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Freeze-Drying/Lyophilization: As a Better Step in Pharmaceutical Process

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Abstract

Freeze-drying is a way of disposing of water via way of means of sublimation of ice crystals from frozen material. Suitable parameters of procedure application allow us to excellent quality products compared to products dried with the traditional methods. In the pharmaceutical discipline, lyophilization has come to be an essential situation for ongoing improvement and expansion. Lyophilization is common, however, value extensive and for this reason, one of the freeze-drying procedure improvements is to decrease the drying time (especially number one drying time, that's the longest of the 3 steps in freeze-drying).

However, growing the shelf temperature into secondary drying earlier than all the ice is eliminated from the product will probably reason disintegrates or eutectic melt. Thus, from a product excellent in addition to procedure economics standpoint, it's far very essential to locate the give up of number one drying. The overview centered on the latest advances and its objectives in close to future. At first, the principle, step involved, method components and significane of lyophilization, techniques of lyophilization with the detection of giving up factor in lyophilization become explained. In the 21st century, in the pharmaceutical discipline, lyophilization has come to be an essential situation for ongoing improvement and expansion. Lyophilization is common, however, value extensively. In vintage days procedure optimization become centered handiest on drying in preference to lyophilization. But lyophilization becomes more similarly essential for the procedure of pharmaceuticals.

Keywords: *- Freeze drying, Freeze drying methods, Lyophilization, Freeze Drying Equipment.*

INTRODUCTION

Lyophilization or freeze drying is a process in which water is frozen, then removed from the sample, sublimated initially (primary drying) and then desorbed (secondary Desiccation). Freezing- drying is a drying process in which water is sublimated from the product after it has been frozen. It is a drying process applicable to the manufacture of some pharmaceuticals and biologics, which are thermolabile or otherwise unstable in aqueous solutions for extended storage periods but which are stable in dry conditions. The word "lyophilization" defines a process in which a product "loves the dry state" is generated.

The word "lyophilization" defines a method for producing a commodity that "loves the dry state." However, the freezing method is not included in this phase. Thus, while lyophilization and freeze-drying are used interchangeably, a more descriptive term is freeze-drying. When aqueous solution stability is a concern, lyophilization is the most common method for producing parentals. In order to maintain stability and require a sterile and gentle preservation procedure, it is central to the safety of materials that require low moisture content (less than 1 percent). For many years, freeze-drying has been used in a variety of applications, most notably in the food and pharmaceutical industries. However, many other processes include the stabilisation of living materials, such as microbial cultures, the preservation of whole animal specimens for museum display, the conservation of books and other water-damaged objects, and the concentration and recovery of reaction products. Freeze-drying or lyophilization is an efficient way to dry materials without harming them. It makes use of the physical sublimation phenomenon, which requires direct transfer without going through the liquid phase between the solid-state and the gaseous state. The frozen product is dried under a vacuum to achieve this, without being able to thaw out. With the advent of recombinant DNA technology, the freeze-drying process has taken on greater prominence in the parenteral industry. Proteins and peptides for medicinal and commercial use must be freeze-dried. Besides freeze-drying, other technologies are available for manufacturing sterile dry

powder drug products, such as sterile crystallisation or spray-drying and powder filling. Freeze-drying is, however, the most common unit method for generating drug products that are too unstable to be sold as solutions.

PRINCIPLE

A system referred to as sublimation is the primary idea concerned with freeze-drying, in which water passes at once from the solid-state (ice) to the vapour state without going through the liquid condition. Water sublimation can arise at pressures and temperatures beneath the triple stage, i.e. 4,579 mm Hg and 0, 0099 degrees Celsius. The fabric to be dried is first frozen, after which uncovered to heat (through conduction or radiation or both) under excessive vacuum, so that it is frozen. Liquid Sublime, leaving the original liquid with only solid, dried parts. The gradient of water vapour concentration between the drying front and the condenser is the driving force for removing water during lyophilization.

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).

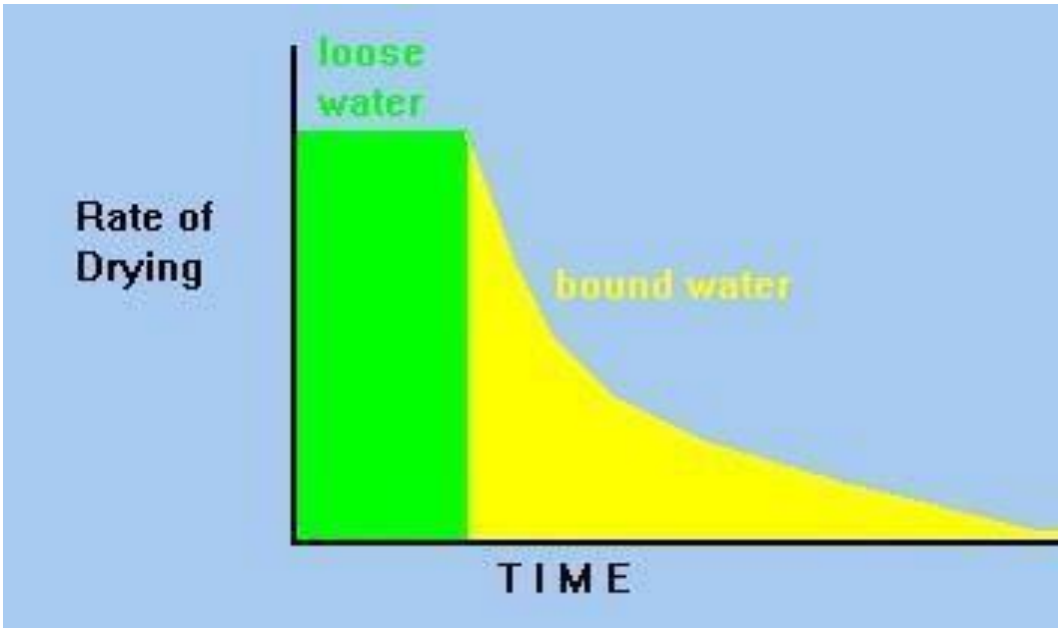

Figure 1: Rate of drying of water

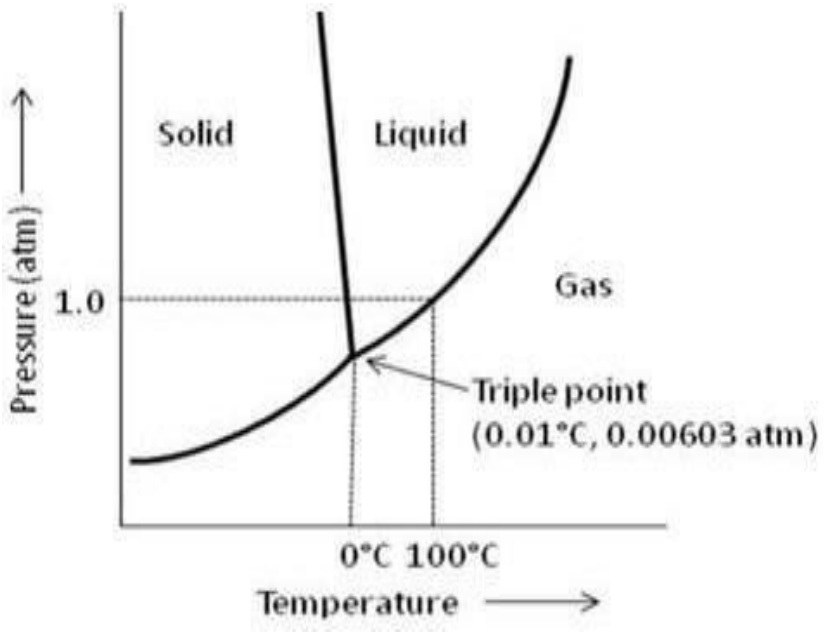

Figure 2: Phase diagram of water

On this physical reality, the theory of freeze/sublimation-drying is based. If the ambient partial water vapour pressure is lower than the partial pressure of the ice at its relevant temperature (Table 1), the ice in the substance is directly converted to water vapour (without going through the "fluid state")

Water sublimation can take place at pressures and temperatures below triple points, i.e. 4,579 mm Hg and 0,0099 degrees Celsius.5 The substance to be dried is first frozen and then heated (by conduction or radiation or both) under a high vacuum so that frozen liquid sublimates, leaving only solid, dried components of the original liquid.

The water vapour concentration gradient between the drying front and the condenser is the driving force during lyophilization for water removal. The technique of lyophilization consists of: to eliminate water from the formulation.

1. Freezing the formulation in order that the water within side the food ends up ice.

2. Under a vacuum, sublimating the ice at once into water vapour.

3. Drawing off the water vapour.

4. Once the ice is sublimated, the foods are freeze-dried and can be eliminated from the machine.

Table 1: Ice vapour pressure data

Temperature (°C)	Vacuum (mbar)	Temperature (°C)	Vacuum (mbar)	Temperature (°C)	Vacuum (mbar)	Temperature (°C)	Vacuum (mbar)	Temperature (°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		

The process of producing a product that "loves the dry state".

Freeze drying is typically used for pharmaceuticals to boost the safety and long-term storage of labile products, also known as lyophilization. In pharmaceutical manufacturing technology, lyophilization or freeze-drying fulfills a significant need by allowing heat-sensitive drugs and biologicals to be dried at low temperatures under conditions that enable water to be extracted by sublimation or a phase change from solid to vapour without passing through the liquid phase. The most common application of pharmaceutical freeze-drying is in the manufacturing process.

Lyophilization or freeze-drying is a a method in which after it is frozen and placed under a vacuum, water is extracted from a substance, allowing the ice to transform immediately from solid to vapour without going through a liquid phase.

At temperature and pressure conditions below the triple stage, lyophilization is performed in order to allow ice sublimation. At low temperature and pressure, the entire process is performed. It is also ideal for drying thermo-labile compounds. In order to achieve the final dried product with the correct moisture content, steps involved in lyophilization

begin with sample preparation followed by freezing, primary drying and secondary drying. The concentration gradient of water vapour between the drying front and the condenser is the driving force during lyophilization for water removal. With an increase in temperature during the primary drying, the vapour pressure of water increases. To prevent the loss of cake structure, the primary drying temperature should therefore be kept as high as possible but below the critical process temperature. This vital process temperature is the amorphous material collapse temperature, or the crystalline substance has a eutectic melt. Ice crystals begin to detach during freezing until the solution becomes maximally concentrated. The solution and ice are separated in phase upon further cooling. **See figure 3 below.**

ADVANTAGES

- Oxidizable materials are nicely protected under vacuum conditions.
- Long preservation duration due to 95%-99.5% water removal.
- Loading amount correct and content material uniform.
- Little contamination due to aseptic process.
- Minimal loss in volatile chemicals compound and heat-sensitive nutrient and aromatic components.
- Minimal changes in the properties because microbe growth and enzyme effect cannot be exerted under low temperature. Transportation and storage under ordinary temperature.
- Rapid reconstitution time.
- Constituents of the dried material remain homogenously dispersed.
- Product is manner within the liquid form.
- Sterility of product can be achieved and maintained.

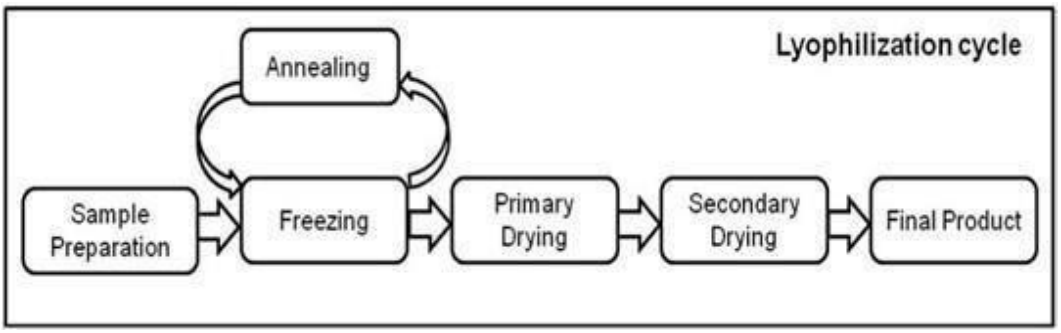

Figure 3: Steps involved in lyophilization from sample preparation to final product formation

DISADVANTAGES

- Volatile compounds can be eliminated by high vacuum.
- Single maximum expensive unit operation.
- Stability issues related with individual drugs.
- Some issues related to sterilization and sterility assurance of the dryer chamber and aseptic loading of vials into the chamber.

APPLICATIONS

Pharmaceutical and Biotechnology

Pharmaceuticals corporations regularly use freeze-drying to growth the shelf existence of merchandise, consisting of vaccines and different injectables. By doing away with the water from the fabric and sealing the fabric in a vial, the fabric may be without difficulty saved, shipped, and later reconstituted to its unique shape for injection.

Food Industry

Freeze-drying is used to keep meals and make them very lightweight. The technique has been popularized with inside the sorts of freeze-dried ice cream, an example of astronaut food.

Technological Industry

Products are often freezed in chemical synthesis to make them more stable or easier to dissolve in water for further use. Freeze-drying can also be used as a late-stage purification technique in bioseparations, as it can extract solvents efficiently. In addition, it is capable of concentrating low molecular weight substances that are too small to be separated by a filtration membrane.

DESIRED CHARACTERISTICS OF FREEZE DRIED PRODUCTS

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

PROCESSING

There are four stages in the complete drying process:

- Pretreatment
- Freezing
- Primary drying
- Secondary drying

Freeze-Drying Process

Freeze drying is primarily used to extract water from sensitive materials, often of biological origin, without harming them, so that they can be easily preserved in a permanently stored state and simply reconstituted by adding water. Antibiotics, bacteria, sera, vaccines, diagnostic drugs, protein-containing and biotechnological materials, cells and biotechnological products are examples of freeze-dried products: Under atmospheric pressure, the substance to be dried is frozen. Then, the water (in the form of ice) is removed by sublimation in an initial drying process, referred to as primary drying; it is removed by desorption in the second step, called secondary drying. Vacuum freeze-drying is performed.

Pre -treatment

Pretreatment consists of any approach of treating the product previous to freezing. This may also include concentrating the product, components revision (i.e., the addition of additives to increase balance and/or enhance processing), reducing an excessive vapor strain solvent or increasing the floor area. In many times the choice to pretreat a product is primarily based totally on theoretical expertise of freeze-drying and its requirements or is demanded through cycle time or product best considerations. Pretreatment methods include: Freeze concentration, Phase Solution concentration, Product Preservation Formulation, Reactive Product Stabilization Formulation, Surface Area Increase Formulation, and High Vapor Pressure Solvent Decreasing. Lyophilization cycle architecture has historically been split into three parts:

1. Freezing, wherein the liquid pattern is cooled till natural crystalline ice forms from part of the liquid and the rest of the pattern is freeze-concentrated into a glassy state where the viscosity is too high to allow further crystallization.
2. Primary drying, in which the ice formed during the freezing is eliminated by sublimation beneath vacuum at low temperatures, leaving a tremendously porous structure in the remaining amorphous solute that is typically 30% water. This step is performed at pressures of 104 to 10-5 atmospheres and a product temperature of –45 to –20°C; Sublimation during primary drying is the result of coupled heat- and mass-transfer processes.
3. Secondary drying, in which maximum of the ultimate water is desorbed from the glass because the temperature of the sample is gradually increased while maintaining low pressures.

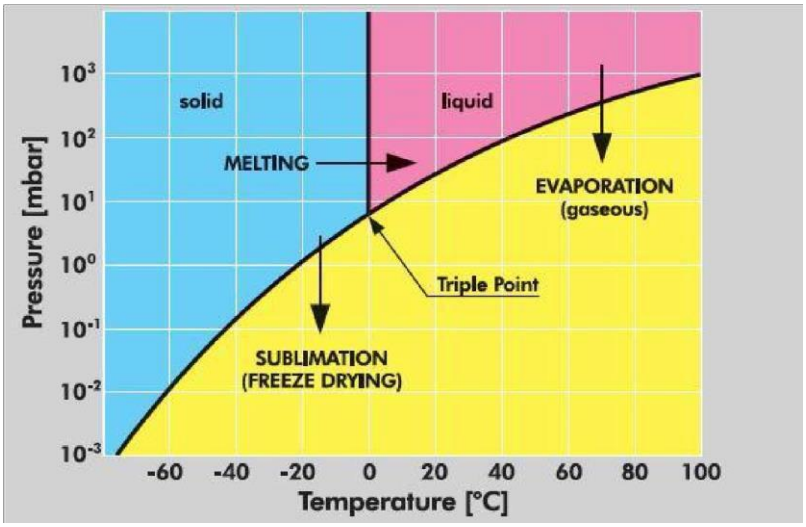

Figure 4: Freeze drying proces

Ideally, the last product is a dry, easily reconstituted cake with a high surface area (ca. 10 m2g).

LYOPHILIZATION EQUIPMENT

There are basically three types of freeze dryers: the freeze-dryer multiple, the freeze dryer rotary and the freeze-dryer type tray. Two components are common to all types of the freezer: a vacuum pump to minimise the pressure of the atmospheric gas in a vessel containing the substance to Be dry and a condenser to extract moisture by condensing to the −40 to −80 ° C (−40 to −112 ° F) cooled floor. Freeze-dryers of the manifold, rotary and tray form vary in the process by which a condenser is interfaced with the dried material. A short, normally circular tube is used in manifold freeze dryers to attach several containers to a condenser with the dried product. The rotary and tray freeze dryers have a single large reservoir for the dried material. Usually, rotary freeze-dryers are used to dry pellets, cubes, and other pourable substances. The rotary dryers have a cylindrical reservoir that is rotated during drying to achieve a more consistent drying across the substance. Tray-style freeze dryers typically have a rectangular reservoir with shelves on which items, such as pharmaceutical solutions and tissue extracts, can be stored in trays, vials and other containers. Manifold freeze dryers are typically used in a laboratory environment when drying liquid substances in small containers and when the product is used in a limited time. A multiple dryers can dry the product to a moisture content of less than 5 percent.

Only primary drying (removal of the unbound water) can be accomplished

without heat. For secondary drying, a heater must be added, which will eliminate the bound water and produce lower humidity content. Usually, tray-type freeze dryers are larger and more powerful than manifold dryers. A variety of materials are used to dry tray-type freeze-dryers. In order to generate the driest product for long term storage, a tray freeze dryer is used. A tray freeze dryer allows the product to be frozen in place and performs freeze-drying both primary (unbound water removal) and secondary (bound water removal), providing the driest possible end product. Tray freeze dryers may dry goods in bulk or in vials or other containers. When drying in vials, a stopping mechanism is given to the freeze dryer that allows a stopper to be pressed into place, sealing the vial until it is exposed to the atmosphere. This is used for storage in the long term, such as vaccines. Improved techniques for freeze-drying are being developed to increase the variety of products that can be freeze-dried, improve the product's consistency, and manufacture the product more efficiently with less labour. A lyophilizer is a vacuum chamber containing commodity shelves that are capable of cooling and heating containers and their contents. The vacuum chamber is connected by a vacuum pump, a refrigeration unit and associated controls. Chemicals are usually stored in containers such as glass vials that are stored within the vacuum chamber on the shelves. Cooling components congeal the substance within the racks. The vacuum pump evacuates the chamber and the product is heated until the product is frozen. Heat is transferred from the shelf, through the vial, and eventually into the substance by thermal conduction.

Lyophilization Container Requirements

The container in which a material is lyophilized must allow for thermal conductivity, be able to be securely sealed at the end of the lyophilization period and reduce the amount of moisture to permeate its walls and seals. The container in which it is handled will only remain properly lyophilized if the container in which it is handled meets these specifications.

Lyophilization Heat Transfer

Effective lyophilization depends heavily on good thermal conductivity. For this purpose, containers used in the process of lyophilization must be capable of meeting a number of specifications for heat transfer. These containers should be made of a material with good thermal conductivity; they should have good thermal contact with the shelf of the

lyophilizer, which is the source of heat during processing; and they should have a minimum of insulation separating the heat source from the heating product. The use of containers made of materials with low heat transfer coefficients is often the result of poor thermal conductivity. It may also be caused by the shape, size or consistency of the container. It can be caused by thermal barriers, such as excessive quantities of material that can serve as insulation, preventing the transfer of energy to the point at which the frozen ice and the dried product interface are transferred.

FREEZE DRYER DESIGN

Essential Components Chamber

This is the box tight with vacuum, also called the chamber or cabinet for lyophilization. The chamber includes shelves or product production shelves. Also, the chamber can fit into a stoppering device. It is generally made of stainless steel and is usually highly polished on the inside and insulated and painted on the outside. The hydraulic or electric motor door locking system.

Shelves

A small research freeze dryer will only have one shelf, but there will be many for all the others. Because of the many roles it has to perform, and the shelf design is made more difficult. The shelf serves as a heat exchanger, extracting energy from the product during freezing and providing the product with energy during the freeze-drying period of the primary and secondary drying segments. The shelves will be connected via either fixed or flexible hoses to the silicone oil system. Shelves can be rendered in sizes of up to 4 m^2 in area.

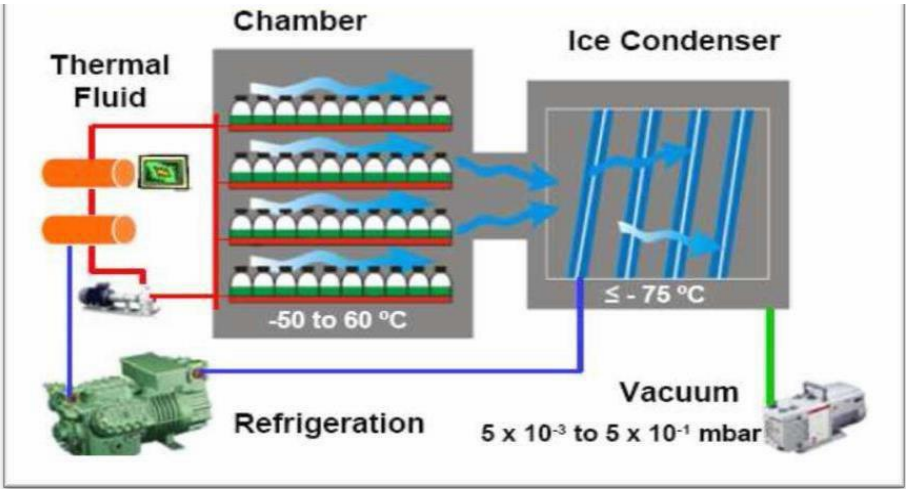

Figure 5: Lyophilizer Design

Process Condenser

Often the phase condenser is called just the condenser or the cold trap. It is built during the drying process to trap the solvent, which is normally water. The process condenser will consist of coils or plates that are cooled to allow temperature at times. Such refrigerated coils or plates may be isolated from the chamber in a vessel, or they may be placed in the same chamber as the shelves. Hence there is classification "external condenser" and "internal condenser." The external condenser is usually positioned physically behind the chamber, but it can be on the side, below or above. The condenser position does not affect the efficiency of trapping. The refrigerated coils or plates are mounted on smaller machines under the shelves for an internal condenser and on larger machines behind the shelves, but again there is no output restriction, only the chamber geometry.

Shelf Fluid System

The freeze-drying process requires that during the drying phases of the cycle, the product is first frozen and then the energy in the form of heat is applied. Traditionally, this exchange of energy is affected by circulating fluid at the desired temperature through the shelves. The temperature is set in an external heat exchange device consisting of heat exchangers and an electric heater for cooling. Normally, the fluid circulating is silicone oil. This will be pumped into a sealed circuit by means of a pump at low pressure around the circuit.

Refrigeration System

The dried product is either frozen in the dryer before or frozen when on the shelves. To this duty, a tremendous amount of energy is needed. The cooling energy is provided by compressors or often liquid nitrogen. Compressors are most often needed to multiply and two tasks may be performed by the compressor, one to cool the shelves and the other to cool the process condenser.

Vacuum System

The vacuum must be applied during the drying process in order to extract the solvent within a reasonable period. Usually, the necessary vacuum level is in the range of 50 to 100μ bar. A two-stage rotary vacuum pump is used to achieve such a low vacuum. Multiple pumps can be used for large chambers.

Control System

For production machines, control can be completely or typically fully automatic. The control elements needed are

temperature, pressure and time of the shelf, as described above. The control software can set such values as the product or method needs. The time may range from a couple of hours to a few days. It is also possible to monitor and monitor other data, such as product temperatures and condenser process temperatures.

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 of state from the solid phase to the gaseous phase, the material must first be sufficiently prefrozen to be freezed dried. The freezing method and the final temperature of the frozen product will affect the material's ability to successfully freeze dry. Rapid cooling results in small ice crystals, which are helpful in preserving structures for microscopic analysis but result in a product that is more difficult to freeze dry. During the drying process, slower cooling results in bigger ice crystals and less restrictive channels in the matric. Depending on the chemical make-up, the goods freeze in two forms. Most of the goods that are subjected to freezing drying consist mainly of water, the solvent and the dissolved or suspended components in the water, the solute. Many samples that are to be dried for freezing are eutectics that are a combination of substances that freeze at lower temperatures than the water around. Changes occur in the solute concentrations of the substance matrix when the aqueous suspension is cooled. And as cooling progresses, as it converts to ice, the water is isolated from the solutes, producing more concentrated areas of the solution. The freezing point of these pockets of condensed materials is lower than water. While a substance may appear to be frozen due to all the ice present, before all the solvent in the suspension is frozen, it is still not fully frozen. The combination of different solute amounts with the solvent constitutes the suspension eutectic. The suspension is completely frozen only when all of the eutectic mixtures are frozen. That's known as the eutectic temperature. Pre-freezing the product to below the eutectic temperature before starting the freeze-drying process is very critical in freeze-drying. Tiny pockets of residual unfrozen content in the product extend and jeopardise the structural integrity of the freeze-dried product. A suspension that undergoes glass-forming during the freezing process is the second

type of frozen product. Instead of creating eutectics, the entire suspension becomes even more viscous as the temperature decreases. At the glass transition point, the substance eventually freezes, creating a vitreous solid. It is incredibly difficult for this kind of substance 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 dried product's electrical resistance almost always increases significantly due to the decreased mobility of the ions and electrons with the transition from the liquid to the solid-state. This means that the freezing point can be measured by calculating the product's temperature and electrical resistance at the same point. Since resistance typically rises very suddenly, the Rx- and T-curves intersection can be taken as the freezing point with a very high degree of precision. Numerous tests of different solutions have confirmed this.

Primary Drying

Using a vacuum pump, the pressure inside the freeze-dryer is reduced after the freezing step is completed. Typical chamber pressures in pharmaceutical lyophilization range from 30 to 300 mTorr and are dependent on the prefered product temperature and container device characteristics. To permit the sublimation of ice and the transport of water vapour to the condenser where it is deposited as ice, the chamber pressure needs to be lower than the vapour pressure of ice at the sublimation interface in the product. By reducing the pressure gradient between the sublimation interface and the container, very high container pressures decrease the sublimation rate, thus minimising the driving force for sublimation and continuing ice removal. If the pressure in the chamber exceeds the vapour pressure at the sublimation interface, there can be no mass transfer. On the other hand, for rapid sublimation speeds, very low pressures (< 50 mTorr) are also counter-productive because they greatly restrict the rate of heat transfer to the commodity. A vapour pressure that is directly proportional to the product temperature is shown by the ice at the sublimation interface (Table 1). When the chamber pressure in the substance decreases below the vapour pressure of ice, sublimation

may occur, i.e. ice is eliminated from the top of the frozen layer and transformed directly into water vapour. Water vapour is taken to the ice condenser and stored on coils or plates that are constantly cooled to a temperature consistent with the condensed ice's very low vapour pressure. Energy (temperature-dependent, about 670 cal / g) is wanted to sublimate water from the product, main to the product being cooled. The energy needed for continued ice sublimation must be supplied from the heated shelves to a given higher temperature. The product temperature is generally the most important product parameter during a freeze-drying process, in particular, the product temperature during primary drying at the sublimation interface. Low product temperature and the resulting low ice vapour pressure lead to lengthy primary drying times. It has been recorded that a 1 ° C rise in product temperature will reduce the total primary drying period by as much as 13 percent, which provides tremendous potential to save process time and manufacturing costs while administering more aggressive product temperatures. However, a rise in product temperatures to temperatures above the "critical formulation temperature" referred to in the "critical formulation" For amorphous materials, Tg leads mainly to the loss of Structure on the cake. If the critical temperature is exceeded, the dried pore structure close to the sublimation front, which still contains high volumes of water, may undergo a viscous flow, resulting in pores fusion and holes developing in the cake structure. This phenomenon is associated with a decrease in the inner surface area as well as elevated moisture content with potentially adverse effects on the time and completeness of reconstitution as well as API stability. Most significantly, because of the lack of beauty, the cake shows shrinkage or may completely collapse, rendering the product unsuitable for sale and application in patients. The critical formulation temperature can be measured using Freeze-Dry Microscopy (FDM), which allows the drying cake structure to be observed under vacuum at varying temperatures. Once the failure temperature is reached, holes in the dried cake structure can be observed forming. As the sample is being dried at some stage in the experiment, the conditions are more similar to lyophilization than alternative methods, making the results more representatives for a vial freeze-drying process. Differential Scanning Calorimetry (DSC), which measures the heat flow and thermal properties of the frozen sample, is another approach to determining the critical formulation temperature. The glass

transition temperature of the maximally freeze-concentrated solution, Tg, can hence be determined, which is indicative of molecular mobility in the amorphous matrix. Because no water elimination is involved, the critical temperature is not as a representative of the collapse temperature determined using FDM for vial freeze-drying. Critical temperature may be improved with the aid of using quantitatively crystallising salts (i.e., buffers, etc.) during freezing or by introducing amorphous excipients with high Tg values such as dextrans or cyclodextrins. If formulations with high crystallising solutes content are lyophilized, a crystalline lattice are formed, which is stable up to product temperatures equal to the eutectic m. Therefore, at temperatures above the Tg' of the amorphous ingredients, formulations with a high ratio of crystallising substances and freeze-dry can be produced, which then collapses onto the crystalline matrix. Thus, there is no global loss of form and the presentation of the cake is remaining elegant. It is vital to pay careful attention to the reliability of the API and the selection of stabilisers in order to achieve a product that is stable over the shelf-life while pursuing such an approach, but it provides tremendous advantages for process optimisation.

Secondary Drying

After the primary freeze-drying is complete and all ice has sublimated, the substance still contains bound moisture. The product appears to be dry, but the residual moisture content can be as high as 7-8%. In order to reduce the residual moisture content to acceptable values, continuous drying is required at warmer temperatures. This method is called "Isothermal Desorption" because the product desorbs the bound water. Secondary drying typically starts at a secondary drying stage. The temperature of the substance above ambient but compliant with substance sensitivity. In contrast to primary drying processing conditions, which use low shelf temperatures and a Moderate vacuum and desorption, drying is enabled by raising the temperature of the shelf and decreasing the chamber pressure. As protein polymerization or biodegradation can result from the use of high processing temperature during secondary drying, caution should be exercised when raising shelf temperature too high. Secondary drying is typically performed for approximately 1/3 or 1/2 of the primary drying period required. The general practice of freezing is to raise the shelf temperature during secondary drying and to reduce the pressure of the chamber to

the lowest possible level. The procedure is focused on the ice is no longer present, and there is no doubt about the "melt route" that the substance can withstand higher heat input. In addition, the water that remains during secondary drying is more tightly bound, thus requiring more energy for removal. It has historically been thought that decreasing chamber pressure to the highest attainable vacuum would benefit the desorption of water.a vacuum pump, the pressure inside the freeze-dryer is reduced after the freezing step is completed. Typical chamber pressures in pharmaceutical lyophilization range from 30 to 300 mTorr and are dependent on the prefered product temperature and container device characteristics. To permit the sublimation of ice and the transport of water vapour to the condenser where it is deposited as ice, the chamber pressure needs to be lower than the vapour pressure of ice at the sublimation interface in the product. By reducing the pressure gradient between the sublimation interface and the container, very high container pressures decrease the sublimation rate, thus minimising the driving force for sublimation and continuing ice removal. If the pressure in the chamber exceeds the vapour pressure at the sublimation interface, there can be no mass transfer. On the other hand, for rapid sublimation speeds, very low pressures (< 50 mTorr) are also counter-productive because they greatly restrict the rate of heat transfer to the commodity. A vapour pressure that is directly proportional to the product temperature is shown by the ice at the sublimation interface (Table 1). When the chamber pressure in the substance decreases below the vapour pressure of ice, sublimation may occur, i.e. ice is eliminated from the top of the frozen layer and transformed directly into water vapour. Water vapour is taken to the ice condenser and stored on coils or plates that are constantly cooled to a temperature consistent with the condensed ice's very low vapour pressure. Energy (temperature-dependent, about 670 cal / g) is wanted to sublimate water from the product, main to the product being cooled. The energy needed for continued ice sublimation must be supplied from the heated shelves to a given higher temperature. The product temperature is generally the most important product parameter during a freeze-drying process; in particular, the product temperature during primary drying at the sublimation interface. Low product temperature and the resulting low ice vapour pressure lead to lengthy primary drying times. It has been recorded that a 1°C rise in product temperature will reduce the total primary drying period by

as much as 13 percent, which provides tremendous potential to save process time and manufacturing costs while administering more aggressive product temperatures. However, a rise in product temperatures to temperatures above the "critical formulation temperature" referred to in the "critical formulation" For amorphous materials, Tg leads mainly to the loss of Structure on the cake. If the critical temperature is exceeded, the dried pore structure close to the sublimation front, which still contains high volumes of water, may undergo a viscous flow, resulting in pores fusion and holes developing in the cake structure. This phenomenon is associated with a decrease in the inner surface area as well as elevated moisture content with potentially adverse effects on the time and completeness of reconstitution as well as API stability. Most significantly, because of the lack of beauty, the cake shows shrinkage or may completely collapse, rendering the product unsuitable for sale and application in patients. The critical formulation temperature can be measured using Freeze-Dry Microscopy (FDM), which allows the drying cake structure to be observed under vacuum at varying temperatures. Once the failure temperature is reached, holes in the dried cake structure can be observed forming. As the sample is being dried at some stage in the experiment, the conditions are more similar to lyophilization than alternative methods, making the results more representatives for a vial freeze-drying process. Differential Scanning Calorimetry (DSC), which measures the heat flow and thermal properties of the frozen sample, is another approach to determining the critical formulation temperature. The glass transition temperature of the maximally freeze-concentrated solution, Tg, can hence be determined, which is indicative of molecular mobility in the amorphous matrix. Because no water elimination is involved, the critical temperature is not as a representative of the collapse temperature determined using FDM for vial freeze-drying. Critical temperature may be improved with the aid of using quantitatively crystallising salts (i.e., buffers, etc.) during freezing or by introducing amorphous excipients with high Tg values such as dextrans or cyclodextrins. If formulations with high crystallising solutes content are lyophilized, a crystalline lattice are formed, which is stable up to product temperatures equal to the eutectic m. Therefore, at temperatures above the Tg' of the amorphous ingredients, formulations with a high ratio of crystallising substances and freeze-dry can be

produced, which then collapses onto the crystalline matrix. Thus, there is no global loss of form and the presentation of the cake is remaining elegant. It is vital to pay careful attention to the reliability of the API and the selection of stabilisers in order to achieve a product that is stable over the shelf-life while pursuing such an approach, but it provides tremendous advantages for process optimisation.

EXCIPIENTS IN LYOPHILIZED FORMULATION

The design of aq lyophilized formulation is based on the active pharmaceutical ingredient (API) specifications and the intended route of administration. A formula may consist of one or more excipients performing one or more functions. Buffers and pH adjusters, bulking agents, stabilisers, and tonicity modifiers can be known as excipients.

Buffers

In pharmaceutical formulations, buffers are needed in order to stabilise pH. The choice of a buffer can be crucial in the production of lyophilized formulations. During freezing, phosphate buffers, especially sodium phosphate, undergo drastic pH changes. Low concentrations of a buffer that undergoes a minimal pH shift during freezing, such as citrate and histidine buffers, are good approaches.

Bulking Agents

The bulking agent's goal is to provide the formulation with bulk. This is relevant in cases where very low active ingredient concentrations are used. An elegant cake structure with good mechanical properties is created by crystalline bulking agents. However, such materials are often unsuccessful in stabilising products such as emulsions, proteins, and liposomes but may be suitable for small chemical drugs and certain peptides. Mannitol can be used if a crystalline form is appropriate. Sucrose or one of the other disaccharides in a protein or liposome product can be used.

Stabilizers

In addition to being bulking agents, disaccharides form an amorphous glass of sugar and during lyophilization have proved to be the most effective in stabilising products such as liposomes and proteins. In stabilising liposome, protein, and virus formulations, sucrose and trehalose are inert and have been used. Glucose, lactose, and maltose reduce sugars, and the mallard reaction will reduce proteins.

Tonicity Adjusters

An isotonic formulation might be needed in several instances. Either the stability requirements of the bulk solution or those for the route of administration can determine the need for such a formulation. Healthy tonicity adjusters are excipients such as mannitol, sucrose, glycine, glycerol, and sodium chloride. If kept in the amorphous phase, glycine will lower the glass transition temperature. Diluent modificators of tonicity can also be used rather than the formulation.

FREEZE DRYING METHODS

Three methods of freeze drying are commonly used:

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

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

Manifold Method

Flasks, ampules, or vials are individually connected to the ports of a multiple or drying chamber in the manifold process. Depending on the type of the product and the amount to be dried to freeze, the product is either frozen in a freezer, by direct submersion in a low-temperature bath or by shell congelation. The pre-frozen product is easily added to the drying chamber or manifold to avoid warming. The vacuum must be quickly produced in the liquid container and the operator relies on evaporative cooling to maintain the product's low temperature. This technique can only be used for goods with high eutectic and collapse temperatures and relatively small volumes. Manifold drying has many benefits over-drying on a batch tray. Since the vessels are individually connected to the manifold, each vial or flask has a clear route to the collector. This eliminates some of the rivalry for molecular space produced in a batch method and is most preferably realised in a cylindrical drying chamber where the distance from the collector to each product vessel is the same. The water molecules that exit the commodity in vessels farthest from the collector undergo some traffic congestion in a "tee" manifold as they pass past the ports of other vessels. It can affect heat input by simply exposing the vessels to Temperature in the atmosphere or in the circulating bath. Manifold drying may not be appropriate for some goods, where precise temperature control is necessary. Several vessels can be housed in a multi-purpose system that allows the drying of different items at the same time, in vessels of different sizes,

with a range of closure systems. Because the items and their volumes can vary, each vessel may be separately removed from the manifold as its drying process is completed. The near proximity to the collector often provides an atmosphere in which drying efficiency is maximised. Each method has a specific purpose, and the method used depends on the product and the final configuration desired.

Batch Method

Large numbers of similar-sized vessels containing like items are put together in a tray dryer during batch drying. Typically the stock is pre-frozen on a tray dryer shelf. It is possible to maintain precise control of the temperature of the product and the quantity of heat applied to the product during drying. Generally, all vials in the batch are handled similarly during the drying process, but there may be some variance in the method. In various locations, minor variations in heat input from the shelf can be encountered. The clear door will radiantly heat vials located in the front portion of the shelf. These minor variations can lead to small differences in residual humidity. Batch drying allows all vials to be closed simultaneously in a tonne, under the same atmospheric conditions. It is possible to avoid the vials in a vacuum or with an inert gas after backfilling. At the same time, stopping all vials guarantees a consistent atmosphere in each vial and consistent consistency of the substance during storage. Batch drying is used to prepare large quantities of one product's ampules or vials and is widely used in the pharmaceutical industry.

Bulk Method

In a tray dryer, bulk drying is normally carried out like batch drying. However, as a single unit, the liquid is poured into a bulk pan and dried. While the product is distributed all over the shelf surface and can be the same thickness as the product dried in vials, the lack of empty spaces inside the product's mass changes the heat input rate. The heat input is primarily limited to that provided by shelf contact, as shown in Figure6.

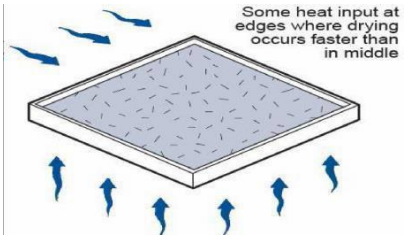

Figure: 6 Bulk drying, heat is provided primarily through conduction from shelf

Under regulated conditions, bulk drying does not lend itself to product sealing, as does manifold or batch drying. Until closure, the product is usually removed from the freeze-dry device and then sealed in air-tight containers. Generally, bulk drying is reserved for secure products that are not particularly susceptible to oxygen or humidity.

DETERMINATION OF END POINT OF FREEZE DRYING PROCESS

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

Dew Point

To calculate the frost point, which is the temperature at which ice has an equilibrium vapour pressure equal to the measured partial water pressure, an electronic moisture sensor may be used. The calculation is based on the idea that the capacitance of a thin film of aluminium oxide, resulting from water adsorption at a given partial pressure, varies. The point at which "dew point" begins to fall, similar to the Pirani, means that the sublimation is "essentially" complete, i.e., the composition of the gas changes from mainly water vapour to nitrogen.

Pressure Rise Test

By rapidly isolating the chamber from the condenser for a short time (about 25 s) and analysing the pressure increase during this duration, MTM is a method for measuring the product temperature during primary drying. This study yields ice vapour pressure at the sublimation interface, product temperature, and dried product mass transfer resistance. However, the data obtained reliably calculate ice vapour pressure only so long as the device remains in primary drying. "There is little to no increase in pressure at the end of primary drying because all ice is gone, and thus the measured" vapour pressure of ice "becomes equal to the pressure of the chamber. Therefore, a similar approach to the chamber pressure of the measured vapour pressure of ice forms the basis of the end criterion for primary drying.

STABILITY OF FREEZE DRIED PRODUCT

The durability of the freeze-dried material can be influenced by many factors. Moisture and oxygen are two of the most essential. Both freeze-dried goods have a small amount of residual moisture left in them. The amount of moisture remaining in the material depends on the product character and secondary drying duration. Residual moisture may be measured by

different means: chemical, chromatographic, manometric, or gravimetric. It's expressed as a percentage weight of the dried product's total weight. For most goods, residual moisture values vary from < 1 percent to 3 percent. By their very nature, freeze-dried materials are hygroscopic and the product can be destabilised by exposure to moisture during storage. The packaging used for freeze-dried products must be impervious to humidity in the atmosphere. The risk of deterioration from exposure to moisture can be minimised by storing goods in low humidity environments. Oxygen is also hazardous to most freeze-dried products' durability, so air must also be impermeable to the packaging used. Temperature relies upon the adverse effects of oxygen and moisture. The higher the temperature of storage, the more easily a product degrades. Most freeze-dried goods can be stored at temperatures in the refrigerator, i.e., 4-8° C. Placing freeze-dried products at lower temperatures increases their shelf life. A freeze-dried product's shelf life can be estimated by calculating the product's degradation rate at an elevated temperature. This is called expedited storage. The rate of product degradation can be predicted at lower storage temperatures by choosing the correct time and temperature relationships at elevated temperatures.

MARKETED FREEZE DRYING/LYOPHILIZES FORMUALTION

Table 2

Drug	Category	Route of administration	Marketed Name
Amphotericin b &Cholestrylsulphate	Anti-fungal	IV Infusion at 2-4 mg/kg/hr	Amphotec (sequus pharmaceuticals)
Chlorthiazide sodium	Diuretic & anti-hypertensive	IV Infusion, IV bolus	Diuril (Merck)
Cisplatin	Anti-neoplastic	IV Infusion	Platinol (Bristol Myers Oncolgy)
Gemcitabine	Anti-neoplastic	IV Infusion over 30 min	Genzer (Lilly)
Thiopental sodium	Short acting anesthetic	IV Infusion	Pentothal sodium (Baxter)

CONCLUSION

As the moisture content of the formulation is significantly reduced, the lyophilization technique has proven to be a benefit for the production of safe injectable dosage type, thereby improving product consistency, ease of handling, rapid dissolution due to the porous nature of the cake and easier transport of the substance during shipping. Approximately 50% of the biopharmaceuticals currently used are lyophilized, reflecting the most popular formulation technique. Chemical or physical degradation reactions are inhibited or sufficiently decelerated in the freeze-dried solid state, resulting in improved long-term stability. For effective lyophilization, understanding the dynamics of the freezing process and its effects on product quality and process efficiency is important. Awareness of how to monitor or at least manipulate the freezing step will help to develop more effective stability-enhanced lyophilization cycles and biopharmaceuticals.

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