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A Review on Freeze Drying Process of Pharmaceuticals

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ABSTRACT

Freeze-drying is a method of removing water by sublimation of ice crystals from frozen material. Suitable parameters of process application allow us to obtain best quality products compared to products dried with traditional methods. In pharmaceutical field lyophilization has become important subject to ongoing development and its expansion. Lyophilization is common, but cost intensive and hence one of the key objectives during freeze-drying process development is to minimize the drying time (mainly primary drying time, which is the longest of the three steps in freeze-drying). However, increasing the shelf temperature into secondary drying before all of the ice is removed from the product will likely cause collapse or eutectic melt. Thus, from product quality as well as process economics standpoint, it is very critical to detect the end of primary drying. This review focused on the recent advances and its targets in near future. At first, the principle, steps involved, formulation aspects and importance of lyophilization, methods of lyophilization with detection of end point in lyophilization was explained.

KEYWORDS- End point of freeze-drying, Freeze drying, Freeze drying methods, Lyophilization.

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TABLE OF CONTENT

INTRODUCTION

The term ‘lyophilization’ describes a process to produce a product that ‘loves the dry state.’ However, this term does not include the freezing process. Therefore, although lyophilization and freeze-drying are used interchangeably, freeze-drying is a more descriptive term.[1] Lyophilization is the most common method for manufacturing parenterals when aqueous solution stability is an issue. It is central to the protection of materials, which require low moisture content (less than 1%) in order to

ensure stability and require a sterile and gentle preservation process.[2] Freeze drying has been used in a number of applications for many years, most commonly in the food and pharmaceutical industries. There are, however, many other uses for the process including the stabilization of living materials such as microbial cultures, preservation of whole animal specimens for museum display, restoration of books and other items damaged by water, and the concentration and recovery of reaction products.[3] Freeze-drying or lyophilisation is an effective way of drying materials without harming them. It makes use of the physical phenomenon of sublimation, which involves the direct transition between the solid state and the gaseous state without passing through the liquid phase. To achieve this, the frozen product is dried under vacuum, without being allowed to thaw out. The process of freeze-drying has taken on greater prominence in the parenteral industry, due to the advent of recombinant DNA technology. Proteins and peptides must be freeze-dried for clinical and commercial use. There are other technologies available to produce sterile dry powder drug products besides freeze-drying, such as sterile crystallization or spray-drying and powder filling. However, freeze-drying is the most common unit process for manufacturing drug products too unstable to be marketed as solutions.[4]

The steps involved in the formulation of freeze dried product are depicted in below figure.(Figure 1)

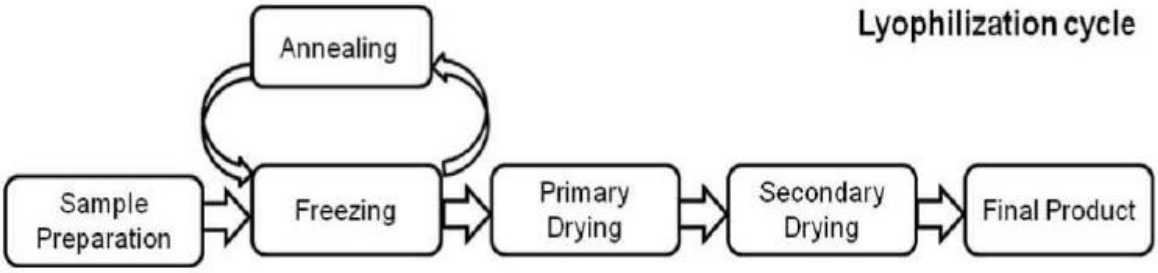

Figure. 1-**Steps involved in lyophilization from sample preparation to final product formation**

ADVANTAGES

- Oxidizable substances are well protected under vacuum conditions.
- Long preservation period owing to 95%-99.5% water removal.
- Loading quantity accurate and content uniform.
- Little contamination owing to aseptic process.
- Minimal loss in volatile chemicals and heat-sensitive nutrient and fragrant components.
- Minimal changes in the properties because microbe growth and enzyme effect can not be exerted under low temperature.
- Transportation and storage under normal temperature.
- Rapid reconstitution time.

- Constituents of the dried material remain homogenously dispersed.
- Product is process in the liquid form.
- Sterility of product can be achieved and maintained.

DISADVANTAGES

- Volatile compounds may be removed by high vacuum.
- Single most expensive unit operation.
- Stability problems associated with individual drugs.
- Some issues associated with sterilization and sterility assurance of the dryer chamber and aseptic loading of vials into the chamber.

DESIRED CHARACTERISTICS OF FREEZE-DRIED PRODUCTS

- Intact cake
- Sufficient strength
- Uniform color
- Sufficiently dry
- Sufficiently porous
- Sterile
- Free of pyrogens
- Free of particulates
- Chemically stable

THE PRINCIPLE OF FREEZE-DRYING

At atmospheric pressure (approx. 1,000 mbar) water can have three physical states

- Solid;
- Liquid;
- Gaseous.

Below the triple-point (for pure water: 6.1 mbar at 0°C), only the solid and the gaseous states exist (Figure.2).

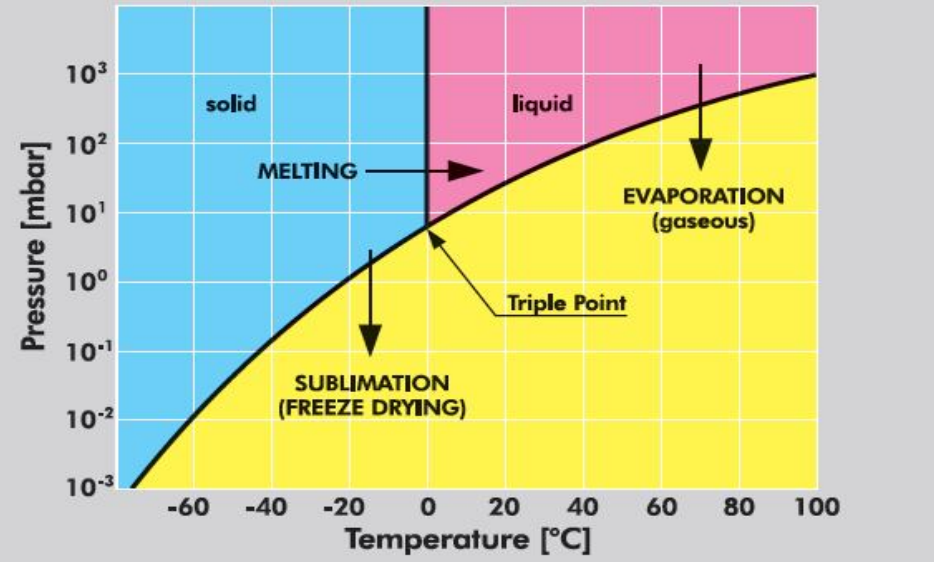

Figure 2- Phase diagram of water

The principle of freeze/sublimation-drying is based on this physical fact. The ice in the product is directly converted into water vapor (without passing through the "fluid state") if the ambient partial water vapor pressure is lower than the partial pressure of the ice at its relevant temperature (Table 1).

Table 1: Ice vapor pressure data

Tempera-ture (°C)	Vacuum (mbar)	Tempera-ture (°C)	Vacuum (mbar)	Tempera-ture (°C)	Vacuum (mbar)	Tempera-ture (°C)	Vacuum (mbar)	Tempera-ture (°C)	Vacuum (mbar)
0	6.110	-16	1.510	-34	0.250	-54	0.024	-70	0.0026
-1	5.620	-17	1.370	-35	0.220	-55	0.021	-71	0.0023
-2	5.170	-18	1.250	-36	0.200	-56	0.018	-72	0.0019
-3	4.760	-19	1.140	-37	0.180	-57	0.016	-73	0.0017
-4	4.370	-20	1.030	-38	0.160	-58	0.014	-74	0.0014
-5	4.020	-21	0.940	-39	0.140	-59	0.012	-75	0.0012
-6	3.690	-22	0.850	-40	0.120	-60	0.011	-76	0.0010
-7	3.380	-23	0.770	-41	0.110	-61	0.009		
-8	3.010	-24	0.700	-46	0.060	-62	0.008		
-9	2.840	-25	0.630	-47	0.055	-63	0.007		
-10	2.560	-28	0.470	-48	0.050	-64	0.006		
-11	2.380	-29	0.420	-49	0.045	-65	0.0054		
-12	2.170	-30	0.370	-50	0.040	-66	0.0047		
-13	1.980	-31	0.340	-51	0.035	-67	0.0047		
-14	1.810	-32	0.310	-52	0.030	-68	0.0035		
-15	1.650	-33	0.280	-53	0.025	-69	0.003		

Sublimation of water can take place at pressures and temperature below triple point i.e. 4.579 mm of Hg and 0.0099 degree Celsius.[5] The material to be dried is first frozen and then subjected under a high vacuum to heat (by conduction or radiation or by both) so that frozen liquid sublimes leaving only solid ,dried components of the original liquid. The concentration gradient of water vapor between the drying front and condenser is the driving force for removal of water during lyophilization.

To extract water from formulation, the process of lyophilization consists of :

1. Freezing the formulation so that the water in the food become ice.
2. Under a vacuum, sublimating the ice directly into water vapour.
3. Drawing off the water vapour.
4. Once the ice is sublimated, the foods are freeze dried and can be removed from the machine.[6]

FREEZE DRYING PROCESS

The freeze drying process consists of three stages:

1. Freezing,
2. Primary drying, and
3. Secondary drying.

FREEZING:

Since freeze drying is a change in state from the solid phase to the gaseous phase, material to be freeze dried must first be adequately prefrozen. The method of freezing and the final temperature of the frozen product can affect the ability to successfully freeze dry the material. Rapid cooling results in small ice crystals, useful in preserving structures to be examined microscopically, but resulting in a product that is more difficult to freeze dry. Slower cooling results in larger ice crystals and less restrictive channels in the matrix during the drying process.

Products freeze in two ways, depending on the makeup of the product. The majority of products that are subjected to freeze drying consist primarily of water, the solvent, and the materials dissolved or suspended in the water, the solute. Most samples that are to be freeze dried

are eutectics which are a mixture of substances that freeze at lower temperatures than the surrounding water. When the aqueous suspension is cooled, changes occur in the solute concentrations of the product matrix. And as cooling proceeds, the water is separated from the solutes as it changes to ice, creating more concentrated areas of solute. These pockets of concentrated materials have a lower

freezing temperature than the water. Although a product may appear to be frozen because of all the ice present, in actuality it is not completely frozen until all of the solute in the suspension is frozen. The mixture of various concentration of solutes with the solvent constitutes the eutectic of the suspension. Only when all of the eutectic mixture is frozen is the suspension properly frozen. This is called the eutectic temperature. It is very important in freeze drying to prefreeze the product to below the eutectic temperature before beginning the freeze drying process. Small pockets of unfrozen material remaining in the product expand and compromise the structural stability of the freeze dried product.

The second type of frozen product is a suspension that undergoes glass formation during the freezing process. Instead of forming eutectics, the entire suspension becomes increasingly viscous as the temperature is lowered. Finally the product freezes at the glass transition point forming a vitreous solid. This type of product is extremely difficult to freeze dry.

The freezing point can be determined by means of,

- Theoretical thermodynamic value
- Cryo-microscope
- DSC (Differential Scanning Calorimetry)
- Measurement of temperature and resistance during the freezing phase

The electric resistance of the product being dried almost always rises dramatically with the transfer from the liquid to the solid state due to the reduced mobility of the ions and electrons. This means that by measuring the product temperature and electrical resistance at the same point it is possible to determine the freezing point. Because there is usually a very abrupt rise in resistance, the intersection of the Rx- and T-curves can be taken as the freezing point with a very high level of accuracy. This has been confirmed by numerous measurements with various solutions.

PRIMARY DRYING

After the freezing step has been completed, the pressure within the freeze-dryer is reduced using a vacuum pump. Typical chamber pressures in the lyophilization of pharmaceuticals range from 30 and 300 mTorr and depend on the desired product temperature and the characteristics of the container system. The chamber pressure needs to be lower than the vapor pressure of ice at the sublimation interface in the product to facilitate sublimation of ice and transport of water vapor to the condenser where it is deposited as ice. Very high chamber pressures decrease the sublimation rate by reducing the pressure gradient between sublimation interface and chamber, thereby mitigating the driving force for

sublimation and continuing removal of ice. If the chamber pressure exceeds the vapor pressure at the sublimation interface, no mass transfer is possible. On the other hand, very low pressures (< 50 mTorr) are also counter productive for fast sublimation rates since they greatly limit the rate of heat transfer to the product. The ice at the sublimation interface shows a vapor pressure that is directly correlated to the product temperature (Table 1). Once the chamber pressure decreases below the vapor pressure of ice in the product, sublimation can occur, i.e. ice is removed from the top of the frozen layer and directly converted to water vapor. Water vapor is transported to the ice condenser and deposited onto the coils or plates which are constantly cooled to a temperature associated with very low vapor pressure of the condensed ice. The sublimation of water from the product requires energy (temperature-dependent, around 670 cal/g), leading to cooling of the product. The energy for continuing sublimation of ice needs to be supplied from the shelves that are heated to a defined higher temperature. The product temperature is in general the most important product parameter during a freeze drying process, in particular the product temperature at the sublimation interface during primary drying.[7] Low product temperature and the corresponding low vapor pressure of ice result in extensive primary drying times. It has been reported that elevation of product temperature by 1°C can reduce the overall primary drying time by as much as 13%, which offers enormous potential of saving process time and manufacturing costs when administering more aggressive product temperatures.[8] However, an increase of product temperatures to temperatures above the "critical formulation temperature" which refers to the eutectic melting temperature, TE, for crystalline and to Tc or Tg for amorphous materials, mostly leads to loss of cake structure. If the critical temperature is exceeded, the dried pore structure close to the sublimation front that still contains high amounts of water can undergo viscous flow, resulting in fusion of pores and formation of holes in the cake structure. This occurrence is associated with a reduction of inner surface area as well as elevated moisture contents with potentially detrimental effects on reconstitution time and completeness as well as API stability.[9] Most importantly, the cake shows shrinkage or may fully collapse, making the product unsuitable for sale and application in patients due to the lack of elegance. The critical formulation temperature can be determined using Freeze-Dry Microscopy (FDM) which allows observation of the drying cake structure under vacuum at varying temperatures.[10] Once the collapse temperature is reached it is possible to observe formation of holes in the dried cake structure. Since the sample is being dried during the experiment, the conditions are more similar to lyophilization than alternative methods, making the results more representative for a vial freeze-drying process.[11] A different approach to determine the critical formulation temperature is Differential Scanning Calorimetry (DSC) which measures the heat flow and thermal properties of the

frozen sample. This way it is possible to determine the glass transition temperature of the maximally freeze-concentrated solute, Tg , which is indicative for molecular mobility in the amorphous matrix.[12] Since no removal of water is involved, the critical temperature is not as representative for vial freeze-drying as the collapse temperature determined using FDM. It is possible to increase the critical temperature by crystallizing salts (i.e. buffers etc.) quantitatively during freezing, or by adding amorphous excipients with high Tg' values such as dextran or cyclodextrines.[13] If formulations with high contents of crystallizing solutes are lyophilized, a crystalline lattice is formed that is stable up to product temperatures equivalent to the eutectic melting point TE which is much higher than common Tg' values. Therefore it is possible to create formulations with a high ratio of crystallizing substances and freeze-dry at temperatures above the Tg' of the amorphous ingredients which then collapse onto the crystalline matrix. Thus no global loss of structure occurs and the cake appearance is still elegant. It is important to pay close attention to API stability and choice of stabilizers to obtain a product stable over the shelf life when following such an approach, but it offers huge benefits for process optimization.[14]

SECONDARY DRYING

In the area where the ice has already been removed, desorption of water from the cake occurs; this process is referred to as secondary drying and already starts in the primary drying phase. Once all ice has been removed from all product containers, the shelf temperature is elevated and typically maintained at a temperature between 20°C and 40°C for several hours. The rate of desorption and the obtainable moisture level is controlled by diffusion within the solute phase and desorption from the surface and therefore depends mostly on product temperature; further reduction of chamber pressure is not required.[15] The ramp rate to the secondary drying temperature needs to be moderate (0.1°C/min to 0.3°C/min) for amorphous substances to avoid surpassing the glass transition of the lyophilized cake and pertaining cake shrinkage. Secondary drying times are usually designed to achieve a reduction of moisture content within the cake to less than 1%. For most lyophilized API's the stability increases with the reduction of moisture, so it is beneficial to reduce the residual moisture as much as possible.[16] However, thermal stresses to the API due to the elevated product temperature need to be considered. Especially for proteins it is necessary to determine optimal secondary drying conditions which result in an optimum moisture content without detrimental effects from heating. For some protein formulations, the stability optimum has been found at intermediate moisture contents, i.e. between 1-3% RM.[17] Targeting of such moisture contents for all vials in the batch is often difficult and hard to monitor.

FACTORS AFFECTING THE PROCESS RATE

From the diagram in Figure 3, it can be seen that the direction of heat and mass transfer causes the top of the product to dry first with drying proceeding downward to the bottom of the vial. Therefore, as drying proceeds, there exists a three-component or layer system in each vial—the upper dry product, the middle sublimation front, and the lower frozen liquid product.

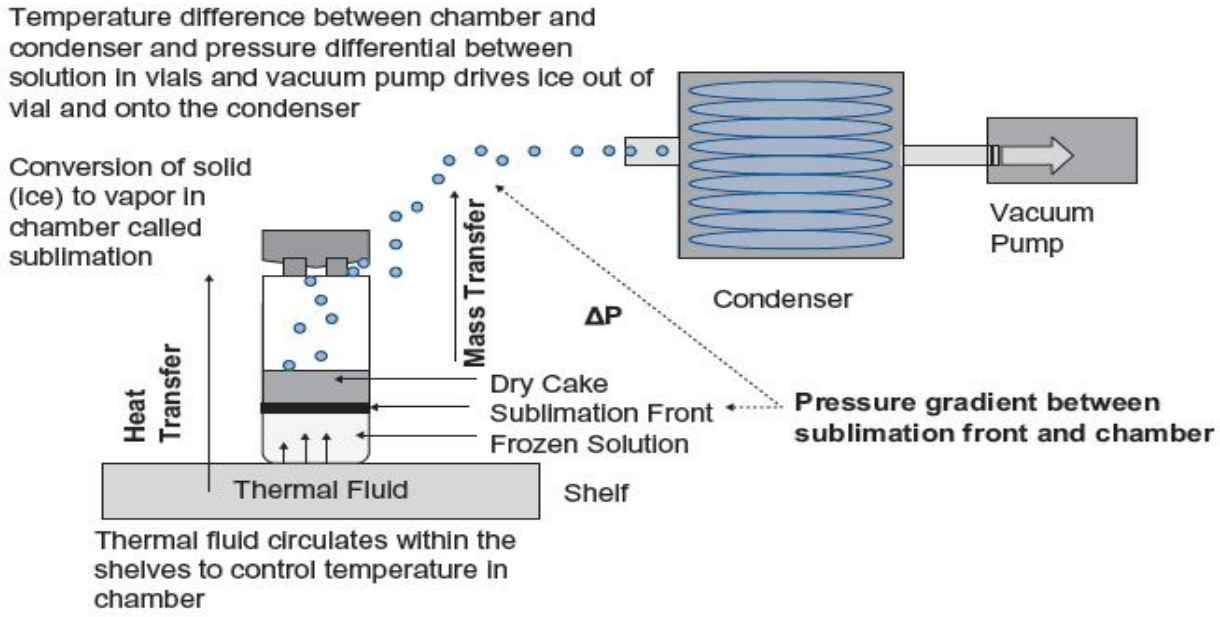

Figure 3- Schematic of heat and mass transfer in the freeze dryer.

As the dried layer increases, it becomes a greater barrier or the source of greatest resistance to the transfer of mass out of the vials. This points out the importance of vial dimensions and volume of product per vial on the efficiency of the freeze-drying process. If large volumes of solution must be processed, the surface area relative to the depth may be increased, utilizing larger vials or by using such devices as freezing the container in a slanted position to increase the surface area. The actual driving force for the process is the vapor pressure differential between the vapor at the surface where drying of the product is occurring (the drying boundary) and at the

surface of the ice on the condenser. The latter is determined by the temperature of the condenser, as modified by the insulating effect of the accumulated ice. The former is determined by a number of factors, including:

1. The rate of heat conduction through the container and the frozen material, both relatively poor thermal conductors, to the drying boundary, while maintaining all of the product below its eutectic temperature.
2. The impeding effect of the increasing depth of dried, porous product above the drying boundary.
3. The temperature and heat capacity of the shelf itself.

The passageways between the product surface and the condenser surface must be wide open and direct for effective operation. The condensing surfaces in large freeze-dryers may be in the same chamber as the product or located in a separate chamber connected by a duct to the drying chamber. Evacuation of the system is necessary to reduce the impeding effect that collisions with air molecules would have on the passage of water molecules. However, the residual pressure in the system must be greater than the vapor pressure of the ice on the condenser, or the ice will be vaporized and pulled into the pump, an event detrimental to most pumps. The amount of solids in the product, the ice crystal size, and their thermal conductance affect the rate of drying. The more solids present, the more impediment will be provided to the escape of the water vapor. The degree of supercooling (i.e., how much lower the product temperature goes below its equilibrium freezing point before ice crystals first form) and the rate of ice crystallization define the freezing process and efficiency of primary drying. The larger the size of ice crystals formed, usually as a result of slow freezing, the larger the pore sizes are when the ice sublimes and, consequently, the faster the rate of drying. A high degree of supercooling produces a large number of small ice crystals, a small pore size when the ice sublimes in the dried layer, and a greater resistance to water vapor transport during primary drying. The poorer the thermal conducting properties of the solids in the product, the slower the rate of heat transfer through the frozen material to the drying boundary. The rate of drying is slow, most often requiring 24 hours or longer for completion. The actual time required, the rate of heat input, and the product temperatures used must be determined for each product and then reproduced carefully with successive processes.[18]

FREEZE DRYING METHODS

Three methods of freeze drying are commonly used:

1. Manifold drying,
2. Batch drying, and
3. Bulk drying.

Each method has a specific purpose, and the method used depends on the product and the final

configuration desired.

MANIFOLD METHOD

In the manifold method, flasks, ampules or vials are individually attached to the ports of a manifold or drying chamber. The product is either frozen in a freezer, by direct submersion in a low temperature bath, or by shell freezing, depending on the nature of the product and the volume to be freeze dried. The prefrozen product is quickly attached to the drying chamber or manifold to prevent warming. The vacuum must be created in the product container quickly, and the operator relies on evaporative cooling to maintain the low temperature of the product. This procedure can only be used for relatively small volumes and products with high eutectic and collapse temperatures. Manifold drying has several advantages over batch tray drying. Since the vessels are attached to the manifold individually, each vial or flask has a direct path to the collector. This removes some of the competition for molecular space created in a batch system, and is most ideally realized in a cylindrical drying chamber where the distance from the collector to each product vessel is the same. In a “tee” manifold, the water molecules leaving the product in vessels farthest from the collector experience some traffic congestion as they travel past the ports of other vessels.

Heat input can be affected by simply exposing the vessels to ambient temperature or via a circulating bath. For some products, where precise temperature control is required, manifold drying may not be suitable. Several vessels can be accommodated on a manifold system allowing drying of different products at the same time, in different sized vessels, with a variety of closure systems. Since the products and their volumes may differ, each vessel can be removed from the manifold separately as its drying is completed. The close proximity to the collector also creates an environment that maximizes drying efficiency.

BATCH METHOD

In batch drying, large numbers of similar sized vessels containing like products are placed together in a tray dryer. The product is usually prefrozen on the shelf of the tray dryer. Precise control of the product temperature and the amount of heat applied to the product during drying can be maintained. Generally all vials in the batch are treated alike during the drying process, although some variation in the system can occur. Slight differences in heat input from the shelf can be experienced in different areas. Vials located in the front portion of the shelf may be radiantly heated through the clear door. These slight variations can result in small differences in residual moisture. Batch drying allows closure of all vials

in a lot at the same time, under the same atmospheric conditions. The vials can be stoppered in a vacuum, or after backfilling with inert gas. Stoppering of all vials at the same time ensures a uniform environment in each vial and uniform product stability during storage. Batch drying is used to prepare large numbers of ampules or vials of one product and is commonly used in the pharmaceutical industry.

BULK METHOD

Bulk drying is generally carried out in a tray dryer like batch drying. However, the product is poured into a bulk pan and dried as a single unit. Although the product is spread throughout the entire surface area of the shelf and may be the same thickness as product dried in vials, the lack of empty spaces within the product mass changes the rate of heat input. The heat input is limited primarily to that provided by contact with the shelf as shown in Figure 4.

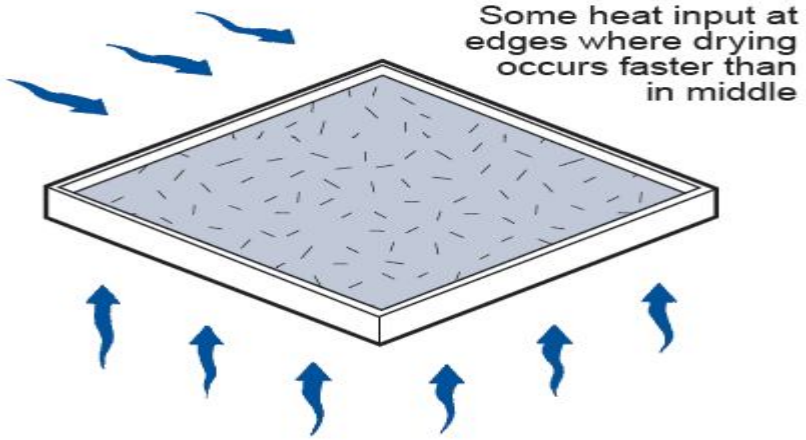

Figure. 4-bulk drying, heat is provided primarily through conduction from shelf.

Bulk drying does not lend itself to sealing of product under controlled conditions as does manifold or batch drying. Usually the product is removed from the freeze dry system prior to closure, and then packaged in air tight containers. Bulk drying is generally reserved for stable products that are not highly sensitive to oxygen or moisture.[19]

DETERMINATION OF END POINT OF FREEZE-DRYING PROCESS

The following are the techniques used for determination of end point of primary drying process,

Techniques based on gas composition in the product chamber:

1. Comparative pressure measurement (i.e., Pirani vs. capacitance manometer)

2. Dew point monitor (electronic moisture sensor)

3. Process H2O concentration from tunable diode laser absorption spectroscopy (TDLAS)

4. Lyotrack (gas plasma spectroscopy)

Others:

5. Product thermocouple response

6. Condenser pressure

7. Pressure rise test (manometric temperature measurement (MTM) or variations of this method)

COMPARATIVE PRESSURE MEASUREMENT (I.E., PIRANI VS. CAPACITANCE MANOMETER)

During the drying step, the chamber pressure is controlled using a capacitance manometer, which measures the absolute pressure in the drying chamber. However, the Pirani vacuum gauge works on the principle of measuring the thermal conductivity of the gas in the drying chamber.[20] The Pirani gauge reads about 60% higher than the capacitance manometer (i.e., MKS Baratron) during primary drying when essentially all of the gas in the chamber is water vapor. This is because the thermal conductivity of water vapor is ~1.6 times the thermal conductivity of nitrogen. With this inherent property, the Pirani vacuum gauge can be used to detect the end of primary drying. The point where the Pirani pressure starts to sharply decrease (i.e., onset) indicates that the gas composition is changing from mostly water vapor to nitrogen; i.e., sublimation is "essentially" complete (Fig. 5).

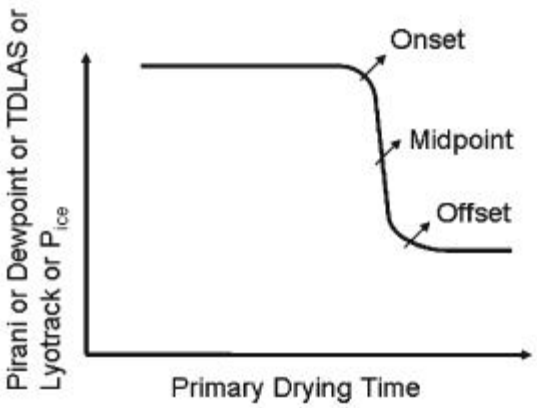

Figure. 5. Pirani pressure, dew point, TDLAS (process [H2O]), Lyotrack (gas composition), and Pice (vapor pressure of ice from pressure rise test) profile during primary drying

DEW POINT

An electronic moisture sensor can be used to measure the frost point, which is the temperature at which ice has an equilibrium vapor pressure equal to the measured partial pressure of water. The measurement is based on the principle of changes in the capacitance of a thin film of aluminum oxide arising from adsorption of water at a given partial pressure. Similar to the Pirani, the point where "dew point" starts dropping indicates that the sublimation is "essentially" complete, i.e. gas composition is changing from mostly water vapor to nitrogen (fig 5).[21]

PROCESS H_2O CONCENTRATION VIA TDLAS

Tunable diode laser absorption spectroscopy (TDLAS) directly measures the water vapor concentration (molecules/ cm3) in the duct connecting the chamber and the condenser. The TDLAS unit is commonly installed with two laser beams, one directed with and the other directed against the vapor flow. TDLAS works on basic spectroscopic principles measuring absorption of radiation by water vapor to monitor the trace concentration of water vapor in real time. A laser beam is passed through a gas mixture containing a quantity of the target gas, and the beam's wavelength is tuned to one of the target gas's absorption lines to accurately measure the absorption of that beam from which one can deduce the average concentration of target gas molecules integrated over the beam's path length. the sublimation rate can be determined from the gas flow velocity and concentration of water vapor. The point where water concentration starts decreasing sharply (i.e., onset) indicates that the gas composition is changing, and hence sublimation is "essentially" complete (Fig. 5).[22]

LYOTRACK (GAS PLASMA SPECTROSCOPY)

This method is the latest addition to the online monitoring devices for freeze-drying and is manufactured by Alcatel Vacuum Technology, France. Lyotrack is based on optical emission spectroscopy and measures water vapor concentration during the drying process. It consists of a plasma generator and an optical spectrometer. Lyotrack gas composition signal was sensitive to gas composition in the chamber as well as the duct but not in the condenser. The wavelengths of the emitted light are the characteristic signatures for the identification of the atom or molecule. The point where water vapor concentration starts sharply decreasing (i.e., onset) indicates that the gas composition is changing, and hence sublimation is "essentially" complete (Fig.5).[23]

PRODUCT TEMPERATURE DURING PRIMARY DRYING

The end point of primary drying can also be determined from the product thermocouple response, assuming the vials containing the thermocouples are representative of the batch as a whole.[24] Product temperature approaching the shelf temperature set point (i.e., "offset" in Fig.6) is commonly taken as an indication of the end of primary drying.

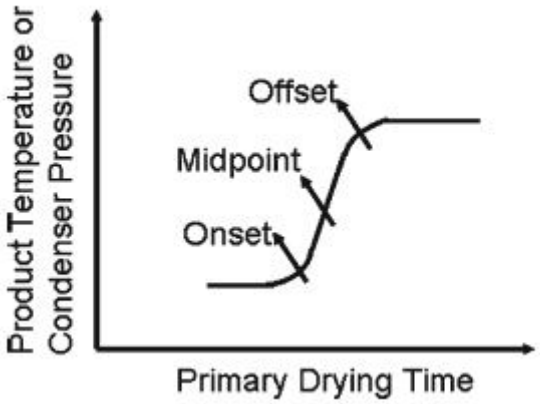

Figure. 6. Product temperature and condenser pressure profile during primary drying

CONDENSER PRESSURE DURING PRIMARY DRYING

Yet another indicator of the end point of primary drying is the condenser pressure. During primary drying, most of the gas in the chamber is water vapor, and because the total vapor flux is high, a high ΔP (difference between chamber and condenser pressure) develops to remove the water from the chamber. However, once primary drying is over, ΔP decreases (i.e., condenser pressure (Pcond) increases since chamber pressure (Pc) is held constant). The point where condenser pressure starts increasing (i.e., onset) indicates that the sublimation is "essentially" over since the high mass transfer portion of the process (i.e., sublimation) is largely over (Fig.6). A capacitance manometer installed in the condenser reads the condenser pressure.

PRESSURE RISE TEST

MTM is a procedure to measure the product temperature during primary drying by quickly isolating the chamber from the condenser for a short time (≈25 s) and analyzing the pressure rise during this period. This analysis yields vapor pressure of ice at the sublimation interface, the product temperature, and the

mass transfer resistance of the dried product.[25] However, the data obtained measure the vapor pressure of ice accurately only as long as the system remains in primary drying. At the end of primary drying, there is little or no pressure rise because all ice is gone, and hence the calculated "vapor pressure of ice" becomes equal to the chamber pressure (Fig. 5). Thus, a close approach of the calculated vapor pressure of ice to the chamber pressure forms the basis of the criterion for end of primary drying.

STABILITY OF FREEZE DRIED PRODUCTS

Several factors can affect the stability of freeze dried material. Two of the most important are moisture and oxygen. All freeze dried products have a small amount of moisture remaining in them termed residual moisture. The amount of moisture remaining in the material depends on the nature of the product and the length of secondary drying. Residual moisture can be measured by several means: chemically, chromatographically, manometrically or gravimetrically. It is expressed as a weight percentage of the total weight of the dried product. Residual moisture values range from <1% to 3% for most products. By their nature, freeze dried materials are hygroscopic and exposure to moisture during storage can destabilize the product. Packaging used for freeze dried materials must be impermeable to atmospheric moisture. Storing products in low humidity environments can reduce the risk of degradation by exposure to moisture. Oxygen is also detrimental to the stability of most freeze dried material so the packaging used must also be

impermeable to air. The detrimental effects of oxygen and moisture are temperature dependent. The higher the storage temperature, the faster a product degrades. Most freeze dried products can be maintained at refrigerator temperatures, i.e. 4-8°C. Placing freeze dried products at lower temperatures extends their shelf life. The shelf life of a freeze dried product can be predicted by measuring the rate of degradation of the product at an elevated temperature. This is called accelerated storage. By choosing the proper time and temperature relationships at elevated temperatures, the rate of product degradation can be predicted at lower storage temperatures.

CONCLUSION

The lyophilized technique proved to be an advantage for development of stable injectable dosage form as the moisture content of the formulation is greatly reduced thus enhancing the stability of the product, ease of handling, rapid dissolution because of porous nature of the cake and easier transport of the material during shipping. About 50% of the currently biopharmaceuticals are lyophilized, representing

the most common formulation strategy. In the freeze dried solid state, chemical or physical degradation reactions are inhibited or sufficiently decelerated, resulting in an improved long term stability.The awareness of the complexity of the freezing process and its

consequences on product quality and process performance is essential for successful lyophilization. The knowledge of how to control, or atleast manipulate, the freezing step will help to develop more efficient lyophilization cycles and biopharmaceutical products with an improved stability.

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