Lyophilization/Freeze Drying - An Review

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INTRODUCTION

Lyophilization or freeze drying is a process in which water is frozen, followed by its removal from the sample, initially by sublimation (primary drying) and then by desorption (secondary drying). Freeze-drying is a process of drying in which water is sublimed from the product after it is frozen [1]. It is a drying process applicable to manufacture of certain pharmaceuticals and biologicals that are thermolabile or otherwise unstable in aqueous solutions for prolonged storage periods, but that are stable in the dry state. The term “lyophilization” describes a process to produce a product that “loves the dry state” [2].

To extract water from foods, the process of lyophilization consists of:
1. Freezing the food 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 [5].

PRINCIPLE

The main principle involved in freeze drying is a phenomenon called sublimation, where water passes directly from solid state (ice) to the vapor state without passing through the liquid state. 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 [3]. 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 [4].

Fig 1. Rate of drying of water

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Process to produce a product that “loves dry state”
Freeze drying also known as lyophilization, is widely used for pharmaceuticals to improve the stability and long term storage of labile drugs. Lyophilization or Freeze drying fills an important need in pharmaceutical manufacturing technology by allowing drying of heat-sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation, or a change of phase from solid to vapor without passing through the liquid phase [6]. The most common application of pharmaceutical freeze drying is in the production of injectable dosage forms, the process is also used in the production of diagnostics and, occasionally, for oral solid dosage forms where a very fast dissolution rate is desired [7].

Lyophilization or freeze drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase [8].

Lyophilization is performed at temperature and pressure conditions below the triple point, to enable sublimation of ice. The entire process is performed at low temperature and pressure, hence is suited for drying of thermolabile compounds. Steps involved in lyophilization start from sample preparation followed by freezing, primary drying and secondary drying, to obtain the final dried product with desired moisture content [9]. The concentration gradient of water vapor between the drying front and condenser is the driving force for removal of water during lyophilization. The vapor pressure of water increases with an increase in temperature during the primary drying. Therefore, primary drying temperature should be kept as high as possible, but below the critical process temperature, to avoid a loss of cake structure. This critical process temperature is the collapse temperature for amorphous substance, or eutectic melt for the crystalline substance. During freezing, ice crystals start separating out until the solution becomes maximally concentrated. On further cooling, phase separation of the solute and ice takes place [10].

Lyophilization is carried out below the triple point to enable conversion of ice into vapor, without entering the liquid phase (known as sublimation).

Fig 2. Phase diagram showing the triple point of water at 0.01°C, 0.00603 atm.

Fig 3. Steps involved in lyophilization from sample preparation to final product formation

Annealing is an optional step, occasionally used to crystallize the formulation component. If the solute separates out in crystalline form, it is known as the eutectic temperature. In contrast, if an amorphous form is formed, the temperature is referred to as the glass transition temperature (Tg). Determination of this critical temperature is important for development of an optimized lyophilization cycle. During primary drying, drying temperature should not exceed the critical temperature, which otherwise leads to ‘meltback’ or ‘collapse’ phenomenon. In the majority of lyophilized
formulations, excipients are included to improve the functional properties and stability of the lyophilized product [11]. The International Pharmaceutical Excipients Council has defined excipients as "substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form".

The fundamental process steps
1. Freezing: The product is frozen. This provides a necessary condition for low temperature drying.
2. Vacuum: After freezing, the product is placed under vacuum. This enables the frozen solvent in the product to vaporize without passing through the liquid phase, a process known as sublimation.
3. Heat: Heat is applied to frozen product to accelerate sublimation.
4. Condensation: Low temperature condenser plates remove the vaporized solvent from the vacuum chamber by converting it back to a solid. This completes the separation process [12]. Resulting product has a very large surface area thus promoting rapid dissolution of dried product [13].

APPLICATIONS
Pharmaceutical and biotechnology
Pharmaceutical companies often use freeze-drying to increase the shelf life of products, such as vaccines and other injectables [14]. By removing the water from the material and sealing the material in a vial, the material can be easily stored, shipped, and later reconstituted to its original form for injection.

Food Industry
Freeze-drying is used to preserve food and make it very lightweight. The process has been popularized in the forms of freeze-dried ice cream, an example of astronaut food.

Technological Industry
In chemical synthesis, products are often freeze-dried to make them more stable, or easier to dissolve in water for subsequent use. In bioprocessing, freeze-drying can be used also as a late-stage purification procedure, because it can effectively remove solvents. Furthermore, it is capable of concentrating substances with low molecular weights that are too small to be removed by a filtration membrane [15].

Other Uses
Organizations such as the Document Conservation Laboratory at the United States National Archives and Records Administration (NARA) have done studies on freeze-drying as a recovery method of water-damaged books and documents. In bacteriology freeze-drying is used to conserve special strains [16].

The advantages of Lyophilization include
- Chemical decomposition is minimized.
- Removal of water without excessive heating.
- Enhanced product stability in a dry state.
- Ease of processing a liquid, simplifies aseptic handling.
- More compatible with sterile operations than dry powder filling.

Disadvantages of Lyophilization include
- Increased handling and processing time.
- Volatile compounds may be removed by vacuum.
- Need for sterile diluents upon reconstitution.

TRADITIONAL LYOPHILIZATION TECHNOLOGY
Traditional lyophilization is a complex process that requires a careful balancing of product, equipment, and processing techniques. For nearly 30 years, lyophilization has been used to stabilize many types of chemical components. In their liquid form, many such biochemicals and chemical reagents are unstable, biologically and chemically active, temperature sensitive, and chemically reactive with one another. Because of these characteristics, the chemicals may have a very short shelf life, may need to be refrigerated, or may degrade unless stabilized. When performed properly, the process of lyophilization solves these problems by putting reagents into a state of suspended activity [17]. Lyophilization gives unstable chemical solutions a long shelf life when they are stored at room temperature. The process gives product excellent solubility characteristics, allowing for rapid reconstitution. Heat- and moisture-sensitive compounds retain their viability. Most proteins do not denature during the process, and bacterial growth and enzyme action, which normally occur in aqueous preparations, can be eliminated. Thus, lyophilization ensures maximum retention of biological and chemical purity [18].

PROCESSING
There are four stages in the complete drying process: pretreatment, freezing, primary drying, and secondary drying.

**Freeze-drying process**
Freeze-drying is mainly used to remove the water from sensitive products, mostly of biological origin, without damaging them, so they can be preserved easily, in a permanently storable state and be reconstituted simply by adding water [19]. Examples of freeze-dried products are: antibiotics, bacteria, sera, vaccines, diagnostic medications, protein-containing and biotechnological products, cells and tissues, and chemicals. The product to be dried is frozen under atmospheric pressure. Then, in an initial drying phase referred to as primary drying, the water (in form of ice) is removed by sublimation; in the second phase, called secondary drying, it is removed by desorption. Freeze drying is carried out under vacuum [20].

**Pretreatment**
Pretreatment includes any method of treating the product prior to freezing. This may include concentrating the product, formulation revision (i.e., addition of components to increase stability and/or improve processing), decreasing a high vapor pressure solvent or increasing the surface area. In many instances the decision to pretreat a product is based on theoretical knowledge of freeze-drying and its requirements, or is demanded by cycle time or product quality considerations [21]. Methods of pretreatment include: Freeze concentration, Solution phase concentration, Formulation to Preserve Product Appearance, Formulation to Stabilize Reactive Products, Formulation to Increase the Surface Area, and Decreasing High Vapor Pressure Solvents.

Traditionally, lyophilization cycle design has been divided into three parts [22]:
1. Freezing, in which the liquid sample is cooled until pure crystalline ice forms from part of the liquid and the remainder of the sample is freeze-concentrated into a glassy state where the viscosity is too high to allow further crystallization.
2. Primary drying, wherein the ice formed during the freezing is removed by sublimation under vacuum at low temperatures, leaving a highly porous structure in the remaining amorphous solute that is typically 30% water. This step is carried out at pressures of 10-4 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, wherein most of the remaining water is desorbed from the glass as the temperature of the sample is gradually increased while maintaining low pressures. Ideally, the final product is a dry, easily reconstituted cake with a high surface area (ca. 10 m²/g) [23].

**LYOPHILIZATION EQUIPMENT**
There are essentially three categories of freeze-dryers: the manifold freeze-dryer, the rotary freeze-dryer and the tray style freeze-dryer. Two components are common to all types of freeze-dryers: a vacuum pump to reduce the ambient gas pressure in a vessel containing the substance to be dried and a condenser to remove the moisture by condensation on a surface cooled to –40 to –80°C (–40 to –112°F). The manifold, rotary and tray type freeze-dryers differ in the method by which the dried substance is interfaced with a condenser. In manifold freeze-dryers a short usually circular tube is used to connect multiple containers with the dried product to a condenser [24]. The rotary and tray type freeze-dryers have a single large reservoir for the dried substance. Rotary freeze-dryers are usually used for drying pellets, cubes and other pourable substances. The rotary dryers have a cylindrical reservoir that is rotated during drying to achieve a more uniform drying throughout the substance [25]. Tray style freeze-dryers usually have rectangular reservoir with shelves on which
products, such as pharmaceutical solutions and tissue extracts, can be placed in trays, vials and other containers. Manifold freeze-dryers are usually used in a laboratory setting when drying liquid substances in small containers and when the product will be used in a short period of time [26]. A manifold dryer will dry the product to less than 5% moisture content. Without heat, only primary drying (removal of the unbound water) can be achieved. A heater must be added for secondary drying, which will remove the bound water and will produce lower moisture content. Tray style freeze-dryers are typically larger than the manifold dryers and are more sophisticated. Tray style freeze-dryers are used to dry a variety of materials. A tray freeze-dryer is used to produce the driest product for long-term storage. A tray freeze dryer allows the product to be frozen in place and performs both primary (unbound water removal) and secondary (bound water removal) freeze-drying, thus producing the driest possible end-product. Tray freeze-dryers can dry products in bulk or in vials or other containers [27]. When drying in vials, the freeze-dryer is supplied with a stoppering mechanism that allows a stopper to be pressed into place, sealing the vial before it is exposed to the atmosphere. This is used for long-term storage, such as vaccines. Improved freeze drying techniques are being developed to extend the range of products that can be freeze dried, to improve the quality of the product, and to produce the product faster with less labor.

A lyophilizer consists of a vacuum chamber that contains product shelves capable of cooling and heating containers and their contents. A vacuum pump, a refrigeration unit, and associated controls are connected to the vacuum chamber [28]. Chemicals are generally placed in containers such as glass vials that are placed on the shelves within the vacuum chamber. Cooling elements within the shelves freeze the product. Once the product is frozen, the vacuum pump evacuates the chamber and the product is heated. Heat is transferred by thermal conduction from the shelf, through the vial, and ultimately into the product [29].

**Lyophilization Container Requirements**

The container in which a substance is lyophilized must permit thermal conductivity, be capable of being tightly sealed at the end of the lyophilization cycle, and minimize the amount of moisture to permeate its walls and seal [30]. The enclosed reagents can only remain properly lyophilized if the container in which they are processed meets these requirements.

**Lyophilization Heat Transfer**

Successful lyophilization is heavily dependent on good thermal conductivity. For this, containers used in the lyophilization process must be capable of meeting a number of heat-transfer requirements. Such containers should be made of a material that offers good thermal conductivity; should provide good thermal contact with the lyophilizer shelf, which is the source of heat during processing; and should have a minimum of insulation separating the source of heat from the product requiring heating. Poor thermal conductivity often results from the use of containers made of materials with low coefficients of heat transfer. It can also be caused by the shape, size, or quality of the container [31]. It may come from thermal barriers, such as excessive amounts of material, which can act as insulation, preventing energy from being transferred to the point at which the frozen ice and dried product interface [32].

**FREEZE DRYER DESIGN**

**Essential Components**

**Chamber**

This is the vacuum tight box, sometimes called the lyophilization chamber or cabinet. The chamber contains shelf or shelves for processing product. The chamber can also fit with a stoppering system. It is typically made of stainless steel and usually highly polished on the inside and insulated and clad on the outside [33]. The door locking arrangement by a hydraulic or electric motor.
**Shelves**
A small research freeze dryer may have only one shelf but all others will have several. The shelf design is made more complicated because of the several functions it has to perform. The shelf act as a heat exchanger, removing energy from the product during freezing, and supplying energy to the product during the primary and secondary drying segments of the freeze drying cycle. The shelves will be connected to the silicone oil system through either fixed or flexible hoses. Shelves can be manufactured in sizes up to 4 m$^2$ in area [34].

**Process Condenser**
The process condenser is sometimes referred as just the condenser or the cold trap. It is designed to trap the solvent, which is usually water, during the drying process. The process condenser will consist of coils or sometimes plates which are refrigerated to allow temperature. These refrigerated coils or plates may be in a vessel separate to the chamber, or they could be located within the same chamber as the shelves. Hence there is designation “external condenser” and “internal condenser”. Physically, the external condenser is traditionally placed behind the chamber, but it may be at the side, below or above [35]. The position of the condenser does not affect trapping performance. For an internal condenser the refrigerated coils or plates are placed beneath the shelves on smaller machines, and behind the shelves on larger machines, but again there is no performance constraint, only the geometry of the chamber.

**Shelf fluid system**
The freeze-drying process requires that the product is first frozen and then energy in the form of heat is applied throughout the drying phases of the cycle. This energy exchange is traditionally done by circulating a fluid through the shelves at a desired temperature [36]. The temperature is set in an external heat exchange system consisting of cooling heat exchangers and an electrical heater. The fluid circulated is normally silicone oil. This will be pumped around the circuit at a low pressure in a sealed circuit by means of a pump.

**Refrigeration system**
The product to be freeze dried is either frozen before into the dryer or frozen whilst on the shelves. A considerable amount of energy is needed to this duty. Compressors or sometimes-liquid nitrogen supplies the cooling energy. Most often multiply compressors are needed and the compressor may perform two duties, one to cool the shelves and the second to cool the process condenser.

**Vacuum system**
To remove solvent in a reasonable time, vacuum must be applied during the drying process. The vacuum level required will be typically in the range of 50 to 100µ bar. To achieve such a low vacuum, a two stage rotary vacuum pump is used. For large chambers, multiple pumps may be used.

**Control system**
Control may be entirely or usually fully automatic for production machines. The control elements required are as mentioned above, shelf temperature, pressure and time. A control program will set up these values as required by the product or the process. The time may vary from a few hours to several days. Other data such as a product temperatures and process condenser temperatures can also be recorded and logged [37].

**THE FREEZE-DRYING CYCLE:**
Lyophilization is the most common method for manufacturing solid pharmaceutical products and is central to the preservation of materials which must be dried thoroughly in order to ensure stability. To meet this requirement, a solution’s lyophilization occurs in three steps: (1) freezing to convert most of the water into ice, (2) primary drying to sublime the ice, and (3) secondary drying to remove unfrozen water by desorption [38]. To technically realize this manufacturing process, a freeze dryer is commonly constructed with two main parts: a “drying” chamber holding temperature controlled shelves is connected by a valve to a “condenser” chamber, which contains coils capable to achieve very low temperatures between -50°C and -80°C. The freeze-drying process consists of three stages.

1) Freezing
2) Primary drying
3) Secondary drying

**Freezing**
Freezing is a critical step, since the microstructure established by the freezing process usually represents the microstructure of the dried product. The product must be frozen to a low enough
temperature to be completely solidify. 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 pre-frozen. The method of prefreezing 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 large ice crystals and less restrictive channel in the matrix during the drying process. Products freeze in two ways, the majority of products that are subjected to freeze-drying consists primarily of water, the solvent and materials dissolved or suspended in the water, the solute. Most samples that are to be freeze dried are eutectics, which are mixtures of substances that freeze at lower temperature than the surrounding water. This is called the eutectic temperature. Eutectic point is the point where all the three phases’ i.e. solid, liquid and gaseous phases co-exist. It is very important in freeze-drying to pre freeze the product to below the eutectic temperature before beginning the freeze-drying process.

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 products freeze at the glass transition point forming a vitreous solid. This type of product is extremely difficult to freeze dry [40,41].

**Primary drying**

After prefreezing the product, conditions must be established in which ice can be removed from the frozen product via sublimation, resulting in a dry, structurally intact product. This requires very carefully control of the two parameters.

1) Temperature and 2) Pressure involved in freeze-drying system.

The rate of sublimation of ice from a frozen product depends upon the difference in vapor pressure of the product compared to the vapor pressure of the ice collector. Molecules migrate from the high-pressure sample to a lower pressure area. Since vapor pressure is related to temperature, it is necessary that the product temperature is warmer than the cold trap (ice collector) temperature. It is extremely important that the temperature at which a product is freeze dried is balanced between the temperature that maintains the frozen integrity of the product and the temperature that maximizes the vapor pressure of the product. This is the balance is key to optimum drying.

**Fig 6. The Typical Phase Diagram Of Water In Primary Drying**

Most products are frozen well below their eutectic or glass transition point (point A), and the temperature is raised to just below this critical temperature (Point B) and they are subjected to reduced pressure. At this point the freeze-drying process is started. Vacuum pump is an essential of a freeze drying system, and is used to lower the pressure of the environment around the product (point C). The other essential is a collecting system, which is a cold trap used to collect the moisture that leaves the frozen product.

The collector condenses all condensable gases, i.e. the water molecules and the vacuum pump removes all non-condensable gases. The molecules have a natural affinity to move toward the collector because its vapor pressure is lower than that of the product. Therefore the collector temperature, (Point D) must be significantly lower than the product temperature.

A third component essential in freeze-drying system is energy. Energy is essential in the form of heat. Almost ten times, much energy is required to sublime a gram of water from the frozen to the gaseous state as is required to freeze a gram of water, (2700 joules per gram of ice). Heat must be applied to the product to encourage the removal of water in the form of vapor from the frozen product. The heat must be very carefully controlled, as applying more heat than the evaporative cooling in the system can warm the product above its eutectic or collapse temperature.
Heat can be applied by several means one method is to apply heat directly through a thermal conductor shelf such as is used in tray drying. Another method is to use ambient heat as in manifold drying [42].

**Heat enters the products by one of several mechanisms:**

1) By direct contact between the container base and the shelf, so here the shape of the container is important.
2) By conduction across the container base and then through the frozen mass to the drying front (also called the sublimation interface)
3) By gaseous convection between the product and residual gas molecules in the chamber.
4) By radiation, this is low due to low temperature encountered in freeze-drying. Convection is certainly the most important of these mechanisms.

**Secondary drying**

After primary freeze-drying is complete, and all ice has sublimed, bound moisture is still present in the product. The product appears dry, but the residual moisture content may be as high as 7-8% continued drying is necessary at warmer temperature to reduce the residual moisture content to optimum values. This process is called 'Isothermal Desorption' as the bound water is desorbed from the product [43].

Secondary drying is normally continued at a product temperature higher than ambient but compatible with the sensitivity of the product. In contrast to processing conditions for primary drying which use low shelf temperature and a moderate vacuum, desorption drying is facilitated by raising shelf temperature and reducing chamber pressure to a minimum. Care should be exercised in raising shelf temperature too highly; since, protein polymerization or biodegradation may result from using high processing temperature during secondary drying. Secondary drying is usually carried out for approximately 1/3 or 1/2 the time required for primary drying.

The general practice in freeze-drying is to increase the shelf temperature during secondary drying and to decrease chamber pressure to the lowest attainable level. The practice is based on the ice is no longer present and there is no concern about "melt track" the product can withstand higher heat input [44]. Also, the water remaining during secondary drying is more strongly bound, thus requiring more energy for its removal. Decreasing the chamber pressure to the maximum attainable vacuum has traditionally been thought to favor desorption of water.

**EXCIPIENTS IN LYOPHILIZED FORMULATION**

The design of an lyophilized formulation is dependent on the requirements of the active pharmaceutical ingredient (API) and intended route of administration. A formulation may consist of one or more excipients that perform one or more functions. Excipients may be characterized as buffers and pH adjusters, bulking agents, stabilizers, and tonicity modifiers [45].

**Buffers**

Buffers are required in pharmaceutical formulations to stabilize pH. In the development of lyophilized formulations, the choice of buffer can be critical. Phosphate buffers, especially sodium phosphate, undergo drastic pH changes during freezing. A good approach is to use low concentrations of a buffer that undergoes minimal pH change during freezing such as citrate and histidine buffers.

**Bulking agents**

The purpose of the bulking agent is to provide bulk to the formulation. This is important in cases in which very low concentrations of the active ingredient are used. Crystalline bulking agents produce an elegant cake structure with good mechanical properties. However, these materials often are ineffective in stabilizing products such as emulsions, proteins and liposomes but may be suitable for small chemical drugs and some peptides. If a crystalline phase is suitable, mannitol can be used. Sucrose or one of the other disaccharides can be used in a protein or liposome product.

**Stabilizers**

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

**Tonicity adjusters**
In several cases, an isotonic formulation might be required. The need for such a formulation may be dictated by either the stability requirements of the bulk solution or those for the route of administration. Excipients such as mannitol, sucrose, glycine, glycerol, and sodium chloride are good tonicity adjusters. Glycine can lower the glass transition temperature if it is maintained in the amorphous phase. Tonicity modifiers also can be included diluent rather than the formulation.

FREEZE DRYING METHODS

Three methods of freeze drying are commonly used [46]

**Manifold method**

In the manifold method, flasks, ampoules or vials are individually attached to the ports of a drying chamber. The product 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 product 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. 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 [47].

**Batch method**

In a batch drying, large numbers of similar sized vessels containing like product 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 during drying process, although some variation in the system can occur. Slight difference in heat input from the shelf can be expressed in different areas. Vials located in the front portion of the shelf may radiantly through the clear door. These slight variations can result in small difference in residual moisture.

Batch drying allows closure of all vials in a lot at the same time, under the same atmospheric condition. The vials can be stoppered in a vacuum, or after backfilling with inert gas [48]. 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 ampoules 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 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.

**Technology transfer**

In pharmaceutical industry “technology transfer” refers to the processes that are needed for successful progress drug discovery to product development to full scale commercialization [49]. Technology transfer can be divided in to 2 types

**Tech transfer**

In tech transfer, the product is developed in lab-scale, subjected to scale-up, exhibit batch to full scale commercialization.

**Site transfer**

In site transfer the products from the outside customer are subjected to lab-scale feasibility trials and then to commercial scale depending on customer need. The importance of technology transfer

- To gather necessary information to transfer technology from R&D to actual
- Manufacturing by sorting out various information obtained during R&D.
- To elucidate necessary information to transfer technology of existing products between various manufacturing places.
In most cases, technology transfer occurs in several stages. Small scale laboratory development from 100 ml to 500 ml can be scaled up to 5-10 liters and then 20-100 liters on an Exhibit batch scale. Production scale can typically range from 200 liters to 1000 liters. For a successful scale-up of freeze drying process, it is important to develop a systematic strategy to correlate the cycle parameters obtained from small-scale operation to final results obtained from full-scale production operations under various operational conditions, such as shelf temperature, chamber pressure, type of vial, and solution depth. The product from manufacturing had lower moisture from the pilot plant batches despite the similarity of the Lyophilization cycles applied at the two facilities. The product temperature during the two steps of secondary drying in pilot plant unit is lower than the attained in a manufacturing lyophilizer [50]. The differences is attributed to different heat transfer characteristics of the lyophilizer, with the manufacturing lyophilizer having a ‘more efficient’ heat transfer coefficient than the pilot plant unit at secondary drying conditions. Freeze drying cycle transfer must be based on equivalent drying rates and extent of drying at the different scales, especially product final moisture content is critical. Appropriate scale-up of a freeze drying process in a cost effective and efficient manner involves smart use of experimental tools to monitor the drying process of product. It is hypothesised that cycles developed and/or used in the laboratory drier will correlate to cycles used in the production dryer [51]. Predicting production freeze dry cycle parameters from laboratory experiments has obvious advantage.

CONCLUSION
Lyophilization (freeze-drying) is often used to prepare dry pharmaceutical formulations to achieve commercially viable shelf lives. The process comprises three steps: freezing, primary drying, and secondary drying. As water freezes in the first step, the dissolved components in the formulation remain in the residual liquid, a phase termed the freeze concentrate. At the point of maximal ice formation, the freeze concentrate solidifies between the ice crystals that make up the lattice. Under appropriate lyophilization conditions, the ice is removed by sublimation during primary drying, leaving the remaining freeze-concentrate in the same physical and chemical structure as when the ice was present. Residual water in the freeze concentrate is removed in the secondary drying step. 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. Besides the advantage of better stability, lyophilized formulations also provide easy handling during shipping and storage. 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 at least manipulate, the freezing step will help to develop more efficient lyophilization cycles and biopharmaceutical products with an improved stability.

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