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Heat and Mass Transfer Scale-up Issues During Freeze-Drying, I: Atypical Radiation and the Edge Vial Effect

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ABSTRACT

The aim of this study is to determine whether radiation heat transfer is responsible for the position dependence of heat transfer known as the edge vial effect. Freeze drying was performed on a laboratory-scale freeze dryer using pure water with vials that were fully stoppered but had precision cut metal tubes inserted in them to ensure uniformity in resistance to vapor flow. Sublimation rates were determined gravimetrically. Vials were sputter-coated with gold and placed at selected positions on the shelf. Average sublimation rates were determined for vials located at the front, side, and center of an array of vials. Sublimation rates were also determined with and without the use of aluminum foil as a radiation shield. The effect of the guardrail material and its contribution to the edge vial effect by conduction heat transfer was studied by replacing the stainless steel band with a low-thermal conductivity material (styrofoam). The emissivities (ε) of relevant surfaces were measured using an infrared thermometer. Sublimation rate experiments were also conducted with vials suspended off the shelf to study the role of convection heat transfer. It was found that sublimation rates were significantly higher for vials located in the front compared to vials in the center. Additional radiation shields in the form of aluminum foil on the inside door resulted in a decrease in sublimation rates for the front vials and to a lesser extent, the center vials. There was a significant decrease in sublimation rate for gold-coated vials ($\varepsilon \approx 0.4$) placed at the front of an array when compared to that of clear vials ($\varepsilon \approx 0.9$). In the case of experiments with vials suspended off the shelf, the heat transfer coefficient was found to be independent of chamber pressure, indicating that pure convection plays no significant role in heat transfer. Higher sublimation rates were observed when the steel band was used instead of Styrofoam while the highest sublimation rates were obtained in the absence of the guardrail, indicating that the metal band can act as a thermal shield but also transmits some heat from the shelf via conduction and radiation. Atypical radiation heat transfer is responsible for higher sublimation rates for vials located at the front and side of an array. However, the guardrail contributes a little to heat transfer by conduction.

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INTRODUCTION

Freeze-drying, or lyophilization, is a process commonly used in the processing of heat-sensitive products where the solvent, usually water, is removed from the frozen solution by sublimation.[1] The freeze-drying process consists of 3 main stages: freezing, primary drying, and secondary drying. Primary drying is the ice sublimation stage, and secondary drying involves removal of water from the solute phase by desorption. In pharmaceutical freeze-drying operations, the solution is filled into vials with stoppers partially inserted into the vial necks to allow for vapor flow.

Compared to other commonly used processes, freeze-drying of pharmaceuticals is expensive. The main focus of process development is to minimize drying times while maintaining product quality. In practice, the shelf temperature and chamber pressure profiles with time are determined by trial and error. Needless to say, however, optimization of the freeze-drying process is extremely important from a process development point of view, and knowledge of principles of

heat and mass transfer pertinent to the process is essential.[2-4]

Efficiency in process development is also important during scale-up of the freeze-drying process from laboratory to production operations and requires a sound fundamental understanding of heat and mass transfer in primary drying. Although scale-up problems in freeze-drying are frequently less severe when compared to those in other pharmaceutical operations, there are key issues that should be taken into consideration, not only from an economic standpoint but also from a product quality point of view.[5,6] Scale-up problems could arise for several reasons: (1) differences in the degree of supercooling between laboratory and manufacturing operations, which in turn lead to differences in primary drying time; (2) differences in dryer design, which could lead to shelf surface temperature variations, thereby causing variability in heat transfer rates; or (3) differences in the efficiency of the condenser or refrigeration system, which could limit the performance of one freeze dryer at a particular thermal load compared to another. All of these variations can lead to significant heterogeneity in sublimation rates and/or desorption rates and hence variations in drying times.

Heat transfer from the source to the sublimation interface is an important rate-limiting process during primary drying and one on which optimization efforts should focus.[7] It is important to understand the dominant mechanism for heat transfer: conduction, convection, or radiation. In pharmaceutical freeze-drying operations, the vial heat transfer coefficient, K_v, is expressed as a sum of 3 contributions:

$$K_v = K_c + K_r + K_g \tag{1}$$

where K_c refers to the contribution arising from direct conduction from the shelf to the vial at the points of contact, K_r is the contribution from radiative heat transfer, and K_g is the contribution from conduction through the gas between the shelf and the bottom of the vial.[4]

The gas conduction term, K_g, may be expressed as a function of pressure:

$$K_g = \frac{\alpha \Lambda_0 P}{1 + l(\alpha \Lambda_0 / \lambda_0) P} \tag{2}$$

where Λ_0 is the free molecular heat conductivity of the gas at 0°C, λ_0 is the heat conductivity of the gas at ambient pressure, P is the gas pressure, I is the constant "effective" distance characterizing the gap between the shelf and the vial bottom, and α is a term related to the energy accommodation coefficient (a_c)[4].

Thermal radiation occurs as a result of thermal excitations of molecules and is emitted in an amount determined by the temperature of the relevant surfaces and also by the thermal emissivity (ε) of the radiating body. Radiative exchange between 2 surfaces may be expressed in terms of the Stefan-Boltzmann equation as

$$\frac{dQ_r}{dt} = A_v \bar{e} \sigma \left(T_2^4 - T_1^4 \right) \tag{3}$$

where A_v is the cross sectional area of the vial, σ is the Stefan-Boltzmann constant and $\bar{e}$ is the effective emissivity for radiation exchange, with T_2 and T_1 being the absolute temperatures of the 2 surfaces. Although thermal radiation is not the dominant mechanism for heat transfer because of the low temperatures encountered in typical freeze-drying operations,[7] radiation heat transfer can become an important issue when relatively warm surfaces are present, i.e. the chamber walls and the door. Also, vials closer to the condenser chamber could lose some energy by radiation exchange with the condenser plate, thereby causing those vials to run colder and sublime more slowly. While modern freeze dryers are constructed to minimize direct "views" of the extreme temperatures of the condenser, the potential for variability in drying rates arising from atypical radiation effects cannot be ignored, especially in the case of vials on the edge of the vial array close to the freeze dryer door or view port.

Heterogeneity in heat transfer rates with respect to position on the shelf may be an important scale-up issue. Vials located along the periphery of a tray, or edge vials, receive more heat during primary drying, and their contents sublime faster. In one study, the average edge vial was reported to sublime 15% faster than a typical interior vial.[1] In another study, samples at the periphery and closer to the glass door dried at approximately twice the rate of those in the middle.[8] This drying heterogeneity could be a serious problem in process control, where the product in these vials is very likely to collapse if primary drying is conducted at temperatures close to the glass transition temperature of interior (ie, middle) vials. In most manufacturing operations, thermocouples are placed in the front row and only the front-row vials are monitored to detect the end of primary drying, leading to erroneous evaluation of drying time. Operation of a freeze dryer with temperature-controlled walls is said to eliminate temperature gradients when the wall temperature is

reduced to several degrees below the internal sample temperature[9]; model simulations have given similar results.[10] It is our thesis that this heterogeneity in heat transfer, or the "edge vial effect," is due to the direct view of edge vials of a much warmer surface, which could be the chamber wall or the door of the freeze dryer. While there is considerable evidence to support the belief that the cause of this heterogeneity in sublimation rates is due to atypical radiation heat transfer, there is one recent study by workers at Merck that indicates that the contributions from radiation heat transfer are negligible.[11] The critical portion of the Merck study that suggested that radiation heat transfer is minimal was based on a comparison of sublimation rates between normal clear vials and gold-plated vials. The gold-plated vials were assumed to have very low emissivity (0.03) relative to clear vials (0.95).[12] If radiation heat transfer is a significant heat transfer mechanism, the gold-plated vials should have had lower sublimation rates. However, the sublimation rates of gold-plated vials were essentially the same as for clear vials.

Understanding the cause of inhomogeneity in heat transfer rates is the first step to successful scale-up of the freeze-drying process. This article attempts to address one of the several scale-up issues discussed above, to clarify the role of atypical radiation heat transfer in the edge vial effect, and to investigate other heat transfer mechanisms that could contribute to this atypical drying behavior. Once the key parameters that have the potential to affect the scale-up of the freeze-drying process are identified and quantitatively accounted for, the development of scale-up algorithms to scale-up product temperature time profiles will be facilitated.

MATERIALS AND METHODS

Materials

All of the sublimation rate experiments were conducted using pure water in 5-cc tubing vials with a 20-mm finish obtained from West Pharmaceutical Company, Lionville, PA. Stainless steel tubes (0.46-cm inner diameter) inserted into the fully stoppered vials were precision cut into small tubes 2 cm in length. The reciprocal of the tube resistance, R_{TB}^{-1}, calculated using theoretical relationships described for gas flow in tubes,[1] was 8.40-mm Hg.hr.g^{-1} at a chamber pressure of 0.15 mmHg.

Freeze-drying

A laboratory scale Lyostar freeze dryer (Kinetics Thermal Systems, Stone Ridge, NY) was used for this study. Sublimation rates were determined gravimetrically as an average of 5 representative vials located at various positions on the shelf. The freezing protocol was kept the same for all the runs and was as follows:

- Ramp at 2.5°C/min to 5°C and hold for 15 minutes;
- Ramp at 2.5°C/min to –5°C and hold for 15 minutes; and
- Ramp at 1°C/min to –40°C and hold for 120 minutes.

Primary drying was conducted using different shelf temperature and chamber pressure settings for times long enough so that about 50% sublimation was complete, after which the experiment was stopped and vials were removed for weighing.

Sublimation Variability Study

Sublimation rate experiments were conducted using vials that were fully stoppered and had precision cut steel tubes inserted fully into the vial neck. This procedure ensured that the resistance to vapor flow was fixed by the geometry of the tube and the chamber pressure and was not subject to variations related to stopper placement and geometry.[4] Uniformity in resistance to mass transfer is critical when determining variation in the heat transfer coefficients of a set of vials. Five experiments were conducted at a shelf temperature of –25°C and a chamber pressure of 0.15 mmHg during primary drying. In each of these experiments, vials were rotated in 6 different positions on the shelf and alternately, a set of 5 vials was chosen at fixed positions and their tubes were rotated in each experiment. Sublimation rates were determined gravimetrically for all the vials.

Gold Plating

Gold plating was performed on a sputter-coating apparatus, Polaron E5100 series 2 (Quorum Technologies, East Sussex, Newhaven, UK) commonly used for scanning electron microscopy experiments. Coating was conducted at a pressure of 0.04 to 0.06 mmHg using a current of 15 mA for 10 minutes.

Emissivity Measurements

The emissivity of the gold-plated surface and representative surfaces such as the chamber wall, the glass door, and so on was determined using an infrared thermometer—Omegascope OS530 from Omega Instruments, Stamford, CT. The instrument uses a laser detector (with a distance-to-spot-size ratio of 30:1) designed to measure surface temperature at a surface spot of known emissivity. The infrared thermometer uses the Stephan-Boltzmann equation for directly calculating the temperature of an object of known emissivity (Equation 3). A sensor inside the thermometer determines the ambient temperature (ie, temperature of the thermometer). In our studies, we measured the temperature of the relevant surface using a thermocouple and determined the emissivity of the surface at that surface temperature by finding the emissivity that resulted in a match of thermocouple and infrared thermometer readings. The infrared thermometer measured values of emissivity ranging from 0.1 to 1 in steps of 0.01.

Suspended Vials Study

Approximately 100 tubing vials were inserted into a wire mesh that was raised and held on Styrofoam bars and metal tubes as supports. Styrofoam is a low–thermal conductivity material that insulated the vial mesh from the shelf. An arrangement of this kind enabled the vials to be raised approximately 11 cm above the shelf.

Experiments with Guardrail

All of the sublimation experiments described above were carried out without the use of a guardrail. To study the effect of the guardrail material on the sublimation rate, 2 different guardrail materials were used: a stainless steel band that is commonly used for freeze-drying experiments, and a band made out of Styrofoam.

RESULTS AND DISCUSSION

Inter-vial Variability Studies

In addition to variation in heat transfer coefficients, variations in sublimation rate can arise from several other sources: (1) variations in the mass transfer coefficient of the metal tubes, (2) variations due to location on the vial on the shelf that originates from variations in shelf surface temperature or radiation effects, and (3) variations due to measurement error or due to variability in the surface area of ice.[1] A vial rotation study was performed as described under Materials and Methods to determine the variability that could be due to one or more of the causes described above. Atypical vials—that is, vials located along the edges and not surrounded by 6 other vials in a hexagonal arrangement—were excluded from this study. Analysis of variance on these sets of sublimation data are shown in **Table 1**. The results of the position rotation experiment indicate that there is no significant position effect (interior vials only), suggesting that the shelf temperature uniformity is excellent. The raw data and corresponding analysis of variance for the metal tube portion of the study (lower portion of **Table 1**) also shows that there is no significant variation in sublimation rate caused by variation in mass transfer coefficient of the metal tubes. Hence, this component of variation can also be neglected.

Table 1. Analysis of Variance on Sublimation Data to Study the Variability Due to Position on the Shelf and Steel Tubes*

	Mean	Variance
Position†		
5_5	0.08534	9.36E-05
7_3	0.0828	2.65E-05
7_10	0.08234	3.63E-05
10_3	0.07844	1.93E-05
12_10	0.0783	1.00E-05
15_6	0.07852	5.94E-05
Stopper‡		
A	0.081	4.21E-05
B	0.084	6.57E-05
C	0.080	1.65E-05
D	0.083	7.62E-05
E	0.080	1.72E-05

*A 1-way analysis of variance determined that the means were not significantly different at the .05 level of significance. Position represents *x*_*y* where *x* = row number, *y* = vial number from the left.
†F = 1.07312; *P* = .39985.
‡F = 0.44925; *P* = .77172.

Figure 1. Arrangement of gold-coated vials and clear vials on the freeze dryer shelf. Note the steel tubes inserted into the stoppers.

Heterogeneity in Heat Transfer Rates of Edge Vials

Gold-plated vials and clear vials were placed at the front, side, and center of the shelf so that the sublimation rates of gold vials could be compared to rates of clear vials. **Figure 1** shows gold-coated vials alternated with clear vials with steel tubes inserted in them. The conditions of the coating process, as described under Materials and Methods, were used to give a uniform coating on the glass vial. The emissivity of a similarly gold-plated flat glass surface was measured to be 0.4. This value is higher than the emissivity value of 0.03 that is generally reported for gold and that was assumed in the Merck study. Evidently, sputter-coated gold has a higher emissivity than polished gold. Experiments were conducted at 3 different shelf temperatures (–25°C, –15°C, and 0°C) and a chamber pressure of 0.15 mmHg during primary drying. There were no other radiation shields, and no guardrail surrounded the vial array. It was observed that unlike in the Merck study, there was a significant decrease in sublimation rates for gold-coated vials placed at the front of the array when compared to clear vials. **Figure 2** shows sublimation rate data for vials placed at 2 different positions and 3 different shelf temperatures. There is a significant difference in the sublimation rate between clear vials and gold-plated vials in the front of the array, with the ratio of sublimation rate of clear vial to that of gold-plated vial decreasing from 1.37 at –25°C to 1.17 at 0°C, indicating that there is a greater relative contribution from radiation at lower shelf temperatures. This observation, in turn, means that the source of radiation is not the shelf but the dryer walls and door. Differences in sublimation rates between gold-plated vials and clear vials located in the center are small, an indication of the shielding effect from side radiation that neighbor vials provide. Also, sublimation rates for gold-plated vials in the front are higher than those for gold-plated vials in the center, suggesting that the gold-plated vial does not have zero emissivity and that gold plating has not entirely eliminated the edge effect. Of course, as indicated earlier, we measure an emissivity of 0.4, not 0, for gold-plated vials. The reasons for the difference in observations between this research and the Merck study are not clear. However, it does appear that the sputter coating used in the Merck study gave a much higher emissivity than we found for our process.

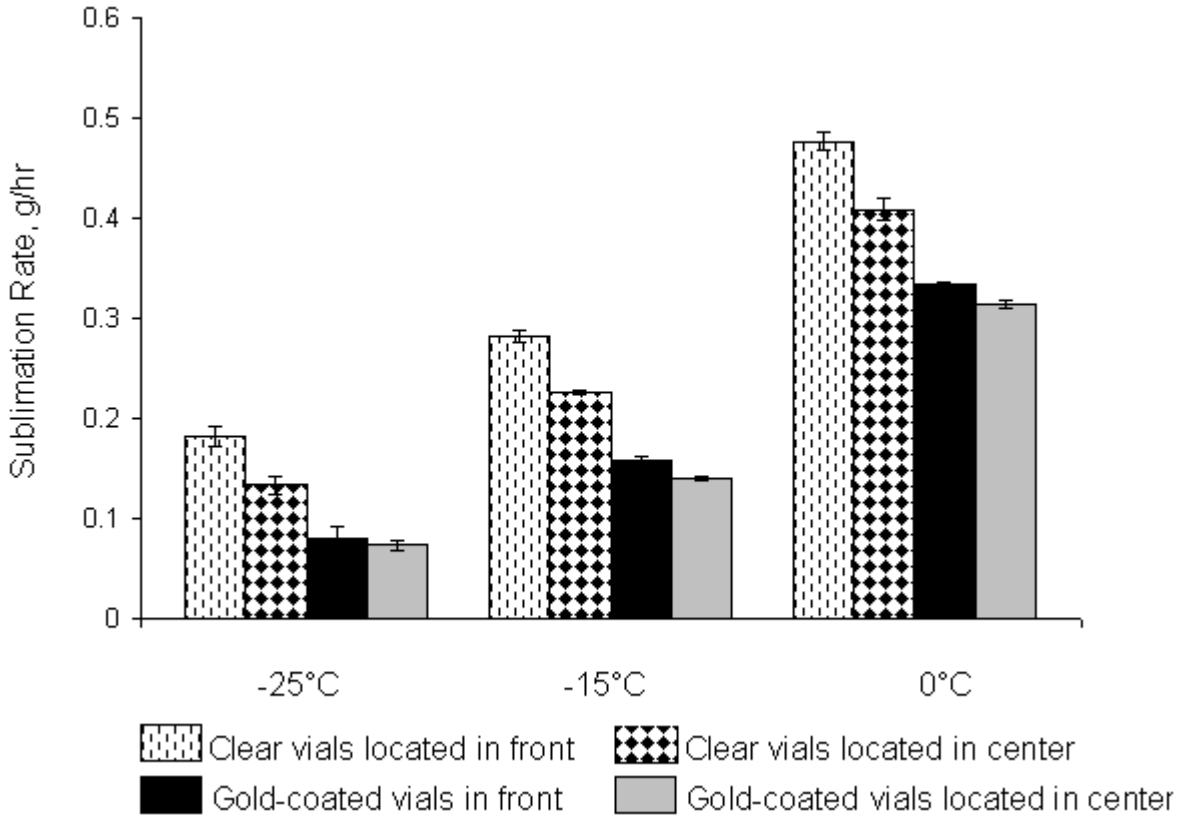

Figure 2. Sublimation rate data obtained as a function of shelf temperature during primary drying for clear and gold-coated vials in the front and in the center. Error bars represent standard deviations. Chamber pressure is 0.15 mmHg for all experiments.

An additional radiation shield in the form of aluminum foil placed on the inside of the freeze dryer door resulted in a significant reduction in sublimation rate for all of the edge vials studied (**Figure 3**). The emissivity of the aluminum foil was approximately 0.15 as measured using the infrared thermometer. Radiation shields constructed from low-emissivity (high-reflectivity) materials can be used to reduce the net radiation heat transfer between 2 surfaces—the Plexiglas door and the vial in this case. With radiation shields, additional resistances to radiation heat transfer are present, and these resistances become very large when the emissivities of the surfaces are small.[12] **Figure 3** represents data obtained for experiments conducted with and without radiation shields at –25°C and 0.1 mmHg during sublimation. There is a clear decrease in sublimation rate for vials located in the front and the side of the array in the presence of radiation shields. Also, as expected, sublimation rates are higher for clear vials when compared to gold-plated vials at the edge locations. However, the presence of radiation shields combined with the gold plating has not been able to eliminate the edge vial effect completely in that the sublimation rate is still significantly higher for the front vials when compared to vials located in the center.

Experiments with Suspended Vials

To assess the role of convection heat transfer, experiments were conducted with vials suspended off the shelf to eliminate heat transfer via conduction through the gas (ie, the separation distance between the shelf and vials is too large to allow significant heat transfer). At large separation distances, l, the heat flow associated with the gas conduction term becomes dependent on the thermal conductivity of the gas, becomes independent of pressure (ie, $l\ (\alpha\Lambda_0/\Lambda_0)P >> 1$ in Equation 2), and reduces to the heat flow equation for moderate-pressure gases. Sublimation experiments were carried out at a shelf temperature of –25°C and at 3 different chamber pressures. Knowledge of the product temperature and shelf temperature and determination of the sublimation rate allowed the vial heat

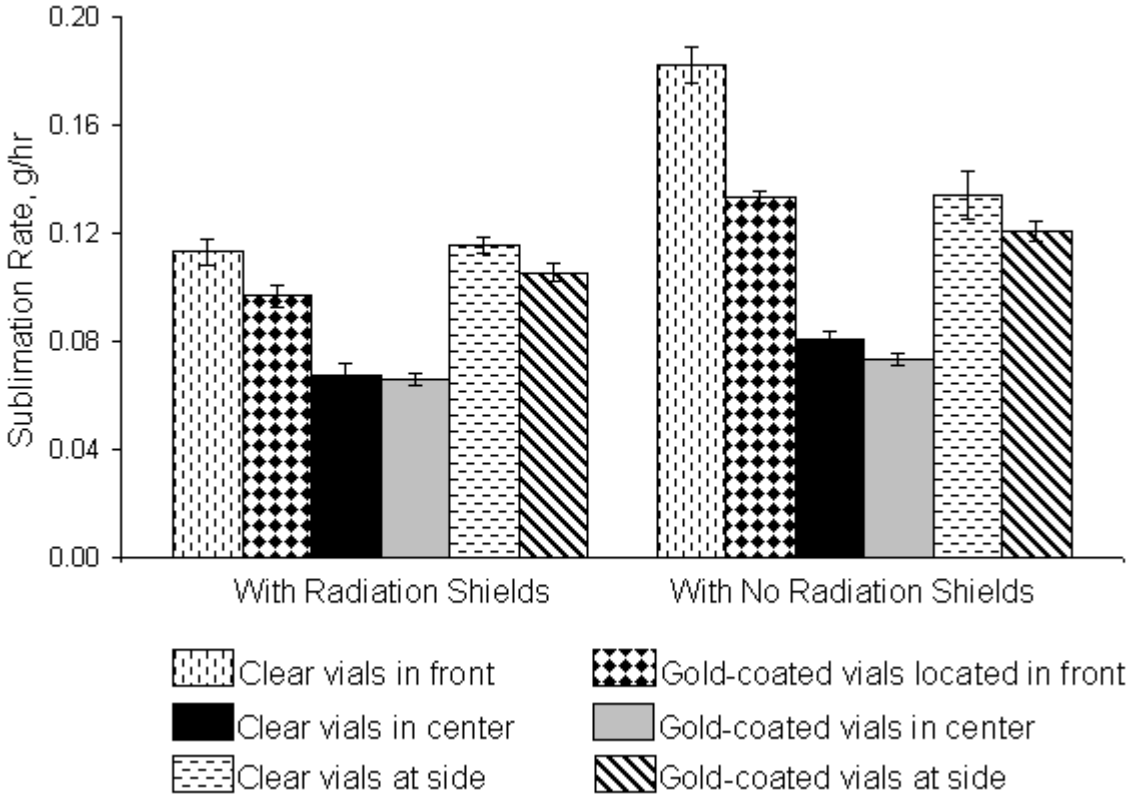

Figure 3. Effect of radiation shields on the sublimation rate at –25°C shelf temperature and 0.1 mmHg chamber pressure for vials. Sublimation rate data are shown for clear and gold-coated vials in the front, in the center, and at the side. Error bars represent standard deviations.

transfer coefficient to be calculated according to Equation 4 for the coupled heat and mass transfer:

$$\frac{dQ}{dt} = \Delta H_s \frac{dm}{dt} = A_v K_v \left(T_s - T_p\right) \tag{4}$$

where dQ/dt is the heat transfer rate from the shelves to the product, ΔH_s is the heat of sublimation of ice, dm/dt is the sublimation rate, A_v is the cross-sectional area of the vial, K_v is the heat transfer coefficient of the vial, T_s is the shelf temperature, and T_p is the product temperature at the vial bottom.

Figure 4 shows heat transfer coefficient data obtained for suspended vials at different locations on the shelf. It is clear that while the vial heat transfer coefficient is higher for edge locations than for those located in the center, as expected, the value of K_v is essentially independent of chamber pressure. This observation is of some significance since the suspended vials experiment was designed to remove all contributions from conduction heat transfer (ie, by suspending the vials). There was obviously no contribution from the heat transfer coefficient due to direct contact, K_c, to the overall heat transfer coefficient. Also, since the vials are suspended well above the shelf, the contribution from conduction through gas molecules may be neglected, as the separation is too great (Equation 2). There has been some speculation that bulk flow (ie, convection heat transfer) of water vapor could be responsible for position dependence of heat transfer.[8] However, the fact that K_v is independent of pressure suggests that convection heat transfer does not play a role. Heat flow due to convection is described by

$$\dot{Q} = hA\Delta T \tag{5}$$

where the heat transfer coefficient, h, is expressed as[13]:

$$\frac{hL}{k} = a\left(\frac{L^3 \rho^2 g \beta \Delta T}{\mu^2} \cdot \left(\frac{c\mu}{k}\right)\right)^m \tag{6}$$

where h is the heat transfer coefficient, L is the height of a vertical surface or length of a horizontal surface, k is the thermal conductivity of the fluid, ρ is the density of gas, g is the acceleration due to gravity, β is the coefficient of thermal expansion of fluid, μ is the vis-

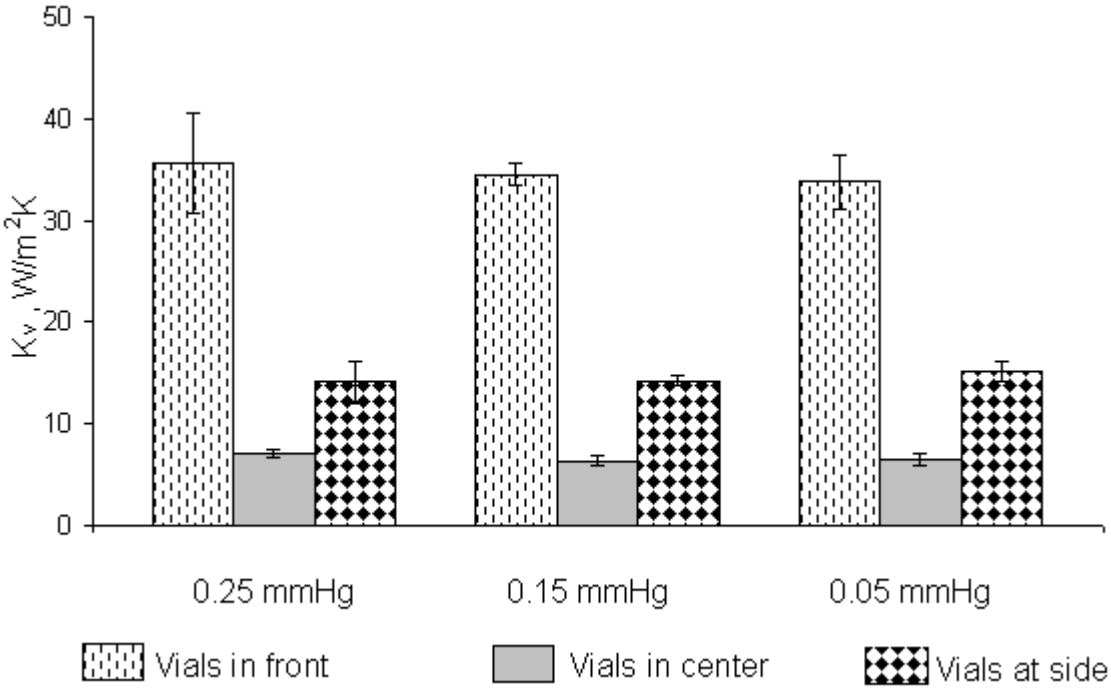

Figure 4. Experiments with suspended vials at a shelf temperature of –25°C showing vial heat transfer coefficient, K_v, obtained as a function of chamber pressure for vials in the front, in the center, and at the side. Error bars represent standard deviations.

cosity of the fluid, ΔT is the temperature difference causing heat flow, c is the specific heat of the fluid at constant pressure, and a and m are constants. Typical a values range from 0.1 to 0.6 and typical m values range from 0.25 to 0.33. According to Equation 6, h is directly proportional to some power of the gas density ρ and therefore should increase with chamber pressure. However, at the low pressures typically encountered during freeze drying, gas density is small and convection heat transfer is negligible.

Effect of Guardrail

Another potential contribution to the higher heat transfer rates of edge vials is the stainless steel guardrail. Vials at the edge of the array are generally in contact with the guardrail, which can impart some thermal energy by way of conduction to the vials in contact with it. Also, in principle, the guardrail may also function as a thermal shield from side radiation. The role of the guardrail material was studied using the commonly used steel band and a band made from styrofoam, a low–thermal conductivity material. Sublimation experiments were performed at –25°C shelf temperature and 0.1 mmHg chamber pressure. A comparison of sublimation rates with the use of these 2 materials and also with no guardrail is shown in **Figure 5**. While the guardrail material or the absence of the guardrail has no significant effect on the sublimation rate of center vials, there is a significantly higher sublimation rate for vials located in the front that have no guardrail when compared to the sublimation rate for vials that have a guardrail surrounding them. Thus, it appears that the guardrail functions as a radiation shield. The sublimation rate for vials that have a steel band is higher than for those that have styrofoam around them, suggesting that there is some contribution from contact conduction with the steel band. Thus, the use of a stainless steel band decreases heat transfer by functioning as a radiation shield but increases heat transfer by direct conduction, with the net effect being a decrease in heat transfer.

CONCLUSION

We have found that atypical radiation heat transfer experienced by edge vials because of their clear view of a warmer surface is responsible for their higher heat transfer rates. One can minimize this effect by the use of suitable radiation shields. Clearly, this effect has to be taken into account during scale-up. Differences exist in the design of laboratory and manufacturing freeze dryers that may affect atypical radia

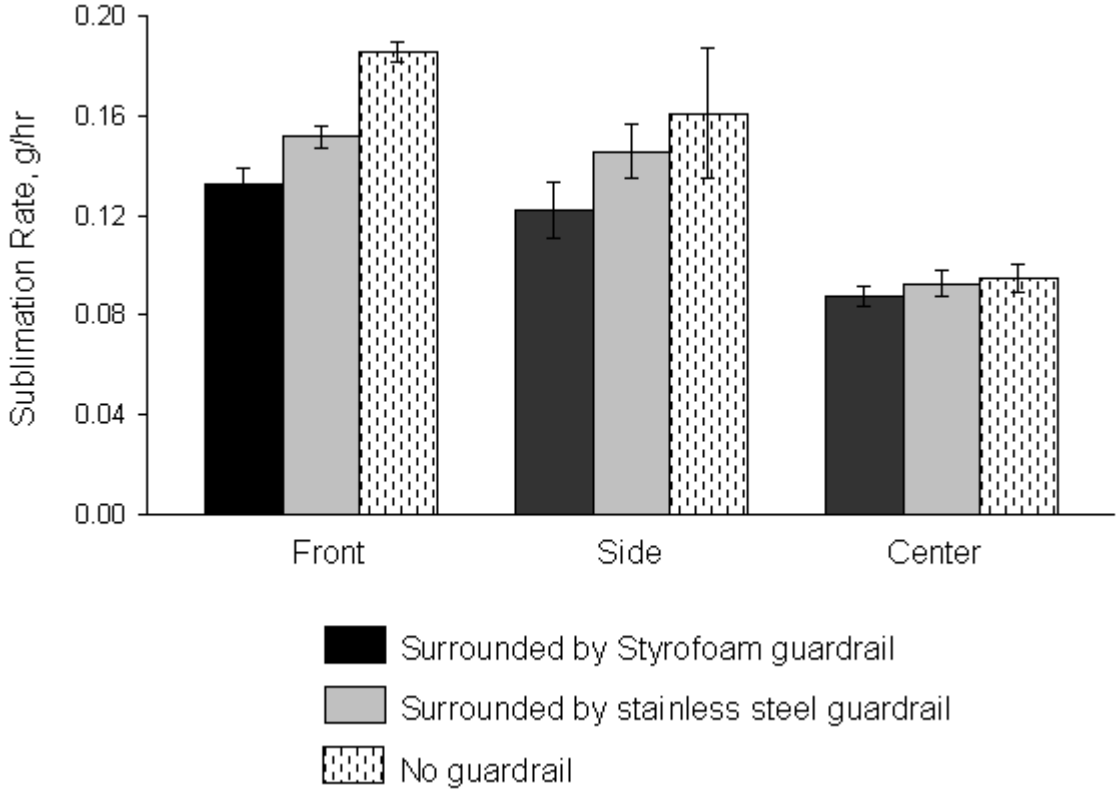

Figure 5. Effect of the guardrail. Sublimation rate data obtained (with shelf temperature –25°C and chamber pressure of 0.1 mmHg) for array of vials surrounded by Styrofoam guardrail, stainless steel guardrail, or no guardrail. Error bars represent standard deviations.

tion heat transfer. For example, with the front door being made of Plexiglas ($\varepsilon \approx 0.95$) for a laboratory freeze dryer and of steel ($\varepsilon = 0.36$) for a manufacturing dryer, and differences in surface temperatures, edge vials in manufacturing will behave differently than the corresponding vials in a laboratory dryer. While the intervial variability and the variability during scale-up cannot be eliminated, use of radiation shields in laboratory freeze-drying can make side and front radiation more like that in a production dryer. A quantitative determination of the relative contributions of various surfaces (eg, the chamber wall, the glass door) to this heterogeneity can help in achieving the process design objective to have similar product temperature profiles for both manufacturing and laboratory dryers. Future studies will focus on developing useful guidelines and algorithms to allow reliable scale-up of heat and mass transfer effects from laboratory to manufacturing scale.

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