Statistical Evaluation of Vial Design Features That Influence Sublimation Rates During Primary Drying

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Purpose. Understanding tubing vial design features that influence sublimation rate provides insight into the development of a more time and cost efficient lyophilization cycle.

Methods. A Plackett–Burman screening experiment was initially used in evaluating multiple design features to predict those that have a statistically significant effect on sublimation rate. Sublimation rates of vials with intentional nominal and extreme dimensions were measured and directly correlated to glass vial design features using conservative and aggressive lyophilization parameters to amplify subtle differences in rates. Purified water, USP was used to alleviate the inhibition to mass transfer due to the presence of excipient and drug substances. Further studies quantified the effect of bottom concavity on sublimation rate while using model preparations to illustrate the impact of processing crystalline and amorphous material.

Results. The results from the Plackett–Burman statistical screening experiment indicate that sublimation rate is influenced by glass type, vial diameter, bottom radius, and fill volume. Results from further studies verify that the influence of concavity on sublimation rate is statistically insignificant.

Conclusions. The results from the Plackett–Burman screening experiment reflect that vial diameter has the greatest impact on sublimation rate. Further studies confirm that various bottom concavities do not substantially influence sublimation rate.

KEY WORDS: sublimation rate; tubing vial; heat transfer; lyophilization; vial design.

INTRODUCTION

An ongoing objective in lyophilization is the development of an effective and efficient freeze-drying process. Appropriate process parameters would minimize time in the freeze-dryer, which would directly affect manufacturing costs. According to Karel, limiting resistance factors to achieve adequate heat and mass transfer would shorten primary drying (1). Pikal *et al.* concluded that molded and tubing vial design features that have a significant influence on heat transfer may be manipulated to provide improved heat transfer and a more efficient lyophilization cycle (2).

Sublimation during primary drying is dictated by coupled heat and mass transfer. In a typical freeze-drying cycle, the product often spends a large portion of time in primary drying where sublimation occurs, a factor influenced by heat transfer efficiencies. A study by Ybema *et al.* reported that the sublimation rate of ice is limited by heat transfer (3). Promotion of heat transfer through the vial would directly influence the amount of energy transferred to the product, thereby increasing sublimation rate. Increasing efficiency of heat transfer should, therefore, promote an increase in sublimation rate. Another study by DeLuca and Lachman found that the thermal conductivity of the product itself has an impact on heat flow through the product and thus drying rate (4). Limiting resistances to mass transfer should also increase sublimation rate.

Pikal showed that poor thermal conductivity among the shelf, the tray, and the vial limits heat transfer among the surfaces due to nominal physical contact and minimal heat transfer through the gas phase (5,6). In studies by Nail, reduced processing times in primary drying associated with increased rates of sublimation were correlated to improved heat transfer through the gas phase when the chamber pressure was elevated (7). A study by Brülls and Rasmuson showed that at lower pressures heat transfer was independent of bottom concavity and the dependency increased with higher pressures (8). This heat transfer dependency on pressure would be expected to have an impact on sublimation rates using various bottom concavities at higher pressures, but not at lower pressures. The rate limiting resistance to heat transfer is the lack of intimate surface area contact between the vial and the dryer shelf and due to the gas phase (3), which is reported to account for more than 93% of the resistance to conductive heat transfer when molded vials are used (7).

Increased heat transfer from the dryer shelf to the product is achieved with an increase in the surface contact between the shelf and the vial bottom. Though of academic value and impractical for routine processing, independent studies by Ybema *et al.* and Patel *et al.* showed that an increase in heat transfer occurs with the use of heat conductive paste or a physical device because it increases the thermal conductivity through direct physical contact and decreases the limitation to heat transfer through the gas phase (3,9). Pikal studied how bottom concavity and the physical contact of the vial affect a vial heat transfer coefficient, although the variable having the greatest contribution was not identified (2). Vials with a small concavity reduce the physical distance the heat has to travel from the shelf through the gas phase before reaching the vial. A vial constructed with a larger cross sectional area increases the direct vial to shelf contact, resulting in improved heat transfer. Adding heat by increasing shelf temperature will increase the sublimation rate only when the additional heat is effectively transferred from the shelf to the product. However, adding excessive heat will cause the product to melt or collapse, particularly in regions close to contact points with the shelf where thermal conductivity is high, such as the bottom corner around the vial perimeter.

Pikal's study thoroughly investigated both molded and tubing vials having different catalog numbers and from two different vendors, representing those typically used in commercial manufacturing. Vial concavity and contact area were evaluated for the affect on the rate of heat transfer where both were found to be an important factor (2). Manufacturing lyophilization vials of particular dimensions for improved heat transfer will be of substantial value if the effect of heat transfer has a significant impact on sublimation rates such that the total time for lyophilization is substantially reduced.

The relative effect of tubing vial design features on heat

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transfer and sublimation rate warrants further investigation. An initial study first evaluated aspects of vial design that may have a pronounced effect on sublimation rate. Statistical analysis of the data was used to assess their relative influence on sublimation rate. Results of such studies were of interest for determining the impact on process efficiency, and therefore processing cost. Focusing on bottom concavity, shown surprisingly in the initial study not to have a statistically significant influence on sublimation, subsequent investigations were to determine the effect of thermal conductivity due to bottom concavity using conservative or aggressive processing conditions. These further studies were a specific focus on measuring the sublimation rates of purified water and of crystalline and amorphous model formulations in specially constructed tubing vials.

MATERIALS AND METHODS

A Plackett–Burman screening experiment, which allowed for a large number of variables to be statistically analyzed using a minimum number of runs, was used to investigate multiple design features and identify those that significantly influence sublimation rate. The results were used as the foundation for further studies. The glass tubing vials for the Plackett–Burman screening experiment were purposely constructed by Comar, Inc. (Buena, NJ, USA) to examine the vial design features that may be expected to have the greatest impact on sublimation rate. Vials within these parameter specifications are commonly used for lyophilization.

Nine vial design features, along with fill volume, were combined statistically to make sixteen different sets for evaluation. Two values for each design feature, a nominal and an extreme, were designated and eight vials from each of the 16 sets, for a total of 128 vials, were tested. The design features included eight variable dimensions, glass type, and product fill volume, as noted in Table I. The vials were assessed at each of the four different cycle parameters as listed in Table II. One-way analysis of variance (ANOVA) was performed on the data and a p value less than 0.01 was considered statistically significant. The steepness of the slope from the resultant line reflects the statistical significance of the respective vial design feature as depicted in Fig. 1. The plot for the high and low value is a combination of results from all four lyophilization cycles.

Table II. Lyophilization Cycle Parameters

Cycle	Shelf temperature (°C)	Pressure (mTorr)	Approximate time in primary drying (h)
For Plackett–Burman screening experiment			
A	–25	50	4.0
B	–25	200	4.3
C	+25	50	4.0
D	+25	200	2.5[a]
For follow-up of initial findings			
E	–12	80	3.0
F	–12	200	3.0
G	+26	80	3.0
H	+26	200	3.0, 4.0[b]
I	–12	50	3.0

[a] Primary drying time was shortened to prevent complete sublimation of ice.
[b] Mannitol solution subjected to primary drying conditions for 3 h. Purified water subjected to primary drying conditions for 4 h.

All vials were paired with stoppers, and labeled. Purified water was produced by reverse osmosis and met requirements for purified water, USP. Before and after each run, the vials were weighed on an analytical balance to the nearest 0.0001 g. For each Plackett–Burman study, the vials were filled with a target of either 3.00 ml or 5.00 ml of purified water. Vial sets were partially stoppered, weighed for initial sample mass, and then loaded together into the freeze-dryer using a bottomless tray. Type T, 32-gauge thermocouples were placed and secured into the bottom-center of selected vials for monitoring sample temperatures during the cycle. A Hull model 2FS8C freeze dryer having a proportional shelf controller and electronic manometer pressure controller was used for processing all samples. Process data was collected using a Kaye Digi-Link 4C, interfaced to a PC using Kaye Collect® software.

Conservative and aggressive parameter combinations for

Table I. Experimental Design Settings for Plackett–Burman Screening Experiment

Run number	Glass type	Vial diameter (mm)	Bottom concavity (mm)	Bottom thickness (mm)	Wall thickness (mm)	Bottom radius (mm)	Shoulder contour (deg)	Vial finish (mm)	Vial height (mm)	Fill volume (cc)
1	Clear	22	0.50	0.7	1.0	3	10	13	50	3
2	Amber	22	0.50	0.7	1.2	3	45	20	58	5
3	Clear	25	0.50	0.7	1.2	2	10	20	58	5
4	Amber	25	0.50	0.7	1.0	2	45	13	50	3
5	Clear	22	0.25	0.7	1.2	2	45	13	58	3
6	Amber	22	0.25	0.7	1.0	2	10	20	50	5
7	Clear	25	0.25	0.7	1.0	3	45	20	50	5
8	Amber	25	0.25	0.7	1.2	3	10	13	58	3
9	Clear	22	0.50	1.0	1.0	2	45	20	58	3
10	Amber	22	0.50	1.0	1.2	2	10	13	50	5
11	Clear	25	0.50	1.0	1.2	3	45	13	50	5
12	Amber	25	0.50	1.0	1.0	3	10	20	58	3
13	Clear	22	0.25	1.0	1.2	3	10	20	50	3
14	Amber	22	0.25	1.0	1.0	3	45	13	58	5
15	Clear	25	0.25	1.0	1.0	2	10	13	58	5
16	Amber	25	0.25	1.0	1.2	2	45	20	50	3

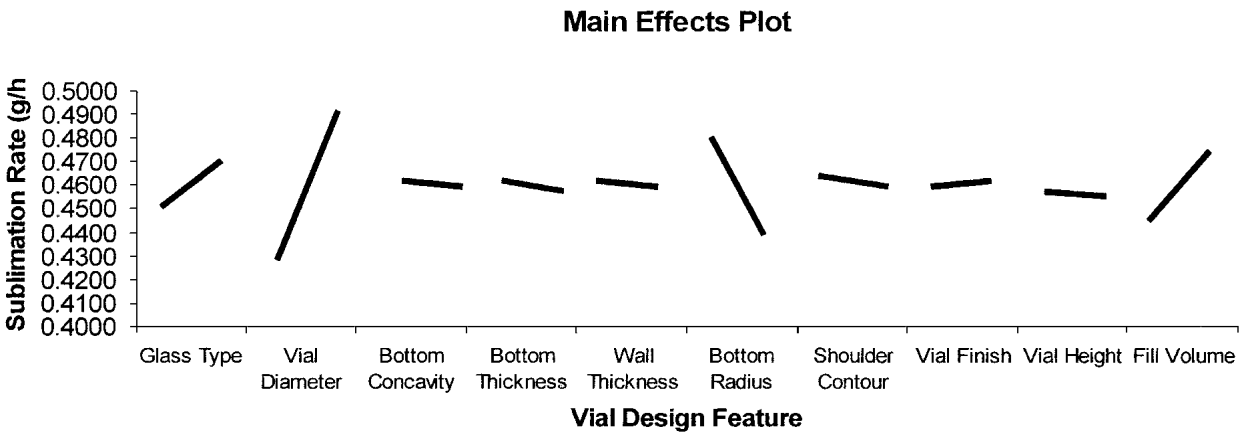

Fig. 1. The Main Effects Plot presents variables identified by the Plackett–Burman screening experiment as statistically significant. The first and second endpoints for each line are the nominal and extreme results, respectively. The values evaluated for the statistically significant design variables include glass type: amber, clear; vial diameter: 22 mm, 25 mm; bottom thickness: 0.7 mm, 1.0 mm; bottom radius: 2 mm, 3 mm; and fill volume: 3 cc, 5 cc. Slopes are based on statistical results from analysis of variance for all four cycles.

shelf temperature and chamber pressure were used to magnify differences in sublimation rates. The cycle consisted of at least 30 min at 5°C to equilibrate the temperature of water or solution in each vial prior to freezing. The shelves were then chilled to a target temperature of at least –35°C at an average controlled rate of 0.5°C min^{-1} and maintained for at least 120 min to allow for complete solidification. The condenser was chilled to below –50°C, the chamber evacuated and the chamber pressure controlled to the target setpoint. Pressure was maintained by bleeding 0.2-μm filtered nitrogen, NF, into the chamber. The shelf temperature was raised to the target primary drying temperature at a controlled rate of 0.5°C min^{-1} (see Table II). Sublimation was allowed to proceed for a predetermined amount of time and terminated by raising the pressure in the chamber to atmosphere by bleeding in filtered nitrogen, NF.

After the chamber pressure reached atmospheric pressure, the vials were stoppered under a nitrogen atmosphere to prevent condensation of water vapor to the partially lyophilized samples from moisture in the air. The vials were brought to room temperature and reweighed for final sample mass. Sublimation rates were then calculated for each vial by the difference of final sample mass from initial sample mass and divided by the time for sublimation during primary drying and are presented as average grams of water per hour for the respective vials. The time interval for sublimation started when the shelf reached the desired target temperature.

For the latter portion of the study, mannitol, USP and maltose reagent grade were purchased from Spectrum Chemical. Comar, Inc. specifically made 10-mL tubing vials with 20 mm finish and designated concavity specifications. The stoppers were two legged, 4416-50, 20 mm Grey Butyl S-87J configuration supplied by West Pharmaceutical Services, Inc. The procedure used to prepare and process the samples was identical to the one used during the initial Plackett–Burman screening experiment. The vials were placed in the center of the shelf. For each study, the vials were filled with a target of 4.00 mL of purified water, USP, and where appropriate, 2% mannitol or 5% maltose. Average sublimation rates for each vial set of each run were calculated from the measured mass loss. ANOVA was performed on the three vial sets from each of the four cycles and a p value less than 0.01 was considered statistically significant. When the average sublimation rates from a cycle were statistically different, multiple comparisons in the form of the Tukey test were calculated for each pair of averages.

These further studies on bottom concavity were conducted using the adjusted cycle parameters noted in Table II, and vials differing only in concavity. Concavity, also designated as the "pushup," reflects the gap that forms between the shelf surface and the vial bottom and is measured from the plane formed along the contact points with the shelf to the top of the arch formed by the vial bottom. To predict the impact when processing actual products of different solute characteristics such as morphology, simple model formulations in individual freeze-drying runs were varied using purified water and crystalline and amorphous solutes, mannitol and maltose, respectively, to evaluate the impact of mass transfer inhibition.

The sets of vial evaluated in the studies following the Plackett–Burman screening experiment consisted of 10-cc tubing vials constructed to be identical with the exception of bottom concavity. The wide range of concavities that were evaluated in the studies following the Plackett–Burman screening experiment were specifically constructed to have bottom concavities spanning 0.00 to 1.14 mm. Vial set 6 has the flattest possible concavity ranging from 0.00 mm to 0.13 mm. Vial set 7 ranges from 0.51 mm to 0.64 mm in concavity and was evaluated to monitor the progression of results over the broad scope of chosen concavities. The extreme concavity of vial set 8 ranges from 1.02 mm to 1.14 mm and was evaluated to obtain results at the upper end of the concavity spectrum. The specific pushups range from 0.00 mm to 1.14 mm, which would be expected to exaggerate any differences in sublimation rates caused by the gap between the vial and shelf.

RESULTS

The results of the study with vials having customized construction dimensions were evaluated using the Plackett–Burman statistical analysis. The analysis shows that glass type,

vial diameter, bottom radius, as well as fill volume have a statistically significant impact on sublimation rate ($p < 0.01$), with vial diameter having the greatest impact on sublimation rate. These results are graphically represented by the Main Effects Plot in Fig. 1. Statistical analysis of the screening experiment eliminated bottom concavity, bottom thickness, wall thickness, shoulder contour, vial finish, and vial height as design features that have a statistically significant influence on sublimation rate ($p > 0.01$). Because bottom concavity was expected to be identified by the Plackett–Burman screening experiment as a key influence on sublimation rate and was not, further investigations were designed to evaluate the empirical effect on sublimation rate.

The screening experiment first presented by Plackett and Burman was used to identify design features for further study by detecting individual significance of each during statistical evaluations, noting potential limitations (10). The possibility exists that error may have been introduced which altered the true effect of a particular vial design feature. Such error can include the impact of synergistic effects or antagonistic effects when different construction dimensions magnify or mask the apparent effect of each other. The lines with the greatest slopes on the Main Effects Plot in Fig. 1 represent the vial design features that exhibit a statistically significant influence on sublimation rate.

Follow-up studies were performed to look more closely at the effect of vial bottom concavity on sublimation rate. Data from four studies using purified water processed at combinations of conservative and aggressive shelf temperature and chamber pressure are presented in Fig. 2. Using ANOVA on the results, the average sublimation rates among vial sets 6, 7, and 8 within each of the four respective lyophilization cycles were statistically compared as noted in Table III. For ice in the absence of a solute, processed using Cycles E, F, and H, the differences in average sublimation rates were not statistically significant for vial sets 6, 7, and 8, respectively ($p > 0.01$). The differences in sublimation rates of the vial sets processed using Cycle G did exhibit a statistically significant difference ($p < 0.01$). The ranking order of average sublimation rates for Cycle G was set 7, set 6, and then set 8. Differences in sublimation rates between set 7 and set 8 were statistically significant. Sublimation rate differences between set 6 and set 7, as well as set 6 and set 8 were not statistically significant.

Table III. p Values from Statistical Evaluation of Plackett–Burman Screening Experiment, and Follow-up Studies of Purified Water, 2% Mannitol, and 5% Maltose

	p value[a]
Plackett–Burman[b]	
Glass type	0.0001
Vial diameter	<0.0001
Bottom	0.11
Concavity	
Bottom	0.02
Thickness	
Wall thickness	0.47
Bottom radius	<0.0001
Shoulder contour	0.10
Vial finish	0.65
Vial height	0.30
Fill volume	<0.0001
Purified Water[c]	
Cycle E	0.09
Cycle F	0.02
Cycle G	<0.001
Cycle H	0.02
2% Mannitol[c]	
Cycle H	0.04
5% Maltose[c]	
Cycle I	0.82

[a] A p value less than 0.01 indicates a statistically significant difference.

[b] Statistical values for each feature were calculated using sublimation rates of eight vials from each of the sixteen sets processed at the respective cycle parameters.

[c] Statistical values for each cycle were calculated using sublimation rates of vial sets 6, 7, and 8 processed at the respective cycle parameters.

In addition to sublimation rates of purified water, solutions of 2% mannitol and 5% maltose, crystalline and amorphous materials, respectively, were evaluated. The lower concentration of mannitol was used to avert incidence of vial breakage during processing (11). The eutectic melt tempera-

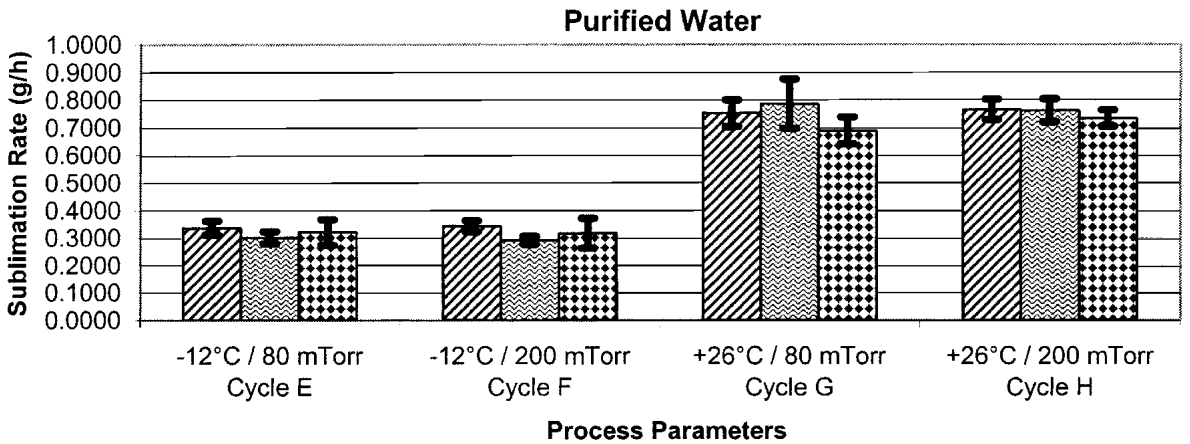

Fig. 2. Average sublimation rates ± standard deviation (SD) for vial sets 6, 7, and 8 filled with purified water. Vials have a finish of 20 mm and concavities are ▨ 0.00–0.13 mm, ▩ 0.51–0.64 mm, or ▣ 1.02–1.14 mm. Cycles were run at a combination of conservative and aggressive shelf temperatures and chamber pressures.

ture of mannitol is –2.2°C (12) and the collapse temperature of maltose is –32°C (13). Statistical values for vial sets 6, 7, and 8 using the mannitol and maltose formulations processed at aggressive and conservative parameters, respectively, are presented in Table III. The average sublimation rates along with standard deviations are plotted as shown in Fig. 3 and Fig. 4.

The mannitol formulation was evaluated using the aggressive parameters identified as Cycle H. Product temperatures were well below –2.2°C during primary drying, precluding any eutectic melt and the resulting influence on drying. Differences in the average sublimation rates of the three vials sets were not statistically significant ($p > 0.01$).

The maltose formulation was processed using Cycle I and evaluated with conservative processing conditions. Such conditions were intended to yield appreciable sublimation rates while preventing product collapse. Drying with retention of initial product structure was confirmed by product temperatures that were below –32°C during primary drying. Statistical results indicate no significant difference in average sublimation rates among vial sets 6, 7, and 8 at such conservative processing conditions ($p > 0.01$).

DISCUSSION

The significance of glass type on sublimation rate was unexpected and may be explained by the differences in composition. The amber vials contain ferrous and ferric oxide, which would be expected to impact heat transfer and thus the rate of sublimation (14). The effectiveness of heat transfer in this case is directly influenced by the thermal conductivity of glass. Plackett–Burman results indicated the construction features that have the largest effect on sublimation rate are those that control the surface contact between the vial and the shelf, identified as bottom radius and vial diameter. Manipulating the dimensions of these two features to create a vial with maximum surface contact should significantly increase sublimation rates. Contact conduction is more efficient than gas conduction and increases in surface contact increases the participation of the former.

Fourier's Law, the fundamental heat transfer equation for conduction, is expressed by:

$$\frac{dQ}{d\theta} = -kA\left(\frac{dt}{dx}\right) \tag{1}$$

where $dQ/d\theta$ is the rate of heat flow, k is the thermal conductivity which is a characteristic property of the material through which the heat flows and varies with temperature, A is the area at right angles to the direction in which the heat flows, and $-dt/dx$ is the rate of change of temperature with the distance in the direction of heat flow (15). Further, the difference in surface area contact between two vials with different diameters is measured using the circle formed by direct surface contact and calculated by:

$$A = \pi(r_1 + r_2)(r_1 - r_2) \quad r_1 > r_2 \tag{2}$$

where A is the difference in surface area between the larger and smaller vial diameters, r_1 is the radius of the larger diameter, and r_2 is the radius of the smaller diameter (15). As the area between the shelf and vial bottom is replaced by increasing surface contact, A, in Eq. (1), the rate of heat flow to the vial also increases, which allows for greater sublimation rates.

A smaller bottom radius would provide an increased area for surface contact between the vial and the shelf, which would promote more efficient heat transfer. A larger vial diameter increases the area of both the surface contact and the sublimation front, simultaneously allowing more ice to sublime. The same fill volume in a larger diameter vial reduces the fill height and increases the surface to volume ratio: the surface area of the ice-vapor interface increases. The smaller fill height also has the effect of reducing resistance to mass transfer of water vapor through the dried layer above the sublimation front by reducing the distance the vapor travels through the dried cake increasing sublimation rates (16). The result of a smaller fill volume in a larger diameter vial is an increase in overall sublimation rates.

Because a greater range in concavities for the bottom of tubing vials was used in the follow-up study, slight differences in sublimation rate would be expected to be magnified. It was initially presumed that this difference was not evident in the Plackett–Burman study because vials having a smaller range of concavities were used. A previous study by Pikal on the

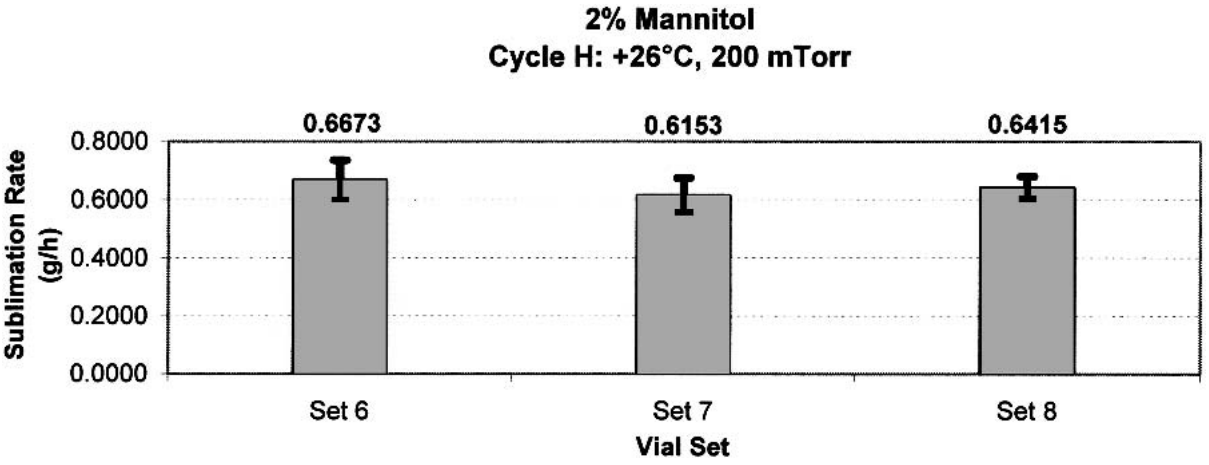

Fig. 3. Average sublimation rates ± SD for vial sets 6, 7, and 8 filled with 2% mannitol. Cycle parameters include an aggressive shelf temperature of +26°C with a chamber pressure of 200 mTorr. Vial finishes are 20 mm and bottom concavities are 0.00–0.13 mm, 0.51–0.64 mm, or 1.02–1.14 mm.

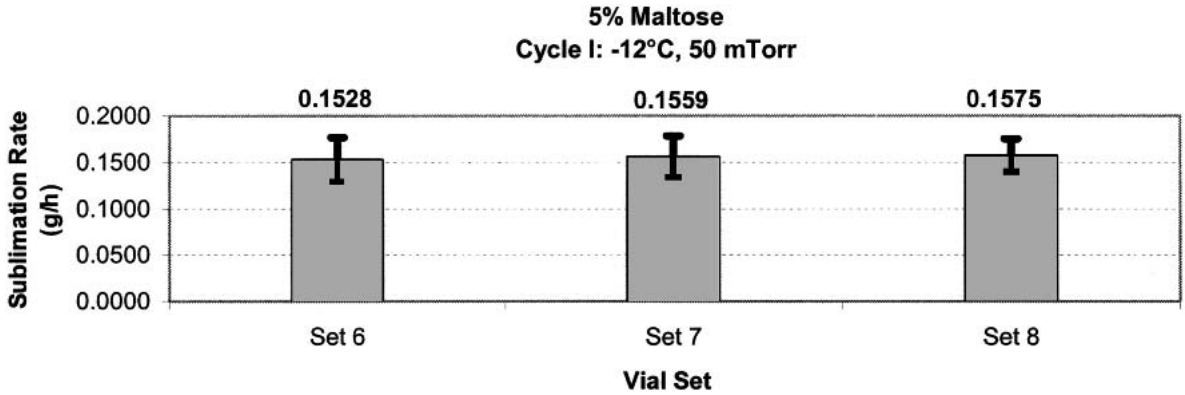

Fig. 4. Average sublimation rates ± SD for vial sets 6, 7, and 8 filled with 5% maltose. Cycle parameters include a conservative shelf temperature of –12°C and a chamber pressure of 50 mTorr. Vial finishes are 20 mm and bottom concavities are 0.00–0.13 mm, 0.51–0.64 mm, or 1.02–1.14 mm.

sublimation rates in vials indicates that bottom concavity along with vial to shelf contact are construction variable that exhibits a significant impact on heat transfer (2). Results of the study presented here with identical vial to shelf contact and multiple permutations indicate that variations in bottom concavity did not result in a statistically significant difference among average sublimation rates. There was no statistically significant difference between sublimation rates of vial sets even when using purified water, except when processed using the parameters of Cycle G. Small differences in actual sublimation rates of the vial sets are attributable to the study error variance.

The difference in results between the work completed in this study and previously published work may be attributed to glass tubing vials constructed with specific dimensions to cover a wide range of concavity, along with the application of rigorous statistical analysis. These vials were constructed to a wide range of concavity in contrast to standard off the shelf tubing and molded vials of varying dimensions. This variation in construction isolates bottom concavity as a controlled variable to provides insight into the variable having the greatest impact on heat transfer, and offer a further explanation to conclusions in the work previously reported and the results of these studies.

An in-depth look at vial heat transfer coefficients illustrates the relationship between vial construction and heat transfer. The vial heat transfer coefficient K_v is expressed by the equation:

$$K_v = K_c + K_r + K_g \quad (3)$$

where K_c is the heat transfer contribution from contact conduction, K_r is the heat transfer contribution from radiation, and K_g is the heat transfer contribution from gas conduction (2). Noting that K_g and K_r are process related and not vial design features, they are dependent upon the surrounding environment, specifically chamber pressure. Since K_v is a coefficient of the vial, it should be dependent only on construction features of the vial, and should be independent of any environmental or processing conditions. Therefore, K_c is comprised of heat conducted by surface contact and is identified by:

$$K_c = k_t (A) \quad (4)$$

where k_t is the thermal conductivity of the glass, and A is the cross-sectional area at right angles to the direction in which the heat flows. If K_r and K_g are not considered when determining the vial heat transfer coefficient, K_v becomes strictly dependent upon conduction at direct points of contact:

$$K_v = k_t (A) \quad (5)$$

For glass of the same composition, the vial heat transfer coefficient is a function K_c and controlled essentially by vial diameter and bottom radius, the two vial design features responsible for A, the surface contact.

Upon comparison, vials with identical contact areas and concavities covering one order of magnitude did not show a statistically significant difference among sublimation rates. Even though the sublimation rate of vial set 7, which had the middle concavity, outperformed the boundary of concavities studied using Cycle G, the realization of actual numerical differences are inconsequential. When applied to the commercial manufacturing scale, such small differences in drying times are negligible when using a 4.00 ml fill volume in a 10 cc glass tubing vial. Data from this study demonstrates that differences in sublimation rates resulting from changes in concavity do not indicate a substantial difference on time in primary drying.

Vial set 7 exhibited the greatest sublimation rate only when processed using the higher shelf temperature and lower pressure of Cycle G. The statistical analysis only showed a significant difference in sublimation rates between vial sets 7 and 8. If the statistically significant difference was strictly due to bottom concavity, then this difference would also be expected between vial sets 6 and 8 as well, since the range of concavity encompasses vial set 7. Because there was no statistically significant difference between vial sets 6 and 8, any difference between rates of all three vial sets is attributed to study error variance. This is evidenced by the large standard deviation in the results of vial set 7 presented in Fig. 2. Actual differences in sublimation rates between vial sets 6, 7, and 8 are considered negligible for primary drying considerations.

Comparing cycles, at increased shelf temperature, sublimation rates of all vial sets increased regardless of chamber pressure. An increase in shelf temperature increases heat transfer, which results in greater sublimation rates that are more partial to mass transfer inhibition due to the presence of a solute. The overall effect of shelf temperature on sublima-

tion rates was much greater than the effect of chamber pressure. Rates of sublimation of all vial sets obtained at the same shelf temperature but different chamber pressure demonstrated a marginal difference, however, statistical analysis was not performed on the data in relation to pressure to determine significance.

CONCLUSIONS

The Plackett–Burman screening experiment is a viable method that allows for the identification of the statistically significant vial design features that influence the rate of sublimation. The two construction variables of tubing vials that the studies show to have the largest impact on sublimation are vial diameter and bottom radius. These two features dictate the extent of heat transfer by direct contact and therefore, have the greatest impact on sublimation rate. Most of the average sublimation rates for tubing vials of various concavities containing purified water were not statistically different within individual lyophilization cycles, and any rate differences were statistically small. Statistically significant differences, while small, were only found in the when processing purified water using an aggressive shelf temperature and conservative chamber pressure. Results in this study showed no statistically significant difference in measured sublimation rates in vials with different concavities with the presence of a crystalline or amorphous solute and the impact on mass transfer of water vapor through the dried layer when processed at aggressive or conservative parameters, respectively.

The results of these studies empirically confirm glass type, vial diameter and bottom radius have a significant effect on sublimation rate. They also confirm that the bottom concavity of tubing vials has no statistically significant effect on sublimation rates when processed at either conservative or aggressive parameters even when using crystalline or amorphous solutes. The results from the latter portion of this study support the initial findings of the Plackett–Burman screening experiment; concavity does not have a statistically significant effect on sublimation rate. Any small differences in average sublimation rates projected to predict processing times are inconsequential relative to the extensive amount of time a product typically spends in primary drying.

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