Vial Lyophilization: Calculations on Rate Limitation During Primary Drying

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Purpose. The aim of this study was to assess the rate limiting factors in the sublimation phase of freeze drying and to propose a simple model on the basis of these rate limitations. *Methods.* A programmable freeze dryer was used. The load consisted of vials of varying size and various contents. To increase heat transfer, conductive paste was applied while the resistance toward mass transport was varied by using different restrictive capillaries. *Results.* It was found that heat transfer limits the rate of sublimation. Presence of the commonly used excipient mannitol did not have a consequence on the rate of sublimation. The same applied for the restrictions towards mass transport. It was found that there exists not only a barrier against heat transport under the vial, but also between the glass wall and the frozen solution. *Conclusions.* From the results, a set of equations is proposed that enables to predict optimum sublimation conditions. For the pharmaceutical technologist this can serve as a simple and useful tool to derive a suitable freeze drying program.

KEY WORDS: freeze-drying; intervening space; optimum pressure; heat transfer; mass transfer.

INTRODUCTION

Freeze-drying or lyophilization is a process whereby water vapor is removed by sublimation from a frozen material at low pressure. The freeze-drying process can be divided into three successive stages: freezing, primary drying, secondary drying. After freezing the product, the pressure is lowered and heat is supplied to provide energy for sublimation during the primary drying stage. During the secondary drying stage the residual moisture, absorbed in the product, diffuses through the dried material.

Freeze-drying has several advantages over other drying processes based on the low temperature character and the favorable pharmaceutical properties of the products. However, the disadvantage is that the process is time consuming and expensive. For this reason, studies on lyophilisation have often been focussed on rate limitation aspects.

Sublimination comprises heat and mass transfer. Pikal (1) proposed that heat transfer takes place by a) direct conduction from the shelf to the vial via points of direct contact between the vial and shelf, b) conduction through the gap between the vial bottom and the shelf, and c) radiative heat transfer. Pikal (1) and Nail (2) demonstrated that the amount of heat transfer is not only controlled by a temperature difference but also by the pressure in the chamber. As the heat conductivity increases with the pressure, a higher chamber pressure shortens the drying time. This means that a significant rate limiting resistance to conductive heat transfer is formed by the gas phase under the vial resulting from lack of intimate contact between the heat source and the product (2). Wolff and Gilbert (3), as well as Yalkowsky and Patel (4,5), confirmed this and proved that the air gap controls the drying kinetics to a large extent.

The sublimation rate may also be limited by mass transfer. Pikal suggested that mass transfer is impeded by three barriers: the dried product layer, the stopper on the semi-stoppered vial, and the chamber to condenser pathway (1,6). The dried product resistance would be the most important controlling factor for the drying rate at a fixed temperature. Since the rate of freezing effects the size of the ice crystals it determines the size of the resulting pores in the material. Generally, the resistance in the dried layer is lower when the size of the pores is bigger (7).

The objective of this study was to determine and to quantify the rate limiting resistances during primary drying. After determining the controlling factors, a model for the sublimation is presented, which can be used to determine the optimum sublimation conditions at a given temperature.

MATERIALS AND METHODS

A Leybold GT 20 freeze dryer was used. This fully automated and programmable apparatus has a total shelf surface area of 0.81 m^2 and a condenser capacity of 20 kg. The condenser is placed in a separate chamber which is connected to the cabinet by a valve. The condenser can be cooled to about −75°C while the temperature of the shelves can be varied from −50°C to 80°C. Experimental data are plotted by a recorder.

The experiments were carried out in 2, 5, and 10 ml type I glass vials. Vials were filled to different fill heights. Vials with and without a neck (open vials) were used and filled with demineralized water or mannitol solutions. As mass transfer barrier, chlorobutyl PH 4104/45 (Pharma Gummi) closures with an opening of 3 mm, or glass capillaries with diameters of 2.71, 2.17, or 1.15 mm were used. On each vial a 1 cm long capillary was fixed with Parafilm (American National Can) in such a way that no gas could flow along the capillary. The gap under some vials was filled with Dow Corning® 340 Heat Sink Compound from Mavom Ltd. This is a paste consisting of a silicon compound with metal oxides. It has a large heat conductivity compared to air, namely 0.42 W/mK versus 0.016 W/mK (at 60 Pa and 0°C).

For each fill height three vials were numbered and weighed. The vials were placed directly on the shelves without having contact with each other. The total load of the freeze dryer was below hundred vials which means that the mass transport is not influenced by limitations in the chamber or valve. The shelves were cooled to −40°C in two hours and kept at this temperature for at least two hours after the contents of the vials were totally frozen. The condenser was cooled to −75°C before evacuation. After having reached the vacuum set point, the shelves were heated to 40°C in two

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hours time. The vials were dried at various chamber pressures, namely 2.5, 12, 19, and 30 Pa.

The process was terminated by breaking vacuum after a predetermined time after which the vials were reweighed. The experiments were repeated for different periods of drying. From the weight loss at various intervals, the sublimation rate was calculated.

RESULTS AND DISCUSSION

Table I presents the sublimation rate for vials filled with varying amounts of water at different pressures. The results show that the sublimation rate increases with the pressure, which confirms Pikal's and Nail's findings. The sublimation rate also increases with the fill height and the diameter of the vial (larger vials have a bigger diameter). This is obviously a consequence of Fourier's law which states that heat flux is proportional to the surface area. Increasing the height or diameter increases the area over which heat transfer takes place. From this it can be deducted that heat transfer takes place not only through the bottom of the vial but also along the vial wall.

Figure 1 shows some representative drying graphs of vials with and without contact paste. As a result of increased heat transfer, the initial sublimation rate increases dramatically. This confirms that the gap under the vial indeed forms a great resistance against heat transport. However, remarkably the sublimation rate slows down until it obtains a comparable value to the vials without contact paste. Because water without further solute was used, it was easy to observe the sublimation front. A very important observation was that the sublimation interface not only sinks but also moves from the vial walls to the center. This means that a gap between the frozen mass and the vial wall develops during sublimation causing a new resistance toward heat transfer. This gap is filled with vapor which has a lower heat conductivity than ice, namely 0.016 W/mK at 0°C and 60 Pa (8) versus 2.1 W/mK (9). A direct implication is that the heat transfer route obviously changes during the cycle. Initially, heat is transferred along the vial directly from the glass wall to the ice causing a high sublimation rate as shown in the left side of Figure 1. After formation of a gap between the ice mass and the vial wall, a new resistance develops causing the sublimation rate to decrease. One can speculate from this that the resistances toward heat transport are situated in the vial instead of under the vial. However, a gap under the frozen mass has not been visually observed.

Table I. Sublimation Rate (mg/min) for Vials with Different Fill Heights (H)

Vial (ml)	Vapour Pressure (Pa)	Φ_m (mg/min) H = 1 cm	Φ_m (mg/min) H = 2 cm	Φ_m (mg/min) H = 3 cm
10	2.5	7.8 ± 0.1	8.5 ± 0.1	11.9 ± 0.1
5	2.5	4.8	5.8	8.5
2	2.5	2.9	5.7	—
10	12	11.2	15.9	19.0
5	12	6.2	10.5	12.3
2	12	5.1	9.1	—
10	30	11.9	18.6	21.6
5	30	7.9	12.6	15.5
2	30	4.6	9.0	—

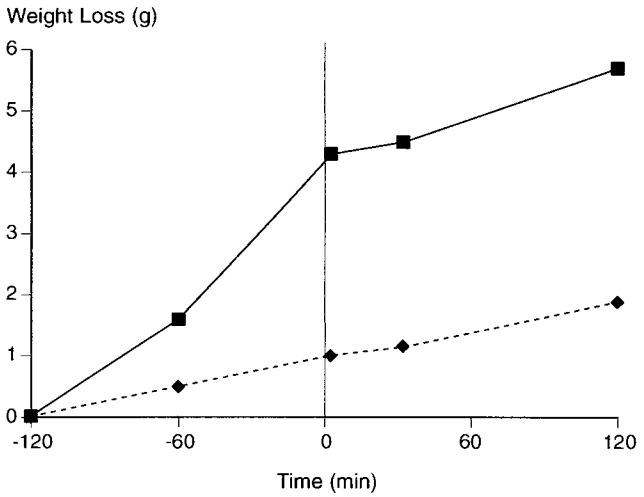

Fig. 1. Weight loss versus time for 10 ml vials filled with water to a fill height of 2 cm with (■) or without (◆) the use of contact paste at a pressure of 2.5 Pa. Shelf temperature increased from −40 to +40°C (zero time) after which the temperature was maintained at 40°C.

Figure 2 shows the weight loss of ice in vials on which capillaries of different sizes have been placed. The parallel lines at equilibrium indicate that the sublimation rates in vials with different restrictions are equal to the sublimation rates in open vials. Clearly mass transfer is not rate limiting in this region. However, during the start up phase, while heating the shelves from −40 to 40°C, the sublimation rate of a vial with a smaller restriction is lower. This phenomenon might be explained by the fact that the pressure in a partially closed vial is slightly higher than in an open vial. The smaller the restriction, the higher the sublimation pressure and consequently, the higher the sublimation temperature. As a result, the temperature difference ($T_{shelf} - T_{subl}$) is also

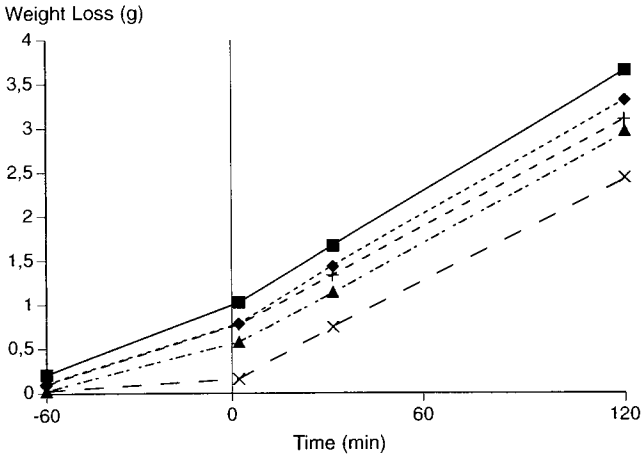

Fig. 2. Weight loss versus time for 10 ml vials filled with water to a fill height of 3 cm and stoppered with a rubber closure (+) or a capillary with a diameter of 2.71 mm (◆), 2.17 mm (▲) or 1.15 mm (×), respectively. As reference, a vial without a neck (■) was used. Zero time is the moment at which the shelves reach the setpoint value of 40°C.

slightly reduced. As the temperature difference is the driving force for heat transfer, the increase in the sublimation temperature results in a smaller heat transfer. At the beginning of the process the temperature difference is small because of the low shelf temperature and a change in the sublimation temperature has a relatively large influence. When the shelf has nearly reached its maximum temperature however, this effect is neglectable on the temperature difference.

The sublimation rate of the frozen solutions appeared not to differ significantly from the sublimation rate of ice. Contrary to Pikal's findings, a thicker dried layer or a more concentrated solution does not exhibit a lower sublimation rate. The dried layer is, therefore, obviously not rate limiting. There exist, however, some differences in the initial phase where the amount of ice sublimated is larger for pure water. In fact, this is a comparable situation as that while using capillaries. In this case the dried cake is to be regarded as an assembly of minute capillaries.

From the conclusion that the speed of sublimation is only limited by heat transfer with main thermal resistances being the gaps around the frozen solution, it is possible to propose some general equations which enable to do rather simple but very useful calculations. This model applies when the temperature is constant, *i.e.*, at equilibrium. The following assumptions apply:

all the energy transported is used for sublimation;
all energy is transferred by conduction;
mass transfer limitation is neglectable, *i.e.*, heat transport is the rate limiting factor;
the sublimation temperature is the temperature corresponding to the vapor pressure in the chamber as presented in the P-T diagram of water.

Heat flux can be described by Fourier's law. Heat transfer takes place along two routes.

Route 1 is from the shelf through the gap under the vial (gap 1), through the glass bottom and the ice mass. The resistances encountered are therefore the resistance of gap 1 ($R_{gap,\ 1}$), the glass bottom (R_{glass}) and the ice mass (R_{ice}). Thus, heat transfer along route 1 is given by:

$$\Phi_{h1} = \frac{A_1(T_{shelf} - T_{subl})}{R_{ice} + R_{glass} + R_{gap,1}} \quad (1)$$

Route 2 is from the shelf to the vial wall. This heat is transferred from the glass wall through the gap between the vial and the ice (gap 2) to the product. The resistances encountered are, therefore, the resistance of the glass wall (R_{wall}), the resistance of gap 2 ($R_{gap,2}$) and the resistance of the ice mass (R_{ice}). Heat transfer along route 2 is given by:

$$\Phi_{h2} = \frac{A_2(T_{wall} - T_{subl})}{R_{ice} + R_{glass} + R_{gap,2}} \quad (2)$$

The total heat transfer is the sum of Φ_{h1} and Φ_{h2}:

$$\Phi_{h,total} = \Phi_{h1} + \Phi_{h2} \quad (3)$$

The sublimation rate (Φ_m) is calculated by dividing Φ_h by the sublimation enthalpy:

$$\Phi_m = \frac{\Phi_{h,total}}{\Delta H_s} \quad (4)$$

The surface area's, A_1 and A_2, can be calculated with the following equations:

$$A_1 = \pi r^2 \quad (5)$$

$$A_2 = 2\pi r h_{water} \quad (6)$$

The resistances of ice and glass can be calculated with the following equations:

$$R_{ice} = \frac{h_{ice}}{\lambda_{ice}} \quad (7)$$

$$R_{glass} = \frac{d_{glass}}{\lambda_{glass}} \quad (8)$$

The resistances of gap 1 and 2 are dependent on the flow condition. The resistance of the gap under the vial is a function of the pressure in the gap and the free molecular heat conductivity (λ_0) as long as free molecular flow applies.[3]

$$R_{gap} = \frac{1}{\lambda_0 P} \quad (9)$$

However, when transition flow or viscous flow applies, the resistance is a function of the depth of the gap and the heat conductivity of the vapor (λ_{vapor}).

$$R_{gap} = \frac{d_{gap}}{\lambda_{vapor}} \quad (10)$$

When viscous flow applies, this heat conductivity is nearly constant and is equal to the heat conductivity at 1 atm., which is 0.02 W/mK.

Knowing that there is no conductive heat transport at 0 Pa and knowing that the heat conductivity increases linearly with the pressure when molecular flow applies, the heat conductivity can be calculated as a function of pressure. In this report it is assumed that the heat conductivity is also linear to the pressure when transition flow applies. The following equation represents the heat conductivity and is calculated by interpolation between the two points mentioned above.

$$\lambda = 2.748 * 10^{-4} P_{vapor} \quad (11)$$

The depth of the gap under the vial can be estimated, whereas the depth of the gap between the vial wall and the ice changes during the process. Visual observations pointed out that the depth increases with the pressure. After filling all known parameters and experimental data in the model, the average depth of the gap between the ice and the vial wall

[3] There are three types of flow: viscous, transition, and molecular flow. The type of flow is determined by the mean free path of the molecule (L) in the gas phase and the dimensions of the space causing the resistance (a). The ratio L/a is called the Knudsen number. When the mean free path is large compared to the dimensions of the system, collisions of molecules with the surrounding walls are more frequent than collisions between the molecules. This is the case with molecular flow. When collisions between the molecules are responsible for the resistance, the flow mechanism is said to be viscous. Transition flow is the less well defined flow region which literally forms a state between molecular and viscous flow.

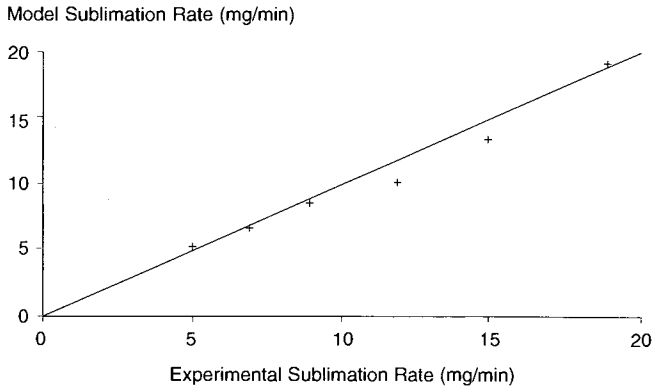

Fig. 3. Correlation between the calculated data and the experimental data for the sublimation rate from various types of vials at a pressure of 19 Pa and a shelf temperature of 40°C.

($d_{gap,2}$) was calculated for two different pressures. These two points were used to derive the following equation:

$$d_{gap,2} = 1.3*10^{-5}P_{vapor} + 1.6*10^{-4} \quad (12)$$

To evaluate this equation the experimental sublimation rates were compared to calculate sublimation rates at a vapor pressure of 19 Pa and at a shelf temperature of 40°C. As can be seen in Figure 3, the sublimation rates calculated are nearly equal to the experimental values, which is in fact a logical consequence of fitting the data.

The model can be used to calculate optimum freeze drying conditions. Figure 4 shows the calculated sublimation rate as a function of pressure. As can be seen, the sublimation rate reaches an optimum. This is a result of the two counteracting parameters involved. Increasing pressure yields a lower resistance toward heat transport. However, simultaneously, the sublimation temperature increases, which does actually mean that the driving force for heat transport drops.

In conclusion, the results point out that in the given set-up sublimation rate is only limited by heat transfer. The greatest resistances toward heat transfer are the gaps under the vial and between the ice mass and the vial wall, respectively. From this, a simple model has been derived which enables the calculation of the sublimation rate at any pressure and shelf temperature.

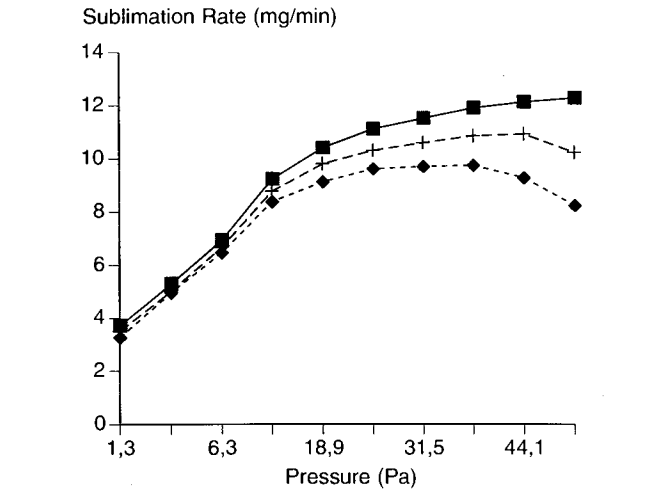

Fig. 4. Sublimation rate versus the pressure for a 5 ml vial filled to a fill height of 2 cm applying a shelf temperature of 0°C (◆), 20°C (+) or 40°C (■), respectively.

ABBREVIATIONS

A	area (m^2)
d_{gap}	depth of the gap (m)
$d_{gap,1}$	depth of the gap under the vial (m)
$d_{gap,2}$	depth of the gap between ice and vial wall (m)
d_{glass}	thickness of the glass wall (m)
ΔH_S	sublimation enthalpy of ice (J/kg)
P	pressure (Pa)
P_{vapor}	vapor pressure in the chamber (Pa)
$R_{gap,1}$	resistance of the gap under the vial (m^2K/W)
$R_{gap,2}$	resistance of the gap between ice and vial wall (m^2K/W)
R_{ice}	resistance of the ice (m^2K/W)
R_{glass}	resistance of the glass wall (m^2K/W)
r	radius of the vial (m)
t	time (s)
T_{shelf}	shelf temperature (°C)
T_{subl}	sublimation temperature (°C)
T_{wall}	temperature of the vial wall (°C)
λ	heat conductivity (W/mK)
λ_0	free molecular heat conductivity (J/m^2sKPa)
Φ_{h1}	heat transfer through the bottom of the vial (J/s)
Φ_{h2}	heat transfer from the vial wall to the ice (J/s)
$\Phi_{h,\,total}$	total heat transfer (J/s)
Φ_m	sublimation rate (kg/s)

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