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A review of lyophilization

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Abstract

Lyophilization is one of the most promising methods for drying. Lyophilization or freeze drying is a technique wherein moisture seems to be covered in ice, including its disposal from the sample, by sublimation (primary drying) and desorption (secondary drying). Lyophilization is prevalent yet generally expensive, and therefore, one of several primary targets throughout freeze-drying process improvement is to reduce the drying time (mainly primary drying time, which would be the lengthiest of three significant steps in freeze-drying). Nevertheless, raising the shelf temperature into secondary drying before removing most ice from the product will probably trigger breakdown or recrystallization melt. Thus, it would be tough to identify the end of primary drying from the product's quality and method economy viewpoint. This overview focused on its latest advancement and goals in the near term. Initially, the basic concept, required steps, formulation elements, significance of Lyophilization, techniques of Lyophilization, and identification of the ultimate conclusion in Lyophilization were clarified.

Keywords: Lyophilization; Primary Drying; Secondary Drying; Freeze Drying Significance

1. Introduction

Lyophilization and freeze drying seem to be methods wherein the liquid has been covered in ice, preceded by its disposal from the sample, initially through sublimation (primary drying) and then by desorption (secondary drying). Freeze drying is a technique of trying to dry wherein the moisture has been sublimed from the product after it has been locked, which is a drying process applicable to manufacture from certain biopharmaceutical as well as biologicals that are thermally unstable and or unsteady along aqueous systems such as prolonged storage periods, and that are secure within the watery nation. Lyophilization seems to be a critical need in modern medicine in which temperature-illicit and naturally occurring substances seem to settle at colder temperatures below conditions that allow water to be eliminated through vaporization. Although the most typical application, pharmaceutical Lyophilization, has been manufacturing injectable dosage forms, the method is used in manufacturing like diagnostic tests. The commercial applications of Lyophilization must not seem to be valued until there emerged a need for large serving sizes of heat-sensitive blood products and newly found antimicrobial drugs [1].

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1.1. Materials that can be lyophilized [2-3]:

Types of materials processed by lyophilization have been summed up as

- Nonbiological, where the procedure has been used to dehydrate or concentrate reactive or heat-liable chemical compounds.
- Non-living bioproducts comprise the main field of application and include enzymes, hormones, antibacterial drugs, vitamin supplements, blood products, antibodies, inactive immunization, etc. One subunit includes biopharmaceuticals that might be used in the diagnosis or therapeutic applications. Bone and other body tissues for surgical or medical utilization of food products with significant organoleptic characteristics. Industrially used bioproducts
- Living life forms seem to have been reconstructed cells ever since drying, and they should be capable of growing and multiplying to produce new offspring. Examples include fungi and bacteria utilized in seed cultures and inactivated viral vaccines.
- Miscellaneous - flood disrupted books, exhibition collection of artifacts, etc.

1.2. Lyophilization Closure system

Ever since Lyophilization, the formulation must be shielded from the atmosphere. Generally, the preparation inside the container is enclosed through a stoppering system controlled in the freeze–dryer, which also depresses the vessel's closure. The stoppering of closure inside the vessel momentarily protects the ultimate product from its surroundings. On finalization of stoppering of the containers, the product can be safely removed from the freeze–dryer, and the stopper can be crimp-sealed with metal or colorful caps to provide a sustainable shield for the product.

1.3. The basic design of freeze–dryers [4]

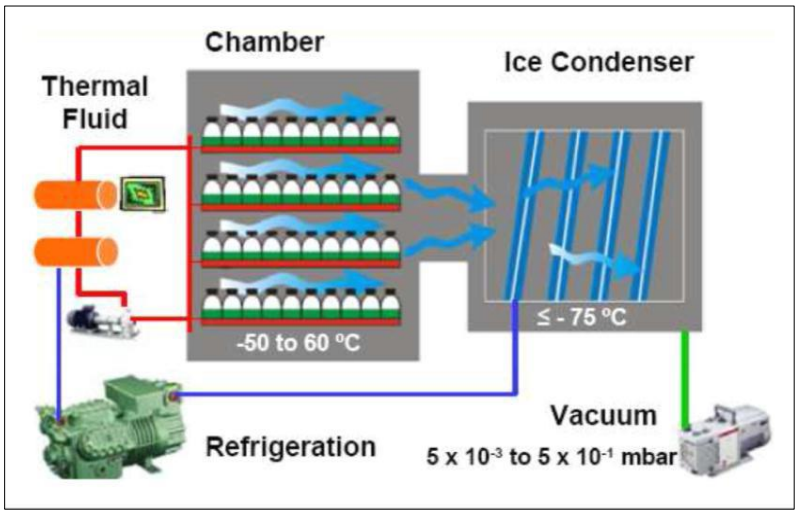

Figure 1 Lyophilizer design

The principal elements of freeze-drying devices are:

- Product chamber/shelves or manifold
- Ice condenser
- Refrigeration system
- Vacuum system
- Control system

The above components are the product chamber, the condenser, and the vacuum pump. Every aspect is essential for the effectiveness of the freeze dryer.

There seem to be two significant types of product chambers: one is for vials, and another for trays (bulk). A vial system will be beneficial when a product is comparatively advanced, molecularly complex, and challenging, subject to re-sale

or aseptic processing. One such methodology gives operators complete control over the parameters that drive the freeze-drying procedure.

When a product has been processed inside a vial dryer, the liquidized product seems to be packed into the vials and loaded over onto the shelf trays of the freeze dryer. There, the commodity is pre-frozen to a temperature possibly a bit under the freezing point of the product, also termed the eutectic point.

During primary drying, the vacuum pump of a freeze dryer eliminates the non-condensable vapors. Such vapors have been formed through leakages inside the equipment and the continuous discharge of non-condensable molecules from the product as the freeze-drying advances. The vacuum pump helps establish an unrestricted vapor path for migrating condensable molecules by eliminating the air from the chamber.

1.4. Essential Components Chamber [5-6]

That's the vacuum-tight box, occasionally termed the lyophilization chamber or cabinet. The compartment consists of shelves for processing products.

1.4.1. Shelves

A small-scale research freeze dryer may only have one shelf, yet all others have had numerous. The shelf layout is created so much more complex due to the several functions it has to operate.

1.4.2. Process Condenser

The process condenser can be called the condenser or the cold trap. The process condenser is constructed to entrap the solvent, usually water, throughout the drying process. The process condenser may encompass coils or even refrigerated plates to permit temperature. Such refrigerated coils or plates might be in a vessel distinct to the chamber and positioned in that chamber as the shelves. Therefore, there is a classification "external condenser" and "internal condenser".

1.4.3. Shelf fluid system

The freeze-drying system needs that perhaps the product is always first frozen, and thereafter, energy in the form of heat is meant to be applied throughout the cycle's drying stages. One such energy transfer has been traditionally done by circulating one liquid through the shelves at an appropriate temperature.

1.4.4. Refrigeration system

The product must also be freeze-dried before entering the dryer or on the shelves. The amount of energy required for something like this process. Air compressors or even sometimes liquid nitrogen resources the cooling energy.

1.4.5. Vacuum system

The vacuum must be applied during dehydration to remove the solvent in such a sensible period. The vacuum required level would be typically in the range of 50 to 100μ bar. A two-phase rotary vacuum pump is used to attain one such low vacuum. For massive amounts of chambers, numerous pumps are used.

1.4.6. Control system

Control might be entirely or pretty much fully automatic for production machines. As discussed in the previous section, the control systems are also necessary for shelf temperature, pressure, and time. A control system will establish such values, even by product or method. The duration could differ from a few hours to many days.

2. The principle of freeze-drying [7-11]

At standard atmospheric pressure (approximately 1,000 mbar), water exhibits three distinct physical states: solid, liquid, and gas. However, below the triple point (where pure water exists at 6.1 mbar and 0°C), only the solid and gaseous states are present, allowing for sublimation. Sublimation can occur at pressures and temperatures below the triple point, such as 4.579 mmHg and 0.0099°C.

The lyophilization process involves freezing the material to be dried, followed by applying a high vacuum and gentle heating (via conduction, radiation, or a combination of both). This causes the frozen water to vaporize, leaving behind

the dried, solid components. The gradient of water vapor concentration between the drying front and condenser drives the elimination of water during Lyophilization.

The lyophilization procedure includes four key steps:

- Freezing: the formulation is frozen, converting the water into ice.
- Sublimation: under vacuum, the ice straightforwardly sublimates into water vapor.
- Water vapor removal: the vapor is removed from the system.
- Final drying: once the ice has sublimated, the lyophilized product can be removed from the equipment.

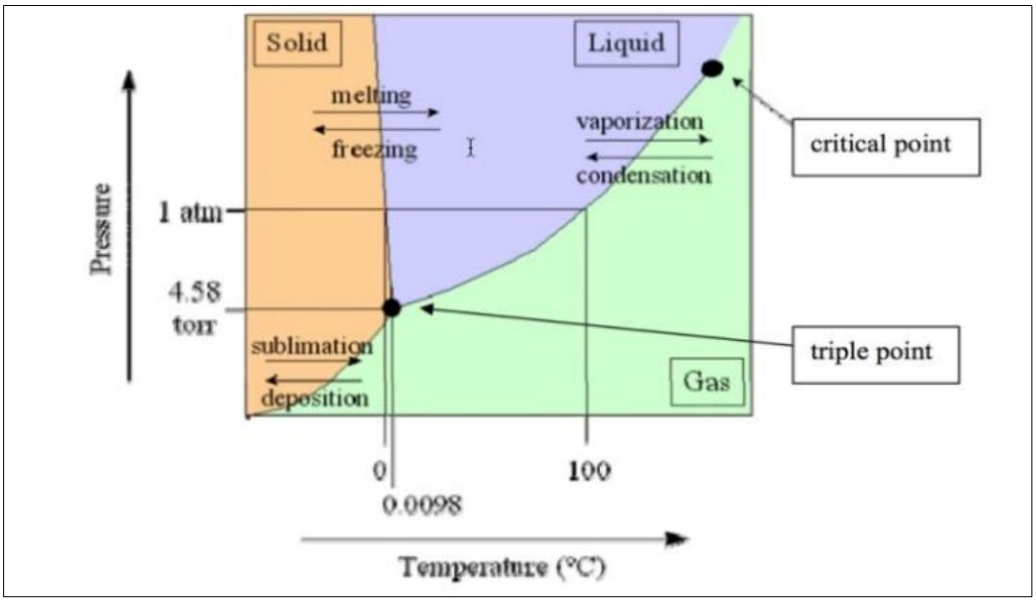

Figure 2 Phase diagram for freeze drying

The lyophilization process comprises three key stages:

- Freezing
- Primary drying
- Secondary drying

Freezing: In this initial stage, water is converted into ice crystals at low temperatures, while the solute remains in the interstitial regions between the ice crystals.

Primary Drying: Once the material is completely frozen, the pressure is reduced, and heat is applied, inducing sublimation of the ice crystals. The condenser plate is crucial in removing the vapors generated during sublimation.

Secondary Drying: Following the primary drying cycle, a small amount of moisture remains in the formulation. The temperature is increased to eliminate this excess moisture, facilitating a process known as "isothermal desorption." This stage ensures the stability of the final product.

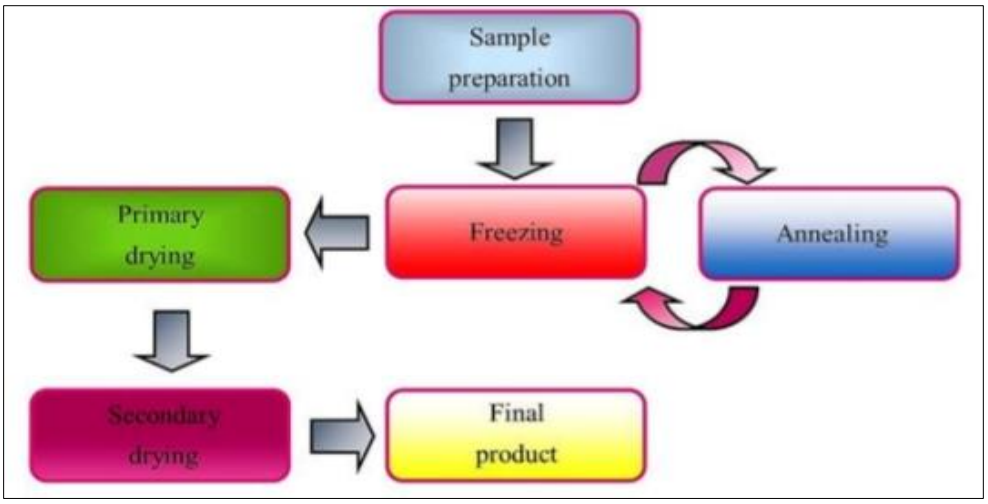

Figure 3 Lyophilization process flow

2.1. Methods of Freeze Drying

- Manifold method
- Batch method
- Bulk method

2.1.1. Manifold method

Figure 4 Manifold method of Lyophilization

This technique connects vials or flasks directly to the drying chamber, facilitating faster drying. Each flask is linked to a separate collector, allowing for individual removal without disturbing other flasks. This method is ideal for small quantities of products with high eutectic and collapse temperatures.

2.1.2. Batch method

Figure 5 Batch method of Lyophilization

This broadly used method in drug companies involves lyophilizing massive amounts of products in a single drying chamber. Multiple vials or vessels are placed in the same chamber, resulting in minimal variability.

2.1.3. Bulk method

In one such method, the formulation is poured inside trays, which seem to be then positioned in the drying chamber. This technique is typically used for products non-sensitive to moisture and oxygen.

2.2. FORMULATION

Determining the composition characteristics of a pharmaceutical product intended for freeze-drying is a critical step influenced by multiple factors. The formulation significantly impacts each stage of the freeze-drying process, including freezing, primary and secondary drying, storage, and reconstitution. When biologically active ingredients are present in low doses, additives (excipients) are incorporated to ensure physical stability. In the case of liquid protein pharmaceuticals, non-toxic excipients with low solubility are often employed to maintain stability.

Excipients, also known as chemical additives, co-solutes, or co-solvents, are added to freeze-dried pharmaceutical formulations to serve various functions, including:

- Cryoprotection
- Bulking
- Buffer stabilization
- Tonicity adjustment
- Structure modification
- Collapse inhibition
- Chemical or biological stabilization

The effects of excipients primarily depend on their concentration within the formulation. However, in some cases, high excipient concentrations can lead to adverse effects.

2.3. Choosing the Right Excipients in Optimal Quantities

Excipients are inert materials added to pharmaceutical products undergoing freeze-drying to enhance stability during the process and improve storage stability. These ingredients serve specific purposes to produce desirable end products. Commonly used excipients in the pharmaceutical, biotechnology, and food industries include mannitol, glycine, trisHCl, sodium phosphate, sodium metabisulphite, lactose, glucose, and dextran.

In freeze-dried product formulations, mannitol, glycine, sucrose, and other disaccharides are bulking agents when the active ingredient concentration is extremely low. Using excipients is crucial in pharmaceutical freeze-drying, and their application requires expertise from professionals knowledgeable about excipients.

Research in the field of excipients has seen significant advancements. However, selecting the appropriate excipients in optimal quantities for specific pharmaceutical formulations to achieve long-term stability, high collapse temperature, and desirable cake appearance while maintaining bioactivity and isotonicity upon reconstitution remains challenging for researchers.

2.4. Optimal Control of Freeze Dryer

Even the most modern industrialized freeze dryers immediately available lack strong process control systems to monitor and analyze data analysis in real time, making it challenging to determine the rate-controlling mechanisms of heat or mass transfer throughout freeze-drying.

The freeze-drying method can be restricted by heat transfer, mass transfer, or both simultaneously. To optimize the process, it is essential to identify whether heat or mass transfer is the limiting factor and adjust the independent variables accordingly, including heat input, chamber pressure, and condenser temperature.

Recent studies have developed a comprehensive framework for optimizing the primary and secondary drying steps. The outcomes show that optimized freeze dryer design features (type I and type ii) exhibit more uniform temperature distributions at the end of the primary drying step than non-optimized designs (figure 6).

Furthermore, applying optimal control policies to freeze-drying, such as milk protein in glass vials, has led to significant minimization in drying periods for both primary and secondary drying stages. The optimized control policy also resulted in even more standardized concentration and temperature profiles of water content all along the length as well as the radius of the vial at the end of the secondary drying stage (figure 7).

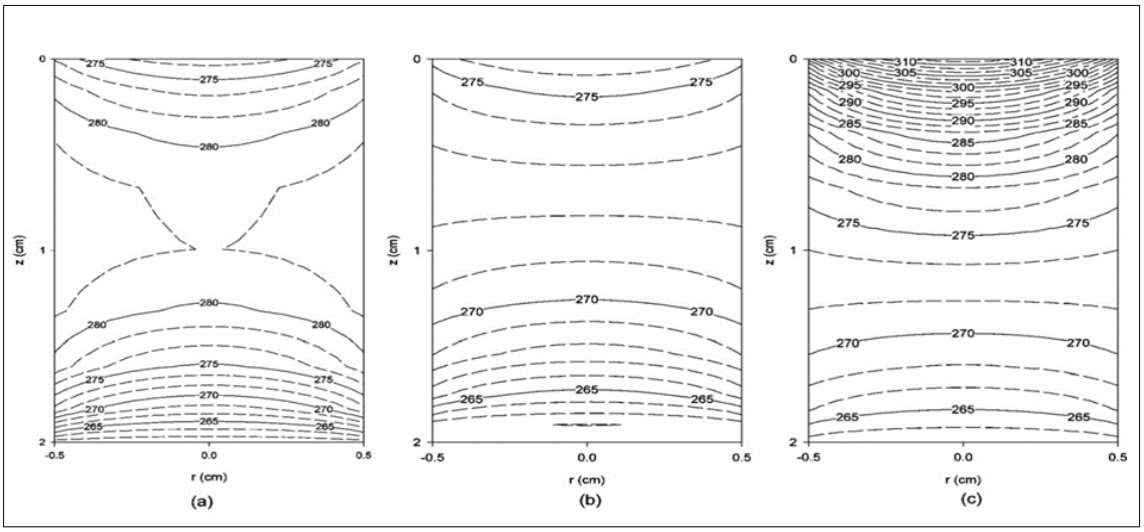

Figure 6 Temperature distribution for the dried layer at the end of the primary drying stage (a) Non–optimized case; (b) Type –Freeze dryer design; and (c) type – II freeze dryer design

2.5. Remote Sensing of Product Temperature

To determine product temperature without sensor contact, researchers developed the "pressure rise technique." the above technique involves briefly closing the nozzle between both the chamber and condenser (5-15 seconds) to allow chamber pressure to rapidly increase initially, followed by a more gradual rise as even the pressure approaches the vapor pressure of sublimated ice. Throughout that period, a software program measured and assessed the increase in chamber pressure.

Based on the pressure rise technique, the manometer temperature measurement method has been used to create an intelligent freeze dryer. This sensible freeze dryer:

- Dynamically adjusts control factors, such as heat and pressure inputs, to achieve optimal product temperature quickly.
- Determines product but also shifting interaction temperature changes using pressure rise approach to avoid collapse during drying.
- Correctly defines the endpoint of primary drying.
- Evaluate leftover water content content in real-time during secondary drying.

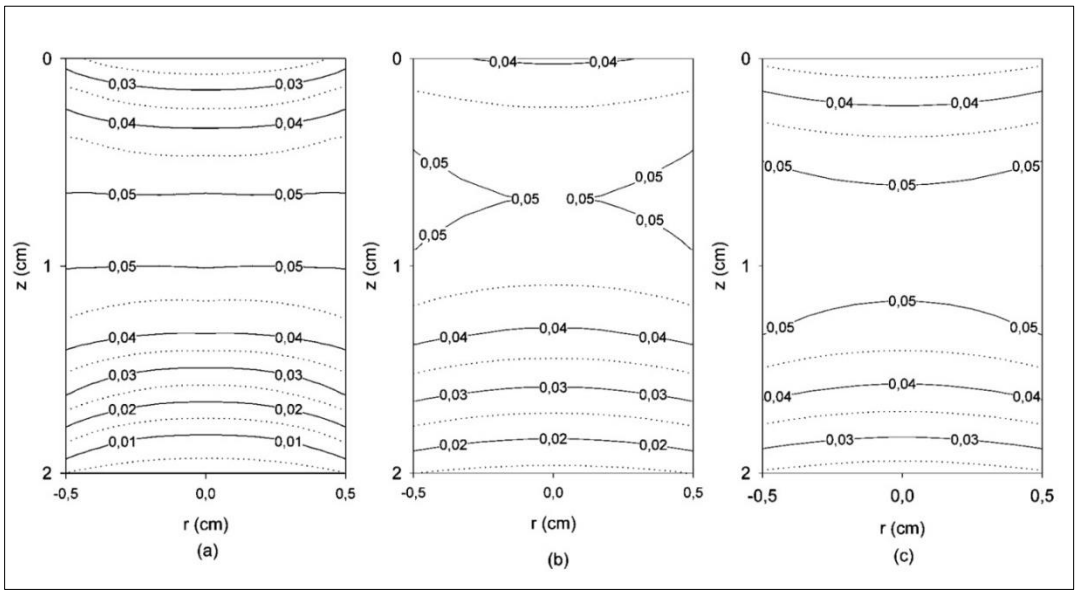

Figure 7 Distribution of concentration of bound water in the material being dried at the end of the secondary drying stage: (a) Non–optimized case; (b) Type –Freeze dryer design; and (c) type – II freeze dryer design

2.6. Lyophilization Container Requirements

When selecting a container for Lyophilization, several key requirements must be met. The container should:

- Provide sufficient Thermal conductivity to enable effective heat transfer during the lyophilization process.
- Be completely closed there after the cycle to prevent re-absorption of moisture.
- Minimize water vapor permeation through its walls and seals, ensuring the integrity of the lyophilized product.

Only containers that satisfy these requirements can ensure that the enclosed reagents remain adequately lyophilized and maintain their stability.

Figure 8 Containers for Lyophilization

2.7. Lyophilization Heat Transfer

Effective Lyophilization relies heavily on optimal thermal conduction. The carton used throughout the lyophilization method should always meet specific heat-transfer requirements to achieve one such. Ideally, these containers should:

- Be made of materials for good thermal conductivity to enable effective heat transfer.
- Focus on providing good thermal interaction with the lyophilizer shelf, the primary heat source, through handling.
- Minimize the insulation between the heat source and the product to ensure direct heat transfer.

Containers with low thermal conductivity, often due to materials with poor heat transfer coefficients, can hinder lyophilization. Factors such as container shape, size, and quality can also impact thermal conductivity. Thermal barriers, including excess material or poor design, can act as insulation, impeding energy transfer to the critical interface between ice and dried product.

3. Excipients in lyophilized formulation [12-15]

The layout of aqueous lyophilized formulations hinges upon that particular requirement of active pharmaceutical ingredient (API) and the intended path of administration. These formulations often include one or multiple excipients that serve various functions, such as buffering, bulking, stabilization, and tonicity modification.

3.1. Buffers

Buffer solutions seem to be essential in pharmaceuticals to maintain pH stability. However, specific buffers like phosphate buffers (e.g., sodium phosphate) can undergo significant pH changes throughout freezing. Low concentrations of buffers like citrate and histidine can be employed to mitigate this, which induces minimal pH changes during freezing.

3.2. Bulking agents

Bulking agents seem to be introduced to provide mass to the preparation, particularly when small quantities of active pharmaceutical ingredients are used. Crystal compounds can yield an elegant cake framework with outstanding mechanical strength.

3.3. Stabilizers

Disaccharides, such as sucrose and trehalose, form an amorphous sugar glass that effectively stabilizes products like liposomes, proteins, and viruses during Lyophilization. In contrast, reducing sugars like glucose, lactose, and maltose can degrade proteins through the Maillard reaction.

3.4. Tonicity adjusters

In many instances, some isosmotic preparation is required to ensure stability or compatibility with the route of administration. Excipients like mannitol, sucrose, glycine, glycerol, and sodium chloride are efficient tonicity adjusters. Notably, glycine could decrease the transition temperature, which would be an essential consideration in lyophilized formulation design.

3.5. Determination of the endpoint of a freeze-drying process [16]

The following are indeed the methodologies in use for the perseverance of the endpoint of the primary drying process, Techniques based on the gas type and concentration inside the product chamber:

- Comparative pressure measurement (i.e., Pirani vs. capacitance manometer)
- Dew point monitor (electronic moisture sensor)
- Process H_2O concentration from tunable diode laser absorption spectroscopy (TDLAS)
- Lyotrack (gas plasma spectroscopy)

Others

- Product thermocouple response
- Condenser pressure

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

4. Comparative pressure measurement (i.e., Pirani vs. Capacitancemanometer) [17-19]

During the drying stage, pressure in the chamber has been monitored using a capacitance manometer that measures absolute pressure inside the chamber. In contrast, the Pirani vacuum gauge measures the gas's thermal conductivity in the chamber.

Notably, the pirani gauge reads approximately 60% more than that of the capacitance manometer (e. G, mksbaratron) all through primary drying, whenever the chamber is predominantly filled with water vapour. The above discrepancy arises from vapor having a thermal conductivity of about 1.6 times that of nitrogen.

This underlying property of the Pirani gauge enables it to detect the end of primary drying. Specifically, the point at which Pirani pressure begins to decrease steeply marks the transition from vapor to nitrogen as the primary gas composition, indicating that sublimation is finished.

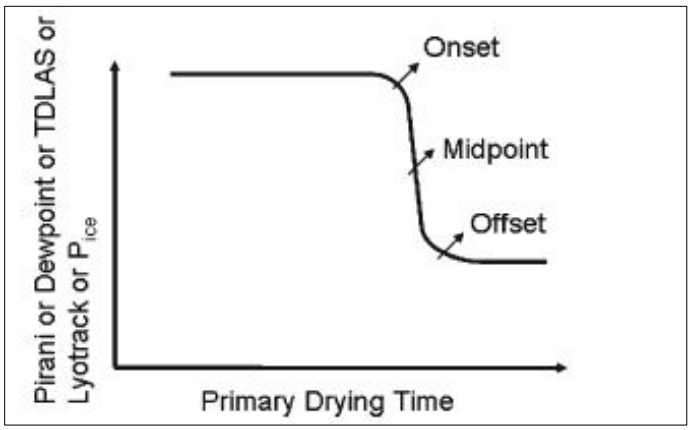

Figure 9 Pirani pressure, dewpoint, TDLAS(process[H2O]), Lyotrack(gas composition), and price (vapor pressure of ice cream from pressure rise test)profile during primary drying

4.1. Dew point

A digital moisture sensor could be employed to determine the ice point, the temperature during which ice exhibits a steady-state vapor pressure equivalent to the evaluated partial pressure of water. This assessment relies on the principle that shifts inside the capacitance of either a coating or aluminum oxide are caused by water adsorption at a given partial pressure. Like the Pirani gauge, the digital moisture sensor can identify the end of primary drying by monitoring the dew point. When the dew point begins to drop steeply, it signifies that sublimation is finished, and the gas type and concentration shift from vapor to nitrogen.

Figure 10 Dew Point

4.2. Lyotrack (gas plasma spectroscopy)

Lyotrack, a system based on optical emission spectroscopy, measures vapour accumulation during dehydration. The system is comprised of a plasma generator as well as an optical spectrometer. The track gas type and concentration notification is responsive to gas composition changes in the drying chamber and duct but not in the condenser. The track system identifies atoms or molecules due to the characteristics of the wavelength range of light emitted. A pointy reduction of water vapor intensity (i.e., onset) suggests a shift in gas composition, signaling that sublimation is finished.

4.3. Product temperature during primary drying

Another method to determine the primary drying endpoint is by analyzing the same product thermocouple response. This approach assumes that the glass vials of the thermocouples have been representing the entire batch. A standard indicator of the end of primary drying would be when the temperature limit methods the shelf temperature set point.

Additionally, monitoring the temperature of the product and condenser pressure profiles all through primary drying can provide valuable insights into the drying process.

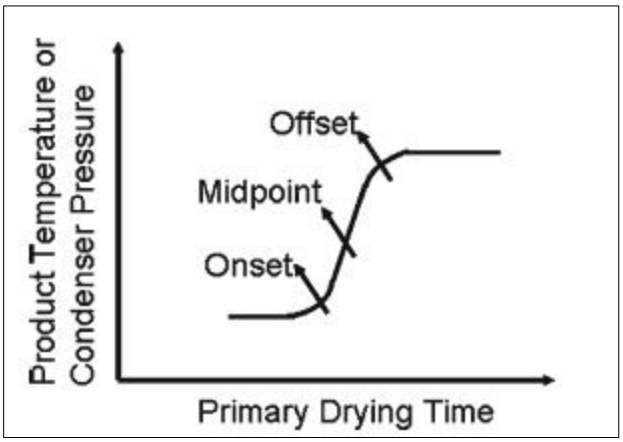

Figure 11 Product temperature and condenser pressure profile during primary drying

4.4. Condenser pressure during primary drying

Another indicator of the endpoint of primary drying is indeed the condenser pressure. The compartment seems to be predominantly filled with water vapor phase through primary drying, resulting in a high total vapor flux. A significant pressure difference (δp) develops between the chamber and condenser to facilitate water removal. However, once

primary drying is complete, δp decreases, causing the condenser pressure (pcond) to increase while the chamber pressure (pc) remains constant.

4.5. Pressure rise test

At the end of the primary drying, the pressure increase is negligible or absent, indicating that all ice has been sublimated. As a result, the vapor pressure of ice becomes equivalent to the chamber pressure. This convergence of ice and chamber pressure's vapor pressure is a reliable means of determining the end of the primary drying.

4.6. Factors affecting the process rate

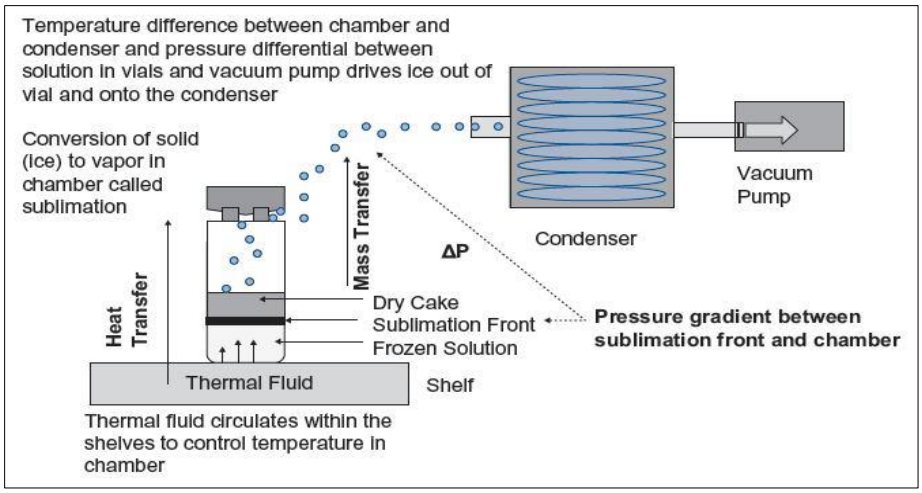

Figure 12 Schematic of heat and mass transfer in the freeze dryer.

During freeze-drying, mass and heat transfer occur directionally, causing the highest product to dry first, followed by progressive drying downwards to the base of the bottle. This creates a three-layer system in each vial: the top dry product, the center sublimation front, and the lower frozen liquid mixture.

As the dried layer grows, it becomes a significant barrier to mass transfer, increasing resistance to water vapor transmission from the vial. This emphasizes the significance of vial dimensions and product volume in determining the effectiveness of the freeze-drying process.

Several factors influence the freeze-drying process, including

- Heat flux through the vessel and frozen content, which are poor thermal conductors, to a drying bounding while preserving the item less than its eutectic temperature.
- The obstructing influence of rising depth of dried, porous product above drying bounding.
- The temperature and heat potential of the rack is its own.

Additionally, the temperature of the condenser, affected by the thermal insulation impact of accumulated ice, also plays a key role in determining the effectiveness of the freeze-drying method.

5. Stability of freeze-dried products [20]

The stability of freeze-dried content is influenced by several factors, with moisture and oxygen being two of the most critical. Freeze-dried products typically retain minimal excessive moisture, which depends on the product's nature and the duration of secondary drying. Excessive humidity could be measured using various methods, including chemical, chromatographic, manometric, and gravimetric analyses. The acceptable moisture level varies among products, ranging from less than 1% to 3%.

Freeze-dried substances have been inherently hygroscopic, and exposure to humidity throughout storage could severely damage the product. Therefore, packaging should be impermeable to atmospheric moisture. Storing products in low-humidity surroundings could indeed minimize degradation due to humidity exposure.

Oxygen could also compromise the stability of freeze-dried content, making it essential to use air-impenetrable packaging. The negative impacts of oxygen and humidity are temperature-dependent, with higher storage temperatures accelerating product deterioration. Most freeze-dried products can be preserved at refrigerator temperature changes (4-8°c), and storing them at cooler temperatures can extend their life span.

The life span of such a freeze-dried product can be anticipated through a measurement system at the speed of deterioration at elevated temperatures.

Table 1 Lyophilized solid Dosage form

Drug	Formulation	Disease	Significances
Duloxetine hydrochloride	Mucoadhesive Tablet	Depression	Improved bioavailability
Silymarin	NanosuspensionTablet	Liver disorder	- Increased stability -Exhibited a faster dissolution rate -Enhanced saturation solubility
Atorvastatin	Dry Emulsion Tablet	Hyperlipidemia	Enhanced dissolution rateIncreasedantihyperlipidemic activity
Chlorpheniramine Maleate	Fast Dissolving Tablet	Allergy, cough, chickenpox	-Increased water solubility -Improved mechanical strength
Griseofulvin	Fast DisintegratingLyophilized Dry EmulsionTablet	Fungal infection	-Improved stability -Showed rapid disintegration

Table 2 Lyophilized Parenteral Formulations

Drug	Formulation	Disease	Significances
Ebola glycoprotein(EBOV-GP),Aluminum Hydroxide	Lyophilized EBOV-GP vaccine	Ebola virus	Maintain immunogenicity Improved thermostable activity
Gadolinium	Lyophilized Injection	MRI contrast agents	Improved stability
Dacarbazine	Injection	Cancer	Improved bioavailability Improved stability

Table 3 Lyophilized Powders

Drug	Formulation	Disease	Significances
Diazepam	Nasal Spray	Anxiety	Improved enzyme stability
Lysosomes	Lyophilizates for dry powder inhalation	Pulmonary disease	Overcome the problem in inhalation of protein and peptide
Betamethasone	Dry Powder Inhaler	Pulmonary disease	Deliver product in deep lungs
Rifampicin	Microspheres	Tuberculosis	Deliver product in deep lungs

6. Conclusion

Lyophilization is a valuable technique in creating steady injectable dosage forms. By significantly reducing the moisture content of the formulation, Lyophilization enhances product stability, relieves going to handle, and quick dissociation due to the porous nature of the resulting cake. Additionally, lyophilized products are easier to transport during shipping. Approximately 50% of biopharma is lyophilized, making this the most prevalent preparation strategy. Freeze-drying inhibits or decelerates chemical and physical degradation reactions, improving the lengthy steady state. Understanding the complexities of the crystallization process and its effect on product value and performance measurement is vital for effective Lyophilization. Controlling or manipulating the freezing step enables the development of much more effective lyophilization periods and biopharma goods with enhanced steady state.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

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