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Freeze-drying and solubility studies

Patel, Suresh Dahyabhai, Ph.D.
The University of Arizona, 1988
FREEZE-DRYING

AND

SOLUBILITY STUDIES

by

Suresh Dahyabhai Patel

A Dissertation Submitted to the Faculty of the
DEPARTMENT OF PHARMACEUTICAL SCIENCES
In Partial Fulfillment of the Requirements
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1988
As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Suresh Dahyabhai Patel entitled FREEZE-DRYING AND SOLUBILITY STUDIES and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

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Dissertation Director 2-11-88

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SIGNED: Suneel D. Patel
To my parents
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ABSTRACT

The medium offering the greatest resistance to heat transfer from the freeze-drying shelf to the moving and subliming surface is the space between the flat shelf top and the concave vial bottom. The resistance to heat transfer can be greatly reduced by improving the thermal conductivity of the intervening space. Several heat transfer augmentation devices, including a multilayered corrugated aluminum quilt and a conformable fluid cushion device, which fill this gap are described.

The devices are inexpensive and easy to use. Experimental data show that the resistance of the intervening space is reduced appreciably and the drying rate is greatly increased. The fluid cushion device is superior to the aluminum quilt as it reduces the consequences of spillage of solution and provides greater interval uniformity among the same batch of vials. Drying times obtained in experiments with and without the fluid cushion device are compared here for different sizes and different types of vials. Product evaluation is conducted by measuring the reconstitution time and observing the product under a microscope.
The solubilities of two univalent electrolytes, sodium chloride and potassium chloride, have been measured in eight cosolvent-water binary systems. The solubility of both the solutes has been found to be adequately described by the log-linear solubility equation, \( \log S_m = \log S_w + f \eta \). The rank order of the desolubilization slopes obtained for the electrolyte solutes is compared with the solubilization of nonelectrolyte solutes. These results indicate that a cosolvent which is most effective in solubilizing a nonelectrolyte is also most effective in desolubilizing an electrolyte.

The solubility of oxacillin sodium in methanol-water mixtures has been determined at various temperatures ranging from +21 to -26 degrees centigrade. The data has been fitted to the log-linear relationship as proposed by Yalkowsky et. al. The heat of solution is determined using the van't Hoff equation and was found to be nearly constant at 1.2 Kcal/mole. There appears to be no dependency of the slope of the \( \log S_m \) vs. fraction cosolvent plot to the temperature. The data suggests that there is a polymorphic or amorphic transition of oxacillin at -14.5 degrees centigrade.
CHAPTER 1

INTRODUCTION

Drying of materials in order to preserve stability has been in use since the early ages of mankind. Undoubtedly, the first attempts involved the sun drying of food. From a historical standpoint the process of freeze-drying, often referred to as lyophilization, received its initial thrust during World War II when whole blood and blood plasma became lifesaving necessities, and adequate supplies were jeopardized because of stability and shipping problems. Soon after World War II, the pharmaceutical industry began considering the process for the preparation of sterile injectable dosage forms which could not be formulated into stable solutions. At the same time the food industry began employing freeze-drying to process and package foods, an application that continues to grow. Another application that has been receiving research attention is the preservation of biological substances, especially those of high value or in short supply. Vital organs and tissues are also preserved by freeze-drying.

Substances that degrade in solution are candidates for freeze-drying. This is superior to storage of the product in a deep-frozen state which presents
solubility problems, is costly, and always has the risk of degradation. Often, freeze-drying offers the only means to stabilize the product and of course shipment and storage of dry material is less expensive than that of a solution.

Although there are those who would consider freeze-drying only as the last resort, there are others who view it as a panacea - a way to get into clinical trials quickly or a way to exclude contaminants and inert particles, especially in comparison with powder filling. Certainly, freeze-drying does offer the advantage over powder filling for dosage accuracy, since the drug is filled into the final container as a solution. Microgram quantities can be filled precisely. Powder filling is used where the required dosage is represented by a large quantity of the drug or where the solubility is not adequate to freeze and sterilization of the powder is possible prior to filling.

THEORETICAL CONSIDERATIONS

Freeze-drying is a process of drying in which water is sublimed from the product after it is frozen. There are four conditions which are essential to the practical freeze-drying technique.

(1) The product must be solidly frozen below its eutectic point.
The freeze-drying system (figure 1.1) generally has six basic components: the vacuum drying chamber (3) containing a shelf (1) that is refrigerated or heated to cool or heat the product (2), a compressor (4) to circulate the refrigerant through pipes within the shelf and to chill the condenser (5) surface to convert water vapor to ice (6), a vacuum pump (7) to evacuate the chamber.

**PROCESS OF FREEZE-DRYING:**

The freeze-drying process can be divided into five stages: sample preparation, freezing, primary drying or ice sublimation, secondary drying or water desorption, and stoppering. The five stages are described below.

**Sample Preparation:**

Sample preparation involves several steps—
(a) dissolving the drug and excipients in a suitable
solvent, generally water;
(b) sterilizing the bulk solution by passing it through a bacteria-retentive filter; and
(c) filling the bulk solution into individual sterile containers (usually vials), and then partially inserting the stoppers into the vial necks (semistoppered position), such that openings for vapor flow are present.

Freezing:

The freezing stage involves the cooling of the solution at a temperature below its lowest eutectic temperature (i.e. temperature of complete solidification). Freezing of the solution is most conveniently accomplished in the chamber to be employed for drying, by placing the containers of solution on a shelf that is cooled by a circulating refrigerant. During the freezing stage, the material is cooled until it is completely frozen.

Primary Drying:

The primary drying stage involves the sublimation of free ice from the product, usually accomplished by reducing the pressure in the drying chamber and providing heat to the product. In this stage:
(a) Heat is transferred from the shelf to the frozen product and conducted to the drying surface (ice
interface).
(b) The ice sublimes and the water vapor formed passes through the dried portion of the product to the surface.
(c) The water vapor is transferred from the surface of the product through the chamber to the condenser.
(d) The water vapor condenses on the condenser.

Secondary Drying:

The secondary drying stage involves the removal of bound water from the frozen product. This is the water which did not separate out as free ice during freezing, and so did not sublime. To accomplish the removal of this water, the product temperature is usually raised and the chamber pressure reduced further. The product is usually processed until there is less than 1% moisture left in the dried product.

Stoppering:

After completion of the drying cycle, a hydraulically operated plate or an expandable rubber diaphragm presses the closures firmly into the neck of the vials and seals them under vacuum.

MECHANICS OF FREEZE-DRYING:

The mechanics of a freeze-drying process may be explained briefly by using a simple binary phase diagram of a drug in water as shown in figure 1.2. The freezing
point of pure water is designated by G; H corresponds to the melting point of the pure drug. The lines GC and HC show the temperatures at which solutions of various compositions are in equilibrium with pure solid water and pure solid drug, respectively. The horizontal straight line is the temperature below which no liquid phase exists. It is instructive to consider what happens when solutions of various concentrations are cooled and dried during the freeze-drying process. On cooling a solution (initially at point A) during the freezing stage, as the temperature falls, a temperature (point B) is ultimately reached when ice starts to form. As the temperature progressively falls (point B to C), more ice comes out of solution and the remaining solution, referred to as "interstitial fluid" (Rey, 1964), becomes more concentrated with the solute drug. A concentration of drug is eventually reached where the remaining solution of drug and water freezes as a mixture (point C). The concentration of drug at this point is known as the eutectic concentration and the temperature at which total solidification of this mixture occurs, the eutectic temperature. The total composition of the frozen product at this stage is denoted by point D.

During the primary drying stage, the system is evacuated and the shelf temperature is increased so as to
keep the product temperature at the inside container bottom a few degrees below the eutectic temperature of the product to avoid "meltback" (i.e. a change from the solid to the liquid state). As more water is removed from the product, the composition of the product will be decreased from that of point D. Primary drying is continued until point E is reached. The primary drying stage usually accounts for approximately 95% of the total water to be removed and about 80% of the drying time.

Secondary drying which involves the removal of bound water is started once the composition reaches point E. The product temperature is raised to point F and drying is continued until the desired amount of moisture is left inside the product. The temperature to which the product is raised during secondary drying depends on the thermal characteristics of the frozen product. This stage of drying accounts for the remaining 5% of water and 20% of drying time.

ECONOMIC FACTORS

As a rule, freeze-drying produces the highest quality product obtainable by any drying method. However, freeze-drying is an expensive form of dehydration of foods and pharmaceuticals because of the slow drying rate and the use of vacuum. Thus, the major disadvantage of freeze-drying relates to energy costs and the lengthy
drying times encountered.

Energy costs are high because the material to be dried must first be frozen, followed by freeze-drying proper where heat must be supplied to sublime the ice and remove bound water. Thus, the latent heat of fusion must first be removed from the product and then resupplied to it. Energy must also be supplied during the freeze-drying process to refrigerate a moisture condensing plate, which provides the driving force for water vapor mass transfer. While it may be possible to recover some of the heat (e.g. by rejecting the condenser heat to the heating surfaces in order to provide the sublimation energy) it is obvious that the process is inherently energy and capital intensive. Also, a significant amount of energy is used to power the vacuum pump for the long periods required for up to 99% moisture removal.

The lengthy drying times are caused by resistances to heat and mass transfer and other factors, which have been investigated extensively (Mellor, 1978; Flink and To, 1978; Liapis and Litchfield, 1979; Litchfield, Liapis and Farhadpour, 1981; Liapis and Marchello, 1984; Flink and Karel, 1972; Flink and Modelina, 1982). A reduction in the drying time can result in reduced energy and labor costs, since throughput may be increased proportionately. Many
different designs and operating procedures of freeze-driers have been proposed (Goldblith, Rey, and Rothmayr, 1975; Mellor, 1978) not all of which are optimal (Liapis and Marchello, 1984). It should be noted that the total drying time must be long enough so that the final moisture content is below about 1 weight percent (wt%) to prevent degradation of the final material during storage. The total residence time of the product within the chamber can range from 24 hours to as long as seven or eight days (Flamberg, 1986).

The following chapters will describe the means by which the freeze-drying process can be made more efficient, so that both time and cost can be reduced.
FIGURE 1.1: TYPICAL FREEZE-DRYING SYSTEM
1. HEATED SHELF  2. VIAL  3. CHAMBER
4. COMPRESSOR  5. CONDENSER 6. ICE
7. VACUUM PUMP
FIGURE 1.2: BINARY PHASE DIAGRAM OF DRUG IN WATER
Freeze-drying is an operation involving a series of rate processes, and the rate of drying is determined by the rate-limiting steps in this series (Perry, 1963):

1. heat flow from the source to the sublimation interface;
2. sublimation, or the change from a solid phase to a gas phase at constant temperature;
3. transport of water vapor from the vaporizing zone to the condensing zone;
4. desublimation, or the change from the vapor phase to a solid phase at constant temperature; and
5. heat flow from the condensed vapor.

Rational optimization of freeze-drying cycles requires a knowledge of which process is inherently slowest for a particular process configuration. This research is based on the configuration illustrated in figure 2.1, where vials of the frozen product are contained on a metal tray which is placed on a heated shelf in an evacuated chamber. Karel (1973) has shown that sublimation (step 2) is much faster than, and is thus limited by, the transfer of heat from the source to
the sublimation interface. Using the same argument, desublimation (step 4) can be disregarded as the rate-limiting step. Flow of heat from the condensed vapor (step 5) will not limit the process, provided that the condenser is designed correctly and that the condenser is defrosted at regular intervals to prevent a large build up of ice.

Mass transfer (step 3) and heat transfer (step 1) are the two potentially rate-limiting processes which are involved during freeze-drying. While passing from the frozen product to the condenser, the mass transport of water vapor is impeded by three barriers or resistances: (a) resistance of the dried product layer above the frozen product, (b) resistance of the semistoppered vial openings, and (c) resistance in transfer from the drying chamber to the condenser.

Fluted stoppers designed to rest on the top of the vials during lyophilization will generally not impede vapor flow enough to limit the overall process, provided that the stopper is properly oriented on the vial. The resistance of the dried product is the limiting resistance, accounting for nearly 80% of the mass transfer resistance (Pikal, Shah, Senior, and Lang, 1983). Mass transfer is an important consideration that
can be rate-limiting in certain situations. For example, when materials with relatively high salt and low protein content such as crude bacterial toxins are freeze-dried, a glassy layer may form on the surface hampering the release of water vapor.

Despite these considerations, heat transfer from the source to the sublimation interface is usually the rate-limiting process, and thus is the process upon which optimization efforts should focus. The importance of heat transfer can be attributed to: (a) the large heat requirement of about 670 calories per gram of ice, (b) the limited temperature difference between the shelf and the product which is allowable without melting the product in contact with the vial, and (c) the high resistance to heat transfer in vial freeze-drying.

Modes of Heat Transfer:

In the lyophilization of pharmaceuticals, the transfer of heat to the product is generally done by circulating a fluid through the shelf on which vials are placed. Thus, the heat is supplied from below and is transferred mainly by conduction (Nail, 1980) through the frozen matrix to the sublimating front. Although other forms of heating have been tried, e.g., microwave heating (Copson, 1958) and radiant heating from above the product (Greaves, 1960), they do not find wide application in the
drying of solutions.

Referring to figure 2.1, it can be seen that heat must be transferred from the shelf to the sublimation interface through a series of resistances:
(1) the shelf,
(2) the tray,
(3) the bottom of the glass vial,
(4) the frozen solution, and
(5) the gaps which are present due to lack of intimate contact between the shelf and the tray, and the tray and the glass vial.

The work of Pikal (1984) and Nail (1980) has shown that the medium offering the greatest resistance to the transfer of heat to the subliming surface is the intervening space between the tray and the shelf (nearly 33%), and between the vial bottom and the tray (nearly 50%). Resistances of the tray and the intervening space between the shelf and the tray are removed if the vial is placed directly on the shelf. It only involves the resistance of the space between the vial bottom and the shelf (nearly 93%).

**Approaches to Optimize the Freeze-Drying Cycle:**

Nearly all of the previous approaches to optimize the freeze-drying cycle have been directed at applications in the food industry. Because of significant
differences between the freeze-drying of food products and pharmaceuticals, these approaches find limited applicability in the pharmaceutical industry. Normally, the heat supply for freeze-drying foods is accomplished by radiative heating of the dried product and subsequent conduction through the dried product to the subliming ice. Second, foods are frequently processed at higher chamber pressures, presumably to maximize heat transfer without scorching the dried product. Third, foods are usually processed in bulk on the tray itself.

One of the first approaches to improving pharmaceutical freeze-drying was made (Pikal, 1987) by pouring nonvolatile oil in the tray before loading it with vials. The oil fills up the space between the vial bottom and the tray. Since the oil is more heat conductive than the gases present at the intervening space, it improves the heat transfer from the tray to the vial bottom. Even though it reduces the drying time, it is messy and impractical. The requirement of cleaning the freeze-dried vials alone would outweigh the advantage gained.

Irregular contact of the vials with the shelf surface due to the buckling of the tray bottom on which the vials rest may cause nonuniformity of drying throughout the lot. This problem can be eliminated by
using a tray assembly developed by Seligmann and Berkeley (1965) which has a movable frame to hold vials securely in place regardless of the number in the tray. It is constructed so that the bottom may be withdrawn from under the vials, thus allowing them to rest directly on the shelf. When drying is complete and the vials are to be removed from the chamber, the tray bottom should be slid under the frame. Using this bottomless tray the resistances offered by the intervening space between the tray and shelf, and the tray itself can be eliminated.

Nail (1980) found that by increasing the total pressure in the chamber, the primary drying rate is greatly increased because of more efficient transfer of heat to the product arising from a higher concentration of gas molecules conducting heat from the shelf to the vial through the intervening space. In support of Nail's work, Pikal et al. (1984) reported that the rate at which water vapor sublimates from a vial increases as the chamber pressure is increased. Similar observations have been made with regard to foods (Oetjen, Ehlers, Hackenberg, Moll, Neumann, 1962), where it was found that increasing the pressure of water vapor within the material greatly increases the internal heat transfer. Rieutord (1960) showed that increasing the pressure of noncondensable gases increases the heat transfer between
the heat source and the product.

Although increasing the chamber pressure results in more efficient transfer of heat to the product, other considerations place a limit on how far the chamber pressure can be raised. Mass transfer can limit the rate of heat transfer in two ways. By increasing the chamber pressure there will be an increase in the number of gas molecules in the intervening space underneath the vial bottom and so there will be enhanced heat transfer from the heat source to the product at the vial bottom. But at the same time, the number of water molecules above the product will also increase due to the increase of the chamber pressure. These molecules will cause return of some of the evaporated molecules to the product surface. So there will be a decrease in the vapor pressure gradient across the free product surface resulting in decreased mass transfer. Some of the excess heat energy supplied is used up as sensitive heat and the product temperature ultimately rises above the permissible temperature. Thus there is a need to optimize the chamber pressure to prevent the product melting.

Since the product temperature has to be maintained below the eutectic temperature to avoid melting, the low eutectic temperature product will have a small number of water molecules coming out of the
product. So in comparison to the high eutectic point product, the mass transfer will become rate-limiting at a much lower chamber pressure for the low eutectic point product. Thus the upper limit of the chamber pressure during the primary drying needs to be controlled according to thermal properties of the product.

There are many solutions which, because of their low eutectic point, must be dried at very low temperatures. Drying at very low temperatures may prolong the cycle so that the whole process becomes time consuming and uneconomical. Ito's studies (1970, 1971) suggest that this problem may be solved by adding another solute which has a high eutectic temperature (if it forms a true eutectic). For example, he found that the collapse temperature of a sorbitol solution can be increased significantly by reducing the sorbitol concentration and adding sufficient mannitol to keep the total solute concentration the same. The resulting ternary solution could be dried at a much higher product temperature without collapse (Ito, 1970).

The bottomless tray and the increased chamber pressure are the two most widely used approaches in the freeze-drying of pharmaceuticals at present. Using the bottomless tray, most of the heat transfer resistance comes from region I as shown in figure 2.2. In
comparison to Naii's approach, heat transfer through this region can be accelerated by filling up this region with a heat conducting medium without affecting the mass transfer of water vapor molecules. The objective of this research is to investigate the feasibility of using a heat transfer augmentation device, namely a multilayered corrugated aluminum quilt.

EXPERIMENTAL

Materials:

The product used for the determination of drying time was a 10% solution of mannitol in glass-distilled water. Mannitol\(^1\) was used as received from the supplier. Solutions were prepared by dissolving the appropriate amount of mannitol in water and then filtering through a 0.45 \(\mu\)m filter to remove particulate matter. The aluminum foil\(^2\) and the plate used were of commercial grade. The vials used were of commercial origin\(^3\) and were selected to yield a representative cross section of vials produced during production. All of the vials were USP type I, molded clear glass vials.

Differential Scanning Calorimetry:

A preliminary study was carried out to determine the eutectic temperature of the mannitol solution used for this study. This information is necessary to ensure that subsequent drying is carried out by sublimation
rather than evaporation which will maintain the desired product quality.

An approximate volume (5 ul) of mannitol solution was placed in a differential scanning calorimeter\(^4\) sample pan using a micropipette. The sample pan was then placed into the sample holder along with an empty cell as a reference sample. The sample was then cooled to \(-40^\circ C\) by using dry ice and acetone, and then heated at \(2^\circ C\) per minute rate while the thermograms were recorded.

**Drying Procedure:**

A research freeze-dryer\(^5\) was used for this investigation. The unit contains 3 heating and cooling shelves, and 3 manual temperature measurement ports. All the basic freeze-drying components are the same as illustrated in figure 1.1.

The product used for testing the device was 10% w/v solution of mannitol in glass-distilled water. Mannitol was used in this study since it is often used as a bulking agent and has a high eutectic point. As it is important to keep the product temperature below the

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1. Aldrich Chemical Co., Milwaukee, WI, 53201
2. Reynolds Metals Company, Richmond, VI 23261
3. Wheaton Glass Company, Millville, New Jersey
eutectic point, the use of a high eutectic point model compound is convenient. The fill volume was 3 milliliters of mannitol solution in a 10 cc molded glass vial resulting in a cake thickness of approximately 1 centimeter. Only the middle shelf was used in all the experiments. Half of the shelf was used for testing the disposable devices 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 the actual production run. Thermistor probes were placed directly on the shelf as well as in the product at the center inside bottom of the vials by using the probe holders. Good thermal contact between the probe and the shelf surface was obtained by applying a thin coat of high-vacuum silicone grease to the contact place. Without grease at the interface the probe could give readings that are dependent on chamber pressure (Pikal, 1984). Thermal contact between the vial bottom and the shelf was improved by applying the mechanical pressure at the neck of the vials. This was done by sliding a perforated aluminum plate over the neck of the vials and then tightening this plate to the flat aluminum plate which was inserted underneath the shelf as shown in figure 2.3.
The product was frozen to $-40^\circ$C for 4 hours. After the chamber was evacuated to the predetermined pressure the shelf temperature was increased to $5^\circ$C to supply heat of sublimation. The shelf temperature was kept constant for all the experiments. The condenser temperature was $-55 + 5^\circ$C. The product temperatures and the shelf temperature were recorded on a six point strip chart recorder $^6$. When the product temperature merged with the shelf temperature drying was terminated.

**Preparation of the Perforated Plate:**

An aluminum plate, 10 x 10 x 1/4 inches in dimension, was cut with circular holes arranged diagonally so as to accommodate a maximum number of vials on the shelf.

**Preparation of the Device:**

Sheets of heavy duty aluminum foil, 10 x 10 x 0.01 inches, were first wrinkled and then stacked into multiple layers. These layers were then stapled together at regular distances.

**Chamber Pressure Control:**

A manually adjusted controlled-leak valve and a calcium carbonate moisture trap were used to bleed dry air into the chamber to maintain a pre-set pressure.

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$^6$ Clears pan P600, Kent Process Control Incorporated, Edison, NJ 08818.
Pressure was measured by a mercury manometer with a range of $10^{-2}$ to 3 mm mercury. Experiments were carried out at pressures ranging from 20 to 1000 micrometer of mercury. No device was used in this study.

Weight Loss Determination:

For each experiment, 10 vials were numbered and weighed after being filled with 3 cc of mannitol solution. These vials were then randomly distributed on a freeze-drying shelf along with the rest of the vials. Since the freeze-drier is not equipped with a sample thief assembly, drying was terminated immediately after the predetermined time period. The vials were stoppered and then weighed immediately to prevent the product from absorbing moisture. These samples were then discarded and another set of fresh samples were used for determining the weight loss at the next time period for the same experiment. This study was carried out for the device at 20 micron pressure, and also without the device at various chamber pressures.

RESULTS AND DISCUSSION

DSC Analysis:

When an aqueous solution is cooled, the water in the solution almost always undergoes some degree of supercooling before crystallizing out as ice. The magnitude of supercooling is an important factor in the
lyophilization process and is largely dependent on the cooling rate (Jennings, 1980). Since the samples are frozen at 2 degrees per minute in the freeze-drying chamber, 10% mannitol solution was cooled and then heated at 2 degrees per minute in a differential scanning calorimeter (DSC). The DSC thermogram obtained is shown in figure 2.4. The cooling (upper) thermogram shows an exothermic peak for ice beginning at -10°C, followed by another exothermic peak which begins at -32°C for the eutectic phase, during the cooling of the solution. This is the temperature at which no liquid state exists in the product and that is why the product was frozen to -40°C. While the heating (lower) thermogram shows a small endothermic peak for the eutectic phase followed by another endothermic peak for ice during the heating of the frozen solution. During heating, the supercooling effect was avoided and the true eutectic temperature was found to be around -2°C. This agrees well with the value reported by Gatlin and Deluca (1980). Product temperature was maintained below this temperature to avoid melting and thus evaporation of the product.

**Heat Transfer Mechanism:**

It is well known that superinsulation consists of a number of highly reflecting metal layers. To minimize the heat transfer between these layers one uses
either metal coated plastic foils or fibrous spacer materials between the metal foils (Kutzner, Wietzke, and Schmidt, 1972, 1973). By limiting the number of uncoated metal layers, the same approach can be used to enhance heat transfer. Since aluminum foil is a good conductor of heat, inexpensive, and can easily conform to the shape of a vial bottom, it was used to make the quilts. Thermal conductivities of various materials are listed in the appendix. The foils were wrinkled first to improve the thermal contacts between them, and also between the device and the concave vial bottom.

The mechanism of heat transfer from the heated shelf through the device to the vial bottom can be explained using figure 2.5. The heat flow through the device consists largely of two modes, heat radiation and heat conduction, since the contribution of heat convection is negligible at low pressure (Nail, 1980). The heat flow by radiation occurs through the space between concentric surfaces of adjacent layers. The heat flow by conduction between adjacent foils consists of the heat conduction by the residual gas, the heat transfer at points of contact between the foils, and the heat conduction along the foils. Since the foils touch each other at different points, the heat must flow along the zig-zag lines as indicated in the figure, i.e. from one
contact point to the next contact point and then through the foils itself. It is true that an increase in the thickness of the aluminum layer or the increase in the number of layers increases the thermal conductivity between the points of contact and thus increases the conductive component of the heat flow. But the space available between the vial bottom and the shelf, and the separation caused by introducing the device at the circular vial bottom contact from the shelf limits this increase in foil thickness or the number of foil layers. Accordingly, when the number of layers was increased in the aluminum quilt from 2 to 5, the drying time was decreased. But when the number was increased to 10, drying time was increased.

Drying Time:

The products with the device as well as without the device were freeze-dried using identical drying conditions in the same experimental run to avoid the interexperimental variations.

The pressure profile obtained for the freeze-dried product is presented in figure 2.6. The product was cooled to -40°C at 1 atmosphere chamber pressure. At the start of drying the chamber was evacuated for about 15 minutes until it reached the pressure of 20 microns mercury. The chamber pressure increased to a maximum
value as soon as the shelf temperature was increased to +5°C.

At the start of drying, there is no dried product present above the subliming interface to inhibit the mass transfer. This will allow the chamber pressure to attain a maximum value. The chamber pressure decreased with further increase in drying time. Initially the decrease is more rapid as it involves the removal of free water. The free water usually accounts for 95% of the total water content. Also the subliming water vapor has to pass through the increasing depth of dried product.

The decrease in chamber pressure becomes more gradual during the later phase of the drying. During this phase of drying most of the bound water is removed. This bound water accounts for approximately 5% of the total water content.

The temperature profile obtained is presented in figure 2.7. Negative values have been assigned for freezing times while positive values have been assigned to drying times. The shelf temperature, product temperature with the device, and the product temperature without the device are presented as the upper, middle, and lower curves, respectively. The product with the device cools faster and attains a lower freezing temperature in comparison to the product without the
device. While during heating this pattern is completely reversed indicating that the product with the device achieves higher temperature faster. Also the product with the device dries faster. Merging of the product temperature lines with the shelf temperature line was taken as the drying end point. This criterion is based on the fact that at the end of drying no more water vapor molecules are coming out of the product. Thus it requires no heat of sublimation and the product temperature rises to the shelf temperature. By the weight loss determination it was confirmed that the product contained less than 0.7% water at the end of drying. Most pharmaceuticals are processed until less than 1.0% moisture is left behind in the product. The product with the device dries in 10.5 hours while without the device it takes as long as 17 hours.

The advantage gained by using the device is much less during freezing than drying. The freezing and drying of the solution were carried out at atmospheric pressure and 20 micron pressure, respectively. And the thermal conductivity of air increases linearly with linear increase in pressure (Hirschfelder, Curtiss, and Bird, 1954). So in comparision to drying, the product temperature curve without the device is closer to that with the device during freezing.
To compare the results of our approach with Nail's increased chamber pressure approach, experiments were carried out at the pressures ranging from 20 microns to 1000 microns without the device. The temperature profiles obtained at five different pressures are shown in figures 2.8-2.9. Since the geometry of the vial bottoms differ significantly, the temperature profiles obtained during freezing are not identical for the different chamber pressures. As the chamber pressure is increased the product attains a higher temperature faster and also the drying time is decreased. This is due to the fact that by increasing the chamber pressure, the number of heat carrying molecules also increases in the intervening space between the vial bottom and the shelf.

**Weight Loss:**

The weight loss obtained at three different time periods for the device as well as without the device at four different chamber pressures is presented in figure 2.10. In all the curves there is a rapid increase in the weight loss rate at the beginning. Then there is a gradual increase as drying continues. Since there is no dried layer present above the frozen product initially, the mass transfer is not affected by this resistance. But as the dried layer thickness increases the increase in mass transfer decreases and so does the weight loss. Also
at any time point there is an increase in weight loss as the chamber pressure is increased. Maximum water loss is obtained by drying the product with the device. By introducing the device, in comparison with increased chamber pressure approach, there is no effect on mass transfer of water vapor molecules and so there is a greater increase in weight loss.

To evaluate the effect of increasing chamber pressure on mass transfer, the weight loss obtained after 5.5 hours is plotted against chamber pressure in figure 2.11. Since at low pressures mass transfer is not affected significantly and also the heat flux increases linearly with the pressure in the free molecular flow region, there is an increase in weight loss with increase in pressure. At higher chamber pressures, resistance to mass transfer becomes increasingly significant and the flow region moves from free molecular to transition to viscous flow region (Dushman and Lafferty, 1962), the weight loss becomes relatively insignificant.

The weight loss and the drying time data are presented in table 2.1 along with average temperatures from the shelf to the product at the vial bottom. This temperature difference was obtained by calculating the area between the product temperature curve and the shelf temperature curve using the linear
trapezoidal rule and dividing it by the total drying time. The initial sublimation rate obtained from the three data points are also presented for comparison. The correlation coefficients obtained using linear regression analysis are presented in table 2.2. As the chamber pressure (without the device) is increased the average temperature difference and the drying time are decreased and there is an increase in the initial sublimation rate. Similar results were also obtained with the device, indicating its efficiency.

Device Modifications:

To enhance the heat transfer through the aluminum quilt the device was modified by changing the geometry and material of the filling in the following ways:

- foils were corrugated first, stacked into multilayers and then made into a quilt,
- aluminum bag filled with strips of aluminum foil and then varying the size of the strips,
- strips of aluminum foil formed into small balls and then filled into an aluminum bag,
- aluminum bag filled with steelwool fibers placed horizontally or vertically.

All of the above modifications excluding the last one proved to be less effective than the parent device. The temperature profiles obtained for the product dried using
the last modification are presented in figure 2.12 and 2.13. The results of this study could lead to a more efficient heat transfer device. Placing the steelwool fibers vertically, the product dried faster than placing them horizontally. The total resistance through the vertically placed fibers is smaller than that with the horizontally placed fibers. This is due to the fact that the reciprocal of the total resistance through the device is the sum of the reciprocals of the individual resistance offered by each steelwool fiber. While in the case of the horizontally placed fibers the total resistance is the sum of individual resistance. An interesting point to note from figure 2.10 and 2.11 is the heat transfer behavior of steelwool fibers observed during freezing and drying of the product. Since freezing is carried out under atmospheric conditions the device acts as an insulator in comparison to the one without the device. While during drying it acts as a heat enhancer, as drying is carried out at 20 micron chamber pressure. It is concluded from this experiment that improved heat transfer can be achieved by attaching the heat conducting fibers to the lower foil with loose upper ends just like carpet.

In summary, using the device the temperature difference across the intervening space between the vial
bottom and the shelf is reduced. The sublimation rate was increased. The drying time is decreased due to the faster cooling and drying of the product. In comparison to Nail's approach, there is no need to modify the device with the change in the product eutectic temperature.
FIGURE 2.1: HEAT TRANSFER RESISTANCES
FIGURE 2.2: HEAT TRANSFER RESISTANCES USING BOTTOMLESS TRAY
FIGURE 2.3: ARRANGEMENT OF VIALS INSIDE FREEZE-DRYING CHAMBER
FIGURE 2.4: DSC THERMOGRAM OF 10% w/v MANNITOL SOLUTION COOLED AND HEATED AT 2 DEGREES PER MINUTE
FIGURE 2.5: MECHANISM OF HEAT TRANSFER THROUGH THE DEVICE (ALUMINUM QUILT)
FIGURE 2.6: CHAMBER PRESSURE DURING FREEZING AND DRYING FOR THE PRODUCT WITH AND WITHOUT DEVICE
FIGURE 2.7: TEMPERATURE PROFILE FOR THE PRODUCT WITH AND WITHOUT DEVICE (ALUMINUM QUILT) □ SHELF TEMPERATURE  † PRODUCT WITH DEVICE  ◆ PRODUCT WITHOUT DEVICE
FIGURE 2.8: TEMPERATURE PROFILE AT 20, 270, AND 1000 MICRON CHAMBER PRESSURES WITHOUT THE DEVICE

+20 MICRON  \(\diamond\) 270 MICRON \(\Delta\) 1000 MICRON

TIME (hours)
FIGURE 2.9: TEMPERATURE PROFILE AT 165 AND 550 MICRON CHAMBER Pressures
WITHOUT THE DEVICE

- 165 MICRON  + 550 MICRON
FIGURE 2.10: WEIGHT LOSS VERSUS TIME PLOTS

- ALUMINUM QUILT
- 1000 MICRON
- 550 MICRON
- 270 MICRON
- 20 MICRON
FIGURE 2.11: PRESSURE VERSUS WEIGHT LOSS
FIGURE 2.12: TEMPERATURE PROFILE FOR THE DEVICE WITH HORIZONTALLY PLACED STEELWOOL FIBRES

- □ SHELF
- + PRODUCT WITH DEVICE
- ◇ PRODUCT WITHOUT DEVICE
FIGURE 2.13: TEMPERATURE PROFILE FOR THE DEVICE WITH VERTICALLY PLACED STEELNOOL FIBRES

- SHELFL PRODUCT WITH DEVICE
- PRODUCT WITHOUT DEVICE
TABLE 2.1: DRYING DATA FOR PRODUCT WITH AND WITHOUT THE DEVICE

<table>
<thead>
<tr>
<th>DEVICE/ PRESSURE IN</th>
<th>T\textsuperscript{a} \text{ave} (°C)</th>
<th>DRYING TIME (hours)</th>
<th>WEIGHT LOSS AFTER 5.5 HRS (GRAMS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum QUILT</td>
<td>7.4</td>
<td>10.5</td>
<td>1.70 (0.280)\textsuperscript{b}</td>
</tr>
<tr>
<td>P\textsuperscript{c} = 20</td>
<td>20.2</td>
<td>17.0</td>
<td>0.84 (0.155)\textsuperscript{b}</td>
</tr>
<tr>
<td>P\textsuperscript{c} = 165</td>
<td>19.5</td>
<td>16.2</td>
<td>0.87</td>
</tr>
<tr>
<td>P\textsuperscript{c} = 270</td>
<td>18.7</td>
<td>15.5</td>
<td>0.95 (0.173)\textsuperscript{b}</td>
</tr>
<tr>
<td>P\textsuperscript{c} = 550</td>
<td>18.3</td>
<td>14.3</td>
<td>1.05 (0.180)\textsuperscript{b}</td>
</tr>
<tr>
<td>P\textsuperscript{c} = 1000</td>
<td>17.2</td>
<td>13.0</td>
<td>1.33 (0.232)\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} average temperature difference from the shelf top to the product at the vial bottom

\textsuperscript{b} sublimation rate (gms/hr) after 5.5 hours of drying

\textsuperscript{c} chamber pressure in microns for the product with no device
TABLE 2.2: WEIGHT LOSS (IN GRAMS) AFTER THREE DIFFERENT TIME PERIODS DURING DRYING - MEAN (S.D.)

<table>
<thead>
<tr>
<th>DEVICE/PRESSURE</th>
<th>WEIGHT LOSS AFTER 2.25 HRS</th>
<th>3.75 HRS</th>
<th>5.5 HRS</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>0.7818</td>
<td>1.3879</td>
<td>1.7019</td>
<td>0.975</td>
</tr>
<tr>
<td>Quilt</td>
<td>(0.068)</td>
<td>(0.086)</td>
<td>(0.112)</td>
<td></td>
</tr>
<tr>
<td>P = 20 μ</td>
<td>0.3416</td>
<td>0.5507</td>
<td>0.8445</td>
<td>0.998</td>
</tr>
<tr>
<td></td>
<td>(0.011)</td>
<td>(0.091)</td>
<td>(0.029)</td>
<td></td>
</tr>
<tr>
<td>P = 165 μ</td>
<td>-</td>
<td>-</td>
<td>0.8692</td>
<td>0.867</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.034)</td>
<td></td>
</tr>
<tr>
<td>P = 270 μ</td>
<td>0.3900</td>
<td>0.6544</td>
<td>0.9539</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>(0.018)</td>
<td>(0.022)</td>
<td>(0.043)</td>
<td></td>
</tr>
<tr>
<td>P = 550 μ</td>
<td>0.4590</td>
<td>0.8031</td>
<td>1.0482</td>
<td>0.990</td>
</tr>
<tr>
<td></td>
<td>(0.011)</td>
<td>(0.019)</td>
<td>(0.049)</td>
<td></td>
</tr>
<tr>
<td>P = 1000 μ</td>
<td>0.5454</td>
<td>0.9233</td>
<td>1.3313</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td>(0.022)</td>
<td>(0.037)</td>
<td>(0.134)</td>
<td></td>
</tr>
<tr>
<td>P = 2000 μ</td>
<td>-</td>
<td>-</td>
<td>1.4605</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.076)</td>
<td></td>
</tr>
<tr>
<td>P = 3000 μ</td>
<td>-</td>
<td>-</td>
<td>1.4800*</td>
<td>-</td>
</tr>
</tbody>
</table>

r is the correlation coefficient
* melting of product observed

r = 0.975, 0.998, 0.999, 0.990, 0.999, 0.999, 1.4800*
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 reliable and uniformly high quality product.

The theoretical arguments of Nail (1980) indicate 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. The previous chapter showed the feasibility of using a heat conducting device. Using the device, the temperature difference across the intervening space is greatly reduced and a significant decrease in drying time is obtained due to faster cooling and drying.

Although the aluminum quilt offers several advantages, it is inefficient in some aspects. It is difficult to sterilize and if improperly handled
accidental flattening of 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 chapter will describe an improved device to enhance the heat transfer from the shelf to the glass vial bottom.

EXPERIMENTAL

Materials:

Mannitol\(^1\) was used as received from the supplier. DSC analysis revealed a purity of greater than 99 mole\%. The aluminum foil\(^2\) and the aluminum plate used were of commercial grade. Polyethylene layered aluminum foil was purchased so that it can be heat sealed to form a bag. It has nylon and polyethylene layers on one side while 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. Reagent grade glycerin\(^3\) was purchased and was vacuum treated before use. Glass-distilled water was used in the preparation of test solutions. All the vials\(^4\) used were of USP type I tubing or molded clear glass vials.

\(^1\) Aldrich Chemical Co., Milwaukee, WI 53201
\(^2\) Ludlo Corporation, Louisiana
\(^3\) Burdick & Jackson Laboratories, Inc., Muskegan, MI 49442
\(^4\) Wheaton Glass Company, Millville, New Jersey
Preparation of the Device:

As shown in figure 3.1, 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 figure 3.1 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 hours. Excess of glycerin was removed by pressing the bag between two flat plates and then the opening was sealed right into the glycerin to avoid the entrapment of air.

Drying Procedure:

A research freeze-dryer was used for this investigation. The product used for testing the device was 10% w/v solution of mannitol in glass-distilled water. Fill volume was 3 milliliters in a 10 cc molded glass vial resulting in a cake thickness of approximately 1 centimeter. The middle shelf was used for all the experiments. For each experiment, half of the vials were placed over the device and the rest of the vials were placed directly on the shelf. Thermistor probes were placed directly on the shelf as well as in the product at the center inside bottom of the vial. The probes were held in position inside the vials by using probe holders.
Thermal contact between the vial bottom and the shelf was improved by sliding a perforated aluminum plate over the neck of the vials and then tightening this plate to the flat aluminum plate which was inserted underneath the shelf. The product was frozen to $-40^\circ C$ for 4 hours. The chamber was then evacuated to a predetermined pressure. The shelf temperature was then increased to $5^\circ C$ and was kept constant for all the experiments. The condenser temperature was $-55 + 5^\circ C$. When the product temperature merged with the shelf temperature, drying was terminated. The product temperatures and the shelf temperature were recorded on a six point strip chart recorder.

**Weight Loss:**

For each experiment, 10 vials were numbered and weighed after being filled with 3 cc of mannitol solution in 10 cc clear molded glass vials. Then the vials were randomly distributed on a freeze-drying shelf with the rest of the vials and were freeze-dried using the same procedure as described above. Since the freeze-drying equipment was not equipped with a sample thief assembly, drying was terminated immediately after the end of the predetermined time period. The vials were stoppered and then weighed immediately to prevent the product from absorbing the moisture. These samples were then discarded and another set of fresh samples were used for
determining the weight loss at the next time period for the same experimental conditions. This study was carried out with the device as well as without the device at a chamber pressure of 20 microns.

**Vial to Vial Uniformity:**

To study the nonuniformity in heat transfer from the shelf to the product at the center of the vial bottom among the set of 10 cc molded vials, thermistor probes were placed at the center of the vial bottoms. The product was then freeze-dried the same way as described above. The maximum temperature difference among the set of vials was calculated for the product both with the device as well as and without the device. To obtain a temperature profile for the maximum number of vials with a limited number of thermistor probes, the product with the device was dried separately from those without the device.

**Vial Size and Type:**

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

**Spill Experiment:**

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 milliliters of the test
solution. Vials were placed over the spilled and the nonspilled areas on the shelf and the device. The product was then freeze-dried as before while monitoring the shelf and product temperatures. The temperature difference was obtained for the vials placed over the spilled area against the nonspilled area.

Boat Experiment:

Flat bottom aluminum boats were made using a thin aluminum foil. They were then filled with glycerin to achieve a thin layer of glycerin just enough to cover the space between the vial bottom and the shelf. Vials were carefully placed inside these glycerin filled boats and were then freeze-dried using the same procedure as described before. A temperature profile was obtained by monitoring the shelf and product temperatures.

Product Evaluation:

Reconstitution time and cake appearance were noted after each experiment. Reconstitution time was measured in the following way: Product was freeze-dried as before and the product vials were immediately stoppered and sealed. Five milliliters of distilled water were added to the inverted stoppered 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. The reconstitution time obtained for the product dried with the device was compared to that without the device.

Cake (i.e. dried product) appearance and the internal porosity were noted under an optical microscope and a scanning electron microscope.

RESULTS AND DISCUSSION

Liquid is used so the device can easily conform to the shape of the vials just as a waterbed conforms to the shape of its occupant. The liquid is contained in a aluminum foil bag which is inexpensive, durable, flexible, and easily sealed. Glycerin is used as a heat conducting liquid in the preparation of the fluid cushion device. Glycerin was chosen because it has a low freezing point and a high boiling point (low vapor pressure) so it will not freeze or evaporate under vacuum. Also it is high in thermal conductivity and heat capacity so it can pick up and give off the required amount of heat of sublimation without appreciable temperature change. It is nontoxic, nonflammable, noncorrosive, inexpensive, and water washable.

5. Olympus Optical Co., Tokyo, Japan
6. International Scientific Instrument, Model DS 130, Santa Clara, California
Heat Transfer Mechanism:

The physical situation to be studied is shown schematically in figure 3.2. In an ideal case, the fluid is contained between two flat horizontal conducting surfaces distance \( d \) apart. The upper surface is held at the temperature \( T_C \) and the lower surface at the higher temperature \( T_H \). In the absence of motion (i.e., convection) the temperature distribution is determined solely by the thermal conductivity and is indicated by the heavy line connecting \( T_H \) and \( T_C \) (Malkus, Veronis, 1958). To determine the contribution of convection, one needs to determine the Rayleigh number

\[
R = \frac{g \beta d^3 \Delta T}{\mu \alpha}
\]  

(3.1)

where \( g \) is the acceleration due to gravity (in cm/s\(^2\)), \( \beta \) is the coefficient of volume expansion (in \( ^\circ C^{-1} \)), \( d \) is the thickness of the fluid layer (in cm), \( \Delta T \) is the temperature difference between the top and bottom plates (in \( ^\circ C \)), \( \mu \) is the kinematic viscosity (in cm\(^2\)/s) and \( \alpha \) is the thermal diffusivity (in cm\(^2\)/s).

An empirically derived plot for any fluid system contained between two flat horizontal plates is given in figure 3.3 (Catton, 1966). The plot describes the change in the Nusselt number (Nu) with change in the Rayleigh
number. The Nusselt number is a dimensionless ratio of heat flow by both conduction and convection to the heat flow solely by conduction. When the Nusselt number is equal to unity, there is no convection and heat is transferred entirely by conduction. The bottom curve in figure 3.3 is for the system with a fluid contained between two flat horizontal plates. A break in the curve is obtained when it exceeds the critical Rayleigh number. This number has to be achieved for convection to occur. For the system with the fluid contained between the top concave plate and the bottom flat plate, the curve will look like the upper curve in figure 3.3. The maximum separation distance of the vial bottom from the shelf and the average temperature across the device were determined experimentally to estimate the Rayleigh number. These data are presented in table 3.1 along with the other property values obtained from the literature. The calculated Rayleigh number is extremely low suggesting that the Nusselt number will be near unity. Therefore the heat flow through the device is largely by conduction and convection is negligible.

**Theoretical Calculation:**

Referring to figure 3.1, it can be seen that heat must be transferred from the heated shelf to the subliming interface 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 device the resistance due to the device is replaced by the intervening gas phase. The contribution of each resistance, with or without the device, is estimated in the following way.

If one takes into consideration the equation governing heat transfer by conduction, under steady-state flow:

\[ Q = k A \frac{\Delta T}{X} \quad (3.2) \]

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, \( \Delta T \) (°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, equation 1 can be written for each of these layers and the overall temperature difference is expressed by:

\[ \Sigma_i \Delta T_i = \frac{Q}{A} \left( \Sigma_i \frac{X_i}{k_i} \right) \quad (3.3) \]

where \( \frac{X_i}{k_i} \) is a measure of the resistance to heat flow,
\[ \Delta T_T = q (\Sigma_1 R_1) = q R_T \quad (3.4) \]

where \( q = Q/A \) in cal cm\(^{-2}\) hr\(^{-1}\). The total resistance, \( R_T \), may be expressed as the sum of four terms:

\[ R_T = R_g + R_v + R_s \quad (3.5) \]

where \( R_g \) is the gas phase resistance between the shelf and the vial bottom, \( R_v \) and \( R_s \) are the resistance of the glass vial and frozen solution, respectively. In the case where the gas boundary is filled with aluminum foil and a heat conducting fluid (glycerin), the term \( R_g \) is replaced in equation 4 by the sum of the resistances of the aluminum foil \( (R_a) \) and the fluid \( (R_f) \).

Based on thermal conductivity values and the thickness of the layers, for the system with aluminum foil and a heat conducting fluid glycerin, one can calculate the resistance of each material. These values are included in table 3.2. The contribution of each of the three phases to the total heat flow resistance was calculated and is presented in table 3.3 along with the reported values (Nail, 1980) 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. And the faster drying will be achieved by minimizing the temperature difference between the shelf and the frozen product.

**Drying Time:**

The products with the fluid cushion device and without the device were freeze-dried using identical drying conditions in the same experimental run to avoid the interexperimental variations. The temperature profile obtained is presented in figure 3.4. Negative values have been assigned for freezing while positive values have been assigned to the drying portion of the time scale. The shelf temperature, product temperature with the device, and the product temperature without the device are presented with the upper, middle, and lower curves, respectively. As with the aluminum quilt the product with the fluid cushion device cools faster and attains a lower freezing temperature in comparison to the product without the device. During heating this pattern is completely reversed as expected, indicating that the product with the device achieves a higher temperature faster. Also the product with the device dries faster. Merging of the product temperature curves with the shelf temperature curve was 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 rises to the shelf temperature. The product with the fluid cushion device dries in 11 hours, while without the device it takes as long as 17 hours. The drying time with the aluminum quilt is 10.5 hours.

An important piece of information missing from figure 3.4 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. Configuration of the container and defects, scratches and other surface irregularities as well as particulate matter can serve to limit the degree of supercooling (Jennings, 1980). But 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. Thus crystals will grow at a relatively lower temperature and a higher degree of supercooling is obtained.
**Weight Loss:**

The weight loss experiments were carried out the same way as described for the aluminum quilt in chapter two. The weight loss data obtained at three different time periods for the fluid cushion device are presented in table 3.4. 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 using 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 using the linear trapezoidal rule, are presented in table 3.4. It is true that the increase in the weight loss obtained requires a higher amount of heat 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 using Fourier's law which states that

\[ q = k \frac{\Delta T}{x} \]  

(3.6)

where heat flux \( q \) (W m\(^{-2}\)) is the heat transfer rate per unit area, \( k \) (W m\(^{-1}\) °K\(^{-1}\)), \( x \) (m) and \( \Delta T \) (°K) are the thermal conductivity, thickness, and temperature.
difference across the medium, respectively. By increasing the chamber pressure or introducing a device, thermal conductivity of the intervening space is increased greatly (see appendix). This will more than offset the decrease in the temperature difference. Thus the heat flux across the intervening space will be much more than the sublimation heat required for increased weight loss. The product temperature will increase resulting in decreased temperature difference between the shelf and the product.

**Vial to Vial Uniformity:**

The vial is an extremely important variable in the freeze-drying process. Although the direct effect of the vial on mass transfer (via closure resistance) is slight, the nature of the vial does significantly affect the rate of heat transfer to the product. The magnitude of variation in the vial heat transfer rate is sensitive to the geometry of the vial bottom. While the thickness of the glass in the vial bottom is not important (Pikal, Roy, Shah, 1984), 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 differences in the vial heat transfer rate exists 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. Indeed, circumstances may arise where a product is routinely freeze-dried with an excellent yield, but a change of supplier for the vial stock results in significant product loss arising from eutectic melt. Results of the nonuniformity in heat transfer from the shelf to the product at the inside center of vial bottom, among the set of vials, are presented in figure 3.5. Maximum product temperature differences obtained among the same lot of vials with and without the device are plotted against time. Temperature difference is plotted only up to three hours, as the product temperature ultimately becomes constant with the shelf temperature. In actual practice the shelf temperature is constantly decreased 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 the distance between the two curves is increased as shown in figure 3.5. 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 this study that by using the device, more even heat transfer can be achieved. It is likely that nonuniformity in heat transfer among the vials manufactured by different suppliers or different lots can also be reduced using the device.

**Vial Size and Type:**

The device was tested for different sizes of vials and the data obtained are listed in table 3.5. The intervening space created between the concave vial bottom and the flat shelf top was measured in terms of weight. 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 using different sizes of vials, the ratio was obtained by dividing the drying time without the device to that with the device. The drying time ratio increased with the increase in vial size. The concavity of the vial bottom increases with the increase in vial size. Thus there is an increase in the importance of space on the vial bottom with the increase in the vial size. The drying time without the device increased more in comparison to that with the device, indicating increased efficiency of the device with increase in the vial size.
Data are also presented for tubing vials in table 3.5. Although the device is equally effective in filling the space at the bottom of the tubing or molded vials, the drying time ratio is decreased for tubing vials in comparison to the same size molded vials. Since the vials manufactured from tubing are generally superior to molded ones, as they have relatively uniform and flat bases, the importance of the space on the vial bottom is decreased. This decrease in importance causes 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 with materials like mannitol, vial breakage is higher (Williams, Lee, Polli, and Jennings, 1986).

**Spill Experiment:**

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 spill experiment was carried out. The data obtained for the vials placed on the spilled and the
nonspillable areas with or without the device are presented in figures 3.6 and 3.7. The vials placed in the spilled area freeze and dry much faster compared to those placed on the nonspillable area without the device. While using the device the freezing portion of both 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 against the nonspillable area were calculated for the vials dried with or without the device and are plotted against time as shown in figure 3.8. Using the device the temperature difference is considerably smaller 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 will make it worse as it entraps the spilled solution between the device and the vial bottom.

**Boat Experiment:**

The purpose of the boat experiment was to check how good the device makes contact with the vial bottom as compared to the vials in direct contact with glycerin. No significant decrease in drying time (half an hour) was observed. This decrease may be due to the contact made by the excess of 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 (i.e. product) 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 the quality of the product. No wet spot or observable differences in quality between the product dried with or without the device was detected. The cake was reconstituted by adding water, but no measurable difference in reconstitution time was observed.

In conclusion, the device has been shown to increase the heat transfer from the shelf to the vial bottom by filling up the intervening space. It reduces the freezing and drying times and increases the sublimation rate. 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.
FIGURE 3.1 - FLUID CUSHION DEVICE
(a) PREPARATION OF THE DEVICE
(b) HEAT TRANSFER THROUGH THE DEVICE
FIGURE 3.2: HEAT TRANSFER BETWEEN TWO SURFACES
(A) HEAT TRANSFER BETWEEN TWO PARALLEL PLATES (HYPOTHETICAL CASE)
(B) HEAT TRANSFER BETWEEN A FLAT SHELF TOP AND A CONCAVE VIAL BOTTOM (ACTUAL CASE)
FIGURE 3.3: NATURAL CONVECTION PLOT FOR AN ACTUAL CASE AND A HYPOTHETICAL CASE
FIGURE 3.4: TEMPERATURE PROFILE FOR FLUID CUSHION DEVICE AT 20 MICRON PRESSURE

☐ SHELF    + PRODUCT WITH DEVICE    ◇ PRODUCT WITHOUT DEVICE
FIGURE 3.5: INTERVAL VARIATION IN PRODUCT TEMPERATURE

- □ PRODUCT WITH DEVICE
- ✫ PRODUCT WITHOUT DEVICE
FIGURE 3.6: SPILL EXPERIMENT WITHOUT THE DEVICE
- VIAL PLACED ON SPILLED AREA
- VIAL PLACED ON NONSPILLED AREA
- SHELF
FIGURE 3.7: SPILL EXPERIMENT WITH FLUID CUSHION DEVICE

- SHELFT
- VIAL PLACED ON SPILLED AREA
- VIAL PLACED ON NONSPILLED AREA
FIGURE 3.8: SPILL EXPERIMENT WITH AND WITHOUT FLUID CUSHION DEVICE

□ PRODUCT WITH DEVICE  + PRODUCT WITHOUT DEVICE
<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity ( (\text{gm cm}^{-1} \text{sec}^{-1}) )</td>
<td>6.8300</td>
</tr>
<tr>
<td>Density ( (\text{gm cm}^{-3}) )</td>
<td>1.0800</td>
</tr>
<tr>
<td>Kinematic Viscosity ( (\text{cm}^2 \text{sec}^{-1}) )</td>
<td>6.3240</td>
</tr>
<tr>
<td>Thermal Diffusivity ( (\text{cm}^2 \text{sec}^{-1}) )</td>
<td>1.0000</td>
</tr>
<tr>
<td>Coefficient of Volume Expansion ( (\degree \text{K}^{-1}) )</td>
<td>0.0005</td>
</tr>
<tr>
<td>Gravitational Constant ( (\text{cm sec}^{-2}) )</td>
<td>980.6650</td>
</tr>
<tr>
<td>Thickness of Device ( (\text{cm}) )</td>
<td>0.1000</td>
</tr>
<tr>
<td>Temperature Difference ( (\degree \text{K}) )</td>
<td>6.2000</td>
</tr>
<tr>
<td>Rayleigh Number</td>
<td>0.481 \times 10^{-3}</td>
</tr>
</tbody>
</table>
### TABLE 3.2: CALCULATED VALUES OF THERMAL RESISTANCES

<table>
<thead>
<tr>
<th>MATERIAL</th>
<th>THICKNESS (cm)</th>
<th>THERMAL CONDUCTIVITY (cal cm/ cm²hr °C)</th>
<th>RESISTANCE (cm²hr°C/cal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen solution</td>
<td>0.80</td>
<td>18.70</td>
<td>4.3 x 10⁻²</td>
</tr>
<tr>
<td>Glass (vial)</td>
<td>0.24</td>
<td>9.40</td>
<td>2.6 x 10⁻²</td>
</tr>
<tr>
<td>Glycerin</td>
<td>0.10</td>
<td>2.43</td>
<td>4.1 x 10⁻²</td>
</tr>
<tr>
<td>Aluminum</td>
<td>0.01</td>
<td>2581.0</td>
<td>3.87 x 10⁻⁶</td>
</tr>
<tr>
<td>Gas phase</td>
<td>0.11</td>
<td>-</td>
<td>1.08</td>
</tr>
</tbody>
</table>
TABLE 3.3: THERMAL RESISTANCES FOR THE SYSTEMS WITH AND WITHOUT THE DEVICE

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>CONTRIBUTION TO HEAT FLOW RESISTANCE, % OF TOTAL SHELF-VIAL BOUNDARY</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas phase</td>
<td>94</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device</td>
<td>37</td>
<td>24</td>
<td>39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3.4: WEIGHT LOSS DATA FOR THE PRODUCT WITH AND WITHOUT THE FLUID CUSHION DEVICE

<table>
<thead>
<tr>
<th>DEVICE/PRESSURE</th>
<th>( T^a_{ave} ) (°C)</th>
<th>DRYING TIME (hrs)</th>
<th>WEIGHT LOSS AFTER 5.5 HRS (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device</td>
<td>6.2</td>
<td>11.0</td>
<td>1.54 (0.278)(^b)</td>
</tr>
<tr>
<td>( P = 20 \ U )</td>
<td>20.2</td>
<td>17.0</td>
<td>0.84 (0.155)(^b)</td>
</tr>
<tr>
<td>( P = 1000 \ U )</td>
<td>17.2</td>
<td>13.0</td>
<td>1.33 (0.232)(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Average temperature difference from the shelf top to the product at the vial bottom

\(^b\)Sublimation rate (gms/hr) after 5.5 hrs
TABLE 3.5: EFFECT OF SIZE AND TYPE OF VIALS ON DRYING OF THE PRODUCT WITH AND WITHOUT THE FLUID CUSHION DEVICE

<table>
<thead>
<tr>
<th>VIAL SIZE (cc)</th>
<th>WEIGHT OF THE INTERVENING SPACE (gms)</th>
<th>DRYING TIME WITH DEVICE (A;hrs)</th>
<th>DRYING TIME WITHOUT DEVICE (B;hrs)</th>
<th>DRYING TIME RATIO (B/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.25</td>
<td>11.0</td>
<td>17.0</td>
<td>1.55</td>
</tr>
<tr>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.20</td>
<td>10.0</td>
<td>14.0</td>
<td>1.40</td>
</tr>
<tr>
<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.43</td>
<td>15.2</td>
<td>25.0</td>
<td>1.65</td>
</tr>
<tr>
<td>30&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.98</td>
<td>14.7</td>
<td>26.7</td>
<td>1.82</td>
</tr>
</tbody>
</table>

<sup>a</sup>Molded Vials

<sup>b</sup>Tubing Vials
The application of the fluid cushion device to enhance the heat transfer from the freeze-drying shelf to the glass vial bottom has been the subject of chapter three. Glycerin has been used as a heat conducting fluid in this device. The device was shown to make near perfect contact with the vial. The only way to make the device more heat conductive is either by changing the fluid or by increasing the thermal conductivity of the fluid.

It is known that the conductivity of water can be increased by dissolving inorganic salts (Perry, 1963). These salts dissociate into cations and anions, and the ions conduct the heat as efficiently as they conduct electricity. Because of its hydroxyl groups glycerol has solubility characteristics similar to those of water, glycols, and alcohols.

Cosolvents such as ethanol, propylene glycol, and polyethylene glycol are routinely used to solubilize drugs in aqueous vehicles. In some cases, the use of an appropriate cosolvent can increase the aqueous solubility of a drug by several orders of magnitude. In other cases, the solubilizing effect is much smaller or even negligible, and in still other cases the addition of a
cosolvent will reduce the solubility of solute in the aqueous vehicles.

It is observed that the solubility of nonelectrolytes increases exponentially as the volume fraction of cosolvent is increased in binary cosolvent-water mixtures (Yalkowsky and Roseman, 1981; Chawla, Pinal, Morris, and Yalkowsky, 1987; Rubino, Blanchard, and Yalkowsky, 1984). This is described mathematically by:

\[
\log S_m = \log S_w + f \sigma \quad (4.1)
\]

where $S_m$ is the solubility of drug in the mixed aqueous system containing the volume fraction $f$ of nonaqueous cosolvent, $S_w$ is the solubility in water, and $\sigma$ is the slope of the $\log S_m$ vs $f$ plot. It was found in these studies that $\sigma$ is dependent on the solute as well as the cosolvent polarities. Recently, Rubino and Yalkowsky (1985a and 1985b) have successfully used the above equation for estimating the solubility of weak organic electrolytes. However, its applicability to strong electrolytes has received only minimal consideration.

This study was undertaken to determine the solubility of electrolytes in cosolvents as well as to test the validity of Equation 4.1 for strong electrolytes and to determine if $\sigma$ is in any way predictable.
EXPERIMENTAL

Materials:

All solutes were obtained in the highest available purity from commercial sources and used as received. The cosolvents were selected to cover a wide range of polarity. These included propylene glycol (PG), ethylene glycol (EG), polyethylene glycol 400 (PEG), dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), methanol (MEOH), and ethanol (ETOH). All solvents were of reagent grade or better and were used as received. Distilled water was used in all experiments.

Sample Preparation:

The solubilities of sodium chloride (NaCl) and potassium chloride (KCl) were determined in different cosolvent-water mixtures. The cosolvent-water mixtures were prepared by mixing 10, 20, 30, ... 70, 80, 90 milliliters of cosolvent with 90, 80, 70, ... 30, 20, 10 milliliters of water, respectively. The volumes of cosolvent and water were measured separately and combined so that the volume fraction of cosolvent, as defined here, would not change if volume shrinkage occurred upon mixing.

Saturated solutions of solute were prepared in the following way: An excess amount of solute was placed
in each of several screw-capped culture tubes containing 1 milliliter of specified amounts of cosolvent-water mixture. These tubes were rotated on a test tube rotator for 24 hours at 25°C and were then centrifuged for 15 minutes. The aliquots of the clean supernatant were diluted with distilled water, and assayed for the given solute as described below.

**Sodium Chloride Determination:**

Mohr's argentimetric titration (Beckett and Stenlake, 1975) was used to determine the sodium chloride content in the various cosolvent-water mixtures. Potassium chromate solution (5 per cent w/v; 1 milliliter), used as an indicator, was added to a conical flask containing the diluted sample, and was then titrated with 0.1 N silver nitrate solution. During the titration the flask was continuously shaken for faster reaction. Dropwise addition of silver nitrate was continued until a permanent faint reddish-brown color was obtained. The silver nitrate used contained 99.9+ percent silver nitrate and therefore was used as a primary standard. Quantitation of sodium chloride was obtained using the following equations:

\[
\text{AgNO}_3 + \text{NaCl} \rightarrow \text{AgCl} \downarrow + \text{NaNO}_3 \quad (4.2)
\]

\[
0.01699 \ g \ \text{AgNO}_3 = 0.005845 \ g \ \text{NaCl} = 1 \ ml \ of \ 0.1 \ N \ \text{AgNO}_3
\]
Potassium Chloride Determination:

Volhard's method (Beckett and Stenlake, 1975) was used to determine the potassium chloride content in the various cosolvent-water mixtures. Dilute nitric acid (15 ml), dibutyl phthalate (5 ml) and 0.1 N silver nitrate (50 ml) were added to the diluted sample contained in a conical flask, and was shaken vigorously for a minute. Ferric ammonium sulphate solution (5 ml) was added to the above solution and then titrated with 0.1 N ammonium thiocyanate (NH₄SCN). Addition of ammonium thiocyanate with shaking was continued until a reddish-brown color, which did not fade away in five minutes, was obtained. Quantitation of potassium chloride was achieved using the following equations:

\[
\text{KCl} + \text{AgNO}_3 \quad \rightarrow \quad \text{AgCl} \downarrow + \text{KNO}_3 \quad (4.3)
\]

\[
\text{AgNO}_3 + \text{NH}_4\text{SCN} \quad \rightarrow \quad \text{AgSCN} \downarrow + \text{NH}_4\text{NO}_3 \quad (4.4)
\]

\[0.00535 \text{ g KCl} = 1 \text{ mL of 0.1 N AgNO}_3\]

The blank reading was subtracted from the sample reading to account for any impurity left behind in the distilled water. The validity of the above two methods was obtained by spiking a known amount of solute in the sample. Linear regression analysis was performed on the data using a statistical analysis program (SAS User's Guide, 1982).
RESULTS AND DISCUSSION

The solubilization curves of sodium chloride and potassium chloride in the various binary mixtures of cosolvents and water are presented in figures 4.1-4.6. Solubilities in acetonitrile, acetone, and isopropanol could not be determined as the solute salts out the cosolvent from the mixture. In general two kinds of profiles were obtained. One being nearly linear throughout the concentration range as shown by ethylene glycol, propylene glycol, and polyethylene glycol. The other profile as seen in the cases of dimethylacetamide, dimethylformamide, dimethylsulfoxide, methanol, and ethanol systems, where the initial linearity is followed by a downward concavity. Downward concavity was also observed in the case of nonelectrolyte solutes (Chawla, Pinal, Morris, and Yalkowsky, 1987).

In nearly all cases there is roughly a linear relationship between log $S$ and $f$ indicating the usefulness of equation 4.1 in describing the electrolyte solubility data. There is an exponential decrease in the solubility of both solutes with a linear increase of cosolvent in the cosolvent-water mixture. The maximum decrease observed is two orders of magnitude for potassium chloride in dimethylacetamide-water mixture. This is due to the fact that the addition of increasing
amount of cosolvent causes the decrease in the polarity of cosolvent-water mixture, and since salts are more polar than these mixtures, the solubility decreases with the addition of cosolvent.

The slopes and the correlation constants for both solutes are presented in tables 4.1 and 4.2. In all cases the value of the correlation coefficient is greater than 0.92.

The addition of cosolvent to water decreases the solubility of electrolyte solutes. The order of the desolubilizing power of cosolvent obtained from the slope of log $S$ vs $f$ (table 4.1) is listed below. The degree of solubilization is similar for both the solutes as would be expected.

NaCl: DMA > DMF > ETOH > DMSO > MEOH > PEG > PG > EG

KCl: DMA > DMF ≈ ETOH > DMSO > MEOH > PEG > PG > EG

While the addition of cosolvent to water increases the solubility of nonelectrolyte solutes. The slopes of log $S$ versus $f$ plots for various nonelectrolytes as reported by Yalkowsky et al. (1987) were averaged and are presented in table 4.1. The solubilization order obtained for various cosolvent-water mixtures is listed below.

DMA > DMF > ETOH > DMSO > MEOH > PG > EG
The above order is the same for the electrolyte solutes indicating that the solvents which salt in the non-electrolyte solute will also salt out the electrolyte solutes in the same order. The desolubilization order obtained in individual groups of compounds, like glycols and mono-hydroxy alcohols, agree with the expected order of polarity (dielectric constant) of the cosolvents.

Regression analysis of the data shown in table 4.1 gives the following results.

(1) Nonelectrolyte slopes (NE) vs NaCl slopes (NACL)

\[ NACL = -2.185 (NE) + 0.676 \]
\[ n = 7, r = -0.998 \] (4.5)

(2) Nonelectrolyte slopes (NE) vs KCl slopes (KCL)

\[ KCL = -2.33 (NE) + 0.698 \]
\[ n = 7, r = -0.958 \] (4.6)

(3) NaCl slopes (NACL) vs KCl slopes (KCL)

\[ KCL = 1.0955 (NACL) + 0.0655 \]
\[ n = 8, r = 0.944 \] (4.7)

Good correlation is obtained in all three cases, suggesting the validity of equation 4.1. The solubilization and desolubilization behavior observed for nonelectrolyte, as well as, electrolyte solutes appear to depend upon the cosolvent in a similar manner.

The solubilities of sodium chloride and potassium chloride are extremely low in all the solvents.
except water. Even though dissolving the salts will decrease the vapor pressure of the solvent, the solubility is not sufficient to increase the thermal conductivity significantly (Pearlstein and Pourier, 1987).

In summary, the solubility of both the electrolyte solutes has been found to be adequately described by the log-linear solubility equation. A cosolvent which is most effective in solubilizing a nonelectrolyte is also most effective in desolubilizing an electrolyte. The solubility of salts in neat organic solvents is insignificant, and therefore would not increase the thermal conductivity of the solvents.
FIGURE 4.1: SOLUBILITY OF SODIUM CHLORIDE IN POLYOL-WATER MIXTURES

- EG
- PG
- PEG
FIGURE 4.2: SOLUBILITY OF SODIUM CHLORIDE IN HYDROALCOHOLIC MIXTURES

□ MEOH  □ ETOH
FIGURE 4.3: SOLUBILITY OF SODIUM CHLORIDE IN DMA, DMF, AND DMSO-WATER MIXTURES

\[ \log S (\text{gm/mL}) \]

VOLUME FRACTION COSOLVENT
FIGURE 4.4: SOLUBILITY OF POTASSIUM CHLORIDE IN POLYOL-WATER MIXTURES

\[
\log S \text{ (gm/ml)}
\]

\[
\text{VOLUME FRACTION COSOLVENT}
\]

\[
\begin{align*}
0 & \quad 0.1 & \quad 0.2 & \quad 0.3 & \quad 0.4 & \quad 0.5 & \quad 0.6 & \quad 0.7 & \quad 0.8 & \quad 0.9 & \quad 1 \\
\end{align*}
\]

\[
\begin{align*}
& -0.5 & \quad -0.7 & \quad -0.8 & \quad -0.9 & \quad -1 & \quad -1.1 & \quad -1.2 & \quad -1.3 & \quad -1.4 & \quad -1.5 & \quad -1.6 \\
\end{align*}
\]

EG \hspace{1cm} PG \hspace{1cm} PEG
FIGURE 4.5: SOLUBILITY OF POTASSIUM CHLORIDE IN HYDROALCOHOLIC MIXTURES
- ME OH  + ET OH
FIGURE 4.6: SOLUBILITY OF POTASSIUM CHLORIDE IN DMA, DMF, AND DMSO-WATER MIXTURES

\[ \text{LOG } S \ (\text{gm/ml}) \]

\[ \text{VOLUME FRACTION COSOLVENT} \]

\( \diamond \) DMA  \( \square \) DMF  \( + \) DMSO

110
### TABLE 4.1: SLOPES OF LOG S VERSUS f PLOTS FOR ELECTROLYTE AND NONELECTROLYTE SOLUTES

<table>
<thead>
<tr>
<th>SOLVENT</th>
<th>NaCl</th>
<th>KCl</th>
<th>NONELECTROLYTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMA</td>
<td>-2.440</td>
<td>-2.644</td>
<td>1.41</td>
</tr>
<tr>
<td>DMF</td>
<td>-2.380</td>
<td>-2.278</td>
<td>1.40</td>
</tr>
<tr>
<td>ETOH</td>
<td>-2.150</td>
<td>-2.274</td>
<td>1.30</td>
</tr>
<tr>
<td>DMSO</td>
<td>-1.644</td>
<td>-2.127</td>
<td>1.07</td>
</tr>
<tr>
<td>MEOH</td>
<td>-1.460</td>
<td>-1.852</td>
<td>1.00</td>
</tr>
<tr>
<td>PEG</td>
<td>-1.306</td>
<td>-1.083</td>
<td>-</td>
</tr>
<tr>
<td>PG</td>
<td>-1.057</td>
<td>-0.977</td>
<td>0.76</td>
</tr>
<tr>
<td>EG</td>
<td>-0.654</td>
<td>-0.582</td>
<td>0.62</td>
</tr>
</tbody>
</table>
TABLE 4.2: CORRELATION COEFFICIENT (r) of LOG S VS f PLOTS FOR ELECTROLYTE SOLUTES

<table>
<thead>
<tr>
<th>SOLVENT</th>
<th>NaCl</th>
<th>KCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>EG</td>
<td>-0.999</td>
<td>-0.995</td>
</tr>
<tr>
<td>PG</td>
<td>-0.990</td>
<td>-0.994</td>
</tr>
<tr>
<td>PEG</td>
<td>-0.948</td>
<td>-0.996</td>
</tr>
<tr>
<td>MEOH</td>
<td>-0.979</td>
<td>-0.978</td>
</tr>
<tr>
<td>ETOH</td>
<td>-0.938</td>
<td>-0.963</td>
</tr>
<tr>
<td>DMA</td>
<td>-0.954</td>
<td>-0.937</td>
</tr>
<tr>
<td>DMF</td>
<td>-0.922</td>
<td>-0.948</td>
</tr>
<tr>
<td>DMSO</td>
<td>-0.975</td>
<td>-0.987</td>
</tr>
</tbody>
</table>
Aqueous solutions of antibiotics are usually very unstable at ambient temperature. One common way to increase the stability is to freeze-dry the product. However, this approach has several disadvantages including the problems with reconstitution, and high processing cost. Another way to increase the stability is to decrease the temperature of the solution. The decrease in solution temperature slows the reaction velocity, and if the solution freezes the reaction will further be diffusion limited by the reduced molecular motion in the frozen solution.

The speed of many reactions decreases about 2 to 3 times with each 10° decrease in temperature. The effect of temperature on the reaction rate is given by the equation, first suggested by Arrhenius,

$$\log k = \log A - \frac{E_a}{2.303 T}$$

(5.1)

in which $k$ is the specific reaction rate, $A$ is a constant known as the frequency factor, $E_a$ is the energy of activation, $R$ is the gas constant, and $T$ is the absolute temperature. The decrease in temperature may also lead to
The purpose of this investigation is to estimate the aqueous solubility of oxacillin sodium at sub-freezing temperatures. The determination of the solubility of any drug in water below zero degrees centigrade is experimentally impossible due to the freezing of water. Cosolvents, like methanol, can be used to get information about the solubility of the drug in aqueous solution at temperatures below zero degrees, as they depress the freezing point of water.

EXPERIMENTAL

Materials:

Oxacillin sodium was obtained from Travenol Laboratories (Morton Grove, Illinois) and was used as received. All other reagents and chemicals used were spectral grade. Double distilled water was used in all the experiments. Water-cosolvent mixtures were prepared by mixing 10, 20, 30, 40, etc., milliliters of cosolvent with 90, 80, 70, 60, etc., milliliters of water. The volumes of cosolvent and water were measured separately and combined so that the mole fraction of cosolvent would not change if volume shrinkage occurred upon mixing.

Solubility Determination:

Solubility determination was conducted in aqueous
methanol by the following procedure: Excess of sodium oxacillin was added to 2 ml of 0, 10, 20, ..., 100 % v/v methanol-water mixture contained in screw-capped culture tubes. The samples were then rotated on a test tube rotator for 6 hours at 21, 12, and 5 degrees, and for 24 hours at -6, -14.5, and -26 degrees centigrade. The samples which did not freeze during equilibration were used for the solubility determinations.

The equilibrated solution was then filtered through a 0.45 micron millipore filter which was thermally equilibrated for 24 hours under similar conditions. The syringe used in the filtration was wrapped with an insulating material as shown in figure 5.1 and was equilibrated for 24 hours. This was done to prevent heat transfer from the atmosphere during filtration. The filtration process was completed in about 15 seconds. The drug was then analysed using a Beckman DU-8 spectrophotometer at 240 nm and the solubility from the standard curve.

Differential Scanning Calorimetry (DSC):

DSC analysis was performed on a Du Pont 1090 thermal analyzer with a 910 DSC module. Aqueous suspension (50 % w/v) of oxacillin sodium was heated from -40 to 15 degrees centigrade at 2 degree per minute rate.
RESULTS AND DISCUSSION

Methanol was chosen as the cosolvent because of its ability to depress the freezing point of water. Also, the viscosity of the methanol-water system is low and does not inhibit filtration. The reported stability of oxacillin sodium in aqueous solution at room temperature is only 24 hours (Chatterji, Hiranaka, and Galleli, 1975). The samples were equilibrated for only 6 hours at higher temperatures. Since the stability of oxacillin sodium at refrigerated temperature is greater, the equilibration time was increased for subzero temperatures.

The solubility data obtained are plotted semi-logarithmically against volume fraction of methanol in figures 5.2-5.7. A linear relationship is observed at all temperatures as expected by the following equation proposed by Yalkowsky and Roseman (1981).

\[ \log S_m = \log S_w + f \sigma \]  

(5.2)

where \( S_m \) is the molar solubility of drug in cosolvent-water mixture, \( S_w \) is the molar solubility of the drug in water, \( f \) is the volume fraction of cosolvent and \( \sigma \) is the slope of the log \( S_m \) vs \( f \) plot. Since the solubility in water is higher than in the cosolvent, the solubility in cosolvent-water mixture shows an exponential decrease
with increasing cosolvent fraction.

Linear regression analysis was performed on the data using SAS. The dependent variable log $S_m$ was regressed against the independent variables, the volume fraction of cosolvent and the reciprocal of temperature. Tables 5.1 and 5.2 give the slope, intercept, and the correlation coefficient for the regression analysis of log $S_m$ vs fraction cosolvent and log $X$ vs reciprocal of temperature, respectively.

The regression slope of log $S_m$ vs fraction cosolvent was found to be nearly constant with an average value of $-0.54$. The slope $\sigma$ is the solubilizing power of the cosolvent, and does not depend on temperature. The intercept of the regressions is the solubility of oxacillin sodium in water at a given temperature. The solubility in water at $-14.5$ degrees was found to be the lowest at 213.8 milligrams per milliliter. Solubility generally decreases until $-14.5$ degrees and then goes up with further decrease in temperature for all methanol-water mixtures. This experiment was repeated three times and gave the same result suggesting the existence of some other form of the drug at that temperature. The DSC curve (figure 5.8) obtained for an aqueous solution oxacillin sodium from $-50$ to $15$ degrees centigrade shows an exothermic transition at $-13.8$ degrees centigrade. This
suggests that some other crystal form of the drug is present below that temperature. The other endothermic transition observed around zero degree centigrade is due to the melting of ice. Similar observation has been observed by Gatlin and Deluca (1980) for nafcillin sodium.

The heat of solution for the drug forming a saturated nonideal solution can be determined from the variation of the equilibrium concentration of drug with temperature. An equation of the following form appears in many texts (Daniels and Albery, 1955; Martin, Swarbick, and Cammarata, 1969):

\[
\ln X = \frac{\Delta H_s}{RT} + \text{constant} \quad (5.3)
\]

where \(X\) is the mole fractional solubility of drug at temperature \(T\), \(R\) is the gas constant, and \(\Delta H_s\) is the heat of solution at saturation. When a plot of \(\log X\) versus reciprocal of temperature is linear, the \(\Delta H_s\) term may be evaluated easily from the slope of that line. The heats of solution calculated from the regression of the van't Hoff plot are presented in table 5.2. Since the slope of these plots changes between temperatures -14.5 and -26, the solubility at -26 degrees centigrade was not considered for the regression analysis. The heat of
solution does not depend on composition or temperature in the +21 to -14 temperature range. The heat of solution is nearly a constant at 1.2 kcal per mole. The solubility is largely independent of temperature in this temperature range. This is expected as the heat of solution is low.

In summary, the present study indicates that the solubility of oxacillin sodium decreases slightly with temperature. However, the results show an increase in drug solubility at temperatures below -14.5 degrees centigrade. This is attributed to a different form of drug and is corroborated by the thermal analysis. Therefore decreasing temperature below -14.5 degrees may improve stability by reducing the reaction rate but not by reducing the drug solubility.
Figure 5.1: Schematic Diagram of Filtration Unit
FIGURE 5.2: SOLUBILITY OF OXACILLIN SODIUM AT 21 DEGREES CENTIGRADE
FIGURE 5.3: SOLUBILITY OF OXACILLIN SODIUM AT 12 DEGREES CENTIGRADE
FIGURE 5.4: SOLUBILITY OF OXACILLIN SODIUM AT 5 DEGREES CENTIGRADE
FIGURE 5.5: SOLUBILITY OF OXACILLIN SODIUM AT -6 DEGREES CENTIGRADE
FIGURE 5.6: SOLUBILITY OF OXACILLIN SODIUM AT -14.5 DEGREES CENTIGRADE
Figure 5.7: Solubility of Oxacillin Sodium at -26 Degrees Centigrade
FIGURE 5.8: DSC THERMOGRAM OF 50% AQUEOUS SUSPENSION
OXACILLIN SODIUM (HEATING CURVE)
<table>
<thead>
<tr>
<th>TEMPERATURE (°C)</th>
<th>SLOPE</th>
<th>INTERCEPT</th>
<th>R SQUARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>-0.49</td>
<td>2.43</td>
<td>0.98</td>
</tr>
<tr>
<td>12</td>
<td>-0.51</td>
<td>2.43</td>
<td>0.97</td>
</tr>
<tr>
<td>5</td>
<td>-0.54</td>
<td>2.41</td>
<td>0.99</td>
</tr>
<tr>
<td>-6</td>
<td>-0.67</td>
<td>2.49</td>
<td>0.92</td>
</tr>
<tr>
<td>-14.5</td>
<td>-0.49</td>
<td>2.33</td>
<td>0.98</td>
</tr>
<tr>
<td>-26.0</td>
<td>-0.54</td>
<td>2.44</td>
<td>0.95</td>
</tr>
<tr>
<td>COMPOSITION</td>
<td>R SQUARE</td>
<td>( \Delta H_s ) (Kcal/mole)</td>
<td>INTERCEPT</td>
</tr>
<tr>
<td>-------------</td>
<td>----------</td>
<td>-------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>0.3</td>
<td>0.99</td>
<td>0.869</td>
<td>-1.42</td>
</tr>
<tr>
<td>0.4</td>
<td>0.92</td>
<td>1.232</td>
<td>-1.22</td>
</tr>
<tr>
<td>0.5</td>
<td>0.99</td>
<td>1.133</td>
<td>-1.34</td>
</tr>
<tr>
<td>0.6</td>
<td>0.89</td>
<td>1.356</td>
<td>-1.19</td>
</tr>
<tr>
<td>0.7</td>
<td>0.94</td>
<td>1.315</td>
<td>-1.29</td>
</tr>
<tr>
<td>0.8</td>
<td>0.87</td>
<td>1.356</td>
<td>-1.33</td>
</tr>
<tr>
<td>0.9</td>
<td>0.93</td>
<td>1.516</td>
<td>-1.28</td>
</tr>
<tr>
<td>1.0</td>
<td>0.93</td>
<td>0.929</td>
<td>-1.78</td>
</tr>
</tbody>
</table>
CHAPTER 6

SUMMARY

Freeze-drying, or lyophilization, is frequently regarded as an expensive process due to often long process times and high capital equipment costs. So there is considerable economic motivation to minimize process times. Indeed, the objective of the freeze-drying process development is to minimize the process time while maintaining high product quality.

Heat transfer from the source to the sublimation interface is usually the rate limiting process and thus leading to lengthy drying cycles. The gas phase resulting from lack of intimate contact between the heat source and the frozen product presents a largest resistance to heat transfer during the lyophilization of parenteral solutions.

Several heat transfer augmentation devices, including a multilayered corrugated aluminum quilt and a conformal fluid cushion device, which fills this gap were described. Using these devices the temperature difference across the embedding space between the vial bottom and the shelf top was reduced due to enhanced heat transfer. The sublimation rate was increased. The drying time was decreased due to the faster cooling and drying of the
product. The fluid cushion device was found to be superior to the aluminum quilt as it does not allow the accidently spilled solution to stay underneath the vials and it provided greater vial to vial temperature uniformity among the same batch of vials. It is likely that it will also increase the batch to batch temperature uniformity and reduce the probability of meltback due to decreased intravial temperature variation.

The solubility behavior of the nonelectrolyte solutes in cosolvent-water mixtures can be expressed by the following expression:

$$\log S_m = \log S_w + f\sigma$$

where $f$ is the volume fraction of cosolvent and $\sigma$ is a coefficient characteristic of a particular cosolvent. The solubilities of sodium chloride and potassium chloride were measured in eight cosolvent-water mixtures using argentimetric titrations. The solubility of both the electrolyte solutes was found to obey the above log-linear relationship. A cosolvent which was most effective in solubilizing the nonelectrolyte solutes was also found to be most effective in desolubilizing the electrolyte solutes.

The solubility of oxacillin sodium was determined in methanol-water mixtures at various temperatures
ranging from +21 to -26 degrees centigrade. The solubility of oxacillin sodium decreased slightly with a decrease in temperature. However, the results showed an increase in drug solubility at temperatures below -14.5 degree centigrade. This anomalous behavior can be attributed to a different form of drug and was corroborated by the thermal analysis. Therefore, decreasing the temperature of the drug solution below -14.5 degrees centigrade might improve the drug stability by reducing the reaction velocity.
APPENDIX

PHYSICOCHEMICAL PROPERTIES
OF
SOME MATERIALS OF INTEREST
<table>
<thead>
<tr>
<th>LIQUID</th>
<th>TEMPERATURE (°C)</th>
<th>THERMAL CONDUCTIVITY (cal cm⁻¹ sec⁻¹ (°C)⁻¹ x 10⁷)</th>
<th>BOILING POINT (°C)</th>
<th>HEAT CAPACITY (cal gm⁻¹ (°C)⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerin</td>
<td>0</td>
<td>0.674</td>
<td>290</td>
<td>0.5399</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>0.684</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylene</td>
<td>0</td>
<td>0.578</td>
<td>197</td>
<td>0.5478</td>
</tr>
<tr>
<td>Glycol</td>
<td>27</td>
<td>0.602</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>0</td>
<td>19.6</td>
<td>357</td>
<td>0.0335</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>20.4</td>
<td></td>
<td>0.0333</td>
</tr>
<tr>
<td>Water</td>
<td>0</td>
<td>1.374</td>
<td>100</td>
<td>1.0042</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>1.454</td>
<td></td>
<td>0.9975</td>
</tr>
</tbody>
</table>

### THERMAL CONDUCTIVITIES

SOME MATERIALS COMMON TO LYOPHILIZATION

<table>
<thead>
<tr>
<th>MATERIAL</th>
<th>TEMPERATURE (°C)</th>
<th>THERMAL CONDUCTIVITY x 10^3 (cal cm⁻¹ sec⁻¹ (°C⁻¹))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borosilicate Glass¹</td>
<td></td>
<td>205.0</td>
</tr>
<tr>
<td></td>
<td>-100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>260.0</td>
</tr>
<tr>
<td>Aluminum²</td>
<td>-73</td>
<td>566.45</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>566.45</td>
</tr>
<tr>
<td>Copper³</td>
<td>-73</td>
<td>987.0</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>958.0</td>
</tr>
<tr>
<td>Steel³</td>
<td>18</td>
<td>112.0</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>107.0</td>
</tr>
<tr>
<td>Air²</td>
<td>-23</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>0.063</td>
</tr>
<tr>
<td>Ice²</td>
<td>-20</td>
<td>4.85</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4.49</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>20</td>
<td>0.833</td>
</tr>
</tbody>
</table>

THERMAL CONDUCTIVITIES OF SOME NONVOLATILE OILS NEAR ROOM TEMPERATURE

<table>
<thead>
<tr>
<th>OIL</th>
<th>TEMPERATURE (°C)</th>
<th>THERMAL CONDUCTIVITY x 10^3 (cal cm⁻¹ sec⁻¹ (°C)⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mineral Oil</td>
<td>20</td>
<td>0.313</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>0.308</td>
</tr>
<tr>
<td>Petroleum Oil</td>
<td>20</td>
<td>0.359</td>
</tr>
<tr>
<td>Silicone Oil²</td>
<td>60</td>
<td>0.237</td>
</tr>
<tr>
<td>(MW 162)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MW 1200)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MW 15800)</td>
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<td></td>
</tr>
<tr>
<td>Transformer Oil</td>
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<td>0.325</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.320</td>
</tr>
<tr>
<td>Castor Oil</td>
<td>20</td>
<td>0.425</td>
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<tr>
<td>Cylinder Oil</td>
<td>81</td>
<td>0.290</td>
</tr>
<tr>
<td>Olive Oil</td>
<td>15.7</td>
<td>0.4515</td>
</tr>
<tr>
<td>Turpentine Oil</td>
<td>12</td>
<td>0.260</td>
</tr>
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REFERENCES


