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Correlation of laboratory and production freeze drying cycles

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Abstract

The purpose of this study was to develop the correlation of cycle parameters between a laboratory and a production freeze-dryer. With the established correlation, key cycle parameters obtained using a laboratory dryer may be converted to those for a production dryer with minimal experimental efforts. In order to develop the correlation, it was important to consider the contributions from the following freeze-drying components: (1) the dryer, (2) the vial, and (3) the formulation. The critical parameters for the dryer are the shelf heat transfer coefficient and shelf surface radiation emissivity. The critical parameters for the vial are the vial bottom heat transfer coefficients (the contact parameter K_{cs} and separation distance ℓ_v), and vial top heat transfer coefficient. The critical parameter of the formulation is the dry layer mass transfer coefficient. The above heat and mass transfer coefficients were determined by freeze-drying experiments in conjunction with mathematical modeling. With the obtained heat and mass transfer coefficients, the maximum product temperature, T_{bmax}, during primary drying was simulated using a primary drying subroutine as a function of the shelf temperature and chamber pressure. The required shelf temperature and chamber pressure, in order to perform a successful cycle run without product collapse, were then simulated based on the resulting values of T_{bmax}. The established correlation approach was demonstrated by the primary drying of the model formulation 5% mannitol solution. The cycle runs were performed using a LyoStar™ dryer as the laboratory dryer and a BOC Edwards™ dryer as the production dryer. The determined normalized dried layer mass transfer resistance for 5% mannitol is expressed as $R_{pN} = 0.7313 + 17.19\ell$, where ℓ is the receding dry layer thickness. After demonstrating the correlation approach using the model formulation 5% mannitol, a practical comparison study was performed for the actual product, the lactate dehydrogenase (LDH) formulation. The determined normalized dried layer mass transfer resistance for the LDH formulation is expressed as $R_{pN} = 4.344 + 10.85\ell$. The operational templates T_{bmax} and primary drying time were also generated by simulation. The cycle run for the LDH formulation using the Edwards™ production dryer verified that the cycle developed in a laboratory freeze-dryer was transferable at the production scale.

Keywords: Collapsing temperature; Correlation; Cycle parameters; Dry layer mass transfer resistance; Heat transfer coefficient; Lactose dehydrogenase (LDH); 5% Mannitol; Mass transfer coefficient; Micro-collapse; Powell's optimization algorithm; Primary drying subroutine; Radiation emissivity

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1. Introduction

For a successful scale-up of a freeze-drying process, it is important to develop a systematic strategy to correlate the cycle parameters obtained from small-scale operation to final results obtained from full-scale production operations under various operational conditions, such as the shelf temperature, chamber pressure, type of vial, and solution depth. While a recent publication focused on prediction of differences in ice nucleation temperatures as a freeze-dry process was scaled-up (Rambhatla et al., 2004), we are unaware of any published studies that correlated cycles developed in a laboratory size freeze-dryer to cycles used in a production size freeze-dryer. This paper describes a correlation between a 4.6 ft^2 laboratory freeze dryer and a 220 ft^2 production freeze-dryer. Studies combined both theoretical and practical methods to demonstrate that sublimation rates are similar between these small and large dryers. It is our hypothesis that cycles developed and/or used in the laboratory dryer will correlate to cycles used in the production dryer. Predicting production freeze dry cycle parameters from laboratory experiments has obvious advantages. Small initial batches conducted in the laboratory dryer will establish an optimal cycle for a product that may be modestly adjusted to transfer the product to a production dryer.

Cycle parameters for freeze-drying under direct control of an operator or control system (independent variables) include the shelf fluid temperature T_f and chamber pressure P_c. Since it is difficult to use a production dryer to optimize or manipulate these variables to obtain desirable cycle parameters for manufacturing, it is preferable to utilize the laboratory dryer to establish these parameters and convert results to the production dryer using the developed correlations.

In order to utilize the modeling and simulation approach for correlation, first, it is important to establish both heat and mass transfer quantitative relationships between a laboratory dryer and a production dryer. Heat transfer coefficients were determined for both dryers. Subsequently, dry layer mass transfer coefficients for a given formulation were determined. The mass transfer mechanisms include the sublimation of ice from the frozen product and the permeation of the sublimated water vapor through the porous dry product layer.

2. Correlation approach

In order to develop a strategy of correlation, it is important to consider the characteristics of the following three areas (correlation components): (1) the dryer, (2) the vial, and (3) the formulation. The characteristics of the dryer include shelf temperature control capabilities, the level of chamber vacuum, and the efficiency of the condenser. The dryer capability can be quantitatively evaluated by the shelf heat transfer coefficient, radiation emissivity, shelf-temperature mapping, and condenser efficiency. The characteristics of the vial include the vial heat transfer coefficients. For correlation of the dryers for a specific formulation, it is necessary to consider collapse of the product during primary drying, and the moisture content and stability of the finished product. The characteristics of the formulation include the collapse temperature and dry layer mass transfer resistance. The dry layer mass transfer resistance can be expressed by an equation containing one of more mass transfer coefficients.

The approach proposed in this paper includes various mathematical modeling and experimental tasks to encompass the three correlation components as presented in Table 1. Task 1 was to evaluate and compare the efficiency of the laboratory and production dryers to ensure that the condenser provides sufficient capability to remove the sublimated water vapor while at the same time properly controlling the chamber pressure. The comparison includes features, such as (1) the ratio of condenser surface area to the shelf surface area, and (2) the ratio of the shelf surface area to the condenser cross-sectional area. The results of the comparison in Table 2 shows that the capabilities of the two dryers are similar in terms of the following two ratios: (1) ratio of condenser surface area to shelf surface area, and (2) ratio of shelf area to condenser opening area. The actual efficiency testing was performed using a weight loss experiment of frozen pure water on the fully-loaded shelf. The freeze-drying of the frozen water represents the maximum sublimation rate at the chosen temperature and pressure, due to the absence of the product mass transfer resistance.

Table 1
Correlation studies between laboratory and production dryers

Task no.	Task	Laboratory dryer	Production dryer	Freeze-drying component
1	Efficiency studies for the laboratory and production dryers	Efficiency comparison studies; weight loss studies of frozen pure water	Efficiency comparison studies; weight loss studies of frozen pure water	Dryer
2	Determine the shelf emissivity	Measure the shelf emissivity	Measure the shelf emissivity	Dryer
3	Vial-top radiation emissivity	Obtained from the literature	Obtained from the literature	Vial
4	Determine shelf heat transfer coefficient	Shelf temperature mapping studies	Shelf temperature mapping studies	Dryer
5	Determine vial-bottom heat transfer coefficients and compare sublimation rates between dryers	Perform sublimation study of pure water; simulation studies	Perform sublimation study of pure water	Formulation
6	Determine mass transfer resistance R_p using the product temp, T_b, profiles and non-linear parameter estimate algorithm	Perform the primary drying studies and measure the T_b profiles	Not required	Formulation
7	Simulate T_b	Simulate T_b as a function of T_s and P_c	Simulate T_b, as a function of T_s and Pc	Dryer, vial and formulation
8	Determine the operating cycle parameters and product temp T_b for the production dryer	Not required	Run simulation to obtain the optimum operating cycle parameters	Dryer, vial and formulation
9	Demonstrate the accuracy of the developed cycle parameters	Not required	Perform a cycle run	Dryer, vial and formulation

Table 2
Important information on freeze dryers used in this study

	LyoStar™	Edwards™
Condenser (external)		
Capacity	30 L	548 L
Surface area	7 ft^2 (0.65 m^2)	301 ft^2 (28 m^2)
Temperature	−85 °C	−80 °C
Chamber		
Shelf dimensions	11 in. × 20 in. (28 cm × 51 cm) 1.53 ft^2 per shelf 3 Shelves = 4.59 ft^2	48 in. × 60 in. (122 cm × 152 cm) 20 ft^2 per shelf 11 Shelves = 220 ft^2
Opening to condenser	3.75 in. (9.525 cm)	24 in. (60.96 cm)
Ratio of condenser surface area to shelf surface areas		
7 ft^2/4.59 ft^2	1.525	
301 ft^2/220 ft^2		1.368
Ratio of shelf area to condenser opening area		
4.61 ft^2/3.14 × $(0.3125)^2$/4	60.2	
219.57 ft^2/3.14 × $(2.0)^2$/4		69.9

Task 2 was to measure the radiation emissivity of the shelf surface e_s for both laboratory and production dryer. This was a relatively simple task, requiring only an infrared pyrometer. Task 3 was to determine the vial-top radiation emissivity e_v for both the laboratory and production dryers. This value is available from the literature using a sophisticated experimental design (Pikal et al., 1984). Task 4 was to determine the shelf heat transfer coefficient K_s of both the laboratory and production dryers using shelf temperature mapping data measured for both dryers. Task 5 was to determine the vial-bottom heat transfer coefficients K_{cs} (the contact parameter) and ℓ_v (the separation distance). This was accomplished by a sublimation study of frozen pure water. Since the vial-bottom heat transfer coefficients are independent of the type of the dryer, the sublimation experiment was performed on the laboratory dryer. Since the sublimation study is a relatively simple weight-loss experiment, it was also performed on the production dryer. The weight-loss results for the production dryer were used to confirm the obtained values of the heat transfer parameters e_s, e_v, K_{cs}, and ℓ_v. Task 6 was to determine the mass transfer resistance R_p for the formulation of interest, such as 5% mannitol solution and a lactate dehydrogenase (LDH) formulation (50.78 mcg/mL LDH, 32.5 mg/mL glycine, 17.5 mg/mL sucrose, QS with water to 2 mL, pH 7.12), using the product temperature profiles T_b and Powell's optimization algorithm (Powell, 1965; Himmelblau, 1972; Kuester and Mize, 1973; Kuu et al., 1992, 1995, in press). This unique method permitted a rapid determination of the mass transfer coefficients. Since the mass transfer coefficients are independent of the type of dryer used, only the laboratory dryer was used to obtain the T_b profiles during primary drying.

After the heat and mass transfer coefficients were obtained from Tasks 2 to 6, various simulation studies were performed using primary drying subroutine PDRYS (Kuu et al., 1995, in press). Task 7 was to simulate T_b as a function of the shelf fluid temperature T_f and the chamber pressure P_c. Task 8 was to perform simulations to obtain the optimum operating cycle parameters. Finally, in order to demonstrate the accuracy of the obtained heat and mass transfer coefficients and developed cycle parameters, actual cycle runs were performed for the formulation of interest using the production dryer (Task 9). The theoretical background and detailed mathematical modeling required for Tasks 4–8 in Table 1 have been presented in the literature (Pikal, 1985; Kuu et al., 1995, in press).

3. Materials and methods

3.1. Weight loss studies of frozen pure water (for direct comparison of the laboratory and production dryers, Task #1, and for determination of vial heat transfer coefficients, Task #5)

In order to compare the efficiency of the LyoStar™ and Edwards™ dryers under identical operating parameters for a fixed period of time, weight loss studies of frozen pure water during primary drying were conducted for both dryers using the same cycle and at a high shelf temperature of 10 °C. A full shelf of 10 mL/20 mm tubing vials (Schott Pharmaceutical Inc.) was filled with 6.7 mL of 0.22μ filtered Milli-Q water in each vial, and partially stoppered with 20 mm lyo stoppers. Selected vials were weighed, and then the following cycle was run: (1) ramp from 20 to −25 °C in 30 min (1.8 °C/min) → (2) dwell at −25 °C for 4 h → (3) turn on vacuum and wait until 100 milliTorr (mT or microns) is reached → (4) ramp to 10 °C in 30 min (1.2 °C/min) → (5) dwell at 10 °C, 100 mT, for 8 h.

Vials were fully stoppered, and when the contents reached room temperature, the selected vials were again weighed. The amount of water lost during sublimation was calculated and compared per equivalent position in each dryer.

In addition to the efficiency comparison of the two dryers, the results of the weight loss studies were also used for determination of the vial-bottom heat transfer coefficients K_{cs} (the contact parameter) and ℓ_v (the separation distance) (Kuu et al., 1995, in press). The vial-bottom heat transfer coefficient is independent of formulation, depending only on the vial and the dryer to be used. In order to separate the effect of the pressure and temperature ramping up period from the actual sublimation phase, a separate run was performed from time zero to the time when the target shelf temperature and chamber pressure was reached. The resulting amount of sublimation is used as the baseline to be excluded from the actual primary drying runs.

3.2. Measurements of radiation emissivities and determination of shelf heat transfer coefficients (Tasks #2–4)

The values of the shelf surface emissivity for both the LyoStar™ and Edwards™ dryers were measured using the Omega OS205 Infrared Pyrometer (Omega Engineering Inc., Omega.com). Shelf surface emissivity is constant for a particular dryer at a particular point in time, independent of the formulation or vial type used. For measurements, thermocouples were placed at various locations of the shelf surface, so that actual temperatures of the shelf surface could be measured. The sensor of the pyrometer was then aimed at the location of shelf surface adjacent to each thermocouple. The emissivity of the pyrometer was adjusted until the temperature reading on the pyrometer was the same as the temperature measured by the thermocouple at the particular location.

For determination of the vial-top radiation emissivity, e_v, Pikal et al. (1985) proposed a novel approach for its measurement. In this paper, e_v was generated by using the single vial procedure and adjusting the shelf temperature so that the shelf surface temperature T_s is equal to the product temperature at the bottom of the vial T_b. Under these conditions, the heat transfer was due to the top radiation term only. The resulting e_v was determined to be approximately 0.84 and independent of the types and sizes of vials tested. Since the experiment requires a highly modified laboratory dryer, it was very difficult (or impossible) to be performed in the dryers available to us. Therefore, this value was used for the simulation studies in this paper. As with the surface emissivity, the vial-top emissivity is independent of formulation or type of vial, depending only on the dryer to be used.

3.3. Determination of mass transfer coefficients for the model formulation 5% mannitol (Task #6)

Mass transfer resistance of the dry layer during primary drying is one of the most important factors affecting the maximum product temperature and drying time. Since the mass transfer coefficients are highly dependent on the type of formulation and concentrations of ingredients, it is necessary to determine them for each formulation. Thus, a simple, rapid and efficient method is preferable. Thus, dry product mass transfer coefficients were determined using temperature profiles T_b generated by the laboratory dryer of the center vials. The proposed approach of using product temperature profiles T_b in conjunction with Powell's optimization algorithm provides a quick and simple approach (Kuu et al., in press). The dry layer mass transfer coefficients depend on the formulation only, independent of the type of vial and the dryer to be used.

Freeze drying was accomplished by filling 3 mL of 5% mannitol into a 10 mL Schott tubing vial, and running the following cycle: (1) precool shelves to 5 °C → (2) freeze shelves to −40 °C (0.5 °C/min) → (3) hold at −40 °C for 9 h → (4) adjust chamber pressure to 100 mT → (5) increase shelf temperature to −15 °C (0.42 °C/min) → (6) maintain shelf temperature of −15 °C for 26.5 h → (7) increase shelf temperature to +45 °C (1.33 °C/min) (8) maintain at +45 °C for 2 h → (9) neutralize chamber, stopper vials.

3.4. Ramping of shelf temperature

The cycle runs for 5% mannitol and the LDH formulations were performed using shelf temperature ramping, rather than "jumped" directly, from the freezing temperature to the primary drying shelf temperature. For 5% mannitol, the ramping was 0.42 °C/min from −40 to−15 °C with a duration of 60 min. For the LDH formulations, the ramping was 0.44 °C/min from −40 to −20 °C with a duration of 45 min. The sublimation of ice during ramping depends on the ramping rate and may not be negligible. Therefore, in the primary drying subroutine PDRYS, the shelf fluid temperature needs to be varied over time, rather than using a fixed value. This is especially important for the LDH formulation, as shown in Fig. 6 where the ramping period lasts for 120 min to avoid collapsing of the product. The shelf temperature is the most important factor affecting the product temperature. In order to ensure the accuracy of computation during ramping, the time interval of integration was set at 1 min. It is clear that during the simulation process, the shelf temperature varies over time, but was not treated as a dependent variable. It was controlled directly by the software of the freeze dryer.

3.5. Simulations for 5% mannitol (Tasks #7 and 8)

After obtaining the heat and mass transfer coefficients, the simulation program developed based on the

primary drying subroutine (Kuu et al., 1995, in press) can be used to simulate the product temperature T_b at various experimental conditions, such as the shelf fluid temperature T_f and chamber pressure P_c. The operating cycle parameters and product temperature T_b for the production dryer can then be determined. With the results obtained from mannitol vial freeze drying experiments, the optimum operating cycle parameters can be determined to maximize the efficiency of the cycle run without causing collapse of the product.

3.6. Practical comparison study for the actual product, the LDH formulation (Task #6–9)

After demonstrating the correlation approach using the model formulation 5% mannitol, a practical comparison study was performed using the actual product, the lactate dehydrogenase (LDH) formulation. The cycle development was performed using the LyoStar™ dryer, where 60 Wheaton 10 mL tubing vials were filled with 2 mL of LDH formulation. The following cycle was run: (1) precool shelves to 20 °C → (2) freeze shelves to −40 °C (0.5 °C/min) → (3) hold at −40 °C for 4 h → (4) adjust chamber pressure to 100 mT → (5) increase shelf temperature to 0 °C (0.31 °C/min) → (6) maintain shelf temperature of 0 °C for 12 h → (7) increase shelf temperature to +25 °C (1.67 °C/min) → (8) maintain at +25 °C for 4 h → (9) increase shelf temperature to 40 °C (1 °C/min) → (10) maintain at +40 °C for 4 h) → (11) decrease shelf temperature to +25 °C (0.5 °C/min) → (12) neutralize chamber, stopper vials.

The above cycle yielded a final product with a cake moisture content less than 1% by Karl Fischer. The same lyophilization cycle developed in the laboratory was used in the production dryer, with water filled placebo vials used to completely fill all shelves of the production dryer with the LDH containing vials interspersed among the placebo vials on all shelves. The enzymatic assay run for LDH was quite variable in both laboratory and production experiments with acceptance limits being 80–120% of initial assay. The moisture content of the dry cakes was measured by Karl Fischer and achieved the acceptance limit of less than 1.0%.

4. Results and discussion

4.1. Weight loss studies of frozen pure water to determine the contact parameter k_{cs} and separation distance ℓ_v, Tasks #1 and 5)

Fig. 1 summarizes the comparison of percent weight loss of water in vials located at different parts of a middle shelf in the laboratory dryer compared to the same locations in the production dryer. The results of weight loss studies of frozen pure water indicate that, for the time period measured, sublimation rates obtained in a lab dryer fell into a range of 91–103% that of the production dryer when both dryers were run under identical conditions, regardless of location. The average weight loss of the center vials for the LyoStar™ and Edwards™ dryers are 3.0912 ± 0.1379 g and 3.0614 ± 0.08976 g, respectively. It is interesting to note the close values for these

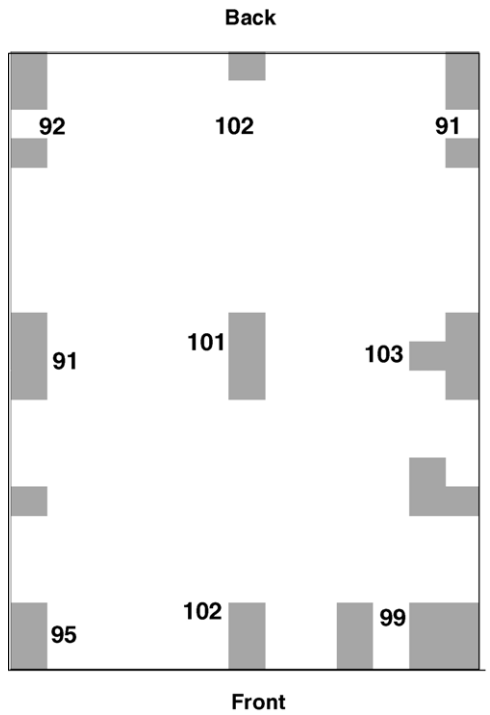

Fig. 1. Correlation of sublimation rates at different locations on a shelf (middle) with data showing laboratory dryer weight loss as percent of production dryer.

two dryers. We calculated the condenser surface area, the shelf surface area and condenser opening area for the two dryers (Table 2). We then calculated the ratios of condenser and shelf surface areas shelf area to condenser opening area for both dryers (Table 2). For such a large difference in the shelf capacity of the two dryers (production dryer is 48 times the size of the laboratory dryer), these ratios were surprisingly close. The ratio of condenser surface area to shelf surface area for the laboratory dryer (1.525) is only 10% higher than that for the production dryer (1.368) while the ratio of the shelf area to condenser opening area for the laboratory dryer (60.2) is only 14% less than that for the production dryer (69.9). The relative closeness of these values suggests similar capabilities of the condenser openings to handle the ice vapor during primary drying for the two dryers that may, in part, explain why the weight loss data are so similar. The weight loss studies indicated that both dryers are capable of performing the subsequent tasks of correlation.

In addition to the efficiency comparison studies for both dryers, based on the sublimation rates of the center vials, we can conclude that the shelf heat transfer coefficient K_s in the center area is approximately the same for both dryers. In addition, it is reasonable to assume that the shelf heat transfer property is uniform for the entire shelf surface.

In our introduction we indicated that results of sublimation studies were used to directly compare sublimation rates between lab and production dryers operating under the same conditions for a fixed period of time, and draw conclusions about how closely the lab dryer compared to the production dryer. Previous discussion has demonstrated the comparability of the two dryers. We also indicated that these sublimation data would be used to obtain values of the vial heat transfer parameters K_{cs} (the contact parameter) and the separation distance ℓ_v (Kuu et al., 1995, in press). This is similar to Section 4.3 described later with the following conditions: (1) The dependent variable is the amount of water sublimated during primary drying; (2) Since the frozen water has no mass transfer resistance, the values of R_0, A_1, and A_2 are set to zero. The obtained contact parameter K_{cs} and separation distance ℓ_v for the 10 mL tubing vial are: $\ell_v = 0.0421$ cm, $K_{cs} = 1.32 \times 10^{-4}$ (cal s^{-1} cm^{-2} °C^{-1}).

4.2. Measurements of radiation emissivities and determination of shelf heat transfer coefficient (Tasks #2–4)

The measured shelf surface emissivity using an Omega® infrared pyrometer, both for the LyoStar™ and Edwards™ dryers, is approximately 0.6. This value is very close to the values reported in the literature for polished 316 stainless steel. Thus, this is a very simple measure contributing to the correlation of lab and production dryers.

As discussed in Section 3, the resulting e_v determined by Pikal et al. (1985) was approximately 0.84 and independent of the types and sizes of vials tested. To measure the shelf surface temperature, thermocouples (copper and constantan, Type T, Omega Engineering Inc.) were placed at various locations of the empty shelf surface and the gas space of the LyoStar™ dryer. The shelf fluid temperature and chamber pressure were set at 40 °C and 500 mT, respectively. The detailed procedure for determination of K_s is presented in the literature (Kuu et al., in press). The obtained value is approximately 0.013 cal s^{-1} cm^{-2} °C^{-1}. The effect of the accuracy of K_s on the overall heat and mass transfer processes is insignificant. For example, for the K_s values of 0.003, 0.01, and 0.03, the simulated corresponding values of the maximum product temperature T_{bmax}, for 3 mL of 5% mannitol in the 10 mL of tubing vial, are −27.68, −27.32, and −27.21 °C, respectively. Likewise, for the same K_s values, the simulated corresponding values of the primary drying time are 18.82, 17.76, and 17.45 h, respectively.

4.3. Determination of mass transfer coefficients for 5% mannitol (Task #6)

The measured product temperature T_b profiles for mannitol of the center vials for the entire cycle run using the LyoStar™ dryer are shown in Fig. 2. The normalized dry layer mass transfer resistance for mannitol can be expressed as (Pikal, 1985)

$$R_{pN} = R_0 + A_1 \ell \quad (1)$$

where R_0 and A_1 are constants (the dry layer mass transfer coefficients) and ℓ is the receding thickness of the dry layer. The best-fit values of the parameters were obtained by minimizing the following sum of the squares, SSQ

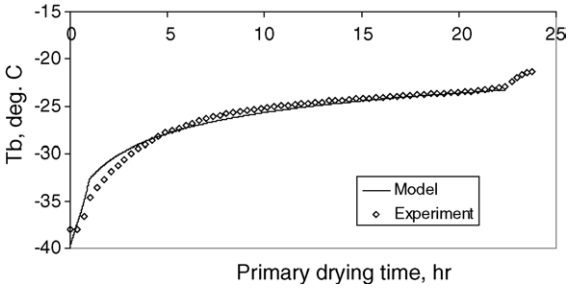

Fig. 2. The experimental and simulated product temperature vs. time profiles of 5% mannitol in 10 mL tubing vial during primary drying $R_{pN} = 0.7313 + 17.19\ell$. The shelf temperature ramping rate is 0.4 °C/min. Constants and parameters used for the simulation are listed below (detailed explanations for other symbols can be found in the literature, Pikal, 1985). Large values of KTC and KTP were chosen to simulate the primary drying without using trays: $A_v = 4.43$, $A_P = 3.58$, $R_0 = 0.7313$, $A_1 = 17.19$, KTC = 100.0, KTP = 100.0, KTD = 1.0, KC = 2.64×10^{-4}, KD = 3.64, $K_P = 3.32 \times 10^{-3}$, $K_I = 0.0059$, $K_s = 0.013$, $S_0 = 4.8$, $S_1 = 169.0$, $K_{cs} = 1.32 \times 10^{-4}$, $e_s = 0.60$, $e_v = 0.84$, $\sigma = 1.35 \times 10^{-12}$, $\lambda_0 = 4.29 \times 10^{-5}$, $\ell_v = 0.0421$.

$$\text{minimize (SSQ)} = \text{minimize} \left(\sum_{i=1}^{n} [(T_b(t) - T_{bi})]^2 \right) \quad (2)$$

where n is the number of data points; T_b (t) and T_{bi} are the theoretically and experimentally determined product temperature, respectively. The most significant advantage of using the product temperature profiles T_b to determine the mass transfer coefficients is that the temperature can be continuously monitored and recorded during primary drying, without interruption of the chamber or the shelf. Determination of mass transfer coefficients of mannitol using T_b was done (Powell, 1965; Kuester and Mize, 1973; Kuu et al., 1992, 1995, in press) in conjunction with the primary drying subroutine described earlier. The resulting normalized dry layer mass transfer resistance R_{pN} in Eq. (1) is expressed by the following equation

$$R_{pN} = 0.7313 + 17.19\ell \quad (3)$$

The obtained mass transfer resistance allows simulation studies to predict the product temperature profiles at various values of chamber pressure and shelf temperature.

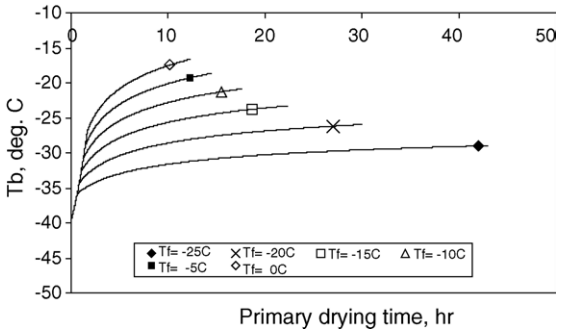

Fig. 3. Simulated product temperature profiles for 5% mannitol as a function of the shelf fluid temperature and the primary drying time. The constants and parameters are the same as those of Fig. 2. The shelf temperature ramping rate is 0.4 °C/min.

4.4. Simulation results for the production dryer for 5% mannitol (Tasks #7 and 8)

The simulated typical product temperature versus time profiles for 5% mannitol in the 10 mL tubing vial, at the chamber pressure of 100 mT and at various shelf fluid temperatures T_f, are presented in Fig. 3. The profiles show that that the shelf fluid temperature has a very profound effect on the primary drying rate and time. The end point of each profile indicates the completion of primary drying, and the corresponding product temperature is termed the maximum product temperature T_{bmax}. In order to develop operation templates for cycle parameters, first it is necessary to simulate numerous product temperature profiles, similar to those in Fig. 3, to encompass the entire range of these parameters. The resulting values of T_{bmax} and the corresponding primary drying times are then determined and presented in Figs. 4 and 5. The purposes of the operation templates are to optimize the cycle parameters by controlling the product temperature below the collapse temperature during the entire course of primary drying and to minimize the primary drying time.

Fig. 4 shows that T_{bmax} proportionally increases with T_f. The values of T_{bmax} for all profiles range between −28.5 and −14.7 °C. The glass transition temperature for 5% mannitol was determined using DSC as approximately −29.22 °C. If one uses this glass transition temperature as the criterion to determine the cycle parameters from Fig. 4, none of the shelf temperatures nor the chamber pressures can be used to run the cycle. However, It is well known that the effect of cooling

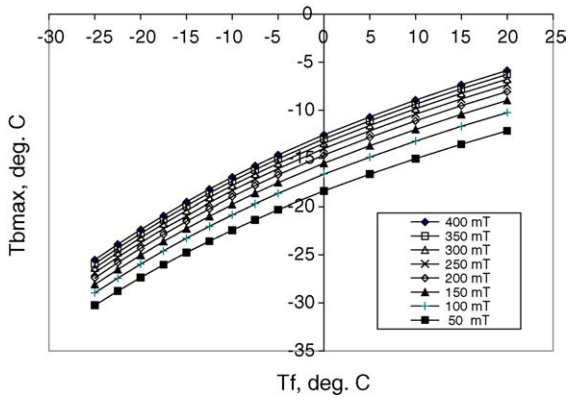

Fig. 4. Simulated maximum product temperature profiles T_{bmax} for the production dryer as a function of the shelf fluid temperature and chamber pressure −3 mL of 5% mannitol in the 10 mL tubing vial. The constants and parameters are the same as those of Fig. 2. The shelf temperature ramping rate is 0.4 °C/min.

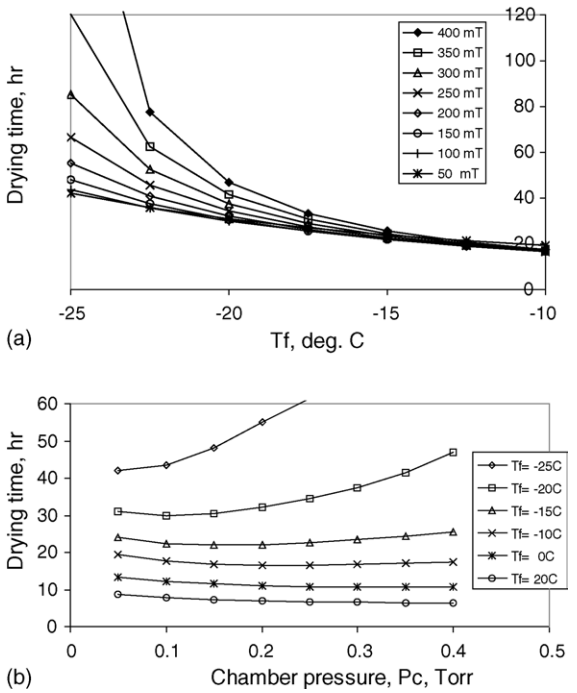

Fig. 5. Simulated primary drying times for the production dryer as a function of the shelf fluid temperature and chamber pressure −3 mL of 5% mannitol in 10 mL tubing vial. The constants and parameters are the same as those of Fig. 2. The shelf temperature ramping rate is 0.4 °C/min. (a) The effect of shelf fluid temperature on drying time at various levels of chamber pressure. (b) The effect of chamber pressure on drying time at various levels of T_f.

rate has a significant effect on the polymorphism of mannitol (Kim et al., 1998). With a proper control of the cooling rate during the freezing stage, the glass transition temperature can be raised. As such, the primary drying can be performed at a much higher shelf temperature. Therefore, in order to apply the results in Figs. 4 and 5 to determine the optimum operating cycle parameters, it is necessary to combine with other "thermal treatment" means, such as controlling of cooling rate or annealing to raise the glass transition temperature. Although reducing the time that a product must remain in the primary drying phase is one way to optimize the length of the entire cycle, the extra time required for these types of treatment steps must be taken into account when choosing optimal parameters for primary drying conditions.

It is interesting to note from Fig. 5 that the primary drying time decreases with the increasing chamber pressure when the shelf fluid temperature is above −5 °C. On the other hand, for the shelf fluid temperature lower than −5 °C, the primary drying time increases much faster than the decreasing rate of the shelf fluid temperature, especially at −25 °C. For example, it requires 85 h of primary drying time for shelf temperature of −25 °C and the chamber pressure of 300 mT. By comparing T_{bmax} in Fig. 4 and the primary drying time in Fig. 5, it is clear that in order to freeze-dry the product at a low shelf fluid temperature, it is important to perform at a low chamber pressure to minimize the drying time.

The effect that a higher chamber pressure results in a shorter drying time was reported by a number of researchers (Nail, 1980; Pikal, 1985; Livesey and Rowe, 1987; Chang and Fisehr, 1995). This phenomenon was explained by Pikal using the conductive heat transfer of the gas between the shelf surface and the glass vial, and the driving force of mass transfer ($P_0 - P_c$). Since the vial heat transfer coefficient through gas conduction K_g (Pikal, 1985; Eq. 28) increases with increasing pressure, the drying rate is higher at a higher chamber pressure. Thus, the drying time normally decreases as the chamber pressure increases. This is true when the shelf temperature is high.

Fig. 5 also shows that when the shelf fluid temperature is lower than −5 °C, the trend appears to be reversed, resulting in the increase of the drying time. This effect was amplified with further decrease of the

shelf temperature. The increase of the drying time is a result of the decrease in the driving force $(P_0 - P_c)$, as P_c increases, as can be seen from the sublimation rate equation $(dm/dt) = (P_0 - P_c)/(R_s + R_p)$. The reversal shelf temperature depends on the mass transfer resistance. Thus, the best way of determining the quantitative effect of the chamber pressure on the drying time is to perform simulation studies of primary drying.

4.5. Practical comparison study (Tasks #6–9)

The product temperature profile T_b for the LDH formulation was obtained from the cycle run in Section 3.6. Similar to 5% mannitol in Section 4.3, dry product mass transfer coefficients for the LDH formulation were determined using the T_b profile, generated by the laboratory dryer of the center vial in conjunction with Powell's optimization algorithm. The resulting normalized dry layer mass transfer resistance is expressed by

$$R_{pN} = 4.344 + 10.85\ell \quad (4)$$

The experimental and simulated profiles are shown in Fig. 6. The initial linearly rising product temperature was due to the ramping of the shelf temperature for 120 min. A close fit between the two profiles can be seen. The obtained mass transfer resistance Eq. (4) allows simulation studies to predict the product temperature profiles at various values of chamber pressure and shelf temperature. Similar to Figs. 4 and 5 for 5% mannitol, the operational templates T_{bmax} and primary drying time are also generated by simulation, and presented in Figs. 7 and 8. It is interesting to note that the profiles in Fig. 7 are similar to those in Fig. 4, since the mass transfer resistance in Eq. (4) is similar to Eq. (3) if one plots R_{pN} against the receding dry layer thickness ℓ.

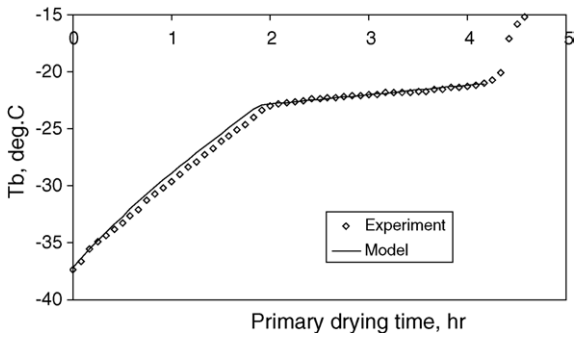

Fig. 6. The experimental and simulated product temperature vs. time profiles of the LDH formulation in 10 mL tubing vial using the mass transfer resistance equation $R_{pN} = 4.344 + 10.85\ell$. The shelf temperature ramping rate is 0.4 °C/min.

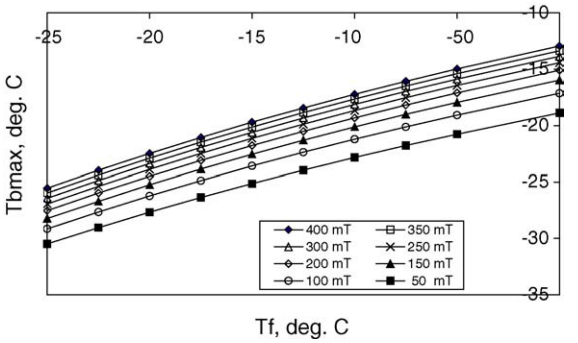

Fig. 7. Simulated maximum product temperature profiles T_{bmax} for the production dryer as a function of the shelf fluid temperature and chamber pressure—the LDH formulation in 10 mL tubing vial. The constants and parameters used for the simulation are the same as those of Fig. 2 except R_0 and A_1. $R_{pN} = 4.344 + 10.85\ell$. The shelf temperature ramping rate is 0.31 °C/min.

The data in Table 3 indicate that the cycle developed in the laboratory dryer that produced a LDH formulation with 80–120% of initial activity and moisture content <1.0% gave similar results when the product was lyophilized in the production dryer. Other studies have shown similar correlations. However, since these studies involve confidential client products, we are unable to report the data.

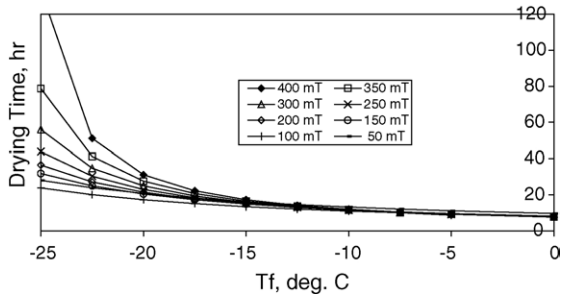

Fig. 8. Simulated primary drying time for the production dryer as a function of the shelf fluid temperature and chamber pressure-the LDH formulation in 10 mL tubing vial. The constants and parameters used for the simulation are the same as those of Fig. 2 except R_0 and A_1. $R_{pN} = 4.344 + 10.85\ell$. The shelf temperature ramping rate is 0.31 °C/min.

Table 3
Karl Fischer moisture data and LDH activity following lyophilization cycle in production dryer using same cycle developed in laboratory dryer

Shelf	Front left		Back left		Center		Rear right		Front right	
	Moisture (%)	LDH (%)	Moisture (%)	LDH (%)	Moisture (%)	LDH (%)	Moisture (%)	LDH (%)	Moisture (%)	LDH (%)
1	–	–	–	–	–		0.55	–	0.51	–
2	–	100.5	–	97.2	–	91.5	–	102.2	–	–
3	–		–	–	0.77	–	0.63	–	0.74	–
4	–	109.6	–	102.9	0.53	–	–	86.3	–	87.9
5	0.55	–	0.70	–	0.97	–	0.42	–	0.69	–
6	–	102	–	96.7	0.58	–	–	107.4	–	108.4
7	0.67	–	0.66	–	0.95	–	0.55	–	0.49	–
8	–	115.5	–	99.4	0.67	–	–	109.9	–	98.4
9	0.69	–	–	–	0.41	–	0.40	–	0.73	–
10	–	100.4	–	–	0.27		–	–	–	99

4.6. Summary

The systematic correlation approach presented in this paper is recaptured and summarized in Fig. 9. The flow chart describes the relationship among the tasks presented in Table 1, and also indicates the sequential and parallel correlation activities. During the correlation studies for the LyoStar™ and Edwards™ dryers, we have experienced the best-case scenario that the dryer heat transfer coefficient and emissivities K_s, e_s and e_v, at the center-vial locations, are virtually the same for both dryers. In addition, the vial used for the LyoStar™ dryer during the cycle development was the same as that for the Edwards™ dryer for production. This scenario simplifies the correlation activities. As such, the operation templates presented in Figs. 4 and 5 for 5% mannitol and Figs. 7 and 8 for the LDH formulation can be used for both the LyoStar™ and Edwards™ dryers. For cases other than the best-case scenario, it may be necessary to perform simulations to generate Fig. 3 for both the LyoStar™ and Edwards™ dryers, and subsequently generate the operation templates for both dryers.

For the purpose of demonstration of the proposed approach, the model formulation studied in this paper is 5% mannitol and actual product is the LDH formulation. For other formulations, it is necessary to re-determine the mass transfer resistance for the for-

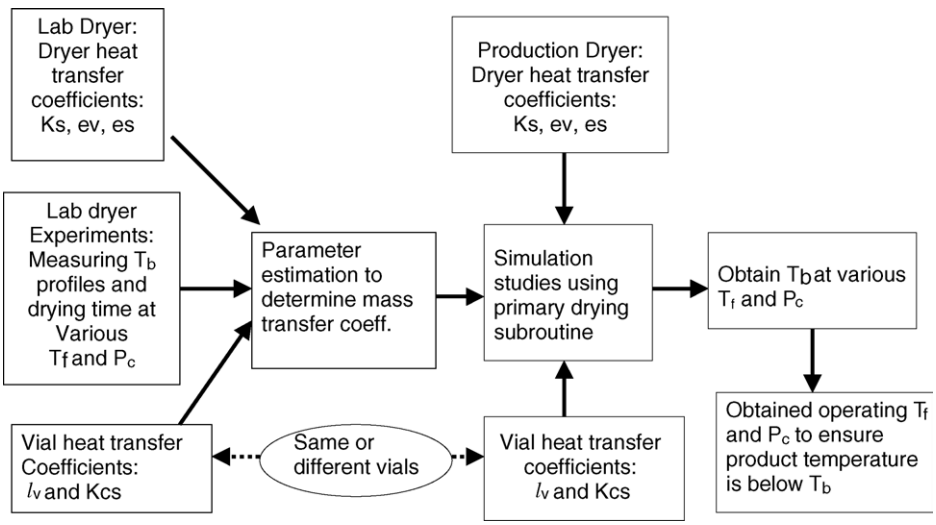

Fig. 9. Summary of the correlation activities.

mulations of interest. This is the most time-consuming task. However, this can be done using the "*Rapid determination of dry layer mass transfer resistance for various pharmaceutical formulations during primary drying using product temperature profiles*" presented in the literature (Kuu et al., in press).

5. Conclusions

We have employed a systematic approach to attempt to show correlation of cycle parameters between our laboratory and production freeze dryers. Methods used include emissivity comparisons, shelf fluid temperature mapping, weight loss determinations that measure rates of sublimation, comparisons of heat and mass transfer rates, and freeze dry cycle simulations.

The results of weight loss studies of frozen pure water indicate that, for the time period measured, sublimation rates obtained in a lab dryer fell into a range of 91–103% that of the production dryer when both dryers were run under identical conditions, regardless of location. Since the most critical variation would be the case of the lab dryer subliming more slowly than the production dryer, the data from these two experiments indicate that a "worst-case" scenario (for formulations without collapse concerns) would be the lab dryer having a sublimation rate 91% that of the production dryer. Therefore, in general, a cycle developed in our lab dryer would be, at worst, within 91% of the cycle time required for the production dryer.

The weight loss data of center vials for both dryers are very close, indicating that the heat transfer rates for both dryers at this location are approximately equal. This conclusion can be confirmed by the similar shelf heat transfer coefficient K_s and shelf surface emissivity e_s determined for both dryers. Finally, the primary drying cycle time, at various levels of the shelf temperature and chamber pressure, can be predicted using the simulation subroutine PDRYS. The product temperature T_b, as a function of the shelf fluid temperature and chamber pressure, can also be obtained by simulation studies. The optimum operating cycle parameters can then be obtained from the simulated results. With the optimum parameters, the cycle run can be performed successfully without product collapse, and yet the cycle time can be minimized.

This paper emphasizes the correlation of the laboratory and production dryers based on the cycle developed for the center vials. Future studies will be directed toward the impact of the edge vials on the correlation results.

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