AAPS PharmSciTech 2006; 7 (4) Article 97 (http://www.aapspharmscitech.org).

Evaluation of Manometric Temperature Measurement (MTM), a Process Analytical Technology Tool in Freeze Drying, Part III: Heat and Mass Transfer Measurement

Submitted: December 22, 2005; Accepted: June 5, 2006; Published: December 22, 2006

Xiaolin Charlie Tang,[1,3] Steven L. Nail,[2,4] and Michael J. Pikal[1]

[1]School of Pharmacy, University of Connecticut, Storrs, CT
[2]Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN
[3]Current address: Formulation Development, Centocor Inc, Radnor, PA
[4]Current address: Baxter Solutions, Bloomington, IN

ABSTRACT

This article evaluates the procedures for determining the vial heat transfer coefficient and the extent of primary drying through manometric temperature measurement (MTM). The vial heat transfer coefficients (K_v) were calculated from the MTM-determined temperature and resistance and compared with K_v values determined by a gravimetric method. The differences between the MTM vial heat transfer coefficients and the gravimetric values are large at low shelf temperature but smaller when higher shelf temperatures were used. The differences also became smaller at higher chamber pressure and smaller when higher resistance materials were being freeze-dried. In all cases, using thermal shields greatly improved the accuracy of the MTM K_v measurement. With use of thermal shields, the thickness of the frozen layer calculated from MTM is in good agreement with values obtained gravimetrically. The heat transfer coefficient "error" is largely a direct result of the error in the dry layer resistance (ie, MTM-determined resistance is too low). This problem can be minimized if thermal shields are used for freeze-drying. With suitable use of thermal shields, accurate K_v values are obtained by MTM; thus allowing accurate calculations of heat and mass flow rates. The extent of primary drying can be monitored by real-time calculation of the amount of remaining ice using MTM data, thus providing a process analytical tool that greatly improves the freeze-drying process design and control.

KEYWORDS: freeze drying/lyophilization, manometric temperature measurement, process analytical technology for freeze drying, vial heat transfer coefficient.

INTRODUCTION

Primary drying is usually the longest stage of the freeze-drying process and significant efforts are required to design and optimize this stage.[1-3] The duration of primary drying, which depends on the ice sublimation rate and fill volume, may range from several hours to weeks. Ice sublimation consumes heat, which is mainly provided by the freeze-dryer shelf and the heat consumption results in a temperature gradient between the freeze-drying product and the shelf. In steady state, the heat removed by ice sublimation or mass transfer is equivalent to the heat transfer from the shelf and other sources (ie, radiation from the freeze-dryer chamber wall and door) to the vials. This phenomenon is denoted "heat and mass transfer coupling."[4] The temperature difference between product and shelf together with the vial heat transfer coefficient (K_v) determines the ice sublimation rate. At fixed shelf temperature and chamber pressure, a higher K_v gives a higher ice sublimation rate and a higher product temperature during primary drying.[4,5] For a given target product temperature and chamber pressure, K_v together with the dry layer resistance determines the shelf temperature needed to achieve the target product temperature.[2,5] Therefore, K_v, which directly impacts heat and mass transfer, is a very important parameter in the freeze-drying process design and control. Ideally, the K_v of a given vial in a given freeze-dryer depends only on the chamber pressure, increasing as chamber pressure increases.[4,6] However, it is found that K_v may vary with vial location, vial arrangement, and can even vary slightly between freeze-dryers. Usually, the center vials have a smaller heat transfer coefficient than the edge vials because the edge vials receive more radiation heat transfer. Because of smaller radiation effects, the vials in manufacturing freeze-dryers typically have smaller heat transfer coefficients than do laboratory freeze-dryers operating at the same chamber pressure and shelf temperature. Therefore, measurement of K_v is a matter of some importance for freeze-drying process transfer and scale-up. K_v can be measured by a gravimetric method.[4,6] The gravimetric method may involve weighing vials after a given time in primary drying or might involve periodically extracting vials from the freeze-dryer using a

Corresponding Author: Michael J. Pikal, School of Pharmacy, U-2092, University of Connecticut, 372 Fairfield Road, Storrs, CT 06269-2092. Tel: (860) 486-3202; Fax: (860) 486-4998; E-mail: pikal@uconnvm.uconn.edu

sample thief and weighing to obtain the ice sublimation rate (dm/dt) and therefore the heat transfer (dQ/dt) by $dQ/dt = \Delta Hs \cdot (dm/dt)$.[7]

In this article, the K_v values are calculated from MTM results, ie, the product dry layer resistance and vapor pressure of ice at the sublimation interface from which the product temperature is calculated. The MTM K_v values are then compared with corresponding data from gravimetric methods. The systematic errors in MTM K_v values are discussed and methodology that can minimize the errors is proposed. The heat and mass transfer rates are also calculated from MTM data and are evaluated for accuracy. Furthermore, for the first time, the extent of primary drying as measured by ice thickness is estimated from MTM data, and the results are evaluated for accuracy. We find that accurate values for K_v, heat and mass transfer rates, and extent of primary drying may be obtained in real time by the MTM method, which means that MTM offers process analytical technology well beyond sample temperature measurement. The success of the calculation of extent of primary drying helps freeze-drying process monitoring and process optimization.

MATERIALS AND METHODS

Sucrose, glycine, and mannitol were purchased from Sigma (St. Louis, MO) and used without further purification. All the reagents were analytical grade. All vials used for freeze-drying were 5-mL serum tubing vials from Fisher (Pittsburgh, PA). The stoppers were gray butyl 20-mm finish, double-vent (Wheaton, Millville, NJ).

Freeze-drying

Freeze-drying was performed with an FTS Dura-Stop/Dura-Top freeze-drier (FTS-Kinetics, Stone Ridge, NY) with the manometric temperature measurement (MTM) software installed. All solutions were prepared by weight volume ratio (wt/vol). Sample vials (150) were loaded on the middle shelf of the freeze-dryer for all freeze-drying runs. Thermal shields or radiation shields were used for some experiments, including empty (dummy) vials surrounding sample vials to cut heat transfer from the freeze-dryer chamber wall and the door, and aluminum foil attached at the inside of the chamber door to reduce the radiation from the door.

The freeze-drying cycles for 5% glycine and mannitol were as follows. (1) Freezing: cool 1°C/min to 5°C, hold for 30 minutes; cool 1°C/min to –25°C, hold for 60 minutes; cool 1°C/min to –40°C, hold for 60 minutes. (2) Primary drying conditions were changed according to the specific experimental design: chamber pressure varied from 60 to 120 mTorr as designed; after pump-down, the shelf temperature was increased at 1°C/min to the assigned shelf temperature (from –30 to 43°C). Primary drying was stopped before all ice was sublimed (ie, near the beginning or near the half-way point of primary drying) to determine the average ice sublimation rate gravimetrically. The sample vials were weighed before and after the freeze-drying experiments, and the mass differences were ice sublimed during primary drying, Δm (g/vial). The average sublimation rate, <dm/dt> (g $hr^{-1}vial^{-1}$) was calculated by Equation 1.

$$\langle \frac{dm}{dt} \rangle = \frac{\Delta m}{\Delta t} \tag{1}$$

where Δt is the time in primary drying.

The freeze-drying cycles for 5% sucrose were as follows. (1) Freezing: 1°C/min to 5°C, hold for 30 minutes; cool 1°C/min to –40°C, hold for 60 minutes. (2) Primary drying: chamber pressure 80 mTorr; ramp at 1°C/min to the assigned shelf temperature, hold until primary drying is completed. The end point of primary drying was determined by combined use of thermocouple product temperature and dew point sensor.

Manometric Temperature Measurement

The manometric temperature measurement (MTM) was made at 1- or 0.5-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 seconds. The MTM equation (Equation 2) or combination of Equations 2 and 3 were fitted to the MTM data, which were the chamber pressure as a function of time by nonlinear regression analysis using a software package (Microcal Origin, Northampton, MA) that uses a Marquardt-Levenberg algorithm.

The MTM equation (Equation 2) describes vapor pressure rise in the freeze-drying chamber (P, Torr) as a function of valve closure time during MTM (it, seconds).[8,9]

$$P(t) = P_{ice} - (P_{ice} - P_0) \cdot \exp\left[-\left(\frac{3.461 \cdot N \cdot A_p \cdot T_s}{V \cdot (\hat{R}_p + \hat{R}_s)} \right) \cdot t \right] + 0.0465 \cdot P_{ice} \cdot \Delta T \cdot \left[1 - 0.811 \cdot \exp\left(-\frac{0.114}{L_{ice}} \cdot t \right) \right] + X \cdot t \tag{2}$$

where P_{ice} is the vapor pressure of ice at the sublimation interface (fit, Torr); P_0 is the chamber pressure (set, Torr); N is the total number of samples vials (known); A_p is the inner cross-section 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 (fit); L_{ice} is the ice thickness (calculated, cm); ΔT is the temperature difference between ice sublimation interface and bottom of the vials (fixed value: 2°C, or evaluated from the data); and X is a constant (fit, Torr/s). We emphasize that the value of ΔT can also be evaluated from the data without introducing new parameters. Steady-state heat and mass transfer theory gives Equation 3.[4]

$$\Delta T = \frac{\left[24.7 \cdot L_{ice} \cdot (P_{ice} - P_0)/(R_p + R_s) - 0.0102 \cdot L_{ice} \cdot (T_s - MTM)\right]}{1 - 0.0102 \cdot L_{ice}} \quad (3)$$

where T (°C) is the product temperature at the ice sublimation interface, which is related to vapor pressure of ice at the sublimation interface by Equation 4.[5,10]

$$T = \frac{-16144.96}{\ln(P_{ice}) - 24.01849} - 273.15 \quad (4)$$

MTM curve fits were performed by use of Equation 2, where ΔT is given by Equation 3, as this is the more accurate procedure.[11]

The converged curve fit yields both vapor pressure of ice, from which product temperature (T) is calculated from Equation 4, and total resistance of stoppers and product dry layer ($\hat{R}_p$+$\hat{R}_s$).[8,9] The resistance of stoppers ($\hat{R}_s$) is constant at constant pressure and often negligibly low. Therefore, the total resistance ($\hat{R}_p$+$\hat{R}_s$) can often be interpreted as the product resistance, $\hat{R}_p$.[4]

Heat transfer coefficient of vials

The heat transfer coefficient of vials was measured by both the gravimetric method and the MTM method. During primary drying, the heat flow in from the shelf to sample vials is equal to the heat consumed by ice sublimation. The heat flow in from shelf during primary drying is calculated by Equation 5.[4]

$$\frac{dQ}{dt}(in) = K_v \cdot A_v \cdot (T_s - T_b) \quad (5)$$

where, dQ/dt is the heat transfer rate (cal hr^{-1} vial^{-1}); A_v is vial cross-sectional area (cm^2); T_s is the shelf temperature (°C); T_b is the temperature of the vial bottom (°C), which can be directly determined by thermocouples or calculated (Equation 2 in Milton et al[9]); and K_v is the vial heat transfer coefficient. The temperature at the vial bottom is related to the temperature at the ice sublimation interface (T) by,

$$T_b = \Delta T + T \quad (6)$$

and ΔT is calculated by Equation 3.

The heat consumed by ice sublimation, dQ/dt (out), is calculated by Equations 7 and 8.

$$\frac{dQ}{dt}(out) = \Delta H_s \cdot \frac{dm}{dt} \quad (7)$$

$$\frac{dm}{dt} = A_p \cdot \frac{P_{ice} - P_c}{\hat{R}_p + \hat{R}_s} \quad (8)$$

where *dm/dt* is ice sublimation rate (g/hour/vial); A_p is internal cross section area of vials (cm^2); P_{ice} is vapor pressure of ice at the temperature of sublimation surface (Torr), which is a paramenter obtained by fit of the MTM equation to the pressure rise data; P_c is the pressure in the freeze-drying chamber (Torr); and $\hat{R}_{ps}$ is the MTM total resistance (cm^2 Torr hour/g). The average mass flow, <dm/dt>, is calculated by Equation 1 when the total mass loss during primary drying time is known.

Therefore, the heat transfer coefficient of vials (K_v) can be calculated by combination of Equations 5 to 8 for the MTM method or by combination of Equations 1, 5, and 7 for the gravimetric method. Note that the MTM values will be accurate as long as $\hat{R}_{ps}$ and P_{ice} are accurate, ie, as long as dm/dt is correct. The gravimetric method yields an average K_v value over the time of primary drying, evaluated from initial and final vial weighings, but since chamber pressure is held constant, K_v should not vary with time. Both methods should yield an "average" K_v for the product load.

$$K_v(MTM) = \Delta Hs \cdot \frac{A_p}{A_v} \cdot \frac{P_{ice} - P_c}{\hat{R}_p \cdot (T_s - T_b)} \quad (9)$$

$$K_v(gravimetric) = \Delta Hs \cdot \frac{A_p}{A_v} \cdot \frac{\Delta m/\Delta t}{<T_s - T_b>} \quad (10)$$

Calculation of ice thickness

Ice sublimation rate is calculated by Equation 8. The mass of ice sublimed, m (t), (g) is calculated by numerical integration of dm/dt over the time of primary drying. The dry layer thickness is then calculated with Equation 11.[6]

$$l(t) = \frac{m(t)}{\rho I A p \varepsilon} \quad (11)$$

where *l(t)* is dry layer thickness (cm) at time t; *m*(*t*) is the mass of ice sublimed at time t (g/vial); ρ_I is density of ice (g/cm^3); ε is the porosity volume fraction of ice, which is ~0.97 for 5% glycine, sucrose, or mannitol and 1.00 for 1% glycine. The mass of ice sublimed is calculated by numerical integration of the ice sublimation rate, dm/dt, using the trapezoidal rule. The mass transfer rate (dm_n/dt) at the time of each MTM measurement (t_n) is calculated by Equation 8 using the MTM resistance, $(\hat{R}_{ps})_n$, and vapor pressure of ice at the sublimation interface $(P_{ice})_n$.

Heat Transfer (Flow) During Primary Drying

The MTM heat flow is calculated using Equation 7 from MTM mass flow as evaluated by Equation 8 and the gravimetric heat flow is calculated by Equation 7 from gravimetric mass flow (Equation 1), which is an average value for the data collection interval. For example, the average mass transfer rate during time interval between t_2 and t_1 is calculated from the mass loss at the time interval $\Delta m_{(2,1)}$ and the time interval $t_{(2,1)}$ (Equation 12). A sample thief was used to extract 3 vials for weighing at each gravimetric time point during primary drying.

$$\langle \frac{dm}{dt} \rangle t_{(2,1)} = \frac{\Delta m_{(2,1)}}{t_{(2,1)}} \qquad (12)$$

Therefore, the MTM heat flow is an instantaneous value while the gravimetric heat flow is the average for the data collection interval.

Thermocouple Placement

Thermocouples were 28-gauge Copper-Constantan thermocouples with an accuracy of ±1ºC verified by calibration against certified mercury-in-glass thermometers. The thermocouple product temperatures were measured at different locations during freeze-drying including edge vials (front and side vials) and internal vials and were placed in the middle of the vials touching the vial bottoms.

RESULTS AND DISCUSSION

Vial Heat Transfer Coefficients

The heat transfer coefficients of vials were determined by both the MTM and gravimetric methods under different freeze-drying conditions for different materials (glycine, sucrose, and mannitol). Glycine and mannitol are both examples of crystalline products, and sucrose is an example of an amorphous product with a low collapse temperature (–34ºC). The heat transfer coefficients determined by the gravimetric method are considered to be true values. Experiments were designed to freeze-dry 5% glycine at a chamber pressure of 80 mTorr and at different shelf temperatures from low temperatures of –20°C and 0ºC to a high temperature of +20ºC, which is close to the ambient temperature of 22ºC. However, the freeze-dryer lost pressure control for the 20°C shelf temperature experiment. Instead of freeze-drying at a chamber pressure of 80 mTorr, the run was conducted at a chamber pressure of 89 mTorr. The reason for the loss of pressure control is that the freeze dryer was overloaded by the high mass flow at high shelf temperature (+20ºC).

Vial heat transfer coefficients determined by both the MTM method (calculated by Equation 9) and the gravimetric method (calculated by Equation 10) are compared in Table 1. Thermal shields means both dummy vials and aluminum foil, with the aluminum foil on either the inside or outside door surface. The MTM data are obtained using ΔT from pressure rise data, and the MTM K_v values were taken at the mid-point of primary drying. The gravimetric data are averages over about one half of primary drying. Results from the 2 methods were in good agreement when high shelf temperature (+20ºC) was used (experiment 6). However, poor agreement was found when low shelf temperature (–20 ºC) was used for primary drying (experiment 2). We also note that the K_v values (gravimetric method) varied among experiments. The K_v for experiment 6 is higher than for experiments 1 to 5, which is likely caused by the higher chamber pressure in experiment no. 6, and the K_v value for experiment 7 (120 mTorr) is much higher. Higher K_v at higher chamber pressure is expected.[4] Moreover, at high chamber pressure (120 mTorr), the K_v values from both methods were in satisfactory agreement. In many cases, the K_v values from the MTM method were much higher than those obtained from the gravimetric method. The difference between K_v values determined by the 2 methods was greatest for 5% sucrose, smallest for 5% mannitol, and in-between for 5% glycine. The systematic difference between K_v values determined by MTM and gravimetric data indicate a systematic error in the MTM method. The most probable source of this systematic error is the systematic error (low value) of MTM resistance $(\hat{R}_{ps})$ caused by atypical radiation. This issue will be discussed in more detail in the following sections.

Product dry layer resistances vary with the nature of the solutes and it seems that high-resistance products yield better MTM K_v results. That is, agreement between K_v data is better for mannitol (high resistance) than for glycine (low resistance). Further, comparing experiments 2 and 3, it is obvious that agreement in K_v data is better for higher concentration (experiment 3) than for lower concentration (experiment 2). Of course, higher concentration means higher resistance.[9] Agreement between MTM and gravimetric K_v data improves as primary drying proceeds (Figure 1) and dry layer resistance increases.

The effect of using thermal shields is also explored in Table 1. The results show that agreement between MTM and gravimetric results is greatly improved when aluminum foil was used at the inside of the chamber door. As expected, attaching aluminum foil at the outside of the chamber door did not improve MTM K_v accuracy. We note that gravimetric K_v method values from the experiment when aluminum

Table 1. Vial Heat Transfer Coefficient (Kv): MTM Method Compared With Gravimetric Method

Exp. No.	Material	T_s, °C	P_c, mTorr	Thermal shields	$K_v \cdot 10^4$ MTM	$K_v \cdot 10^4$ Gravimetric
1	1% glycine	–20	80	No	5.53	3.09
2	5% glycine	–20	80	No	3.87	3.05
3	10% glycine	–20	80	No	3.07	3.06
4	5% glycine	0	80	No	3.71	3.16
5	5% mannitol	–20	80	No	3.11	3.06
6	5% glycine	20	89	No	3.56	3.42
7	5% glycine	–20	120	No	4.18	4.46
8	5% glycine	–20	80	Inside	2.80	2.74
9	5% sucrose	–30	80	Outside	5.08	2.50
10	5% sucrose	–30	80	No	4.11	3.11
11	5% sucrose	–30	80	Inside	2.67	2.42

shields were used were smaller than those from the corresponding experiment when no thermal shields were used, ie, experiment 2 versus experiment 8 and experiment 10 versus experiment 11. The K_v differences are caused by radiative heat transfer coefficient (K_r) differences. The K_r values are reduced by using thermal shields, which cut the radiation from the freeze-drying chamber door and walls. The improvement in K_v with application of aluminum foil has significance for scale-up because manufacturing freeze-dryers do not have plastic doors of high emissivity. Therefore, the same vials will have a smaller K_v value in manufacturing freeze-dryers than in laboratory freeze-dryers. The smaller K_v means longer primary drying time under the same freeze-drying conditions. Thus, it is strongly suggested that radiation shields (thermal shields) be used for freeze-drying process development experiments performed in laboratory freeze-dryers.

The MTM K_v is calculated by Equation 9, in which the resistance ($\hat{R}_{ps}$) and vapor pressure of ice at the sublimation interface (P_{ice}) are required. Consequently, the accuracy of MTM K_v values are dependent upon accuracy of the $\hat{R}_{ps}$ and P_{ice} values. Usually, the MTM P_{ice} values are accurate.[12] However, the MTM-determined resistance parameter, $\hat{R}_{ps}$, is typically below the actual value due to fast vapor pressure rise from warm vials at the edge of the vial array.[11] In Equation 9, the K_v is inversely proportional to $\hat{R}_{ps}$. Therefore, the small R_p value will cause a large K_v value. Typically, the K_v values from the MTM method were greater than the actual K_v values determined by the gravimetric method (Table 1). The MTM K_v values were improved when higher chamber pressure, higher shelf temperature, or thermal shields were used because the MTM $\hat{R}_{ps}$ values were improved when freeze-drying is performed under these conditions.[11] The accuracy of MTM $\hat{R}_{ps}$ values is also product resistance sensitive, ie, the difference between MTM $\hat{R}_{ps}$ and actual values tends to be smaller at higher $\hat{R}_{ps}$. This is likely the reason why high concentration of glycine and the higher resistance materials gave more accurate MTM K_v values. The resistance for 5% sucrose is less than that for 5% glycine, and $\hat{R}_{ps}$ of 5% glycine is less than $\hat{R}_{ps}$ of 5% mannitol (Table 1).[11] The trend in Figure 1 can also be explained as a direct result of the increase in dry layer resistance with increasing primary drying time. In summary, the MTM method gives accurate K_v values whenever the MTM P_{ice} and $\hat{R}_{ps}$ values are accurate.

Heat Flow During Primary Drying Determined by MTM

The significance of heat flow rate (or mass flow rate) calculation during primary drying is that we can estimate the potential for dryer overload, as long as the maximum heat and mass flow rate for the dryer is known from operational qualification (OQ) data.

The MTM heat flow calculated by Equations 3 and 4 is compared with heat flow via the gravimetric method in Figure 2. The MTM data were obtained with ΔT being evaluated from the data; both dummy vials and Al foil on the inside of the

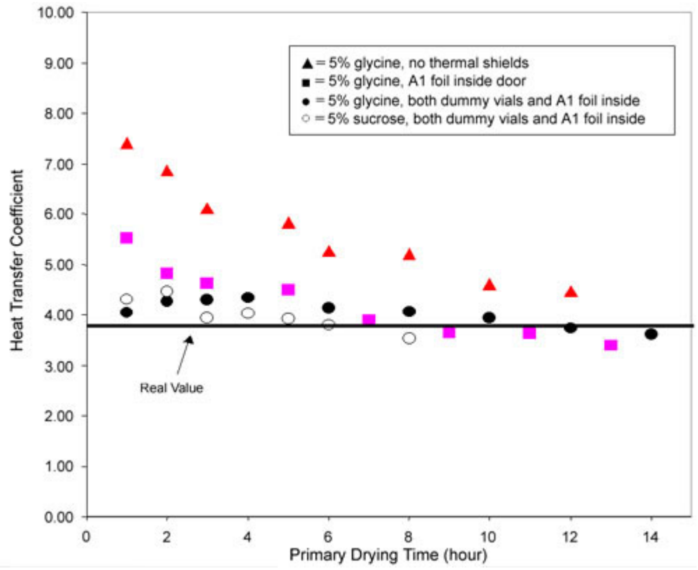

Figure 1. The MTM K_v values through primary drying under different conditions. MTM data with ΔT evaluated from data.

Table 2. Vial Array Effects in the Sublimation Rate, dm/dt, During Primary Drying 5% Sucrose at a Shelf Temperature of –30ºC and a Chamber Pressure of 80 mTorr

Condition	dm/dt Interior	dm/dt Side	dm/dt front	dm/dt Overall	dm/dt MTM
Metal guard	0.72 ± 0.05	0.85 ± 0.06	1.07 ± 0.04	0.75	0.76
No metal guard	0.66 ± 0.03	0.92 ± 0.12	1.51 ± 0.04	0.78	0.85

door were used as thermal shields. The error bars in the gravimetric data give the standard deviation for 3 vial samples. Good agreement is observed. This result is expected since accuracy in heat flow depends on the accuracy in $\hat{R}_p$ and P_{ice}. Thus, whenever $\hat{R}_p$ and P_{ice} are accurate, the heat flow will be accurate.

The heat flow during primary drying decreases with time as expected because the product dry layer resistance increases with primary drying time, and a higher resistance causes slower ice sublimation, thus smaller heat flow. The resistance increased more than 3-fold from the beginning to the end of its primary drying (data not shown). However, the heat flow only decreased ~20% because of the increasing product temperature in primary drying (more than 2°C product temperature increase from the beginning to the end of primary drying). The standard deviation for gravimetric heat flow values is relatively large, likely reflecting the inter-vial ice sublimation heterogeneity during primary drying. The high variation in heat flow means large sublimation heterogeneity between vials, which might be caused by heterogeneity in super-cooling or by heterogeneity in glycine crystallization.

Ice sublimation rate by MTM: vial array effects

In Table 2 are given the ice sublimation rates calculated by Equation 4 for MTM results and by Equation 5 for gravimetric data. Values of dm/dt in columns 2 to 5 refer to values

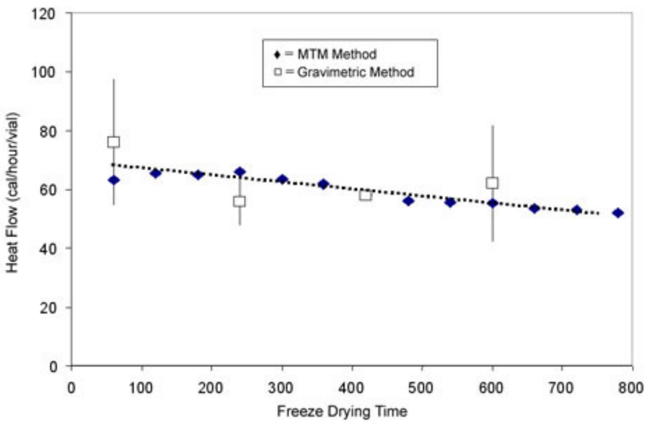

Figure 2. Heat flow determined by MTM and gravimetric methods. The 5% glycine was freeze-dried at a shelf temperature of –20ºC and a chamber pressure of 80 mTorr.

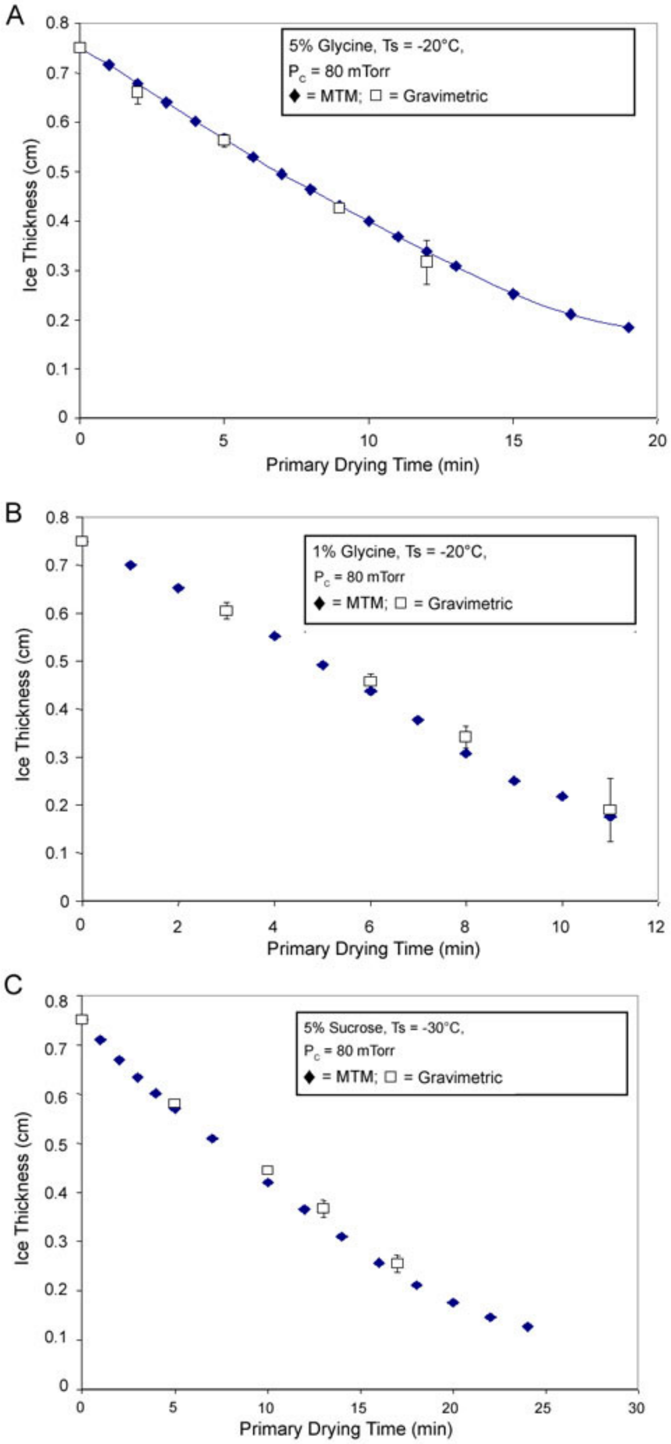

Figure 3. Ice thickness determined by MTM and gravimetric methods under different freeze-drying conditions.

calculated from individual vial thermocouple data while the last column gives the MTM result. Here, no thermal shields (ie, Al foil or dummy vials) are used. The overall and MTM ice sublimation is the result for a total 150 vials. Freeze drying was stopped at about one half the total primary drying time, and the MTM results were taken at the midpoint of the run. Uncertainty is the standard error from 6 replicates.

Excellent agreement between the MTM and gravimetric methods is observed when the metal guard band is used. This is expected because the metal band functions as a partial radiation shield, thereby providing more uniform heat flow. Sublimation rate was highest for the front vials and smallest for interior vials. The rates of ice sublimation for side vials were in-between the front and interior vials and were essentially the same as back vials. Ice sublimation heterogeneity was even less than shown in Table 2 when dummy vials and Al foil were used (data not shown).

Monitoring the extent of primary drying (ice thickness calculation) by MTM

Currently, there is no convenient way to estimate the extent of primary drying in real time. It would be very helpful in process monitoring and freeze-drying process optimization if the extent of primary drying could be estimated. If the time left in primary drying can be estimated, an informed decision can be made as to whether further adjustment of primary drying conditions is necessary or not. For example, a reliable estimate of the extent of primary drying would allow one to decide if a product temperature change is real or just caused by the completion of ice sublimation.

Ice thickness data determination from both MTM and gravimetric methods are plotted in Figure 3 for runs with 5% glycine, 1% glycine, and 5% sucrose. MTM data were obtained with ΔT evaluated from the data, and both dummy vials and Al foil on the inside of the door were used as thermal shields. The MTM results are instantaneous values while the gravimetric results represent an average for the time interval of mass loss determination. The error bars represent standard deviations for 3 samples.

For all systems, MTM and gravimetric data are in good agreement from the beginning to the end of primary drying. As with K_v, heat flow, and sublimation rate, accurate ice thickness data by MTM is a direct result of accuracy in both $\hat{R}_{ps}$ and P_{ice}.

Usually, the only product parameter measured during primary drying is the product temperature. The use of MTM provides much additional information about the freeze-drying process, allowing monitoring of critical process variables and conditions such as ice thickness, heat transfer, and dry layer resistance and is a valuable process analytical technology tool.

CONCLUSIONS

The vial heat transfer coefficients determined by the MTM method may be larger than the actual values, especially at the early stage of primary drying, if freeze-drying is conducted at low shelf temperature, low chamber pressure, and low concentration solids. This high K_v problem is caused by systematic errors in the MTM dry layer resistance (ie, $\hat{R}_{ps}$ is too low), but these errors can be essentially eliminated if thermal shields are used in freeze-drying.

ACKNOWLEDGMENTS

This project was sponsored by the National Science Foundation–Center for Pharmaceutical Processing Research (NSF/CPPR).

REFERENCES

1. Pikal MJ. Freeze-drying of proteins Part I: process design. *BioPharm.* 1990;3:14–26.

2. Tang XC, Pikal MJ. Design of freeze-drying processes for pharmaceuticals: practical advice. *Pharm Res.* 2004;21:191–200.

3. Nail SL, Gatin LA, eds. Freeze-drying: principles and practice. *Pharmaceutical Dosage Forms: Parenteral Medications.* New York, NY: Marcel Dekker, Inc; 1993:163–233.

4. Pikal MJ, Roy ML, Shah S. Mass and heat transfer in vial freeze-drying of pharmaceuticals: role of the vial. *J Pharm Sci.* 1984;73:1224–1237.

5. Pikal MJ. Use of laboratory data in freeze drying process design: heat and mass transfer coefficients and the computer simulation of freeze drying. *J Parenter Sci Technol.* 1985;39:115–139.

6. Pikal MJ, Shah S, Senior D, Lang JE. Physical chemistry of freeze-drying: measurement of sublimation rates for frozen aqueous solutions by a microbalance technique. *J Pharm Sci.* 1983;72:635–650.

7. Overcashier DE, Patapoff TW, Hsu CC. Lyophilization of protein formulations in vials: investigation of the relationship between resistance to vapor flow during primary drying and small-scale product collapse. *J Pharm Sci.* 1999;88:688–695.

8. Tang X, Pikal MJ, Nail S. Mass transfer in freeze drying: measurement of dry layer resistance by a non-steady state method (the MTM procedure). *AAPS PharmSci.* 1998;S1:Abstract 2198.

9. Milton N, Pikal MJ, Roy ML, Nail SL. Evaluation of manometric temperature measurement as a method of monitoring product temperature during lyophilization. *PDA J Pharm Sci Technol.* 1997;51:7–16.

10. Jancso G, Pupezin J, Van Hook WA. The vapor pressure of ice between 0.01 and –100 C. *J Phys Chem.* 1970;74:2984–2989.

11. Tang XC, Pikal MJ. Evaluation of manometric temperature measurement (MTM) in freeze drying, part II: measurement of dry layer resistance. *AAPS PharmSciTech.* 2006;7:E93.

12. Tang XC, Pikal MJ. Evaluation of manometric temperature measurement (MTM) in freeze drying, part I: product temperature measurement. *AAPS PharmSciTech.* 2006;7:E14.