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Research Article

Theme: Team Science and Education for Pharmaceuticals: the NIPTE Model
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Impact of Natural Variations in Freeze-Drying Parameters on Product Temperature History: Application of Quasi Steady-State Heat and Mass Transfer and Simple Statistics

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Abstract. Inter- and intra-batch variability in heat and mass transfer during the drying phase of lyophilization is well recognized. Heat transfer variability between individual vials in the same batch arise from both different positions in the vial array and from variations in the bottom contour of the vials, both effects contributing roughly equally to variations in the effective heat transfer coefficient of the vials, K_v. Both effects can be measured in the laboratory, and variations in average K_v values as a function of vial position in the array for lab and production can be calculated by use of the simple steady-state heat and mass transfer theory. Typically, in the laboratory dryer, vials on the edge of the array, "edge vials," run 2–4°C warmer than "center vials," but differences between laboratory and manufacturing temperatures are modest. The variability in mass transfer can be assigned to major variations in ice nucleation temperature (both intra-batch and inter-batch), including major differences between laboratory and manufacturing. The net effect of all random variations, for each class of vial, can be evaluated by a simple statistical model-propagation of error, which then allows prediction of the distribution in product temperatures and drying times, and therefore prediction of percent of vials dry and percent of vials collapsed and proximity to the edge of failure for a given process. Good agreement between theoretical and experimentally determined maximum temperatures in primary drying and percent collapsed product demonstrates the calculations have useful accuracy.

KEY WORDS: freeze-drying; statistics of variability in product temperature; heat and mass transfer; scale-up.

INTRODUCTION

It is well recognized that due to variation in container geometry, location effects, and stochastic freezing, not all product vials freeze dry at the same temperature nor do they finish primary drying at the same time. Product in vials that exceed the collapse temperature during primary drying will lead to cake collapse. Similarly, when the shelf temperature is increased for secondary drying, any vials still containing ice will likely have collapsed product, again resulting in likely product rejects. To minimize vials exceeding the collapse temperature, the shelf temperature is set colder and lower pressure is used, which means primary drying is longer. Additionally, to minimize product collapse during the early part of "operational secondary drying" due to some vials still containing ice, the low primary drying shelf temperature is maintained much longer, which ultimately prolongs the freeze-drying cycle time. This conservative and empirically driven approach to select cold shelf temperature, very low chamber pressure, and extending primary drying time leads to an inefficient process. Pharmaceutical companies with a significant number of lyophilized products in their portfolio often are strongly encouraged to devise means to reduce cycle times to maximize usage of their lyophilization capacities.

Freeze-drying is one process where the fundamental physics is relatively well understood, and the process may be mathematically modeled with useful accuracy (1). Furthermore, existing

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studies have addressed sources of the variation in heat and mass transfer properties and their impact on product temperature in primary drying and on primary drying time (1–4). Therefore, simple modeling techniques can be used in process design, including the assessment of the distribution in drying behavior that is the subject of this report. Appropriate use of modeling allows a rational, data based, evaluation of design space for optimal process design.

MATERIALS AND METHODS

Materials and Freeze-Drying

Vials used for heat transfer coefficient measurements were 20 cc tubing vials (Nipro Glass Americas (Formerly Amcor) (Millville, NJ)). Rubber stoppers were 2-pronged 20 mm lyophilization stoppers (Fisher Scientific, USA), and sublimation was carried out using pure water for vial heat transfer coefficient measurements.

Heat and Mass Transfer Theory and Data

Heat transfer during lyophilization can be represented as follows:

$$Q = A_v.k_v.(T_S - T_P) \tag{1}$$

where, Q is the heat flow rate per vial, A_v is the horizontal cross-sectional area of vials, K_v is vial heat transfer coefficient, T_S is the shelf surface temperature, and T_P is the product temperature at the bottom center of the vial.

Mass transfer during lyophilization can be represented as:

$$m = A_p \cdot \frac{P_0 - P_c}{\hat{R}_{ps}} \tag{2}$$

where, m is sublimation rate per vial, $\hat{R}_{ps}$ is the dry layer resistance plus stopper resistance, A_p is the internal cross-sectional area of the vial, P_0 the vapor pressure of ice at the sublimation interface, and P_c the chamber pressure. In quasi steady state, heat and mass transfer are coupled by, $Q = m\Delta H_S$, where ΔHs is the heat of sublimation of ice, so combination of Eqs. 1–2 leads to one equation, and one unknown, product temperature at the sublimation interface, T:

$$\frac{\Delta H_s (A_p/A_v) \cdot (P_0(T) - P_c)}{\hat{R}_{ps}} - K_v(T_s - T - \Delta T) = 0 \tag{3}$$

$\hat{R}_{ps}$ **Resistance of product plus stopper**
ΔT temperature difference between bottom of frozen layer (Tp) and sublimation interface (T)

An iterative approach of using Eq. 3 was introduced many years ago (1) and in recent years has been commonly referred to as the "LyoCalculator." This model is currently available as an Excel spreadsheet to those who are interested. Input parameters are introduced, and the program calculates the product temperature history, giving three key parameters for construction of a design space: maximum product temperature, drying time, and the maximum sublimation rate. The LyoCalculator is a key part of the calculations carried out in the present study.

Estimation of mean values and variance (relative standard deviation) of the two parameters, K_v and $\hat{R}_{ps}$, central to the use of LyoCalculator is described in the next sections.

Evaluation of Vial Heat Transfer Coefficients

The LyoCalculator and the statistical analysis use the mean K_v of vials at a given location (*i.e.*, center vials which are those surrounded by six other vials, edge at the outer edge touching the band, and inner edge not touching the band; Fig. 1) and the standard deviation in K_v arising from variations in the bottom contour of the vials. The center vial K_v data for vials from Kimble and Wheaton in Table I have been taken from reference (2). Sections below describe the procedure used to calculate mean K_v and standard deviation for the Amcor and "Proprietary Vials" ("P vials", Table I).

Experimental Methodology

For vials from Amcor and "P vials," heat transfer coefficient determinations used 10 cc of water and procedures similar to those described in the literature (2) for a vial array described by Fig. 1, using a gravimetric procedure that allows not only the average K_v to be determined but also allows the relative standard deviation of K_v to be calculated. The procedure for this gravimetric method is to weigh each vial before and after the steady-state sublimation run designed to sublime no more than about 30% of the ice, such that the sublimation rate can be obtained for each vial, and the raw (uncorrected) K_v value for each vial is obtained (2). A key feature is that a precision cut stainless

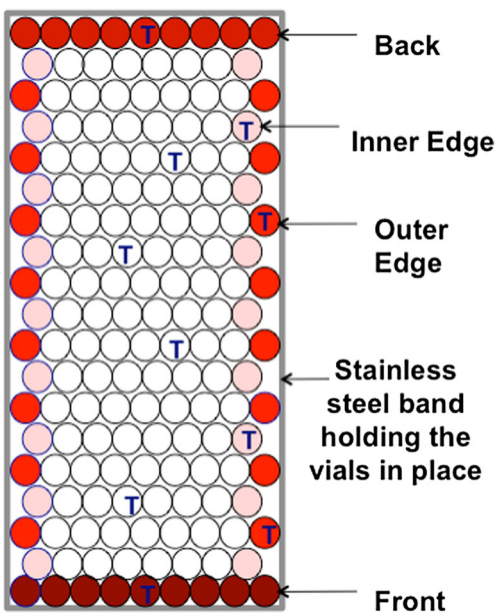


Fig. 1. The vial array (with trays): the different classes of edge vials

Table I. Values of Vial Heat Transfer Coefficients, $10^4 K_v$ (cal $s^{-1}cm^{-2}K^{-1}$) for 20 cc Tubing Vials in a Laboratory Dryer

Vial ID	P_c, mTorr	$10^4 K_v$ (center)	$10^4 K_v$ (inner edge)	$10^4 K_v$ (outer edge)	%RSD K_v (center)	%RSD K_v (edge)
P	55	2.86	3.34	3.82	6.7	10.7
A	60	2.72	3.23	3.83	6.4	8.6
W	68	3.47	4.02*	5.08*	4.0	6.8*
K	68	3.79	4.34*	5.40*	4.2	7.0*
A	100	3.55	4.22	4.96	6.4	8.6
W	100	4.22	4.82*	5.90*	3.8	6.6*
K	100	4.69	5.29*	6.37*	5.1	7.9*
A	150	4.45	5.25	6.25	6.4	8.6

All experiments used pure water
P proprietary (2015), *A* Amcor (2013), *W* Wheaton (reference 2), *K* Kimble (reference 2)
*Estimated from "A" data and calculated ΔK_v^E data in Table II.

steel tube is placed through each stopper such that the resistance to the flow of water vapor out of the vial is identical for all vials in the study, meaning that the variability in sublimation rate is determined entirely by variation in heat transfer to the vials. A full tray of vials (Fig. 1) was loaded into a LyoStar 3 laboratory freeze dryer (SP Scientific, USA) using "bottomless trays," and the bottom was removed such that all vials were directly touching the shelf surface. In Fig. 1, the circles represent vials, and the gray rectangular line surrounding the vial array represents the stainless steel band. Filled circles represent edge vials nominally touching the band ("outer" edge vials), and edge vials not touching the band ("inner" edge vials) are depicted by shaded circles. "T" indicates thermocouple-containing vials, where 30-gauge thermocouples were placed bottom center in the vial. *Calculation of the Edge Vial K_v.* Mean values of K_v for edge vials were obtained by calculating edge K_v using a recently published theory that allows calculation of the edge vial effect, specifically the difference between the K_v of a given type of edge vial and center vial (5). This calculation also operates from an Excel spreadsheet that will be made available to interested parties. This spreadsheet is illustrated in Fig. 2. Input parameters are listed, including standard operating parameters, such as P_c, T_s, fill volume, vial dimensions, product temperature estimate, and dryer dimensions of importance such as shelf spacing and "view factors" representing views of the vial to the band and dryer walls emissivity for radiation heat transfer. The outputs are the average edge vial effect and the edge vial effect for the various types of edge vials (*i.e.*, front and back outer vials, and side inner and outer edge vials). We note that we used a slightly modified calculation from that in (5) in the present study. A significant part of the heat transfer from the band to the vial is *via* gas phase conduction, where the average distance between the edge vial and the band is important. The original calculation of the average separation distance (5) assumed all outer edge vials actually make perfect contact with the band. We recognize that not all outer edge vials actually touch the band, and have increased the calculated average separation distance by 1 mm. This refinement allowed much better agreement between calculation and experiment with small vials, 10 and 5 cc, where the effect of separation distance variation is much more significant (data not shown).

Table I summarizes values of the K_v, and corresponding relative standard deviations in the K_v. Data are provided as a function of chamber pressure for several 20-cc tubing vials, representing vials from different vendors as identified in the Table. Only the "P" and "A" vial vendors products were determined in this research. Notice that at low pressure, the difference in K_v for center vials among vendors is small, but becomes quite large at 100 mTorr. There is also a considerable difference in the uniformity of K_v data among vendors; % RSD in K_v varies by nearly a factor of 2 among these vendors.

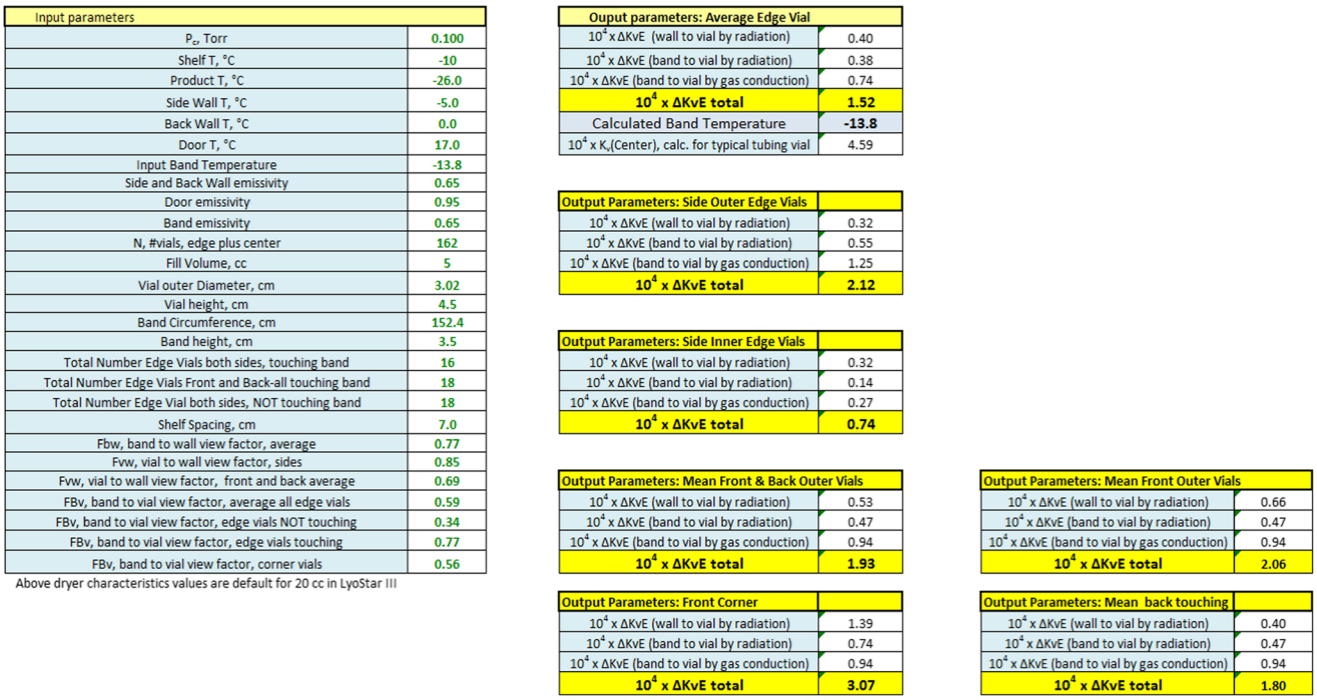
Table II provides a comparison of the calculated edge vial effect and the corresponding experimental values for the K_v experiments using pure water as product. Generally, the agreement is good and the trends with pressure are correctly predicted by theory. The values in Table II refer to the edge vial effect when pure water is the product. Since the edge vial effect depends on shelf temperature and product temperature (Fig. 2), and these input values vary with the nature of the "product" being freeze dried, the edge vial effect for a given model product (*i.e.*, mannitol, sucrose, sucrose-protein) is slightly different than for pure water. Edge vial effects for the model products selected for this research are given in Table III. Note that for actual products, the edge vial effect, $\Delta 10^4 K_v$, is slightly larger than found for pure water.

Variance Calculation for K_v. Duplicate runs were performed with identical vial placement in the array. Three sources of variance in K_v were considered to calculate total variance (and standard deviation) in K_v: relative standard deviation in raw K_v values, relative standard deviation between duplicate runs due to random error, and relative standard deviation in shelf surface temperature.

The relative standard deviation in the $K_v(\sigma_{K_v})$ is calculated by:

$$\sigma_{K_v} = \sqrt{\left(\sigma^2_{Total} - \frac{\sigma^2_{error}}{2} - \sigma^2_{K_v(T_s)}\right)} \tag{4}$$

σ^2_{Total} **total variance in raw K_v**
σ^2_{error} **error variance**
$\sigma^2_{K_v(T_s)}$ **variance in apparent $K_v$due to shelf surface temperature variation**



Input parameters	
P_c, Torr	0.100
Shelf T, °C	-10
Product T, °C	-26.0
Side Wall T, °C	-5.0
Back Wall T, °C	0.0
Door T, °C	17.0
Input Band Temperature	-13.8
Side and Back Wall emissivity	0.65
Door emissivity	0.95
Band emissivity	0.65
N, #vials, edge plus center	162
Fill Volume, cc	5
Vial outer Diameter, cm	3.02
Vial height, cm	4.5
Band Circumference, cm	152.4
Band height, cm	3.5
Total Number Edge Vials both sides, touching band	16
Total Number Edge Vials Front and Back-all touching band	18
Total Number Edge Vial both sides, NOT touching band	18
Shelf Spacing, cm	7.0
Fbw, band to wall view factor, average	0.77
Fvw, vial to wall view factor, sides	0.85
Fvw, vial to wall view factor, front and back average	0.69
FBv, band to vial view factor, average all edge vials	0.59
FBv, band to vial view factor, edge vials NOT touching	0.34
FBv, band to vial view factor, edge vials touching	0.77
FBv, band to vial view factor, corner vials	0.56

Above dryer characteristics values are default for 20 cc in LyoStar III

Ouput parameters: Average Edge Vial	
10^4 x ΔKvE (wall to vial by radiation)	0.40
10^4 x ΔKvE (band to vial by radiation)	0.38
10^4 x ΔKvE (band to vial by gas conduction)	0.74
10^4 x ΔKvE total	**1.52**
Calculated Band Temperature	-13.8
10^4 x K_v(Center), calc. for typical tubing vial	4.59

Output Parameters: Side Outer Edge Vials	
10^4 x ΔKvE (wall to vial by radiation)	0.32
10^4 x ΔKvE (band to vial by radiation)	0.55
10^4 x ΔKvE (band to vial by gas conduction)	1.25
10^4 x ΔKvE total	**2.12**

Output Parameters: Side Inner Edge Vials	
10^4 x ΔKvE (wall to vial by radiation)	0.32
10^4 x ΔKvE (band to vial by radiation)	0.14
10^4 x ΔKvE (band to vial by gas conduction)	0.27
10^4 x ΔKvE total	**0.74**

Output Parameters: Mean Front & Back Outer Vials	
10^4 x ΔKvE (wall to vial by radiation)	0.53
10^4 x ΔKvE (band to vial by radiation)	0.47
10^4 x ΔKvE (band to vial by gas conduction)	0.94
10^4 x ΔKvE total	**1.93**

Output Parameters: Mean Front Outer Vials	
10^4 x ΔKvE (wall to vial by radiation)	0.66
10^4 x ΔKvE (band to vial by radiation)	0.47
10^4 x ΔKvE (band to vial by gas conduction)	0.94
10^4 x ΔKvE total	**2.06**

Output Parameters: Front Corner	
10^4 x ΔKvE (wall to vial by radiation)	1.39
10^4 x ΔKvE (band to vial by radiation)	0.74
10^4 x ΔKvE (band to vial by gas conduction)	0.94
10^4 x ΔKvE total	**3.07**

Output Parameters: Mean back touching	
10^4 x ΔKvE (wall to vial by radiation)	0.40
10^4 x ΔKvE (band to vial by radiation)	0.47
10^4 x ΔKvE (band to vial by gas conduction)	0.94
10^4 x ΔKvE total	**1.80**

Fig. 2. The edge vial effect Excel spreadsheet: input is representative of a sucrose/protein formulation in a LyoStar II lab freeze dryer

where, σ_{Total} is the total relative standard deviation in the raw K_v values, and σ^2_{error} is the measurement error variance, as evaluated from the duplicate run data. To cancel the effect of small systematic errors in the experimental measurement of K_v, perhaps mostly due to the difficulty in establishing the time at which steady-state sublimation begins, each vial K_v for run 2 was normalized by multiplying by the ratio of the average K_v of run 1 to the average of run 2. The mean error variance (σ^2_{error}) of all vials in that location (center or edge vial type) was then computed from the average of the variance calculated from the replication data (runs 1 and 2 normalized). For our studies, this error variance (σ^2_{error}) translated in an "error" standard deviation in K_v of 4.3%.

The variance in apparent K_v arising from shelf surface temperature variations, $\sigma^2_{K_v(T_s)}$, is computed from the measured variation in shelf surface temperature in the dryer of interest as a function of sublimation rate. Rearrangement of the equation yields:

$$K_v = \frac{Q}{A_v(T_s - T_p)} \tag{5}$$

Taking derivatives of Eq. 5, and interpreting a differential as a variation (standard deviation), we may write:

$$\sigma_{K_v(T_s)} = \frac{\sigma_{T_{surface}}}{(T_s - T_p)} \tag{6}$$

where σ_{T_s} is the standard deviation in shelf surface temperature for the dryer at a given sublimation rate, which is determined from experimental data obtained during operational qualification of the dryer and σ_{K_v} is the corresponding % relative

Table II. Comparison of Experimental and Calculated Values of the Edge Vial Effect

	$10^4 K_v\left(\frac{cal}{cm^2 \cdot sec \cdot K}\right)$ Experimental			$10^4 \Delta K_v^E\left(\frac{cal}{cm^2 \cdot sec \cdot K}\right)$ Calculated	
P_c, mTorr	Center	Inner edge	Outer edge	Inner edge	Outer edge
60	2.72	0.50	1.11	0.47	1.29
100	3.55	0.67	1.41	0.55	1.47
150	4.45	0.80	1.80	0.63	1.55
Mean		*0.66*	*1.44*	*0.55*	*1.44*

Amcor 20 cc vials, −10°C shelf in a LyoStar III dryer, 5°cc water fill $10^4\,\Delta K_v^E = 10^4\,K_v(edge) - 10^4\,K_v(center)$
Outer edge vials (nominally) touching the band, *inner edge* edge vials not touching the band (Fig. 1)

Table III. The Edge vial effect for the model Product formulations and processes

System	Shelf temperature, °C	Chamber pressure, mT	$10^4 \Delta K_v^E$, inner edge	$10^4 \Delta K_v^E$, outer edge
5% Sucrose	−18	60	0.60	1.61
5% Sucrose	−18	100	0.71	1.74
5% Sucrose	−18	150	0.86	1.82
5% Sucrose + 5% protein	−10	100	0.56	1.45
5% Mannitol	+10	150	0.53	1.16

Amcor 20 cc vials. $10^4 \Delta K_v^E = 10^4 K_v(edge) - 10^4 K_v(center)$
Outer Edge vials (nominally) touching the band, *inner edge* edge vials not close to touching the band (see Fig. 1)

standard deviation in K_v. We find (Table III) that over the sublimation rate range of interest, $\sigma^2_{K_v(T_s)}$ and the sublimation rate, dm/dt are related, with higher sublimation rate producing higher $\sigma^2_{K_v(T_s)}$. Experiments with the LyoStar 3 show very small variations in shelf temperature from fluid inlet to outlet regions with the experiments done to evaluate K_v (which present relatively high sublimation rates) and the contribution of shelf temperature variation to K_v is therefore small, $\sigma^2_{K_v(T_s)} \approx 0.9\%$.

Evaluation of Dry Layer Resistance

We also need to evaluate the dry layer resistance and corresponding relative standard deviation for input into the LyoCalculator calculations. Dry layer resistance can be determined by manometric temperature measurement (7) or by analysis of the temperature history in primary drying and knowledge of the vial heat transfer coefficient, K_v. For the latter method, one determines the product temperature, and then calculates the corresponding vapor pressure of ice, P_0.

The resistance of the dry layer and stopper (mostly dry layer), $\hat{R}_{ps}$, is then calculated by:

$$\hat{R}_{ps} = \frac{A_p(P_0 - P_c)}{(dm/dt)} \tag{7}$$

where dm/dt is the sublimation rate calculated from the heat flow, dQ/dt, as given by rearrangement of Eq. 2 at each ($T_s - T_p$) time point of interest during primary drying. The difference between the product temperature at the sublimation interface and the experimentally measured T_p at the vial bottom can also be evaluated from the sublimation rate. An Excel spreadsheet that executes the calculations is available to interested parties. A more elegant and complex calculation can also be carried out which may give more accurate results (8). Parameters that allow dry layer resistance to be calculated as a function of dry layer thickness are given in Table IV for the three model formulations considered in this report. *Calculation of Variance in* $\hat{R}_{ps}$. Due to natural variations in ice nucleation temperature, significant variations in ice structure and $\hat{R}_{ps}$ occur in the usual freezing process (6). The variation in $\hat{R}_{ps}$ within a batch can be evaluated from knowledge of the variation within a batch of the specific surface area, SSA, and the linear relationship between SSA and $\hat{R}_{ps}$ established in laboratory studies (6) using controlled ice nucleation to achieve different degrees of supercooling.

From data, we evaluate the derivative of $\hat{R}_{ps}$ with respect to SSA and the derivative of the SSA with respect to ice nucleation temperature, T_n, to obtain the derivative of $\hat{R}_{ps}$ with respect to T_n by the product of the two. Using the experimentally determined value of the standard deviation in ice nucleation temperature (9), σ_{Tn} of 3.9°C, the relative standard deviation in $\hat{R}_{ps}$ may be determined as the product of σ_{Tn} and dln $\hat{R}_{ps}$/dTn. This relationship is a re-statement of the relationship, $\frac{d\hat{R}_{ps}}{\hat{R}_{ps}} = \frac{\partial ln \hat{R}_{ps}}{\partial T_n} \cdot dT_n$, where we identify a differential as a standard deviation in this context. Data for three representative materials (5% sucrose, 5% mannitol, and 5% protein/5% sucrose) are given in Table V.

Statistics Methodology: Propagation of Errors. Assuming a Gaussian distribution in the input variables and no significant covariance as a first approximation, a simple method for evaluating the standard deviation in drying time and maximum product temperature can be developed. For this purpose, we use the formula describing propagation of errors (standard deviation) in calculated quantities from the known errors (standard deviation) in the independent variables, which for drying time, t_{dry} and maximum product temperature in primary drying, T_{pmax}, may be written as:

$$\sigma_{t_{dry}} = \sqrt{\left(\frac{\partial t_{dry}}{\partial K_v}\right)^2 \cdot \sigma^2_{tdry} + \left(\frac{\partial t_{dry}}{\partial V_{fill}}\right)^2 \cdot \sigma^2_{V_{fill}} + \left(\frac{\partial t_{dry}}{\partial R_p}\right)^2 \cdot \sigma^2_{R_p} + \left(\frac{\partial t_{dry}}{\partial T_s}\right)^2 \sigma^2_{T_s}}$$
$$\sigma_{T_{p_{max}}} = \sqrt{\left(\frac{\partial T_{Tpmax}}{\partial K_v}\right)^2 \cdot \sigma^2_{K_v} + \left(\frac{\partial t_{Tpmax}}{\partial V_{fill}}\right)^2 \cdot \sigma^2_{V_{fill}} + \left(\frac{\partial t_{Tpmax}}{\partial R_p}\right)^2 \cdot \sigma^2_{R_p} + \left(\frac{\partial T_{Tpmax}}{\partial T_s}\right)^2 \sigma^2_{T_s}} \tag{8}$$

where K_v, V_{fill}, $<R_p>$, and T_s represent the vial heat transfer coefficient, fill volume, mean product-stopper resistance $\hat{R}_{ps}$

Table IV. Dry Product Resistance $\left(\hat{R}_{ps}\right)$ Parameters, R0, A1, A2 $\hat{R}_{ps} = R0 + \frac{A1 \cdot l}{1 + A2 \cdot l}$, l = dry layer thickness

Product	R0	A1	A2
5% Sucrose	0.2	26.2	1.5
10% Protein-Sucrose	0.2	25	2.5
5% Mannitol	1.4	16	0

Table V. Input Data for Shelf Temperature Uniformity During Primary Drying

	σ_{T_s}			
Product	<dm/dt>	LyoStar 1	LyoStar 3	LyoMax
5% Sucrose	0.14	0.38	0.08	0.24
10% Protein-Sucrose	0.26	0.70	0.15	0.45
5% Mannitol	0.49	1.21	0.29	0.82

Standard deviation in shelf surface temperature for three representative products of varying average sublimation rates. Data for a laboratory dryer (LyoStar 1, LyoStar 3, and a manufacturing dryer (LyoMax)). $\boldsymbol{\sigma_{T_s}}$ is the standard deviation in shelf temperature, °C, and < dm/dt > is the average sublimation rate for primary drying

during primary drying, and shelf surface temperature, respectively.

Additional Consideration for Use of K_v. In general, K_v would be replaced by K_{vs}, where K_{vs} represents the combination of heat transfer barriers presented by both the vial and heat transfer within the shelf:

$$K_{vs}^{-1} = K_v^{-1} + K_s^{-1}, \tag{9}$$

where K_s represents the heat transfer coefficient from the shelf as determined from the difference in temperature from the shelf fluid (usually inlet) and the shelf surface (average) at a known thermal load. K_s is normally much larger than K_v. Therefore, in the absence of K_s data, use of K_v data directly or rough estimates of K_s in Eq. 9 will likely give results of useful accuracy.

Methodology in Using the LyoCalculator

Each of the derivatives in Eq. 8 may be evaluated numerically by using the heat and mass transfer theory (*i. e.*, the LyoCalculator) to calculate changes in drying times for small variations centered around the mean value. Calculations demonstrate approximate linearity in the dependence of the dependent variable (t_{dry} or T_{pmax}) on the independent variables of interest (K_v, $<R_p>$, V_{fill}, T_s) over the ranges of interest. For example, calculation of drying times for +5% and −5% changes in vial heat transfer coefficient would serve to evaluate the derivative, $\partial t_{dry}/\partial K_v$. Calculations are done separately for center (or interior) vials and for each class of edge vials. Further calculations in Excel then use the value of standard deviation and the mean value for a given parameter, primary drying time or maximum product temperature, to evaluate the distribution in each parameter, assuming normal distributions, but recognizing that the center vials and edge vials of each location class have their own distributions, meaning their own means and standard deviations. We then predict what fraction of vials would be defects (*i.e.*, exceed collapse temperature or not finish primary drying in the allotted time) under a given set of cycle parameters using the statistical functions available in excel.

Figure 3 illustrates the Excel spreadsheet for calculation of the drying statistics, with 5% sucrose as the example product. Input variables are listed on the left and output parameters in the "box" on the right. Also, given at the bottom are two figures, the cumulative distribution for the drying time for all vials and the distribution of maximum product temperature during primary drying. Of course, the limiting factor for drying time is the drying time for the center vials since the average K_v for center vials $\left(2.72 \times 10^{-4} \frac{cal}{cm^2 \cdot sec \cdot K}\right)$ is lower than the average K_v $\left(3.32 \times 10^{-4} \frac{cal}{cm^2 \cdot sec \cdot K}\right)$ for inner edge vials, with the difference being quite significant for the edge vials that touch the band surrounding the vial array $\left(4.33 \times 10^{-4} \frac{cal}{cm^2 \cdot sec \cdot K}\right)$ (Fig. 1, Table I). The distribution of maximum product temperature is dominated by the distribution for the vials touching the band since here, the average K_v value is quite high relative to the center vials and edge vials that do not touch the band (Table I). The output parameters include the percent of the vial batch that collapsed (here about 10%), the "six sigma" value for drying time (39 h), and the product temperature "safety margin." The term "six sigma" is the value of drying time that provides less than ≈3 defects (*i.e.*, non-dry and collapsed) per million. Here, the "safety margin" is simply the difference between the collapse temperature and the actual average product temperature for the conditions used for this cycle. Here, and for the other processes we have studied, this safety margin is about 2°C as long as the % collapse is low, interestingly close to the prediction made many years ago (1). We note here that the collapse temperature for sucrose is assigned as −28°C, which is the value provided by the optical coherence tomography method previously described (10) and is the most accurate a prediction we have of collapse occurring when freeze-drying in vials or other commercial containers. However, it must be recognized that there is still uncertainty in this collapse temperature, about ±1°C.

RESULTS AND DISCUSSION

Impact of the Variables: Components of Variance

Figure 4 shows the relative contributions of the four components of variance (fill volume, product resistance, effective vial heat transfer coefficient, K_{vs}, and shelf surface temperature variation) for freeze-drying three representative products. The relative standard deviation of fill volume was arbitrarily taken as 1%, and the other variances arise from experimental measurements summarized by Tables I, V, and VI. Results are quite specific to the product, which largely reflects the specific drying conditions used for each product. The vial heat transfer coefficient dominates for primary drying time, but product resistance and vial heat transfer coefficient variances can be of roughly equal importance for maximum product temperature in primary drying.

Impact of Position Variation in K_v on Maximum Product Temperature and Drying Time

The impact of vial position in the array, center, outer edge vials touching the band, inner edge vials not touching the band are examined in Fig. 5 (primary drying time) and Fig. 6 (maximum

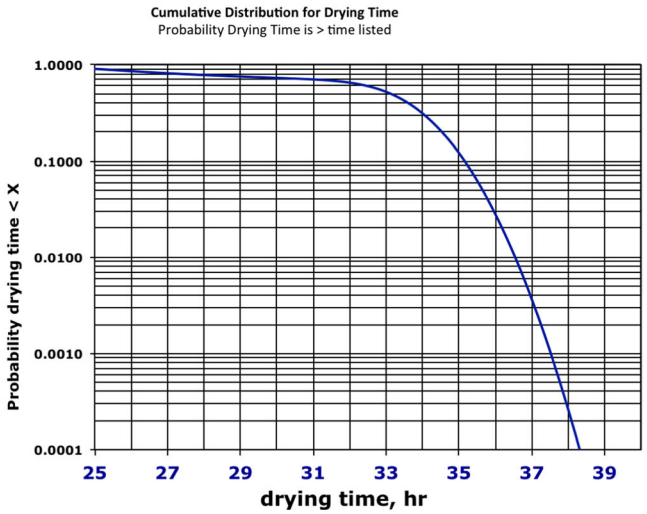
Input Parameters and then go to STAT Calculations and Run STATS

input Parameters	Value
Shelf Temperature, T_S K	255.2
Standard deviation in shelf temperature, K	0.08
Chamber Pressure, Torr	0.06
Vfill, Fill volume, mL	5
%RSD Vfill	1
Solute concentration, g/g	0.05
R0, product resistance parameter	0.2
A1, product resistance parameter	26.2
A2, product resistance parameter	1.5
fR, multiplier for Rp to include variations	1.00
%RSD fR	11.9
Vial inner area from ID, Ap	5.73
Ratio of vial outer area to inner area, Av/Ap	1.2
Shelf Heat Transfer Coefficient, 10^4 K_S	139
10^4 K_v, Center Vials	2.72
%RSD 10^4 K_v, center vials	6.4
Fraction of Center vials	0.683
10^4 K_v, Edge vials not touching	3.32
Fraction of Edge vials not touching	0.099
10^4 K_v, Edge vials touching	4.33
<10^4K_v>, batch avg	**3.03**
%RSD 10^4 K_v Edge vials	8.6
Fraction of Edge Vials Touching	0.211
Collapse Temperature, °C	-28
Desired Primary Drying Time, hr	38

Output Parameters	Value
% Collapse	9.9
% Good Vials	90.1
% Vials Not Dry@desired t	0.03
Average Drying Time	31.1
6 sigma drying time, hr	**39.3**
average product Tmax	**-29.5**
safety margin, °C	**1.5**

% Contributions to Total Variance

Property	Tdry	tp, Max
Vfill	7.4	0.2
Resistance	18.9	43.5
K_{vs}	72.9	55.6
T_S	0.8	0.7



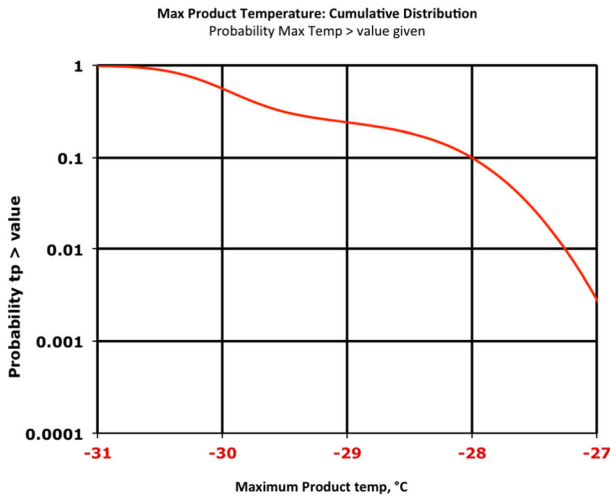


Fig. 3. Excel spreadsheet for variance calculations: 5% sucrose with $T_s = -18°C$ and $P_c = 0.06$ mTorr

product temperature) for the three representative formulations considered in both laboratory and manufacturing environments. These effects arise from position differences in K_v. Here, average dry layer resistance is used, and it is assumed that dry layer resistance is the same for both laboratory and manufacturing. The case of different average ice nucleation temperature differences between lab and manufacturing will be addressed later. Measured wall temperatures are needed for optimally accurate estimates of the edge vial effect for K_v. For Figs. 5 and 6, wall temperatures were evaluated from multiple experiments for the laboratory examples and estimated from data for the manufacturing examples from these laboratory data and one production run. We would not expect variations between manufacturing dryers to have a major impact on these calculations. As expected, drying times are longer for center vials, by roughly 30%, the exact value depending on the type of edge vial and the formulation. Correspondingly, the maximum product temperatures are higher for edge vials by about 2–3°C, depending on the formulation and location of the edge vial. It is significant to note that differences between laboratory and manufacturing temperatures are small (≈ 1°C or less) for the examples presented, which are for vials in trays along the edge of the shelf. If no trays are used in manufacturing, the product temperatures are expected to be slightly lower (≈ 0.3°C) and drying times slightly longer (≈ 5%), but the exact values depend on formulation (and corresponding appropriate process) and wall temperatures. The "bottom line" is that scale-up effects are small for manufacturing when the product resistances are essentially the same for both lab and manufacturing, and unless the process is running close to the edge of failure, should not have practical impact. Of course, unless controlled ice nucleation is employed, or appropriate annealing during freezing is used, significant differences in ice nucleation temperatures do

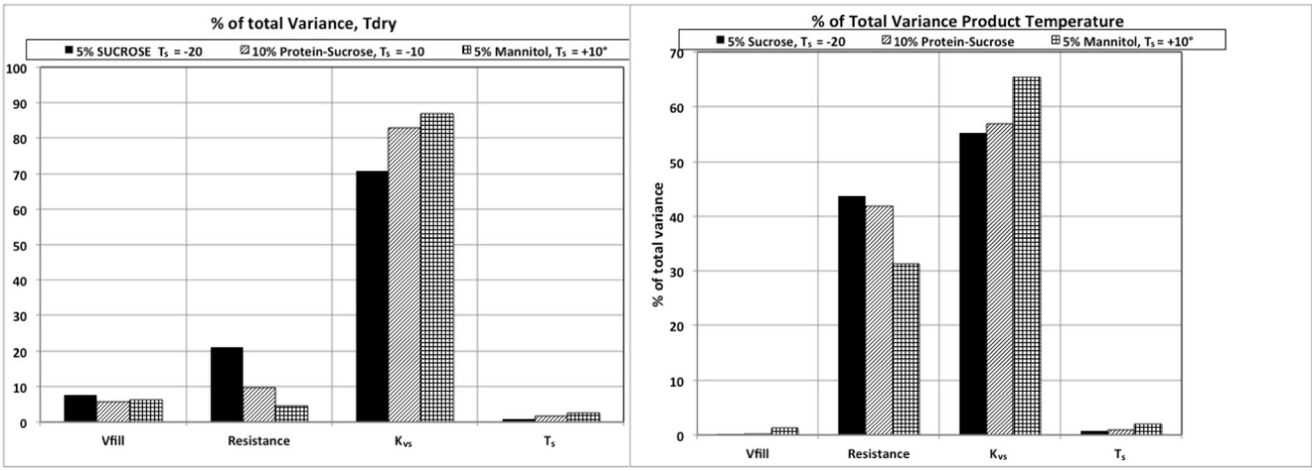


Fig. 4. Relative contributions of the four components of variance (fill volume (Vfill), product resistance, effective vial heat transfer coefficient (K_{vs}), and shelf temperature (T_s)) to the variance in primary drying time, Tdry, and product temperature. Calculated for laboratory dryer but comparable for a manufacturing dryer. Calculations use 1% standard deviation in fill volume, standard deviations for K_{vs}, for product resistance, and for shelf surface temperature from Tables I, VI, and V, respectively. Calculations refer to freezing with no control over ice nucleation and without annealing

likely occur with significant impact on product resistance, which in turn impact both drying time (≈ 10–30% longer) and product temperature (≈ 1–3°C higher). This impact is considered later.

Impact of Parameter Variation on Collapse Behavior and Drying Time

Shelf Temperature Variation. If one is operating close to the edge of failure (typical for low collapse temperature formulations), the calculations predict the frequency of collapse increases very sharply with increases in shelf temperature. Figure 7 illustrates this sensitivity for 5% sucrose as a function of shelf temperature. Here, we assume −28°C for the collapse temperature as determined by optical coherence tomography (10). It should be noted that the % collapse is negligible at the lowest shelf temperatures displayed, but an increase in shelf temperature by a small amount (1°C at 100 mTorr or 2°C at 60 mTorr) increases the collapse frequency dramatically into a range of practical concern. Of course the quantitative details of Fig. 7 will vary with the formulation and input variances (particularly with vial heat transfer coefficient and product resistance). However, the generalization is that movement of shelf temperatures by even a few degrees can have a significant effect on collapse frequency. Much the same can be said of modest changes in chamber pressure.

Table VI. Data for calculation of standard deviation in dry product resistance, $\hat{R}_p$

5% solutions of	$\frac{d\hat{R}_p}{dSSA}$	$\left\|\frac{dSSA}{dT_n}\right\|$	$\left\|\frac{d\hat{R}_p}{dT_n}\right\|$	$\left\langle \hat{R}_p \right\rangle$	$10^2 \cdot \frac{d \ln \hat{R}_p}{dT_n}$	$\%\sigma\left(\hat{R}_p\right)$
Sucrose	2.1	0.029	0.061	2.0	3.0	11.9
Mannitol	1.8	0.090	0.162	6.5	2.5	9.7
Dextran	2.2	0.040	0.088	3.9	2.3	8.8

Standard deviation in ice nucleation temperature taken as 3.9°C (reference 9)

Information Regarding Safety Margin in Drying Time. It is also of interest to estimate the six sigma (6σ) drying times and compare these quantities to the corresponding average quantities. At least for the 5% sucrose example (Supplemental Information), the six sigma drying time is about 25% longer than the average drying time. For both average and six sigma drying times, the drying time is determined by behavior of center vials. Thus, the "safety margin," defined as the difference between six sigma behavior and average behavior, is about 25% for drying time. These results are close to the safety margins suggested many years ago (1) that were based on observation and some limited calculations.

Variation in K_v. The K_v data in Table I demonstrate that not all 20-cc tubing vials are equivalent, either in the average K_v at a given pressure or the relative standard deviation of the K_v in a nominally equivalent batch of vials. With both the "W" vials and the "A" vials in Table I, we have determined that the vendors do provide equivalent vials from different batches produced at different times, at least over a modest time interval. Experimental data (not shown here) indicate the average K_v between lots of vials was well within the variation in the average K_v data, which is typically 3–5% using our gravimetric procedures (2). However, mean K_v can differ between vendors by about 10%, with nearly a factor of 2 difference in relative standard deviation in K_v. Of course, we have limited data comparing vendors, and even larger differences might be found with a larger sample of vendors. Therefore, in Fig. 8, we compare the sensitivity of collapse and drying time to changes in average K_v. Note that, at identical conditions of shelf temperature and chamber pressure, the % collapse varies from 0.3 to 4.9 to 11.2%, and the six sigma drying time varies from 46 to 39 h between the extremes ("A vials" to "K vials"). It should be clear that one cannot assume the same vial type (20-cc tubing vial) from various vendors will give the same freeze-drying results. This caution is particularly important when operating close to the edge of failure.

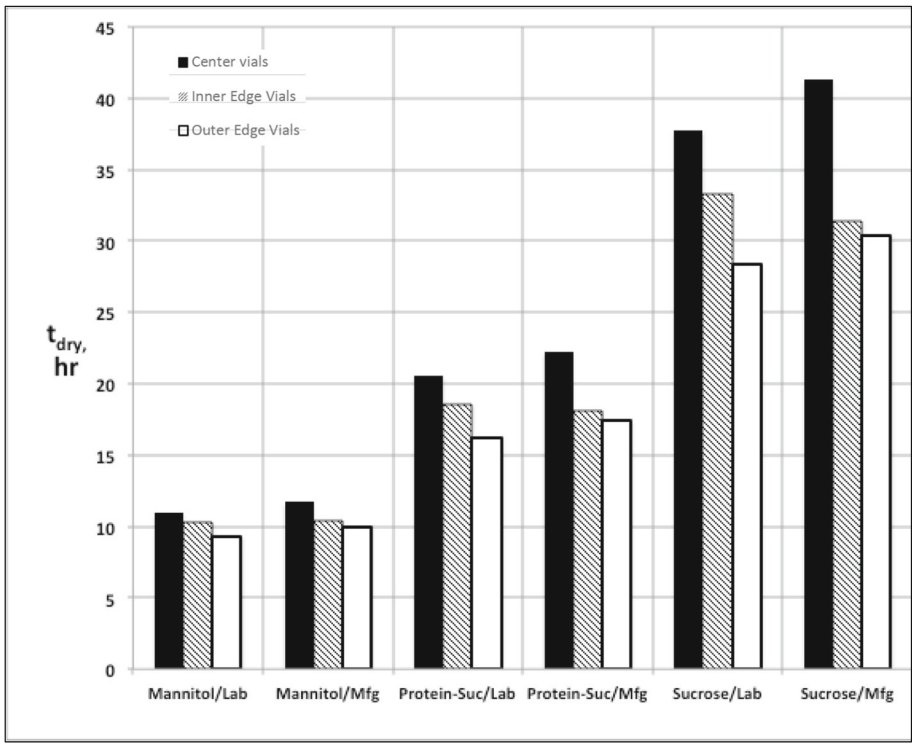


Fig. 5. Impact of vial position on primary drying time: comparison of formulation and scale (lab *vs.* mfg). For estimated wall temperatures for mfg, see text. Assumed same ice nucleation temperature distribution in lab and mgf scales

As Fig. 9 illustrates, it is not sufficient to have the same average K_v from various vendors; it is also important to have the same relative standard deviation in K_v to provide equivalent drying behavior. The results in Fig. 9 show the

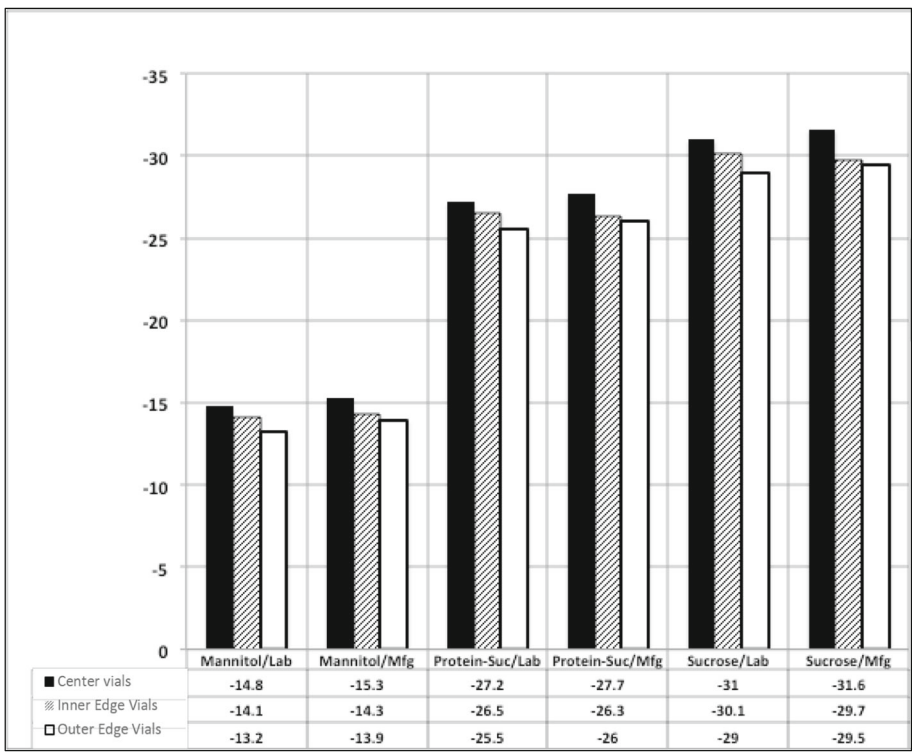


Fig. 6. Impact of vial position on maximum product temperature in primary drying. For estimated wall temperatures for mfg, see text. Assumed same ice nucleation temperature distribution in lab and mgf scales

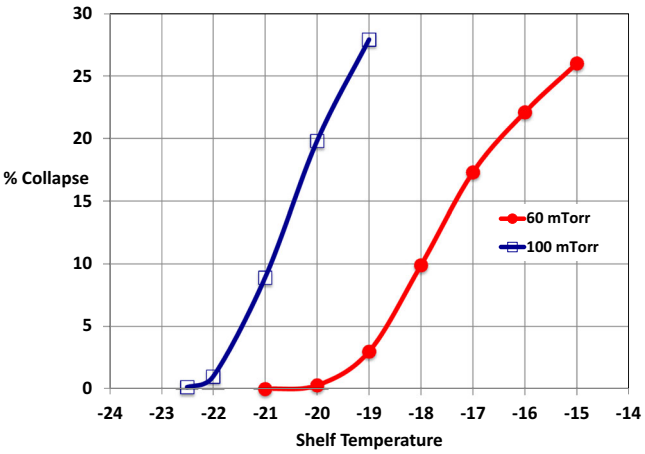


Fig. 7. Sensitivity of % collapse to shelf temperature, 5% sucrose formulation. Input data are for the laboratory dryer. Calculations use −28°C for the collapse temperature, heat transfer coefficients from Table I (A vials) and Table III, standard deviation in cake resistance from Table VI, and standard deviation in shelf temperature from Table V

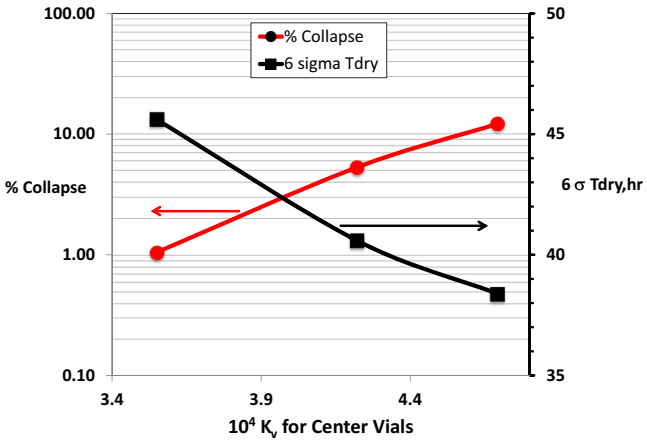


Fig. 8. % Collapse and primary drying time to assure no more than three vials per million contain ice (6σ Tdry) as a function of vial K_v. From low to high K_v, the data are for "A" vials, "W vials," and "K vials" as given in Table I. Data are for 5% sucrose dried at a shelf temperature of −22°C and chamber pressure of 100 mTorr

impact of the relative standard deviation in edge vial K_v calculated using the "A vial" K_v. Note that, even over the range we have found for relative standard deviation in the edge vial K_v, the % collapse increases from about 1.5% to nearly 3.5%. Again, this sensitivity reflects behavior when operating at the edge of failure. Operating at a lower (by only 2°C) shelf temperature, and all other conditions the same, the % collapse for a RSD in K_v of 10.7% is 0.04% and only 0.004% for a RSD of 6.1%. Obviously, operating near the edge of failure carries high risk, and even minor variations in K_v and/or RSD in K_v can cause a change from "acceptable" results to serious failure to preserve product quality.

Scale-Up to Manufacturing: Impact of Variation in Vial Heat Transfer Coefficient and Dry Later Resistance

All the calculations presented previously apply to manufacturing processes that have the same average product resistance behavior as found in the laboratory. This is a useful approximation only if the average ice nucleation temperature in the laboratory and manufacturing are essentially the same, or a suitable annealing process is used during the freezing cycle. The available data indicate about a 10°C lower average ice nucleation temperature for the manufacturing environment (3), and although this is the only published account of such behavior, we have noted a similar freezing bias in another production operation (unpublished observations). Therefore, it seems clear that ice nucleation behavior cannot be assumed to be essentially the same for both laboratory and manufacturing operations. Systematic differences in ice nucleation behavior between laboratory and manufacturing mean systematic differences in resistance of the "dried" product to vapor transport (9). It should be noted that if controlled ice nucleation is employed, this freezing bias between laboratory and manufacturing should vanish completely. Also, if the freezing cycle contains an appropriate annealing step, the resulting ice structure and product resistance differences caused by differences in ice nucleation temperature are at least significantly moderated (11). Thus, annealing should significantly improve the agreement between product resistance measured in the laboratory and that characteristic of manufacturing.

Given the relationship between specific surface area (SSA) and product resistance (6) as described earlier (see Table VI), one can obtain an estimate of the difference in mean product resistance between laboratory and manufacturing from the difference in SSA between laboratory and manufacturing and the sensitivity of resistance to SSA. The data in Table VI were calculated based on data within a batch, but the same procedure can be used to estimate the difference in mean resistance between laboratory and manufacturing scales arising from the freezing bias. Using 10°C for the freezing bias (difference in mean ice nucleation temperature), we calculate an average 30% increase in product resistance for 5% sucrose in scaling up from laboratory to manufacturing, 23% for dextran, and 25% for mannitol. The estimate for 30% *w*/*w* moxalactam (an

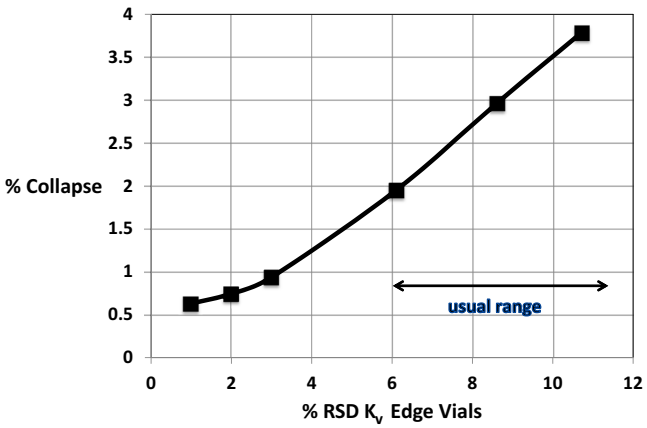


Fig. 9. Impact of %RSD of Kv edge vials on % collapse. Calculated for 5% sucrose using 60 mTorr chamber pressure and −18°C shelf temperature in Amcor vials (Vial "A" K_v data from Table I)

Table VII. Impact of Both Ice Nucleation Temperature and K_v Differences on Scale-Up for Representative Formulations

Product-dryer	T_s °C	Six sigma T_{Dry} hr	% Collapse
Mannitol/Lab	10	12.3	–
Mannitol/Mfg	10	13.8	–
Protein-sucrose/Lab	−3	17.3	0.14
Protein-sucrose/Mfg	−3	19.8	8.4
Protein-sucrose/Lab	−5	18.5	0.002
Protein-sucrose/Mfg	−5	21.1	1.3
Sucrose/Lab	−19	43.4	0.32
Sucrose/Mfg	−19	49.1	16
Sucrose/Lab	−21	45.7	0.008
Sucrose/Mfg	−21	54.5	0.9

Calculations performed with K_v data for "A" vials (Table I), calculated ΔKvE, where manufacturing is assumed to be lower emmisivity dryers without use of trays, and assuming a 10°C lower ice nucleation temperature for manufacturing. Chamber pressure was 60 mTorr for sucrose, 100 mTorr for protein-sucrose, and 150 mTorr for mannitol

antibiotic) provided years ago was 33% increase in mean product resistance (3). Of course, these estimates (except the data for moxalactam) implicitly assume linearity in resistance *vs.* SSA, which are valid over the ice nucleation temperature ranges assessable to experiment (*i.e.*, down to about −12°C). The linear relationship was extrapolated to the ice nucleation temperature range directly relevant to our current problem, which runs down to lower than −25°C.

For our calculations described in Table VII, we assume a 30% increase in average product resistance over the primary drying time, consistent with the values for both 5% sucrose and 30% moxalactam, and the 10°C bias in freezing behavior current observations suggest. As we scale-up from lab to manufacturing, we assume the manufacturing dryer has the typical highly polished stainless steel shelves and walls, with low emissivity of about 0.3. The lab dryers typically have emissivities of about 0.65. We also do the calculations for manufacturing dryers with autoloader systems where trays are not used, and for our calculations, we assume a raised edge of the shelf of 1.5 cm. The differences between lab and manufacturing are twofold. First, the difference in heat transfer is dominated by the differences in shelf emissivities but with some contributions from differences in the edge vial effect. Differences in heat transfer means primary drying runs longer and colder in manufacturing. Secondly, the higher product resistance in manufacturing translates into higher product temperatures and longer primary drying times. The two effects, heat transfer and mass transfer differences together, consistently result in a longer primary drying time by about 12 to 18% (Table VII). The higher product resistance in manufacturing contributes most to the temperature difference, resulting in consistently higher product temperature and greater collapse in manufacturing than in the lab, at least for the examples considered, and likely is a general effect (Table VII). Note that even a 2°C reduction in shelf temperature results in a dramatic reduction in % collapse. It should be emphasized that these results are typical only for processes operating near the edge of failure. Certainly, one would not advise using −3°C shelf temperature for the protein-sucrose product considered here or −19°C shelf temperature for the sucrose-based product.

Design Space

The same Excel spreadsheet that was used to evaluate propensity for collapse and six sigma drying time can be used to evaluate a design space for primary drying from the same set of input parameters and the user's choice of acceptable collapse and/or an acceptable "safety margin" to avoid collapse under any reasonable operating condition. The purpose of the design space is to identify the entire space of shelf temperature and chamber pressure that give acceptable product quality, and from the industry viewpoint, reasonable process economics. Two applications of design space are: (1) to have the design space cover the possible combinations of shelf temperature and chamber pressure variations due to either control fluctuations or calibration errors, and (2) to allow the user (industry) to change the process within the design space without consulting the regulatory agency. The calculations in the Excel spreadsheet are equally valid for conditions outside the design space (*i.e.*, shelf temperatures and chamber pressures producing temperatures above the collapse temperature and sublimation rates in excess of those the dryer can maintain at each chamber pressure), allowing better identification of the "edge of failure" for collapse. We recognize that in addition to collapse, which is evaluated in this version of design space, product quality includes other attributes including product stability and often reconstitution time. Of course, it is not possible to explore the infinite number of combinations of shelf temperature and chamber pressure during cycle development to evaluate all product quality attributes at each combination. Ideally, during "robustness testing," limited combinations of chamber pressure and product temperature near the boundaries of the design space as calculated from the Excel spreadsheet would be used in small scale to produce drug product that is representative of commercial scale which can be placed in the stability program and evaluated for other relevant product quality attributes.

Figure 10 summarizes the input required and the output of most interest, with 5% sucrose as the example. The input parameters are given in the upper left corner of the page and the top center, and include the usual fill volume, dry product resistance parameters, and vial heat transfer coefficient parameters. The desired settings for chamber pressure and shelf temperature, as well as the desired shelf temperature isotherms, are given in between the input resistance parameters and the input heat transfer coefficient data. In the shaded insert at the bottom left is provided calculated mean product temperature maximum for edge vials touching the band, and the safety margin, defined here as the magnitude of the difference between the calculated product temperature and the collapse temperature. The calculated % collapse at the target conditions of shelf temperature and chamber pressure is also given. Given an initial value of shelf temperature and chamber pressure, % collapse is calculated. If the % collapse is sufficiently low to present low risk, that combination of shelf temperature and chamber pressure are

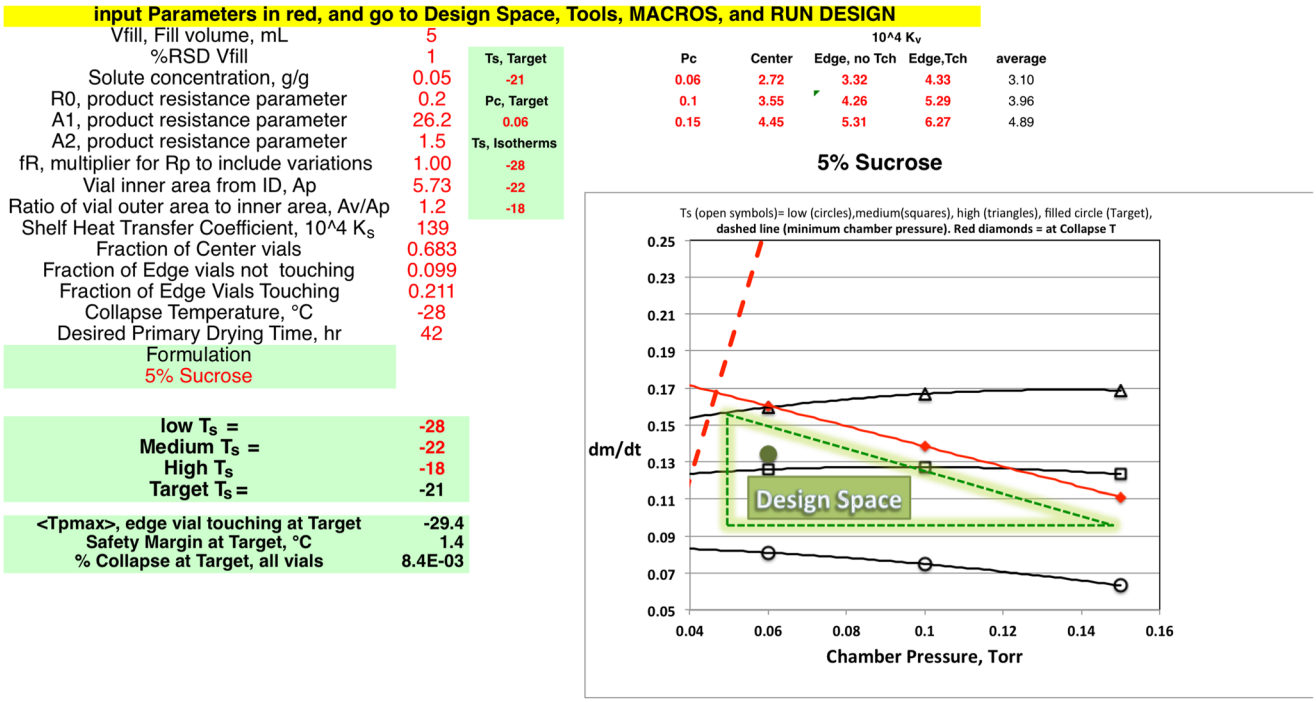


Fig. 10. Input and output for design space calculation for 5% sucrose

in the design space. If the risk is too high (% collapse is higher than acceptable), that combination is outside of the design space. The user would input a lower shelf temperature and/or a lower chamber pressure.

The plot in Fig. 10 is one version of a design space for primary drying with axes of sublimation rate and chamber pressure, based on typical "LyoCalculator" calculations. The dashed line running from left to right with a steep slope represents the dryer overload condition, commonly referred to as the "choked flow" curve. Here, it is calculated from historical manufacturing data, but in real applications it should be evaluated from data on each dryer of interest. Shelf temperature isotherms are calculated for the low, medium, and high shelf temperatures provided as input in the lower left corner, as well as the product temperature isotherm that corresponds to the collapse temperature. This product temperature isotherm is the red straight line (filled diamonds) corresponding to the product temperature that corresponds to product at the edge vials touching the band that are running at the collapse temperature. Obviously, one needs to use shelf temperatures and chamber pressures that keep the product temperature well below the collapse line. The large filled circle corresponds to the target conditions, and is selected to be "safely" away from the "choked flow" line and well away from the collapse line. In fact, as calculated for this choice of target conditions, the expected collapse frequency is 84 per million vials, which is essentially zero for each batch. The design space is the region enclosed by the triangle formed by the dashed lines, and is labeled "Design Space." Assuming the quality attribute one is attempting to control is lack of collapse, the region defined by the "Design Space" represents the combination of shelf temperature and chamber pressure that will produce quality product, and any variation in process variables that falls within that space produces "quality product" (at a reasonable drying time), and the cycle can be changed within this design space without any regulatory implications.

Robustness testing for stability and other quality attributes would presumably be performed for conditions near the upper left corner and lower right corner of the design space. Using the LyoCalculator, the product temperature history could be obtained for these or any other choices.

Note that the design space is expected to appear quite different as we change from a low collapse, slow drying product like a sucrose dominated formulation to a protein-sucrose combination with intermediate collapse temperature and drying rate to one with essentially no collapse liability and fast drying like a mannitol based formulation. Figure 11 illustrates examples of design spaces for two other typical products, a sucrose-protein formulation and a mannitol-based formulation. Here, particularly for the mannitol formulation, the major constraint is to stay safely below the maximum allowable sublimation rate such that chamber pressure may be controlled. For the sucrose-protein formulation, both product temperature and dryer overload constraints are operative.

Accuracy of Calculations: Impact of Usual Errors in Input Values

Even with the best of procedures, essentially all input parameters involve some natural experimental error. Determination of parameters like vial heat transfer coefficient, K_v, and dry product resistance, R_p, have measurement errors, and shelf temperature and chamber pressure are subject to calibrations errors. Table VIII explores the impact of such "usual errors" for a process running at the edge of failure where small variations in input parameters can have a large effect on the predicted % collapse. The example here is 5% sucrose operating at 60 mTorr chamber pressure and −19°C shelf temperature (actually the fluid inlet temperature, in this

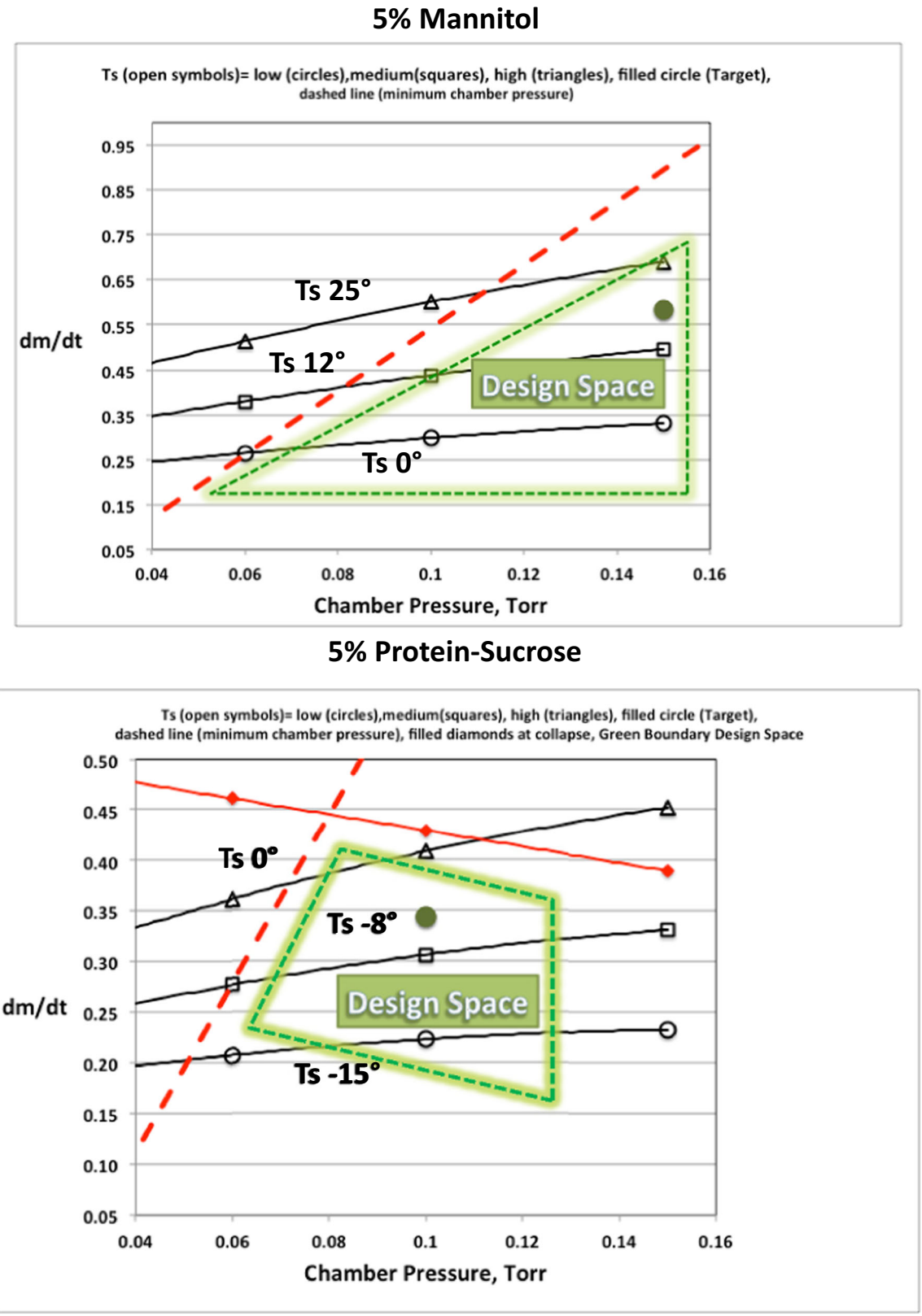


Fig. 11. Design spaces for representative product formulations

example), where our standard input predicts 3.0% collapse and average maximum temperature of −28.5°C at the end of primary drying for those outer edge vials, where the K_v is highest. Note that even a shelf temperature error of −1°C reduces the % collapse from 3.0% to only 0.3%. Typically shelf temperature calibrations are accurate to only about 1°C,

Table VIII. Impact of Usual Errors in Input Values for Statistical Calculations on % Collapse for Process at the Edge of Failure

Using above parameters without error ➔		% Collapse = 3.0	T_p^{Max} = 28.5°C
Measurement of:	Error	% Collapse	T_p^{Max}, °C
Shelf temperature, T_s	−1°C	0.3	−28.9
Chamber pressure, P_c	+10 mT	6.7	−28.2
Chamber pressure, P_c	+5 mT	5.2	−28.3
Product resistance, Rp	+10%	9.1	−28.1
Product resistance, Rp	−10%	0.4	−29.0
Vial heat transfer coefficient, K_v	+5%	4.5	−28.4

For 5% sucrose undergoing primary drying at $T_s = -19$°C and $P_c = 60$ mTorr, where the R_p A1 parameter = 26.2 and $10^4 K_v$ for an outer edge vial is = 4.33. The predictions for % collapse is 3.0% and for T_p^{Max} *is* $-28.5°C$

so this is a significant effect. Note that a +10 mTorr error in chamber pressure results in the % collapse changing to 6.7%. In our view, allowing a 10-mTorr uncertainty in chamber pressure, particularly when operating at a low chamber pressure setting is unacceptable. However, maintaining accuracy within 5 mTorr is perhaps near the lowest tolerance that is practical, and a +5% increase in chamber pressure causes an increase in % collapse by nearly a factor of 2. Product resistance measurements are difficult to carry out with an accuracy much better than about 10%, and if the error is +10%, the resulting % collapse is 9.1%, again a very large effect. Conversely, if the error is −10%, the calculated % collapse is only 0.4%. The determination of K_v, if properly executed usually gives accuracy within 5%. An error of +5% in K_v causes about a factor of 1.5 increase in % collapse. Note that the differences in average maximum product temperature for outer edge vials, T_p^{Max}, are quite small with variations being typically less than 0.5°C.

The major point here is that with normal errors in input data, the predicted errors in % collapse are often a factor of 2 or more off, but as stated earlier, this level of error is of practical significance only if operating near the edge of failure. Thus, the % collapse predicted in this manuscript are only semi-quantitative, but semi-quantitative is still useful to avoid the edge of failure in the design of an efficient and robust process.

Accuracy of Calculations: Impact of Approximations

Some of the approximations used in the current approach may also introduce significant errors in estimation of % collapse, as well as six sigma drying time. The major limitations of this statistical approach are that we assume no covariance and normal distributions for all input variables. However, we emphasize that we do consider the three classes of vial positions in the array, center, inner edge, and outer edge. Each of these vial position classes is assumed to have a normal distribution in vial heat transfer coefficient. The available data suggest that a normal distribution may be a good first approximation, but in reality, insufficient data are available for a clear conclusion. We have no data that indicate covariance would cause a significant difference from the results provided by ignoring covariance. If covariance were significant, we would expect our results would over-predict the % collapse under fixed conditions of shelf temperature and chamber pressure.

Another limitation is that we assume the dry layer resistance, $\hat{R}_{ps}$, is essentially independent of temperature. Some data (1) suggest a dependence of product resistance on product temperature as the product temperature reaches or closely approaches a eutectic temperature or a collapse temperature; that is, the resistance decreases with increasing temperature which, in principle, would increase the collapse temperature, meaning that ignoring this effect when present would cause a high estimate of % collapse. However, we do not attempt to include such effects. The possible effect of temperature on $\hat{R}_{ps}$ has not been explored in detail, and we have insufficient information to include such an effect at this time. We do note, however, that using a temperature independent product resistance for 5% sucrose, we predict the maximum temperature in primary drying to be only 0.1°C colder than found experimentally for a chamber pressure of 60 mTorr and a shelf temperature of −18 °C and only 0.3 °C warmer at a shelf temperature of −16°C. Given the difficulty in accurately determining the maximum product temperature in primary drying, these differences are well within experimental error in the temperature measurements as well as less than the effect of normal errors in input values and calibrations. The point is that if the prediction of maximum product temperature in primary drying matches the experimental values, the predictions of % collapse should be fairly accurate. Moreover, as discussed below, good agreement between calculation and experiment for % collapse with 5% sucrose is satisfactory, suggesting the calculations do have useful accuracy.

Comparison of Predictions of % Collapse with Experimental Data

At this point, we do have some data that suggest our predictions do have useful accuracy. We have data for 5% sucrose, where comparison of experiment with calculated values is acceptable. Assuming −28°C for the collapse temperature, as measured by optical coherence tomography (10), for 60 mTorr chamber pressure and −18°C shelf temperature, predicted % collapse was 10% and measured was 3% in arrays where all side edge vials touched the band. When the shelf temperature was raised to −16°C, the measured % collapse was 15% compared to the calculated value of 22%. It is important to note that if we instead assume a collapse temperature only 0.5°C lower, the calculated %

collapse values are 3% ($-18°$ T_s) and 16% (-16 T_s). Thus, if the real collapse temperature is only 0.5°C lower than reported, agreement is essentially exact. Given the difficulty in identifying minor collapse in 5% sucrose, and the uncertainty in the collapse temperature, this agreement is quite satisfactory.

In a study of a proprietary formulation where annealing during freezing was employed, collapse on the order of 2% was detected in both laboratory and manufacturing. Our calculations suggested operation on the edge of failure with % collapse ranging from 1% in manufacturing to 6% in the laboratory, or an average of about 3.5%. Given the difficulty of experimentally evaluating collapse, the extreme sensitivity of % collapse to small variations in conditions when operating at the edge of failure, and uncertainty in the input data such as wall and band temperatures, this agreement is satisfactory. Thus, we conclude the calculations are sufficiently accurate to provide useful predictions of collapse frequency.

CONCLUSIONS

Using experimental data for the variance of input parameters, such as fill volume, vial heat transfer coefficient, dry product resistance, and shelf surface temperature, it is possible to use simple statistics, within an Excel spreadsheet, to predict with useful accuracy the impact of natural variations on collapse frequency and six sigma primary drying time. We also have characterized, quantitatively, the impact of switching vial suppliers on product temperature history and product quality as well as the impact of freezing differences between manufacturing and laboratory scales. The bottom line is that if the process is well removed from the edge of failure, none of the differences discussed above will cause losses in product quality. However, close to the edge of failure, changes in vial supplier or even small changes in cycle conditions can cause a batch to go from essentially zero defects to a defect level that has significant economic and regulatory implications. Perhaps the greatest utility of what has been presented here will be to guide process development such that reasonably economical processes that avoid the edge of failure may be efficiently developed that are but. The work presented provides procedures and quantitative comparisons that should be useful in efficient process design of robust cycles for manufacturing; that is, finding the edge of failure and avoiding the edge of failure without undue extension of the process.

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