/dt)_{MB}$; set the shelf temperature to the calculated new T_s value.

Step 10) Calculate the final optimum chamber pressure (P_c) by Eq. (13) using the target product temperature as evaluated above using the safety margin selected based upon the estimated primary drying time;

Step 11) Adjust the chamber pressure to P_c calculated in stage IV, step 10;

Step 12) Collect MTM pressure vs. time data, and fit the MTM data. Calculate T_p MTM by Eq. (3);

[1] This method is based upon the experimental results from heat flow estimation by Method B.

Step 13) Calculate the nominal heat flow, $(dQ/dt)_{MB}$ as before in Section IV, Step 5;
Step 14) Calculate ice thickness using **Method 2**:

Method 2

- Calculate mass flow by Eq. (4) for all MTM measurements made;
- Calculated total mass of ice sublimed by numerical integration of all dm/dt values calculated from Eq. (4) from the start of primary drying;
- Calculate ice thickness (L_{ice}) by Eq. (8);

Step 15) Re-calculate the "optimal" shelf temperature (T_s) using **Method 1**, and adjust the shelf temperature to this value of T_s.
Step 16) Collect MTM pressure vs. time data periodically (usually every 15 min for one hr and hourly thereafter), and fit the MTM data.
Step 17) Calculate T_p MTM by Eq. (3):
If, $|T_p$ MTM $- T_p(\text{target})| > 1°C$, then re-calculate T_s by Eq. (9) [using $(dQ/dt)_{MB}$] and adjust the shelf temperature to this calculated T_s, else leave the shelf temperature setting unchanged.
Step 18) Calculate ice thickness as in Section IV, step 14.
If $L_{ice} > (1/3)*(L/0.918)$ and if $|T_p - T_p(\text{target})| > 1°C$, then calculate T_s by **Method 1** as described in Section IV, step 9, and adjust the shelf temperature to this value of T_s, else leave T_s unchanged. Here, T_p means T_p MTM or product temperature evaluated experimentally by temperature sensors (i.e., thermocouples) placed directly in several vials, whichever method of temperature measurement is being employed. Note: if primary drying is more than 2/3 complete, we leave the shelf temperature unchanged until primary drying is fully over.
$T_p(\text{target})$ is used to denote the calculated desired product temperature.
Step 19) If $P_{ice} \leq P_c + 5$ mTorr for two successive MTM measurements, primary drying is over. Go to Section V, Secondary drying stage.

V. Secondary Drying Stage: Operator Selects Either Procedure A or Procedure B (Default Is Procedure A)

Procedure A: Fixed Time Operation

- For formulation with crystalline products and/or crystalline bulking agents
  Step 1) Adjust shelf temperature to 40°C at 0.3°C/min; hold for 60 min.
  Step 2) Adjust shelf temperature to 50°C at 0.3°C/min.
  Step 3) Maintain shelf temperature at 50°C for 180 min; Cool to 25°C at 2°C/min, and terminate the experiment when convenient.
- For non-crystalline formulations (Drug and Stabilizer Amorphous):
  Step 1) Adjust shelf temperature to 40°C at 0.1°C/min;
  Step 2) Maintain the shelf temperature at 40°C for 240 min (if the concentration of formulation $\leq$ 5% w/w); or
  Step 3) Maintain the shelf temperature at 40°C for 360 min (if the concentration of formulation > 5% w/w).
  Step 4) Cool to 25°C at 2°C/min, and terminate the experiment when convenient.

Procedure B:

Step 1) Maintain the shelf temperature at the primary drying setting for 1 hr following the end of primary drying. Then, using a sample extractor, or other suitable method, remove several vials and determine the residual moisture content by a suitable technique, such as Coulometric Karl Fischer titration.
Step 2) Close the valve separating the drying chamber from the condenser chamber, as in the MTM procedure described earlier, and accumulate the pressure vs. time data by this "pressure rise experiment."
Step 3) Calculate the weight percent residual moisture from the accumulated loss of moisture determined from Eq. (11) and the total mass of solute in the dryer.
Step 4) Ramp the shelf temperature to 40°C at 0.3°C/min (crystalline products) or at 0.1°C/min (amorphous products); hold for 60 min.
Step 5) Repeat steps 2–4 (Section V, Method 2) at hourly intervals until either (A) the calculated residual moisture is less than or equal to the target residual moisture. If the target residucal moisture is not specified in the input data, the target will be taken as 0.5%, or (B) the total time elapsed since the beginning of this step exceeds 4 hr. If (A) is true, go to step 7 below; if (B) is true, go to step 6 below.
Step 6) Adjust shelf temperature to 50°C; hold for 60 min, and then repeat steps 2–4 at hourly intervals until either the calculated residual moisture is less than or equal to the target residual moisture or the total time elapsed in this step exceeds 4 hr. Then go to step 7 immediately below.
Step 7) Cool to 25°C at 2°C/min, and terminate the experiment when convenient.

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