Acceleration of Heat Transfer in Vial Freeze-Drying of Pharmaceuticals. II. A Fluid Cushion Device

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A simple device for the improvement of freeze-drying efficiency is described. The device is an aluminum foil bag which contains a small amount of glycerin. The device can be either reusable or disposable. When placed on a freeze-drying tray the liquid is about 1 mm thick. When vials are placed on the device it conforms to the shape of the vial bottoms. Since both the aluminum foil and the glycerin are better heat conductors than a vacuum, the device improves heat transfer from the shelf to the vial. Drying times obtained with and without the device are compared for different sizes as well as different types of vials. In most cases the use of the device reduces the drying time by nearly a factor of two. The use of the device also increases vial-to-vial uniformity and minimizes the effect of spillage.

KEY WORDS: freeze-drying; vials; heat transfer; fluid cushion device.

INTRODUCTION

Freeze-drying is generally the most expensive single-unit operation in the production of a lyophilized product and is a significant factor in the final cost of that product. For this reason, there is a continuing interest in the optimization of production freeze-drying cycles, that is, minimizing freeze-drying cycle times while providing a product of uniformly high quality.

Nail (1) argued that the temperature differences across the frozen product, across the glass at the vial bottom, and across the metal tray bottom are small, and therefore, the largest temperature differences or thermal resistances are across the intervening spaces between surfaces. A previous investigation (2) showed the feasibility of using a heat conducting device, namely, an aluminum quilt. By the use of this device, the thermal resistance of the intervening space is greatly reduced and a significant decrease in drying time is obtained due to better heat conduction.

Although the aluminum quilt offers several advantages, it is inefficient in some aspects. It is difficult to sterilize, and if it is improperly handled, accidental flattening of the device could result before use. It is not likely to be effective in eliminating the consequences of spillage and, in fact, may worsen them. This report describes an extremely efficient device to enhance the heat transfer from the shelf to the glass vial bottom.

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MATERIALS AND METHODS

Materials

Polyethylene layered aluminum foil was purchased so that it could be heat-sealed to form a bag. It has nylon and polyethylene layers on one side and only a polyethylene layer on the other side. This gives strength to the normally brittle aluminum foil to withstand the handling of the device during processing. The aluminum foil (Ludlo Corporation, LA) and the aluminum plate used were of commercial grade. The bags were 25 × 25 cm.

Reagent-grade glycerin (Burdick & Jackson Laboratories, Inc.) was purchased and was vacuum-degassed before use. One hundred milliliters of glycerine was placed in each bag, which was then heat-sealed through the glycerine to ensure that no air was entrapped.

Mannitol (Aldrich Chemical Co.) was used as received from the supplier. DSC analysis revealed a purity greater than 99 mol%. Glass-distilled water was used in the preparation of test solutions.

All the vials (Wheaton Glass Co.) used were of USP type I tubing or molded clear glass vials.

Preparation of the Device

Two layers of aluminum foil laminated with polyethylene were sealed together on four sides using a heat sealer, leaving a small opening for air/gas removal. The top side of the device was designed as shown in Fig. 1 for easy removal of air from the bag. Dissolved gases and air were removed from the glycerin as well as the bag sealing by applying vacuum for 24 hr. The bag was pressed between two flat plates to remove the excess glycerin and then the opening was sealed right through the glycerin to avoid the entrapment of air.

Drying Procedure

A Virtis model 15 SRC-3X freeze-dryer was used for this investigation. A 10% (w/v) aqueous mannitol solution was used for testing the device. Fill volume was 3 ml in a 10-ml molded clear glass vial. Only the middle shelf was used for this study. Half of this shelf was used for testing the device and the remaining half was used without the device. For each experiment, half of the vials were placed over the device and the rest of the vials were placed directly on the shelf. The shelf was used to its fullest capacity to simulate an actual production run. Thermistor probes were placed directly on the shelf as well as in the product touching the center inside bottom of vials. The probes were held in position inside the vials with probe holders. Thermal contact between the vial bottom and the shelf was improved by a perforated aluminum plate which was placed over the necks of the vials and then tightened to the flat aluminum plate inserted underneath the shelf.

The product was frozen to −40°C for 4 hr. The chamber was then evacuated to a predetermined pressure. The shelf temperature was increased to 5°C and was kept constant for all the experiments. The condenser temperature was −53 ± 3°C. When the product temperature merged with the shelf

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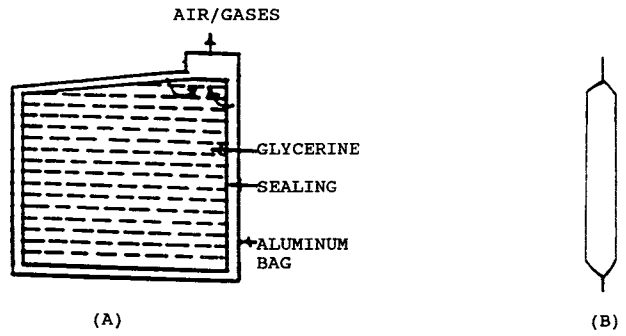

Fig. 1. Preparation of fluid cushion device. (A) Top view; (B) side view.

temperature, drying was terminated. The product temperatures and the shelf temperature were recorded on a Clearspan P600 strip chart recorder (Kent Process Control Inc.). All studies utilized six temperature probes and were run in duplicate with virtually identical results.

Weight Loss

For each experiment, four 10-ml clear molded glass vials were numbered and weighed after being filled with 3 ml of mannitol solution. The vials were then randomly distributed on a freeze-dryer shelf with the rest of the vials and were freeze-dried using the same procedure as described above. Since the freeze-dryer was not equipped with a sample thief assembly, drying was terminated at predetermined time periods. The vials were stoppered and then weighed immediately to minimize the effect of absorbed moisture. Additional sets of fresh samples were used for the determination of weight loss at each time period under the identical experimental conditions. This study was carried out with and without the device at a 20-μm chamber pressure.

Vial-to-Vial Uniformity

The thermistor probes were positioned at the center inside bottoms of a set of 10-ml glass vials to study the variability in heat transfer from the shelf to the product. The product was then freeze-dried the same way as before. The maximum temperature differences among the set of vials were calculated for the product dried with and without the device. To obtain a temperature profile for the maximum number of vials with a limited number of thermistor probe attachments, the product with the device was dried separately from that without the device.

Vial Size and Type

Drying times were also obtained for different sizes and different type of vials for the product with the device as well as without the device.

Effect of Spillage

In order to simulate the effects of an accidental spill, the surfaces above the device as well as the shelf were partially puddled with 25 ml of the test solution. Vials were placed over the spilled and also the nonspilled areas of the shelf and the device. The product was then freeze-dried as before while the shelf and product temperatures were monitored. The temperature differences were obtained for the vials placed over both the spilled area and the nonspilled area.

Comparison to a Liquid Conduction Medium

Flat-bottom aluminum boats were made using a thin aluminum foil. They were then filled with glycerin to achieve a thin fluid layer to cover the space between the vial bottom and the shelf top. Vials were carefully placed inside these glycerin-filled boats and were then freeze-dried using the same procedure as described earlier. The shelf and product temperatures were monitored to obtain a temperature profile.

Product Evaluation

Reconstitution time and cake appearance were noted after each experiment. Reconstitution time was measured in the following way: after the product was freeze-dried the vials were immediately stoppered and sealed. Three milliliters of distilled water was added to the inverted sealed vial using a syringe. The vial was inverted to avoid the initial contact of water with the freeze-dried product and to remove the needle. The product was then agitated on a roller test tube rotator at a controlled constant speed until completely dissolved as determined by visual observation. The reconstitution time obtained for the product dried with the device was compared to that without the device. Cake appearance and internal porosity were observed under an optical microscope (Olumpus Optical Co.) and a scanning electron microscope (Model DS 130, International Scientific Instrument).

RESULTS AND DISCUSSION

It is a well-accepted fact that the intervening space between the vial bottoms and the shelf is the major resistance to heat transfer in freeze-drying and that filling that space with a conducting medium will improve heat transfer and reduce drying time (1). Since vial bottoms are not uniform, it is not possible to design a solid shelf that will uniformly fill all of the void spaces. A simple device that facilitates heat transfer is described. This device conforms to the shape of the vials just as a water bed conforms to the shape of its occupant.

The fluid cushion device consists of glycerin contained in an aluminum foil bag. It is inexpensive, durable, flexible, easily sealed, and easily sterilized. A fluid is used so that the device can easily conform to the shape of a variety of vial sizes and types. Glycerin was chosen as the liquid because it has a low freezing point and a high boiling point. It will not evaporate under normal freeze-drying conditions. (Vaporization at very low pressures will cause expansion and bursting of the bags.) Also, its high thermal conductivity and heat capacity enable it to pick up and give off the required heat of sublimation without appreciable temperature change. Glycerin has the additional attributes of being nontoxic, nonflammable, noncorrosive, inexpensive, and water washable.

Theoretical Calculation

Figure 2 demonstrates that heat must be transferred from the heated shelf to the moving and subliming interface

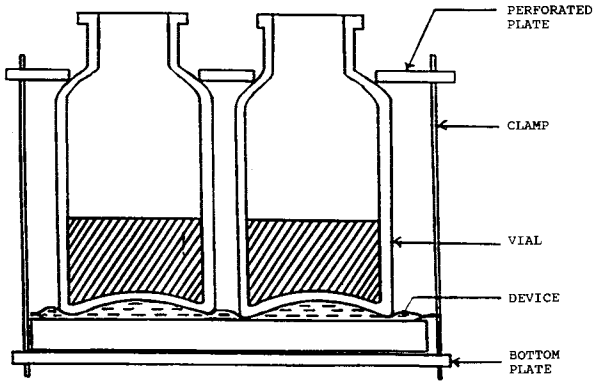

Fig. 2. Arrangement of vials inside freeze-drying chamber.

of frozen product through a series of resistances: the bottom of the glass vial, the frozen product layer, and the device (aluminum foil, glycerin, and aluminum foil in series). In the absence of the device the resistance due to the device (and the tray if present) is replaced by the resistance of the intervening gas phase. The total resistance, R_T, may be expressed as the sum of three terms:

$$R_T = R_g + R_v + R_s \quad (1)$$

where R_g is the gas phase resistance between the shelf and the vial bottom, and R_v and R_s are the resistances of the glass vial and frozen solution, respectively. In the case where the gas phase is replaced by the aluminum foil and a heat-conducting fluid such as glycerin, the term R_g in Eq. (1) is replaced by the sum of the resistances of the aluminum foil, R_a, and the fluid, R_l. Conductive heat transfer under steady-state conditions for each resistance is given by

$$Q = kA \frac{\Delta T}{X} \quad (2)$$

where Q (cal/hr) is the heat flow, k (cal cm^{-2} hr^{-1} °C) is the thermal conductivity of material, A (cm^2) is the area normal to the heat flow, ΔT (°C) is the temperature difference across the material, and X (cm) is the thickness of material. For unidirectional conduction through n parallel slabs of material where the cross-sectional area is constant, Eq. (2) can be written for each of these layers, and the overall temperature difference is expressed by

$$\Sigma_i \Delta T_i = (Q/A)(\Sigma_i X_i/k_i) \quad (3)$$

Table I. Convection Data

Parameter	Value
Viscosity (g cm^{-1} sec^{-1})	6.8300
Density (g cm^{-3})	1.0800
Kinematic viscosity (cm^2 sec^{-1})	6.3240
Thermal diffusivity (cm^2 sec^{-1})	1.0000
Coefficient of volume expansion (K^{-1})	0.0005
Gravitation constant (cm sec^{-2})	980.6650
Thickness of device (cm)	0.1000
Temperature difference (K)	6.2000
Rayleigh number	0.481×10^{-3}

Table II. Calculated Values of Thermal Resistances

Material	Thickness (cm)	Thermal conductivity (cal cm/cm^2 hr °C)	Resistance (cm^2 hr °C/cal)
Frozen solution	0.80	18.70	4.3×10^{-2}
Glass (vial)	0.24	9.40	2.6×10^{-2}
Glycerin	0.10	2.43	4.1×10^{-2}
Aluminum	0.01	2581.0	3.87×10^{-6}
Gas phase	0.11	—	1.08

where X_i/k_i is a measure of the resistance to heat flow, R_i.

$$\Delta T_T = q(\Sigma_i R_i) = qR_T \quad (4)$$

where $q = Q/A$ (cal cm^{-2} hr^{-1}).

Based on thermal conductivity values and thickness, one can calculate the resistance offered by each layer for the system with aluminum foil and glycerin. These values are included in Table I. The contribution of each of the three phases to the total heat flow resistance was calculated and is presented in Table II along with the reported values (1,3) of the gas phase system. Replacing the gas phase system with the heat-conducting fluid system, the resistance of the shelf-vial boundary is reduced by half. So an improvement in heat transfer can be accomplished by introducing a heat-conducting system in the intervening space.

Heat Transfer

The products with the fluid cushion device and without the device were freeze-dried in the same experimental run to avoid the interexperimental variations. The temperature profile obtained is presented in Fig. 3. Negative values are assigned to the freezing portion, while positive values are given to the drying portion of the time scale. In other words the imitation of drying is assigned $t = 0$. The shelf temperature, product temperature with the device, and product temperature without the device are presented as the upper, middle, and lower curves, respectively. It can be seen that

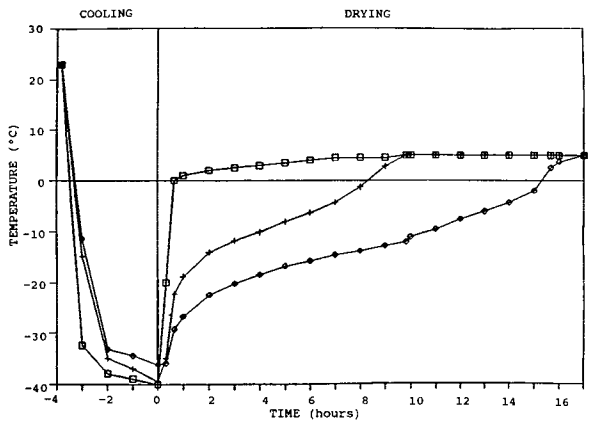

Fig. 3. Temperature profile for freeze-drying at 20-μm pressure. (□) Shelf; (+) product with device; (♦) product without device.

the product with the fluid cushion device cools faster and attains a lower freezing temperature in comparison to the product without the device. This pattern is completely reversed during drying, in which the product with the device achieves a higher temperature faster.

Drying Time

The merging of the product temperature curves with the shelf temperature curve is taken as the end point of the drying cycle. This criterion is based on the fact that, at the end of drying, no more water molecules are coming out of the product. Thus it requires no heat of sublimation and the product temperature reaches and remains constant at the shelf temperature. The product with the fluid cushion device dries in 10 hr, while without the device it takes as long as 17 hr. The drying time with the aluminum quilt is 10.5 hr (2).

Supercooling

An important piece of information missing from Fig. 3 is the supercooling effect observed during freezing of the solution. It is not included in the figure since the degree of supercooling observed was not consistent in all the product vials. This is due to the fact that the degree of supercooling is dependent on a number of parameters involving the product, container, and cooling process. The configuration of the container and defects, scratches, and other surface irregularities as well as particulate matter can serve to limit the degree of supercooling (4).

The degree of supercooling observed for the product with the device is consistently greater than that without the device. Since the product with the device is cooled faster, it does not allow enough time for the ice nuclei to grow into crystals at higher temperature. Thus crystal growth will be accomplished at a relatively lower temperature and a higher degree of supercooling is obtained.

Weight Loss

The weight loss data obtained during three time periods are presented in Table III. Data obtained at different chamber pressures without the device are included here for comparison. There is an increase in weight loss at any particular time period for the product with the device. The sublimation rate was also increased, with a consequent decrease in the drying time. The average temperature differences from the shelf to the product at the vial bottom, calculated by application of the linear trapezoidal rule, are also presented in Table III. It is true that the increase in weight loss obtained requires a higher amount of thermal energy, and so the average temperature difference between the product and the shelf should increase. In contrast, a decrease in the average temperature difference was obtained. This can be explained by Fourier's law, which states that

$$q = k \frac{\Delta T}{X} \tag{5}$$

where q, k, X, and ΔT are the heat flux, thermal conductivity, thickness, and temperature difference across the medium, respectively. With the increase in chamber pressure or introduction of the device, the thermal conductivity, k, of the intervening space is increased greatly. This will more than offset the decrease in the temperature difference, ΔT. Thus the resultant heat flux, q, across the intervening space will be increased much more than the sublimation heat required for increased weight loss. This surplus heat flux will increase the product temperature and a decreased temperature difference between the shelf and the product results.

Table III. Weight Loss Data for the Product with and Without the Fluid Cushion Device

Device/ pressure	T_{ave} (°C)[a]	Drying time (hr)	Weight loss after 5.5 hr (g)
Device	6.2	11.0	1.54 (0.278)[b]
P = 20 U	20.2	17.0	0.84 (0.155)
P = 200 U	17.2	13.0	1.33 (0.232)

[a] Average temperature difference from the shelf top to the shelf bottom.
[b] Sublimation rate (g/hr) after 5.5 hr in parentheses.

Vial-to-Vial Uniformity

The nature of the vial is an important variable in the freeze-drying process. Even though the direct effect of the vial on mass transfer via the closure resistance is not appreciable, the nature of the vial can significantly affect the rate of heat transfer to the product. The magnitude of variation in the vial heat transfer rate is sensitive to the configuration of the vial bottom. While the thickness of the glass in the vial bottom is not important, both the average separation distance between the vial bottom and the shelf and the degree of physical contact between the vial and the shelf are critical factors. It is true that large temperature differences in the vial heat transfer rate exist between different types of vials. Even vials of nominally the same specifications, manufactured by different suppliers, differ significantly in their heat transfer characteristics. A freeze-drying cycle, optimized using one type of vial, cannot be expected to perform satisfactorily with a different vial. Situations may arise in which a product routinely freeze-dried with an excellent yield results in significant product loss due to eutectic melt with the change in bulk vial supplier (5).

Uniformity of Drying. Results of the nonuniformity in heat transfer from the shelf to the product at the inside center of the vial bottom, among the set of vials, are presented in Fig. 4. Maximum product temperature differences obtained among the same lot of vials with and without the device are plotted against time. The temperature difference is plotted only up to 3 hr, as the product temperature ultimately becomes constant with the shelf temperature. In actual practice the shelf temperature is decreased at a constant rate with automatic controls. The temperature variation observed without the device is significantly greater than that observed with the device. Since drying is carried out under vacuum and cooling is not, the distance between the two curves is greater for drying than for cooling. Also, the device is equally effective during freezing as well as drying (identical vertical distances), indicating near-perfect contact of the device with the vial bottoms. Therefore it is concluded from

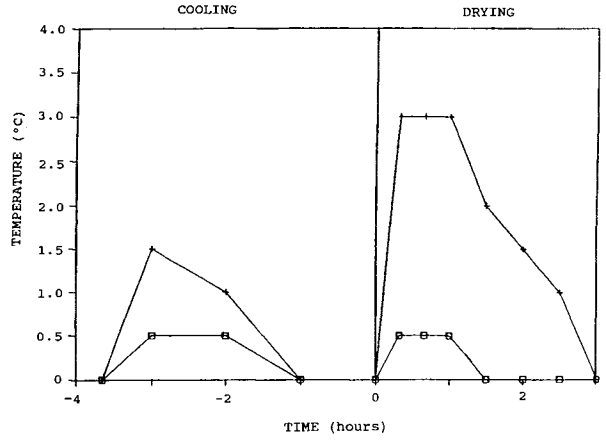

Fig. 4. Interval variation in product temperature. (□) Product with device; (+) product without device.

this study that more even heat transfer can be accomplished by the use of the device. It is likely that nonuniformity in heat transfer among the vials manufactured by different suppliers or of different lots can also be reduced by use of the device.

Vial Size and Type. The device was tested for different sizes and different types of vials and the data obtained are listed in Table IV. The intervening space created between the concave vial bottom and the flat shelf was measured. This was done by filling the space on the vial bottom with modeling clay and removing the excess by pressing the vial bottom against a flat surface. To account for variations caused in the drying time by the use of different sizes of vials, the ratio was obtained by dividing the drying time without the device by that with the device. The drying time ratio increased with an increase in vial size. Since the concavity of the vial bottom increases with the increase in vial size, there is an increase in the importance of space on the vial bottom with an increase in vial size. The drying time without the device increased more in comparison to that with the device, indicating increased efficiency of the device with large vials.

Data for tubing vials are also presented in Table IV. Although the device is equally effective in filling the space at the bottom of the tubing or molded vials, the drying time ratio is less for tubing vials in comparison to the identical size molded vials. Vials manufactured from tubing are generally superior to molded ones, as they have relatively uniform and flat bases. Therefore the importance of the space on the vial bottom is decreased. This decrease in importance corresponds to a smaller decrease in drying time for the product with the device, and so the drying time ratio decreases. But judicious use of these vials is required, as they are more expensive, less resistant to thermal or physical shock, and more prone to breakage and spillage (6).

Table IV. Effect of Size and Type of Vials on Drying of the Product with and Without the Fluid Cusion Device

Vial size (cm^3)	Relative volume, intervening space (g)	Drying time: With device (A; hr)	Drying time: Without device (B; hr)	Ratio (B/A)
10[a]	0.25	11.0	17.0	1.55
10[b]	0.20	10.0	14.0	1.40
20[a]	0.43	15.2	25.0	1.65
30[a]	0.98	14.7	26.7	1.82

[a] Molded vials.
[b] Tubing vials.

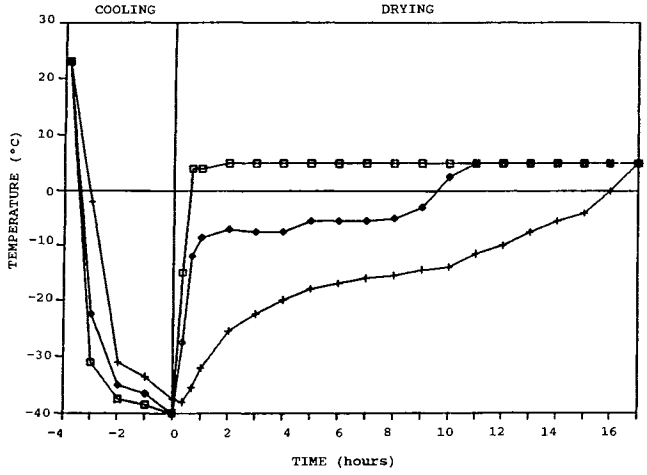

Fig. 5. Influence of spillage on freeze-drying temperature profile without the device. (□) Shelf; (+) vial placed on nonspilled area; (♦) vial placed on spilled area.

Effect of Spillage

One of the commonly encountered problems of the freeze-drying process is the spillage of solution over the surface containing the vials due to improper filling or handling of vials. If this spilled solution is not properly wiped out, it could cause uneven heat transfer from the shelf to the product at the vial bottom. To check the efficiency of the device in alleviating this problem, a simple spill experiment was carried out. The data obtained for the vials placed on the spilled and the nonspilled areas with and without the device are presented in Figs. 5 and 6. The vials placed in the spilled area freeze and dry much faster compared to those placed on

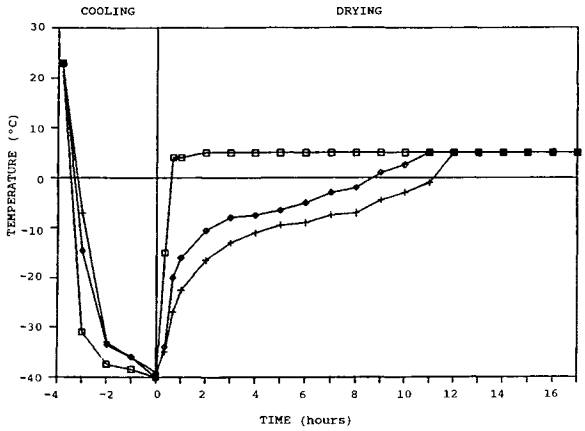

Fig. 6. Influence of spillage on freeze-drying temperature profile with fluid cushion device. (□) Shelf; (♦) vial placed on nonspilled area; (+) vial placed on spilled area.

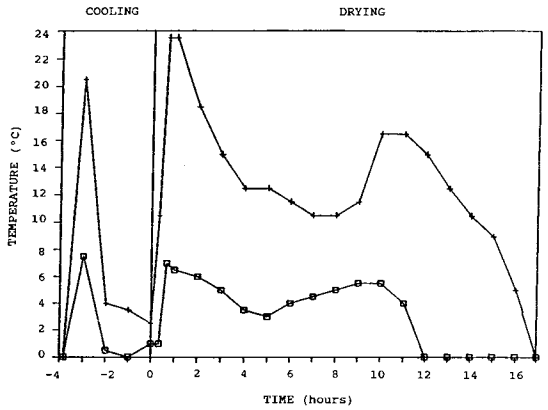

Fig. 7. Spill experiment with and without fluid cushion device. (□) Product with device; (+) product without device.

the nonspilled area without the device. With the device the freezing portions of both the curves are almost identical and also the nonuniformity caused by the spilled solution during drying is considerably reduced. The temperature differences between the vials placed on the spilled area and those on the nonspilled area were calculated for the vials dried with or without the device and are plotted against time as shown in Fig. 7. By use of the device the temperature difference is greatly minimized during freezing as well as drying. The fluid cushion device essentially removes or does not allow the spilled solution to remain underneath the vial. The aluminum quilt, described in previous investigation (2), will make the problem worse, as it entraps the spilled solution between the device and the vial bottom.

Comparison to Liquid Conduction Medium

The purpose of the boat experiment was to check how well the device makes contact with the vial bottom as compared to the vials in direct contact with glycerin. Only a slight decrease in drying time (half an hour) was observed. This decrease may be due to the contact made by the excess glycerin in the boat with the outside of the vial wall. This study suggests the near-perfect contact of the device with the vial bottom.

Product Evaluation

In all cases, the resultant freeze-dried cake was white and uniform in color, approximately the same shape and size as the solution. The cake was observed under the optical and scanning electron microscope for the appearance and quality of the product. No wet spot or observable difference in quality between the product dried with and that dried without the device was detected. The cake was reconstituted by adding water, but no measurable difference in reconstitution time was observed.

CONCLUSION

The fluid cushion device has been shown to increase the heat transfer from the shelf to the vial bottom by filling up the intervening space, thereby reducing the freezing and drying times. Also, it provides greater vial-to-vial uniformity. In contrast to the aluminum quilt, it offers easy sterilizability and physical stability and reduces the consequences of spillage. It is likely that the fluid cushion device will also increase the intravial and the batch-to-batch uniformity.

REFERENCES

1. S. L. Nail. The effect of chamber pressure on heat transfer in the freeze-drying of parenteral solutions. *J. Parent. Drug Assoc.* 34:358–368 (1980).
2. S. D. Patel, B. Gupta, and S. H. Yalkowsky. Acceleration of heat transfer in vial freeze-drying of pharmaceuticals. I. Corrugated aluminum quilt. *J. Parent. Sci. Technol.* 43:8–14 (1989).
3. J. H. Perry. Chemical Engineer's Handbook, McGraw–Hill, New York, 1973, pp. 242–245.
4. T. A. Jennings. Optimization of the lyophilization schedule. *Drug Cosmet. Indust.* 127:43–52 (1980).
5. M. J. Pikal, M. L. Roy, and S. Shah. Mass and heat transfer in vial freeze-drying of pharmaceuticals. *J. Pharm. Sci.* 73:1224–1237 (1984).
6. N. A. Williams, Y. Lee, G. P. Polli, and T. A. Jennings. The effects of cooling rate on solid phase transitions and associated vial breakage occurring in frozen mannitol solutions. *J. Parent. Sci. Technol.* 40:135–141, (1986).