

# Heat and Mass Transfer Scale-Up Issues During Freeze-Drying, III: Control and Characterization of Dryer Differences via Operational Qualification Tests

Submitted: January 15, 2004; Accepted: February 9, 2006; Published: April 21, 2006

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## ABSTRACT

The objective of this research was to estimate differences in heat and mass transfer between freeze dryers due to inherent design characteristics using data obtained from sublimation tests. This study also aimed to provide guidelines for convenient scale-up of the freeze-drying process. Data obtained from sublimation tests performed on laboratory-scale, pilot, and production freeze dryers were used to evaluate various heat and mass transfer parameters: nonuniformity in shelf surface temperatures, resistance of pipe, refrigeration system, and condenser. Emissivity measurements of relevant surfaces such as the chamber wall and the freeze dryer door were taken to evaluate the impact of atypical radiation heat transfer during scale-up. “Hot” and “cold” spots were identified on the shelf surface of different freeze dryers, and the impact of variation in shelf surface temperatures on the primary drying time and the product temperature during primary drying was studied. Calculations performed using emissivity measurements on different freeze dryers suggest that a front vial in the laboratory lyophilizer received 1.8 times more heat than a front vial in a manufacturing freeze dryer operating at a shelf temperature of  $-25^{\circ}\text{C}$  and a chamber pressure of 150 mTorr during primary drying. Therefore, front vials in the laboratory are much more atypical than front vials in manufacturing. Steady-state heat and mass transfer equations were used to study a combination of different scale-up issues pertinent during lyophilization cycles commonly used for the freeze-drying of pharmaceuticals.

**KEYWORDS:** Operational qualification, freeze-drying, scale-up.

## INTRODUCTION

An important objective of freeze-drying process design is the development of a process that is robust, is economical, and can be easily transferred to all freeze dryers irrespective

of size and design. To be fully transferable, the process should be equivalent—that is, the product temperature:time profile should be identical—when the same freeze-drying process is performed on different freeze dryers. Achieving this objective poses some challenges. First, the freeze dryer under consideration must be tested for performance under conditions of thermal load that it would typically experience during the process. This requirement means that the performance of all components (ie, the condenser, the refrigeration system, and the chamber) that influence the flow of water vapor during primary drying must be tested. Furthermore, those components that affect process design that differ from one dryer to another need to be identified, and the process has to be developed such that the impact of dryer performance may be taken into consideration in the development of equivalent cycles. An ideal process is one where the product, not the equipment, limits the process time.

It is important to design appropriate qualification protocols such that all qualification data needed to translate freeze-drying cycles between dryers are obtained. The commonly employed procedure of testing the freeze dryer “clean, dry, and empty” does not give usable scale-up data. Variation of shelf temperature during known representative loads (ie, during sublimation at known rates) and vapor removal capacity under conditions of known high load are examples of important data not obtained with the usual protocols. The principal test designed to obtain such data, the “sublimation test,” requires running a controlled pseudo-steady-state sublimation test using pure ice where the sublimation rate and the thermal load (ie, the heat transfer rate) are known. It is important that the thermal loads and chamber pressures span the range needed for the anticipated applications. The reader is referred to earlier work<sup>1</sup> regarding generation of heat transfer data for interpretation of sublimation test results.

An assessment of variations in shelf surface temperature is important in the assessment of the inter-vial variation in sublimation rate. In general, one may assume that the shelf surface temperature is not perfectly uniform during primary drying.<sup>2</sup> A limited amount of data obtained for a pilot scale dryer<sup>3</sup> indicate that temperature differences between different positions on the same shelf exist and that these

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differences are proportional to the heat transfer rate. The variation in product temperature due to variations in shelf surface temperature across the shelf is an important scale-up issue, one that can affect process. Identification of the “hot” and “cold” spots (ie, regions of differing temperature) on the shelf surface can direct process modification so as to account for these variations.

The vial heat transfer coefficient is also affected by the emissivities of relevant surfaces: the shelf surface, the side and back walls of the chamber, the door,<sup>4</sup> and the view port. Values of emissivity may vary depending on the freeze dryer design and the deterioration of the “polish” on the freeze dryer with use. This variation in emissivity needs to be recognized in process design because it can affect the contribution of radiation heat transfer to the overall vial heat transfer coefficient, particularly at a low shelf temperature and low chamber pressure, where radiation effects are relatively more important.

It has been found with both laboratory and production dryers that at a particular sublimation rate the thermal load becomes too high for the dryer and chamber pressure control is lost.<sup>5</sup> Data for the minimum chamber pressure and maximum condenser temperature at “high” thermal load allow calculation of the thermal load at which loss of pressure control will occur.<sup>6</sup> As part of this research, the theoretical predictions will be compared with experimental results obtained from the sublimation test.

Given the operational qualification (OQ) data on both laboratory and production dryers and the known variance in vial heat transfer coefficient, we will describe the estimation of the interval variation in heat transfer for a production operation. The corresponding variation in product temperature and drying time will then be calculated. This research aims at developing reliable scale-up procedures and guidelines that also consider several other scale-up issues, such as the edge-vial effect and the effect of heterogeneity in nucleation temperatures.<sup>7,8</sup> With the aforementioned information, steady-state heat and mass transfer theory can then be used to define the manufacturing process that provides essentially the same product temperature: time history as found in the laboratory process.

## MATERIALS AND METHODS

### Materials

De-ionized water was used in sublimation experiments. Fast response thermocouples (Omega Instruments, Stamford, CT) with self-adhesive backing were used to record shelf surface temperatures during sublimation tests. The emissivity of representative surfaces such as the chamber wall and the dryer door was determined using an infrared thermometer.

### Equipment

OQ sublimation tests were performed on different lyophilizers. Two laboratory lyophilizers, Durastop and Lyostar I (Kinetics Thermal Systems, Inc); a pilot lyophilizer, Edwards Lyofast S20; and a manufacturing lyophilizer, Lyomax (BOC Edwards Inc), were used. We also obtained data from a sublimation test performed in an earlier study on a manufacturing scale (Stokes) dryer. The basic characteristics of the lyophilizers are shown in Table 1.

### OQ Sublimation Tests

Deionized water was loaded into trays made from thin plastic bags ( $\approx 0.003$  cm). Equal amounts of water were added to each shelf of the lyophilizer; this amount varied depending on the size of the lyophilizer. The intent was to add enough water to provide  $\approx 1$  cm ice thickness. The plastic sheet (black garbage bags) was fastened to the steel band (commonly used as part of a bottomless tray) and formed the bottom of the tray. The plastic, being very thin, does not impose a significant heat transfer barrier and, when filled with water, deforms to fit the contour of the shelf. Flat adhesive thermocouples were placed on the shelf surface at representative shelf positions. To insulate the thermocouple from the bottom of the tray, several layers of aluminum foil and thin plastic (transparency film) were placed between the thermocouple joint and the tray bottom. Temperature measurements are generally subject to random error of about  $\pm 0.2^\circ\text{C}$ , but shelf surface temperatures are also subject to a systematic error due to heat exchange with the ice above the temperature sensor. That is, insulation of the thermocouple is not perfect. This impact of this effect is

**Table 1.** Basic Characteristics of Lyophilizers\*

Characteristics	Laboratory (KTS)		Pilot Lyofast (Edwards)	Manufacturing	
	Durastop	Lyostar I		Lyomax (Edwards)	Stokes
Total shelf surface, m <sup>2</sup>	0.38	0.35	2	39	24.2
Condenser surface, m <sup>2</sup>	0.64	0.37	2	43	24.6
Chamber to condenser pathway	D = 0.05 L = 0.27	D = 0.1 L = 0.48	D = 0.25 L = 0.75	D = 0.91 L $\approx$ 1.5	D = 0.9 L = 0.9

\*D and L are the diameter (m) and length (m) of the chamber to condenser pathway, respectively. KTS indicates Kinetics Thermal Systems.

discussed in the next section. Additionally, thermocouples were placed on the surface of the plastic-bottomed tray to measure the product temperature. The sublimation test was performed using the following protocol:

1. Ramp to  $-15^{\circ}\text{C}$  at  $10^{\circ}\text{C/hr}$ ; hold for 1 hour.
2. Ramp from  $-15^{\circ}\text{C}$  to  $-40^{\circ}\text{C}$  at  $60^{\circ}\text{C/hr}$ ; hold for 4 hours.
3. Pull vacuum to 80 mTorr; ramp from  $-40^{\circ}\text{C}$  to  $-5^{\circ}\text{C}$  at  $30^{\circ}\text{C/hr}$ ; hold for 3 hours. These conditions will give a sublimation load of  $\approx 0.5 \text{ kg hr}^{-1}\text{m}^{-2}$ .
4. Set vacuum to 120 mTorr; ramp at  $60^{\circ}\text{C/hr}$  to  $25^{\circ}\text{C}$ ; hold for 2 hours. This step provides a sublimation rate of  $1.09 \text{ kg hr}^{-1}\text{m}^{-2}$ .
5. Change pressure to 0 mTorr; ramp to  $40^{\circ}\text{C}$  at  $60^{\circ}\text{C/hr}$ ; hold for 3 hours. Determine the “steady state” minimum chamber pressure attained under these conditions. Lower the shelf temperature to  $30^{\circ}\text{C}$  if pressure rises above 0.4 Torr.
6. Set pressure to 400 mTorr; hold at  $40^{\circ}\text{C}$  for 3 hours; visually check ice distribution on condenser plates. Lower the shelf temperature to  $30^{\circ}\text{C}$  if there is loss of pressure control.

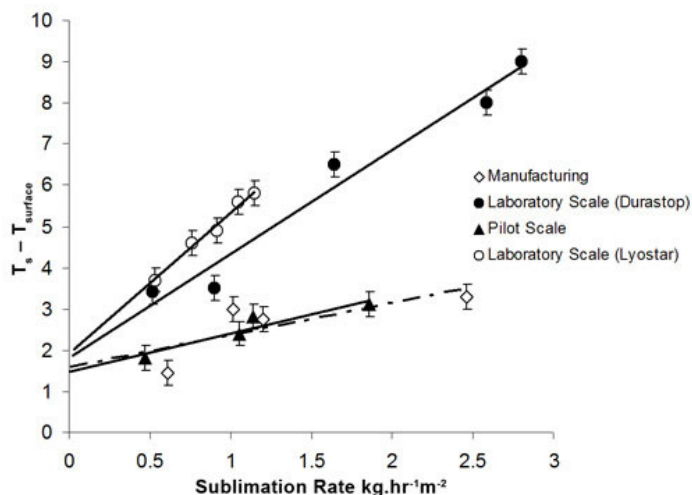
### Emissivity Measurements

The infrared thermometer, Omegascope (Omega Instruments, Samford, CT), uses a laser sight (with a distance-to-spot-size ratio of 30:1) designed to measure surface temperature at a given surface spot of known emissivity. The infrared thermometer uses the Stefan-Boltzmann equation<sup>7</sup> for directly calculating the temperature of an object of known emissivity. A sensor inside the thermometer determines the ambient temperature (ie, the temperature of the thermometer). In our studies, we measured the temperature of the surface using a thermocouple and determined the emissivity of the surface at that surface temperature by finding the emissivity that resulted in a match of thermocouple and infrared thermometer readings. With this technique, the infrared thermometer measures values of emissivity ranging from 0.1 to 1 in steps of 0.01.

## RESULTS AND DISCUSSION

### Temperature Differences

Shelf surface temperature measurements were taken during the sublimation test at representative locations on the shelf surface. Figure 1 illustrates differences between the shelf temperature as reported on the data output (the fluid inlet temperature,  $T_s$ ) and the shelf surface temperature ( $T_s - T_{\text{surface}}$ ) as a function of sublimation rate for the various lyophilizers studied. Shelf surface temperatures generally decreased systematically by several  $^{\circ}\text{C}$  from near the inlet to near the outlet, and the shelf surface temperatures given



**Figure 1.** Difference between shelf temperature ( $T_s$ , fluid inlet) and shelf surface temperature ( $T_{\text{surface}}$ ) obtained as a function of sublimation rate for different lyophilizers. Error bars represent estimated errors ( $\pm 0.2^{\circ}\text{C}$ ) in thermocouple measurements.

in Figure 1 represent the mean of measured shelf surface temperatures. Note that there is a nonzero intercept of  $\approx 1.5^{\circ}\text{C}$  at zero sublimation rate, representing the error in measurement of the shelf surface temperature. This effect arises from incomplete thermal insulation of the thermocouple from the ice and seems to be roughly the same from one run to another. A replication experiment was performed with another laboratory (Lyostar) unit, and it was found that the mean temperature difference between corresponding values in the 2 runs was  $\approx 0.2^{\circ}\text{C}$  and the difference in the slope of temperature difference versus sublimation rate (ie, as in Figure 1) was 9%. Furthermore, the mean slope for the “replication runs,” 1.74, agrees well with the slope given for the Lyostar dryer in Figure 1 (2.0).  $T_s - T_{\text{surface}}$  is much higher in the case of the 2 laboratory freeze dryers than for the pilot or the manufacturing dryer. The slopes of the linear fits to the data are quite different (Table 2), being much higher for the 2 laboratory lyophilizers than for the pilot and manufacturing dryers. These differences in slopes translate into differences in shelf heat transfer coefficient,  $K_s$  (Table 2), with small temperature differences meaning large values of  $K_s$ , or efficient heat transfer within the shelf. A shelf mapping study of this nature may be used to identify “hot” and “cold” spots or regions on the shelf surface. We emphasize that it is the shelf *surface* temperature at a particular location and not the shelf temperature set point that determines the sublimation rate under a given load. A maximum difference of  $\approx 5^{\circ}\text{C}$  between the fluid inlet temperature and the shelf surface temperature was observed in a pilot lyophilizer, resulting in the cold spot running 5 degrees colder than the fluid inlet temperature. Relative hot spots closer to the fluid inlet run warmer and are at most 1 degree lower than the fluid inlet temperature. Shelf surface temperature differences across the shelf

**Table 2.** Shelf Heat Transfer Coefficient ( $K_s$ ) for Various Lyophilizers Calculated From Data Obtained During Operational Qualification Tests and Calculated Using Regression Analysis of the Data\*

Lyophilizer	Slope $\text{hr.m}^2.\text{Kg}^{-1}.\text{°C}^{-1}$	Intercept ( $\text{°C}$ )	$K_s \cdot 10^3$ , $\text{cal.s}^{-1}.\text{cm}^{-2}.\text{K}^{-1}$ Calculated From Slope
Laboratory (Lyostar I)	3.4	1.9	$5.4 \pm 1.9$
Laboratory (Durastop)	2.6	1.5	$8.0 \pm 2.3$
Pilot (Edwards)	0.77	1.5	$18.1 \pm 4.3$
Manufacturing (Stokes)	0.93	1.7	$13.9 \pm 8.5$

\*Regression analysis was performed according to the equation  $Q(\text{cal s}^{-1} \text{cm}^{-2}) = K_s \cdot (T_s - T_{\text{shelf surface}} - \Delta T_{\text{error}})$ , where  $T_{\text{shelf surface}}$  represents average shelf surface temperature measured across the shelf and  $\Delta T_{\text{error}}$  represents the shelf surface temperature measurement error (ie, the intercept in Figure 1). Both  $K_s$  and  $\Delta T_{\text{error}}$  were determined by regression analysis, and the uncertainties given represent the standard error in the parameter as given by the regression analysis.

translate to variations in heat flow and in turn, to variations in primary drying time. Such differences need to be considered during scale-up. For example, consider a process to be transferred from a laboratory freeze dryer to the pilot scale lyophilizer. Consider a hypothetical product of low resistance ( $2.5 \text{ Torr.hr.cm}^2\text{g}^{-1}$ ) of  $\approx 1.4 \text{ cm}$  fill depth in a vial whose internal surface area is roughly  $4.9 \text{ cm}^2$ . The heat transfer coefficient of the vial is  $3.7 \cdot 10^{-4} \text{ cal.sec}^{-1}.\text{cm}^{-2}.\text{K}^{-1}$ . The primary drying conditions for shelf temperature and chamber pressure are  $-5\text{°C}$  and  $80 \text{ mTorr}$ , respectively. Suppose that the lyophilization cycle for this product is  $\approx 22$  hours in a freeze dryer where the differences between shelf fluid inlet temperature and shelf surface temperature at various locations is essentially zero. The product temperature during sublimation is  $-31.8\text{°C}$  in this case. However, suppose, as with the pilot scale freeze dryer, the difference between the shelf fluid inlet temperature and the coldest spot on the shelf surface is  $5\text{°C}$  (ie, the cold spot is  $-10\text{°C}$ ). Using the coupled heat and mass transfer equations,<sup>8</sup> the lower shelf temperature translates to 26 hours of primary drying and a product temperature of  $-32.8\text{°C}$ . This would mean that the translated drying cycle would have to incorporate an additional 4 hours in primary drying time to ensure that primary drying is complete for the vial in the vicinity of the cold spot. However, the shelf temperature set point could be raised by as much as  $1\text{°C}$  (ie, to  $-4\text{°C}$ ) since the relative “hot” spot is 1 degree colder than the fluid inlet temperature. This increase would mean the cold spot is now  $-9\text{°C}$  and would result in an increase of primary drying time of 3 hours instead of 4 hours. Such evaluations become important in process design to ensure that primary

drying is complete for all the vials before the shelf temperature is raised for secondary drying. These evaluations are more critical when the process is designed to run close to optimum.

### Shelf Heat Transfer Coefficient Studies

Sublimation tests were performed according to the protocol mentioned in the OQ Sublimation Tests section. The heat transfer coefficient of the tray,  $K_v$ , was determined earlier (M. Pikal and M. Roy, unpublished data, June 16, 1994) and is represented as a function of pressure as follows:

$$10^4 K_v (\text{cal} \cdot \text{s}^{-1} \cdot \text{cm}^{-2} \cdot \text{°K}^{-1}) = 0.70 + \frac{33.2P}{1 + 2.88P}, \quad (1)$$

where P is the chamber pressure in Torr (ie, mm Hg). With the heat transfer coefficient,  $K_v$ , characterized as a function of chamber pressure for this configuration and knowledge of shelf surface temperature, the exact sublimation rate ( $dm/dt$ ) in  $\text{kg.hr}^{-1}.\text{m}^{-2}$  may be calculated according to Equations 2 and 3:

$$\frac{dm}{dt} = 53.25 \cdot K_T (T_{\text{shelf inlet}} - T_{\text{ice}}) \quad (2)$$

$$\frac{dm}{dt} = 53.25 \cdot K_v (T_{\text{shelf surface}} - T_p), \quad (3)$$

where the total heat transfer coefficient  $K_T$  is expressed as follows:

$$K_T = \frac{K_v}{\left(1 + \frac{K_v}{K_I} + \frac{K_v}{K_s}\right)}, K_I = \frac{0.0066}{L_{\text{ice}}} \quad (4)$$

In the above set of equations,  $T_{\text{shelf inlet}}$  is the fluid inlet temperature that the equipment records,  $T_{\text{shelf surface}}$  is the directly measured mean temperature of the shelf surface,  $K_v$  is the heat transfer coefficient of the “plastic” bottom tray,  $T_{\text{ice}}$  is the temperature of ice at the ice vapor interface,  $T_p$  is the directly measured ice temperature at the bottom of the pan,  $K_I$  is the heat transfer coefficient of ice,  $L_{\text{ice}}$  is the thickness of ice, and  $K_s$  is the heat transfer coefficient of the shelf itself. All heat transfer coefficients are in. The number 53.25 comes from the conversion of units for the heat of sublimation of ice ( $53.25 = 3600 \cdot 10\,000 / 676\,000$ ).  $K_s$  may be evaluated from sublimation rate data according to the following equation:

$$\frac{dm}{dt} (\text{kg} \cdot \text{hr}^{-1} \cdot \text{m}^{-2}) = 53.25 \cdot K_s \cdot (T_{\text{shelf inlet}} - T_{\text{shelf surface}}), \quad (5)$$

where the difference between the shelf inlet temperature and the shelf surface temperature is assumed to be proportional to the sublimation rate,  $dm/dt$ . In our case,  $K_s$  was determined by regression analysis of sublimation rate and shelf temperature data.

Table 2 shows a comparison of values of shelf heat transfer coefficients obtained for freeze dryers used in this study. We note that earlier work (M. Pikal and M. Roy, unpublished data, June 16, 1994) evaluated  $K_s$  for a laboratory scale Virtis 25SRC-X freeze dryer as  $6.8 \cdot 10^{-3}$  and for a Stokes production dryer as  $\approx 3 \cdot 10^{-3}$ .<sup>2</sup> Note that the value of  $K_s$  determined for the manufacturing dryer studied in this research (Table 2) is much higher than that determined for the “literature” Stokes production dryer, while the laboratory lyophilizers studied here have values of  $K_s$  comparable to those evaluated earlier for the Virtis 25SRC-X.

### Sublimation Tests

Sublimation test results were used to evaluate the minimum chamber pressure and maximum condenser temperature attainable at a given load, using the simplified Kobayashi's relationships.<sup>1</sup> The steps of the sublimation test used to define different steady-state periods and the results obtained for a pilot scale Edwards freeze dryer are presented in Table 3. The first setting, 80 mTorr and  $-5^\circ\text{C}$  shelf temperature, was chosen to give a moderate sublimation rate,  $0.5 \text{ kg}\cdot\text{hr}^{-1}\text{m}^{-2}$ , a process typically used in the freeze drying of a material of low collapse temperature and low dried product resistance. There was good control of both chamber pressure and shelf temperature.

The second condition, 120 mTorr and  $25^\circ\text{C}$  shelf temperature, was designed to give a higher load of  $1.09 \text{ kg}\cdot\text{hr}^{-1}\text{m}^{-2}$ . No oscillations in shelf temperature and chamber pressure were observed; however, the chamber pressure could not be controlled at the set point. Instead, the chamber pressure was controlled at 146 mTorr, higher than the set point

chamber pressure of 120 mTorr, and the corresponding sublimation rate was slightly greater than planned. The third condition,  $40^\circ\text{C}$  and 0 mTorr, was designed to determine the minimum chamber pressure attainable under conditions of very high load (greater than  $1 \text{ kg}\cdot\text{hr}^{-1}\text{m}^{-2}$ ). In this case the shelf temperature did not experience any oscillations and the chamber pressure reached a steady-state value of 158 mTorr within 20 minutes. The condenser temperature measured  $-60.5^\circ\text{C}$  in this condition. The last condition,  $30^\circ\text{C}$  and 400 mTorr, was designed to test the freeze dryer under severe load conditions. The nominal load in this case was  $1.86 \text{ kg}\cdot\text{hr}^{-1}\text{m}^{-2}$ , and the shelf temperature and chamber pressure were both well controlled. The condenser temperature was  $-57^\circ\text{C}$ . These observations show that the pilot scale freeze dryer performed satisfactorily in the OQ sublimation test except for the inability to control pressure at the set point of 120 mTorr in step 2. Note also that even in steps 1 and 4, the pressure was not *exactly* at the set point. This is, however, not due to an overload of the condenser and probably represents an offset in the control system.

Table 4 shows a summary of results obtained for the laboratory scale Durastop freeze dryer. It may be observed that while the shelf temperature was well controlled, the chamber pressure was not under control in steps 1 and 2 of the sublimation test. Since we did not observe an increase in the condenser temperature, the refrigeration resistance may be ruled out as a cause for the lack of pressure control. The design of the condenser system is such that blockage of full vapor flow seems unlikely or impossible. Hence, we may deduce that the mass transfer resistance of the chamber to condenser pathway is likely responsible for the freeze dryer's inability to control pressure in this case. A separate test established that the chamber pressure and shelf temperature were well controlled at a shelf temperature of  $20^\circ\text{C}$  and a chamber pressure of 250 mTorr. The sublimation rate under these conditions was  $1.08 \text{ kg}\cdot\text{hr}^{-1}\text{m}^{-2}$ . Thus, a study of this kind is useful in identifying inherent

**Table 3.** Parameters of the Steady-State Process Obtained for a Pilot Scale Edwards Freeze Dryer

	Steady-State Process			
	Step 1	Step 2	Step 3	Step 4
Shelf temperature setting, $^\circ\text{C}$	-5	25	30	30
Chamber pressure setting, mTorr	80	120	0	400
Shelf temperature reading (readout from instrument recorded as the shelf temperature), $^\circ\text{C}$ , $T_{\text{inlet.readout}}$	-4.5	23.2	28.3	29.4
Chamber pressure reading, mTorr	84	141	158	419
Calculated ice surface temperature, $T_{\text{ice}}$ , $^\circ\text{C}$	-41	-36	-35	-26.5
Condenser temperature, $^\circ\text{C}$	-70.0	-62.8	-60.5	-57.0
Ice bottom temperature, $T_p$ , $^\circ\text{C}$	-39	-29.5	-29.8	-21
Average shelf surface temperature, $T_{\text{shelf surf}}$ , $^\circ\text{C}$	-8.3	20.8	25.3	26.6
Sublimation rate ( $\text{kg}\cdot\text{hr}^{-1}\text{m}^{-2}$ ), calculated using $T_p$	0.51	1.09	1.21	1.80

**Table 4.** Parameters of the Steady-State Process Obtained for a Laboratory Scale (Durastop) Freeze Dryer

	Steady-State Process			
	Step 1	Step 2	Step 3	Step 4
Shelf temperature setting, °C	-5	25	50	50
Chamber pressure setting, mTorr	80	120	0	400
Shelf temperature reading (readout from instrument recorded as the shelf temperature), °C, $T_{inlet,readout}$	-5	25	50	50
Chamber Pressure reading, mTorr	270	319	353	403
Calculated ice surface temperature, $T_{ice}$ , °C	-30	-25.8	-28.3	-26.5
Condenser temperature, °C	-70.2	-73.5	-76.0	-77.8
Ice bottom temperature, $T_p$ , °C	-29	-26	-26	-28
Average shelf surface temperature, $T_{shelf\ surf}$ , °C	-8.5	18.5	42	41
Sublimation rate ( $kg \cdot hr^{-1} \cdot m^{-2}$ ), calculated using $T_p$	0.68	1.64	2.58	2.80

design issues that can lead to a lyophilizer’s failure to control pressure at the selected set point under the required load conditions.

**Evaluation of Dryer Performance Parameters**

Information obtained from the sublimation test was used to calculate mass and heat transfer resistances of the freeze dryer, namely the resistance of the chamber to condenser pathway (or pipe resistance),  $R_c$ ; the resistance to transport of water vapor in the condenser and conversion to ice,  $R_c^*$ ; and the resistance of the refrigeration system to removal of heat coming from the conversion of vapor to ice,  $R_R^*$ . Briefly, the calculations involve an evaluation of the relevant resistances from mass flow rate data obtained from the sublimation test using our approximate version of Kobayashi’s theory.<sup>1</sup>

The mass flow rate,  $dm/dt$  (kg/s), may be expressed as the ratio of the pressure difference and the relevant resistance:

$$\frac{dm}{dt} = \frac{(P_{ch} - P_{cd})}{R_c} = \frac{(P_{cd} - P_r^*)}{R_c^*} = \frac{(P_r^* - P_R^*)}{R_R^*}, \quad (6)$$

where  $P_{ch}$  is the chamber pressure;  $P_{cd}$  is the pressure at the entrance to the condenser;  $P_r^*$  is the vapor pressure of ice at the condenser temperature,  $T_r^*$ ; and  $P_R^*$  is the vapor pressure at the minimum temperature of the condenser,  $T_R^*$  (ie, no load temperature). The vapor pressure of ice (Torr) at a particular temperature may be calculated according to the following equation:

$$\ln(P_i^*) = 24.01849 - \frac{6144.96}{T_i^*}, \quad (7)$$

where  $T_i$  is the temperature (K) of the ice.  $R_c$ ,  $R_c^*$ , and  $R_R^*$  were evaluated for different sublimation rates. Details of the calculations have been discussed elsewhere.<sup>1,5</sup>

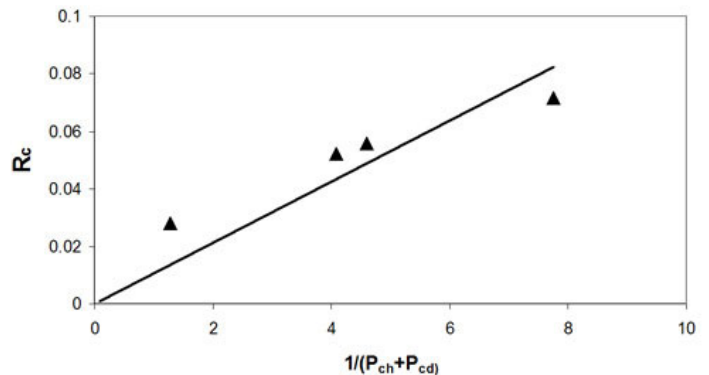
At each steady-state condition of the sublimation test, standard resistance constants KP, KC, and KR were calculated according to the following equations:

$$RC = \frac{KP}{P_{ch} + P_{cd}} \quad (8)$$

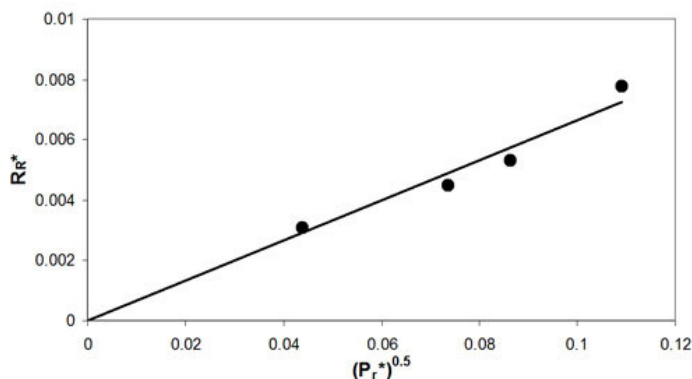
$$R_c^* \cong KC \cdot (P_{cd} + P_r^*) \quad (9)$$

$$R_R^* = KR \cdot \sqrt{P_r^*} \quad (10)$$

KP and KR were determined from the slopes of the linear plots according to Equations 8 and 10. Plots of  $R_c$  versus  $\frac{1}{P_{ch} + P_{cd}}$  and  $R_R^*$  vs  $(P_r^*)^{0.5}$  obtained for the pilot scale freeze dryer are shown in Figures 2 and 3. Linearity was satisfactory. The distribution of data points for  $R_c^*$  and  $(P_{cd} + P_r^*)$  did not allow for a meaningful test of linearity. Basically, the data consisted of 2 points close to one another and one data point well removed so that linearity was



**Figure 2.** Resistance of the chamber to condenser pathway ( $R_c$ ) as a function of  $(P_{ch} + P_{cd})^{-1}$  for the pilot scale lyophilizer. The straight line represents the linear fit to the data. Equation for linear fit:  $R_c = 0.011/(P_{ch} + P_{cd})$ ;  $R^2 = 0.9696$ .



**Figure 3.** Resistance of the refrigeration system ( $R_R^*$ ) as a function of  $(P_r^*)^{0.5}$  for the pilot scale lyophilizer. The straight line represents the linear fit to the data. Equation for linear fit:  $R_R^* = 0.0701 (P_r^*)^{0.5}$ ;  $R^2 = 0.9451$ .

essentially ensured. Here, values of KP were simply calculated at each point according to Equation 9 from values of  $R_c^*$  and  $(P_{cd} + P_r^*)$  and an average value of KC was calculated. Values of KP, KC, and KR obtained for the 3 dryers appear in Table 5. Standard resistance constants obtained in an earlier study<sup>1</sup> for a manufacturing freeze dryer were  $KP = 0.0046$ ,  $KC = 0.32$ , and  $KR = 0.13$ ; the units were consistent with those in Equations 6 to 10 (ie, sublimation rate in  $\text{kg}\cdot\text{hr}^{-1}\cdot\text{m}^{-2}$ , resistance in  $\text{Torr}\cdot\text{hr}\cdot\text{m}^2\cdot\text{kg}^{-1}$ , and pressure in Torr).

Values of KR are higher for the manufacturing freeze dryers than for the pilot and laboratory lyophilizers. On the other hand, KC and KP values are lower for the manufacturing freeze dryers than for the pilot and laboratory freeze dryers. Also, KP is much higher for the laboratory freeze dryer. Assuming the results obtained here are representative, the resistance of the chamber to condenser pathway is a more likely limiting factor for laboratory freeze dryers, thus providing a higher possibility of choked flow in laboratory units. On the other hand, the refrigeration resistance may become an issue for manufacturing freeze dryers. Thus, we observe that an evaluation of resistance constants can provide a broad idea of the variation in resistances in different lyophilizers. However, the important point is not that the trends from laboratory to manufacturing dryers noted here are preserved when other dryers are considered. The

major point is that design factors can be different and there are tests than can allow quantitative comparison of different dryers.

The minimum chamber pressure,  $P_{c, \text{min}}$ , calculated assuming no air leaks, may be determined as follows:

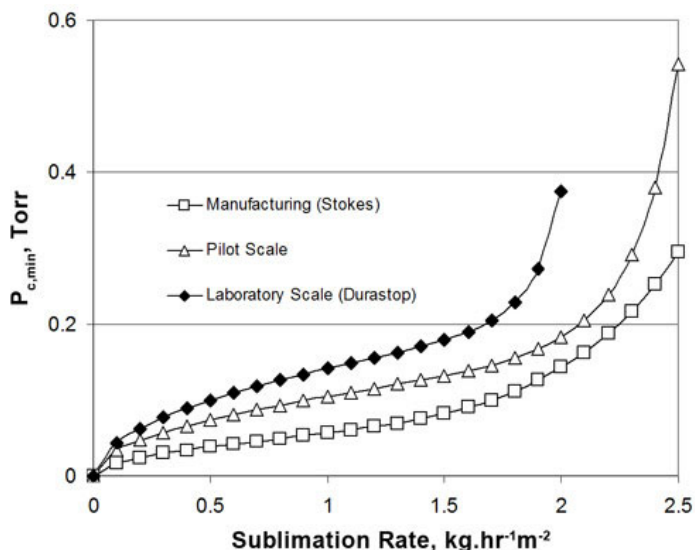
$$P_{c, \text{min}} = \sqrt{G \cdot KP + (KR \cdot G)^4 \left( \frac{1 + G \cdot KC}{1 - G \cdot KC} \right)^2}, \quad G \equiv \frac{dm}{dt} (\text{kg hr}^{-1} \text{m}^{-2}), \quad (11)$$

where  $P_{c, \text{min}}$  refers to the minimum chamber pressure attainable at a given sublimation rate in the absence of an air leak. Minimum pressure values calculated using the appropriate constants (Table 5) at conditions corresponding to the sublimation test runs gave values (mTorr) of 57, 129, and 391 for the production dryer, pilot dryer, and Durastop lab dryer, respectively. Corresponding minimum pressures determined experimentally (Tables 3 and 4, step 3) are 70, 158, and 353 mTorr. As expected, the minimum pressures measured experimentally are generally (ie, except for the Durastop) slightly higher than those evaluated from Equation 11. The minimum pressure attainable in the dryers with zero sublimation load is  $\approx 10$  to 20 mTorr, so agreement between the calculations and the experiment is satisfactory. Figure 4 shows a plot of the calculated minimum chamber pressure as a function of sublimation rate for 3 different freeze dryers. The minimum chamber pressure remains low for low sublimation rates but begins to rise sharply at higher sublimation rates for all 3 freeze dryers. While this increase in minimum chamber pressure is not particularly sharp in the case of the manufacturing freeze dryer, the minimum chamber pressure rises very steeply in the case of the pilot and the laboratory freeze dryers at higher sublimation rates. One can conclude from this study that the minimum chamber pressure attainable at any given thermal load varies from one freeze dryer to another. Thus, a particular thermal load that is easily controlled by one freeze dryer will not necessarily perform the same way for a different freeze dryer. This variability in performance could be due to one or more of several design characteristics of the freeze dryer; a thorough understanding of these characteristics is essential to proper scale-up and is extremely useful in setting design specifications.

**Table 5.** Values of Standard Resistance Constants (KP, KC, and KR) and Emissivity Values of Relevant Surfaces Determined for the Different Lyophilizers\*

Lyophilizer	KP	KC	KR	$\epsilon_{\text{wall}}$	$\epsilon_{\text{door}}$
Manufacturing	0.003	$0.262 \pm 0.017$	$0.097 \pm 0.02$	0.65	0.35
Pilot	0.011	$0.360 \pm 0.035$	$0.066 \pm 0.003$	0.66	0.63
Laboratory (Durastop)	0.020	$0.450 \pm 0.120$	$0.064 \pm 0.004$	0.75	0.90

\*KR and KC are expressed as value  $\pm$  standard error, as given by the regression analysis. Estimated uncertainties for KP are  $3.0 \cdot 10^{-4}$  for all the lyophilizers.



**Figure 4.** Comparison of minimum chamber pressure ( $P_{c,min}$ ) as a function of sublimation rate.

### Emissivity Measurements

The emissivities of relevant surfaces such as the chamber walls and the front door were measured in an attempt to assess the variability in heat transfer coefficient associated with radiation heat transfer arising because of a view of a warmer surface. Table 5 shows emissivity values obtained for various freeze dryers. While the emissivities of the chamber walls are not dramatically different, the emissivity of the door is high for the laboratory freeze dryer and very low for the manufacturing freeze dryer. This can be a serious issue during scale-up, as the vials located in the front row closest to the door are under a direct view of a warmer surface (ie, the front vials receive more heat than the center vials because of an additional contribution from radiation heat transfer). Furthermore, this variation in emissivity values of freeze dryers would mean that the contribution from radiation heat transfer to edge vials would vary for different freeze dryers.

Scale-up considerations should also include the effect of a variation in emissivity when transferring a process from one lyophilizer to another. Vial heat transfer coefficients were determined from sublimation rate experiments performed in a previous study<sup>7</sup> using the following equation:

$$\Delta H_s \cdot \frac{dm}{dt} = \frac{dQ}{dt} = A_v \cdot K_v \cdot (T_s - T_p), \quad (12)$$

where  $\Delta H_s$  is the heat of sublimation of ice,  $dm/dt$  is the sublimation rate,  $dQ/dt$  is the heat transfer rate,  $A_v$  is the outer cross-sectional area of the vial,  $K_v$  is the heat transfer coefficient of the vial, and  $T_s$  and  $T_p$  are temperatures of the shelf and product, respectively. The heat

transfer coefficient of a typical center vial was calculated as  $3.02 \cdot 10^{-4} \text{ cal} \cdot \text{s}^{-1} \cdot \text{m}^{-2} \cdot \text{°K}^{-1}$ , while that of a vial located in the front of the array was  $\approx 10 \cdot 10^{-4} \text{ cal} \cdot \text{s}^{-1} \cdot \text{m}^{-2} \cdot \text{°K}^{-1}$ . These values of heat transfer coefficients correspond to a 120% increase in sublimation rate at a shelf temperature of  $-25\text{°C}$  and a chamber pressure of 150 mTorr during primary drying (from calculations performed using the steady-state heat and mass transfer equations). This excess heat is primarily due to the proximity of front vials to a warmer higher-emissivity surface (ie, the Plexiglas door), which means that there is a greater contribution from radiation heat transfer to the overall heat transfer coefficient for the front vials. A manufacturing lyophilizer, however, has a steel door and emissivity measurements show that a steel door has an emissivity value of 0.3, as compared with a value of 0.95 for the Plexiglas door. This lower emissivity value means a lower contribution from radiation heat transfer. Quantitative differences in radiation heat transfer are best calculated by recognizing the “ $T^4$ ” temperature dependence of radiation heat exchange. The area normalized heat transferred by radiation  $dQ/dt$  from a body at temperature  $T_1$  to a surface at temperature  $T_2$  is given as follows:

$$\left(\frac{1}{A}\right) \times \left(\frac{dQ}{dt}\right)_{\text{radiation}} = \varepsilon \sigma (T_1^4 - T_2^4), \quad (13)$$

where  $\sigma$  is the Stefan-Boltzmann constant and has a value of  $1.35 \cdot 10^{-12} \text{ cal} \cdot \text{s}^{-1} \cdot \text{m}^{-2} \cdot \text{°K}^{-1}$  and  $\varepsilon$  is emissivity. Using the individual emissivities of a steel door (0.35) as opposed to a glass door (0.9), one can estimate the heat transfer contributions to a front vial in manufacturing and laboratory, respectively. Here,  $T_1 = 293 \text{ K}$ ;  $T_2 = 243 \text{ K}$ ;  $A =$  cylindrical half cross section of the vial  $= \pi r h$ ;  $r$  and  $h$  are the radius and height of the cake, respectively;  $r = 1.25 \text{ cm}$ ; and  $h = 0.7 \text{ cm}$ . For top and bottom radiation,  $A = \pi r^2$ .

Calculations using these quantities show that a front vial in a laboratory dryer receives  $\approx 1.8$  times greater heat transfer by radiation than a front vial in a manufacturing freeze dryer. Knowing the increase in sublimation rate corresponding to the increase in radiation heat transfer, one can estimate the corresponding differences in primary drying time, as will be demonstrated later.

### Overall Effect of Variations During Scale-Up

The steady-state-coupled heat and mass transfer equation may be used to calculate primary drying time variation arising from differences in dryer design and the lyophilization cycle. The impact of the degree of supercooling on the primary drying process has been addressed in earlier work,<sup>8</sup>

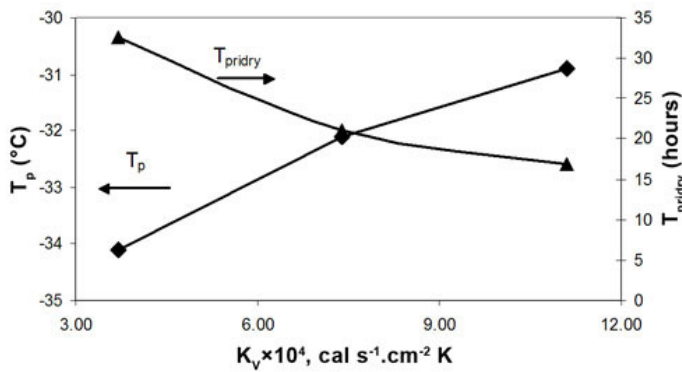


where the correlation between product resistance and specific surface area in a laboratory lyophilizer was used to estimate the increase in product resistance in a manufacturing environment. This difference in product resistance between laboratory and manufacturing was used to determine the primary drying time differences and accordingly alter the freeze-drying cycle to bring about equivalence in freeze-drying cycles.

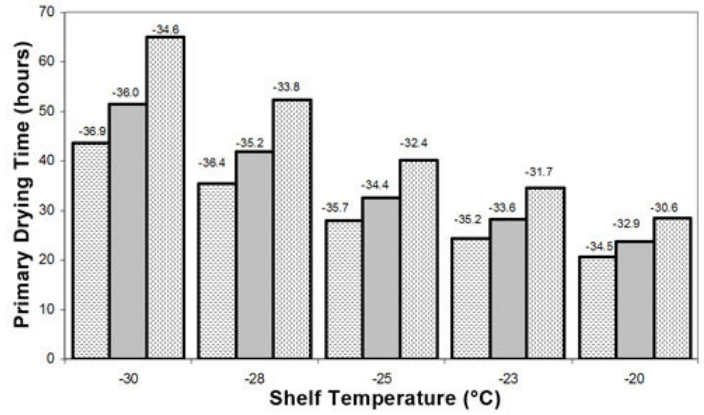
Coupling between heat and mass transfer may be expressed as follows:

$$\Delta H_s \left( \frac{P_0 - P_c}{R_{ps}^{\wedge}} \right) \left( \frac{A_v}{A_p} \right) - A_v K_v (T_s - T_p) = 0, \quad (14)$$

where  $R_{ps}^{\wedge}$  denotes the sum of the area normalized resistance of the product and stopper, and  $P_0$  is the vapor pressure of ice. From Equations 7 and 14, the product temperature can be obtained, and from this one can evaluate the sublimation rate (Equation 12) and the effect of changes in the parameters  $R_{ps}^{\wedge}$ ,  $T_s$ , and  $K_v$ . The effect of a change in heat transfer coefficient that could arise from differences in radiation heat transfer is illustrated in Figure 5. Here, moderate shelf temperature and chamber pressure conditions of  $-25^{\circ}\text{C}$  and 100 mTorr are used for a medium-resistance ( $R_{ps}^{\wedge} = 4.3 \text{ cm}^2 \cdot \text{Torr} \cdot \text{hr} \cdot \text{g}^{-1}$ ) material at a fill depth of 7.5 mm. Low resistance ( $R_{ps}^{\wedge} = 2.5 \text{ cm}^2 \cdot \text{Torr} \cdot \text{hr} \cdot \text{g}^{-1}$ ) and high resistance ( $R_{ps}^{\wedge} = 7.7 \text{ cm}^2 \cdot \text{Torr} \cdot \text{hr} \cdot \text{g}^{-1}$ ) are considered in the following examples. A 3-fold increase in  $K_v$  leads to a nearly 60% decrease in primary drying time and a corresponding 6-degree increase in product temperature. Figure 6 shows the effect of a change in shelf temperature that could arise from the presence of “hot” or “cold” spots. Shelf surface temperature variations can lead to significant differences in primary drying time, especially in high-resistance materials. For a material of medium resistance, a 5-degree decrease in

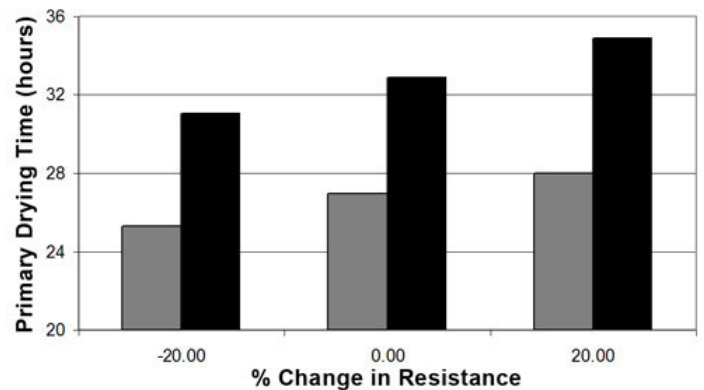


**Figure 5.** Effect of variation in heat transfer coefficient ( $K_v$ ) on the product temperature (closed diamonds) and primary drying time (closed triangles). The shelf temperature and chamber pressure are  $-25^{\circ}\text{C}$  and 100 mTorr, respectively. The resistance was medium. Pridry indicates primary drying.



**Figure 6.** Effect of variation in shelf surface temperature on the primary drying time for a low-resistance (left bar), medium-resistance (middle bar), and high-resistance (right bar) product. Numbers on bar charts represent primary drying product temperatures.

shelf temperature from the set point ( $-25^{\circ}\text{C}$ ) can lead to an increase in primary drying time of nearly 15 hours, which obviously would necessitate significant process modification. Figure 7 shows the effect of a change in product resistance (arising from a change in the degree of supercooling) on the primary drying time for low- and high-resistance materials. From this plot, one can obtain an estimate of the difference in primary drying time due to a difference in the resistance that could occur because of a change in the degree of supercooling. In our previous study,<sup>8</sup> we determined that a change of 5 degrees in supercooling leads to approximately a 20% change in product resistance, which results in modest but significant (ie, 5%-10%) changes in primary drying time (Figure 7). Calculations of this kind are useful since changes in degree of supercooling do occur between laboratory and manufacturing cycles and a knowledge of the impact of this change on the freeze-drying cycle would be vital when transferring the lyophilization cycle.



**Figure 7.** Effect of change in product resistance on the primary drying time for a low-resistance (solid gray) and high-resistance (solid black) product.

## CONCLUSIONS

OQ data obtained from sublimation tests may be used to test the performance of lyophilizers under conditions of known thermal load and provide the data needed to ensure equivalence of freeze-drying cycles from one freeze dryer to another. Given the different performance factors between dryers, simple steady-state heat and mass transfer equations may be used to estimate the effect of dryer variations on the lyophilization cycle, particularly the primary drying time and the product temperature during primary drying. Such theoretical calculations are extremely important in both the optimization of the freeze-drying process and scale-up of the laboratory process into manufacturing.

## ACKNOWLEDGMENTS

The authors would like to thank Ernesto Renzi and Mike Stella at BOC Edwards Inc (Tonawanda, NY) for their help with OQ tests on the production freeze dryer. Madhav Kamat and Myron Ludzinski at Bristol Myers Squibb (Parsippany, NJ) are acknowledged for their assistance with the sublimation tests on the pilot freeze dryer. This project was funded by a grant from the National Science Foundation's Center for Pharmaceutical Processing Research.

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