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Review Article

# Enhancing Lyophilization Efficiency: A Review of Processes, Parameters and Product Preservation Strategies

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**ABSTRACT**

Lyophilization, often known as freeze-drying, is a critical process widely utilized in pharmaceuticals and biotechnology to preserve sensitive materials. This paper examines key parameters influencing lyophilization quality and efficiency, focusing on temperature control, pressure levels, ramp rate and duration, formulation and composition, container design, process parameters, material properties, and environmental factors. Precise temperature control is essential throughout the process to ensure uniform freezing, efficient sublimation, and preservation of product stability. Optimal pressure levels and ramp rates/durations are crucial for achieving uniform drying, preventing collapse, and maintaining product integrity. Formulation factors such as excipients, solvents, and stabilizers play vital roles in product stability, while container design influences heat transfer and drying efficiency. Advanced control systems and monitoring techniques are employed to optimize process parameters and achieve reproducible outcomes. Understanding material properties and environmental factors further enhances lyophilization success, ensuring high-quality lyophilized products with desirable characteristics and stability.

**Keywords:** Freeze-drying, Lyophilization, Pressure regulation, Ramp Duration, Ramp rate, Temperature control.

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## INTRODUCTION

Lyophilization also known as freeze-drying, stands as a cornerstone technique in various industries, including pharmaceuticals, biotechnology, and food preservation. This process involves the removal of water from a product in its frozen state under controlled conditions of temperature and pressure, resulting in a stable, dry product with an extended shelf life.

Among the myriad of parameters governing this complex process, temperature control, pressure levels, ramp rate and duration, formulation and composition, container design and configuration, process parameters and control, material properties, and environmental factors emerge as pivotal determinants of lyophilization efficacy and product quality.[1]

Temperature control is paramount in lyophilization, influencing every stage of the process and ultimately dictating the quality of the lyophilized product. Precise temperature regulation ensures uniform freezing, efficient sublimation, and preservation of product stability. Pressure levels within the lyophilization chamber also play a crucial role, affecting vapor pressure, sublimation rates, and drying kinetics. Optimal pressure conditions are essential to prevent collapse, ensure uniform drying, and maintain product stability. Ramp rate and duration govern ice crystal formation, drying kinetics, and product stability, necessitating careful optimization to achieve desired outcomes.[2]

Formulation and composition are fundamental considerations, profoundly impacting product stability, drying kinetics, and reconstitution properties. Container design and configuration significantly influence heat transfer, drying efficiency, and product uniformity. Precise control and monitoring of process parameters throughout the lyophilization process are imperative for ensuring reproducibility and maintaining product quality. Material properties and environmental factors also exert critical influences, underscoring the intricate interplay of factors shaping lyophilization outcomes.[3]

In this review article, we delve into the multifaceted aspects of lyophilization, exploring the significance of temperature control, pressure levels, ramp rate and duration, formulation and composition, container design and configuration, process parameters and control, material properties, and environmental factors. By comprehensively understanding and optimizing these factors, manufacturers can achieve high-quality lyophilized products with desired characteristics and stability, advancing

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the efficacy and applicability of this indispensable preservation technique.

## STEPS INVOLVED IN LYOPHILIZATION

There are three main steps in this process: freezing, primary drying and secondary drying (Figure 1). In the initial freezing stage, the water present in the sample is frozen, allowing it to separate from other solutes in the mixture. This stage typically takes a few hours. Whereas in the primary drying stage, sublimation occurs, where adequate temperature and vacuum levels facilitate the absorption of heat by the sample, causing the solid water to become vapor. The vapor is directed to a collecting chamber, where it condenses on a coil (usually below -40ºC) and turns back into ice. This stage takes the longest time (up to 3 days) and depends on various factors such as sample volume, solute concentration, thickness, surface area, collector temperature, and vacuum level (usually 0.03-0.2 mbar). The secondary drying stage involves removing non-freezing water to reduce the water content to acceptable levels. It is considered the most critical step since residual water can affect product quality and stability. Samples containing volatile substances, such as solvents other than water, pose challenges to freeze-drying. These substances can affect the eutectic temperature, increase vapor pressure at the sample surface, and require less heat for sublimation, causing the samples to melt at room temperature. Additionally, the presence of volatile substances can damage equipment parts and affect overall equipment performance.

### Freezing

Freezing is the earliest stage of lyophilization, and it has a direct effect on the kinetics of drying. This step includes nucleation and Crystal growth. Kinetics of ice nucleation and the subsequent growth of crystals play a crucial role in defining the physical characteristics and structure of the frozen cake. This directly correlates to rate of sublimation during both primary and secondary drying.[4]

The ice crystal sizes need to be sufficiently large to provide quickest primary drying time. Development of many tiny ice crystals in the freezing step causes a significant resistance to mass transfer, whereas formation of a few large ice crystals cause minor resistance. Although, in order to accelerate secondary drying time, their sizes must be reduced to give an enormous surface area for the dried matrix. This result in removal of non-frozen water from pores on the surface of the amorphous matrix occurs faster. Thus, the freezing method should be chosen after considering the primary and secondary drying processes. If secondary drying requires extended time, it could be quickened by adjusting the freezing conditions to obtain many tiny ice crystals more quickly.[1]

In some cases the sample are kept at a determined subfreezing point; Temperature above the glass transition temperature $T_g$, this process known as annealing which impacts the size distribution of ice crystals and mass transfer, simply it refers to a controlled heating process applied to the frozen product before the primary drying phase. Presence of this stage may vary product to product.

### Primary Drying

It is second stage in lyophilization this mainly involves ice sublimation. In the process of primary drying, the material is heated to release the latent heat of sublimation and the pressure is lowered down below the triple point. The frozen water must vaporize at this heat. Primary drying usually takes ten hours or so. Approximately 95% of the water in the solid is typically removed during the initial drying process for crystalline eutectic systems.[5]

Figure 2 depicts the conditions inside the solid during primary drying. The low vapour pressure inside the chamber is preserved when vaporized water escapes the solid and is taken to a condenser. A layer of dried material forms when the solid's top layer of water is removed. As more drying occurs, this layer gets thicker and the remaining frozen substance that contains water gets thinner. The sublimation front, which causes vaporization, consequently descends down the drying material's depth from the top of the solid.

In order to remove water vapor from the material during primary drying, mass transfer is necessary. The dry solid layer that develops above the sublimation front is the main barrier preventing mass transfer. The drying rate diminishes with time as the dried layer's thickness rises. As mentioned in freezing, the parameters applied during the freezing phase of the freeze-drying process which leads to formation of large and tiny crystals also have an impact on mass transfer rates. When the porosity is high, there is a greater mass transfer of water vapor through the solid.[6]

### Secondary Drying

Secondary drying, also known as desorption drying, involves applying low pressure and simultaneously heating the product to the get assumed water content which is different for each raw material. During this stage, the rate of drying is much slower compared to the sublimation process (Primary Drying) because of the limited amount of water, strong heat resistance, mass transfer through the porous layer, and water particles bonding with the components of the dry substance, particularly those forming a monolayer. During secondary drying, temperatures are elevated and pressures are reduced compared to primary drying.[7] During this stage there is no movement of the sublimation front.[8]

Secondary drying stage is responsible for final moisture content. Appropriate moisture content in the finished lyophilized product plays a crucial role in quality and stability of product. An unfavorable outcome results from moisture content that is either too high or too low; too high moisture is not suitable for long-term storage stability whereas, too low moisture may damage the active material.

If there are many amorphous components present, the storage stability of the product could be impacted by the water content following sublimation drying. Its content may be 5-20% of the initial water content, which depends on solids content in preparation[1].So for the amorphous product higher temperature can be preferred but at slow ramp rate in secondary drying which helps to avoid collapse of cake.[9]

Following the secondary drying process, the water content of the majority of dried materials is decreased by 1 to 4% by weight. Target dry matter concentrations for pharmaceutical goods are frequently as high as 98-99% or higher.

The study conducted by KyuYoon *et al.* the main consequence they found was low rate of mass transfer due to heat resistance, which can be sorted by developing some alternative heating technologies such as microwave drying[10]which will help to remove the bound(unfrozen) water.

## FACTORS INFLUENCING LYOPHILIZATION

### Temperature Control

Temperature control is a critical factor in lyophilization, influencing every stage of the process and ultimately dictating the quality of the lyophilized product. During the freezing phase, precise temperature control is essential to ensure uniform freezing and the formation of small, evenly distributed ice crystals. Slow and controlled cooling rates are preferred to minimize the formation of large ice crystals, which can damage the structure of sensitive materials.[11] Rapid freezing or fluctuations in temperature can lead to heterogeneous ice crystal formation, resulting in product defects such as collapse of cake.[12] In the primary drying phase, low temperatures are typically employed to prevent thermal degradation of heat-sensitive compounds while maximizing sublimation rates. However, excessively low temperatures can prolong drying times and increase energy consumption.[13,14] In the secondary drying phase, temperature control is crucial to ensure the complete removal of bound water without causing thermal degradation of the product. Elevated temperatures are often used to accelerate the removal of bound water while maintaining product stability, but excessive temperatures can lead to product degradation or collapse, particularly for heat-sensitive materials.[13] In conclusion, precise temperature control throughout the lyophilization process is essential for achieving high-quality lyophilized products by ensuring uniform freezing, efficient sublimation, and preservation of product stability.

### Pressure Levels

Pressure levels during Lyophilization have a great influence on the efficiency and quality of the process. The pressure within the lyophilization chamber affects the vapor pressure solvent, which in turn influences the rate of sublimation-the process by which frozen water molecules transition directly from the solid to the vapor phase. Controlling pressure levels is crucial for achieving optimal drying rates, preventing collapse or shrinkage of the dried material, and ensuring uniform drying throughout the product.[15]

Several studies have highlighted the importance of pressure control in lyophilization processes and its effects on product quality. For example, a study by Pikal, Shah, and Roy (1984) investigated the heat and mass transfer dynamics during freeze-drying of pharmaceutical products. They found that variations in pressure levels within the lyophilization chamber significantly affected drying kinetics and product characteristics. Optimal pressure conditions were identified to prevent collapse and ensure uniform drying, leading to improved product quality and stability.[12]

Furthermore, research by Wang, Liu, Zhao, Zhang, and Wu (2020) explored the optimization of freeze-drying parameters for Dendrobium officinale water extraction. This study emphasized the importance of controlling pressure levels to enhance drying efficiency and preserve the bioactive compounds present in the botanical material. By adjusting pressure conditions within the recommended range, the researchers achieved improved lyophilization outcomes and enhanced product quality.[16]

In addition to its direct impact on drying kinetics, pressure levels also influence the stability of the lyophilized product. High pressures can lead to collapse or shrinkage of the dried material, affecting its physical structure and appearance.[17,18] Conversely, excessively low pressures may result in prolonged drying times and increased risk of product degradation.

To optimize pressure levels in lyophilization, precise control and monitoring of process parameters are essential.[19] Advanced lyophilization systems are equipped with automated pressure control mechanisms to maintain optimal conditions throughout the drying process. By carefully adjusting pressure levels according to the specific requirements of the material being lyophilized, manufacturers can achieve consistent and reproducible drying outcomes, resulting in high-quality lyophilized products with desirable characteristics and stability.

In summary, pressure levels play a critical role in lyophilization, influencing drying kinetics, product stability, and overall process efficiency. By understanding the effects of pressure on the lyophilization process and implementing appropriate control strategies, manufacturers can optimize lyophilization protocols to produce high-quality products with enhanced stability and shelf life.

### Ramp Rate and Duration

The ramp rate and duration during lyophilization, referring to the rate at which temperature changes and the time taken to achieve specific temperature transitions, respectively, are critical factors influencing the quality of lyophilized products. These parameters affect ice crystal formation, drying kinetics, and product stability,

thereby playing a significant role in determining the final product characteristics.[2]

Optimizing the ramp rate and duration is essential for controlling ice crystal size and distribution, which can profoundly impact product quality. A slower ramp rate and longer duration during freezing can lead to the formation of larger ice crystals due to prolonged exposure to sub-freezing temperatures. Conversely, a faster ramp rate and shorter duration leads in the formation of tiny ice crystals by minimizing the time available for water molecules to arrange into larger structures. Studies have shown that controlled temperature transitions can significantly affect ice crystal morphology and size distribution, ultimately influencing product stability and reconstitution properties.[12]

Furthermore, the ramp rate and duration also influence drying kinetics during the primary drying phase. Slower temperature transitions can prolong primary drying times by reducing the rate of sublimation, whereas faster transitions accelerate sublimation rates. However, excessively fast ramp rates may lead to uneven drying and product collapse if not carefully controlled. Therefore, selecting optimal ramp rates and durations based on material properties and formulation characteristics is crucial for achieving uniform drying and preserving product integrity.[12,20]

In short, the ramp rate and duration are critical parameters in lyophilization processes, affecting ice crystal formation, drying kinetics, and product stability. Optimizing these parameters is essential for controlling product quality and ensuring reproducible lyophilization outcomes.

## Formulation and Composition

The formulation of the product being lyophilized plays a key role in determining success and quality of lyophilization process. The choice of excipients, solvents, and active ingredients can significantly impact various aspects of lyophilization, including product stability, drying kinetics, and reconstitution properties. Formulation factors such as pH, buffer concentration, and availability of stabilizers must be carefully considered to optimize lyophilization outcomes.[21]

Excipients play a vital role in lyophilization formulations by stabilizing the active ingredients, enhancing solubility, and promoting uniform drying. Common excipients used in lyophilization formulations include sugars (e.g., sucrose, trehalose), bulking agents (e.g., mannitol, lactose), and surfactants (e.g., polysorbate 80). These excipients help protect the product from degradation during freezing and drying stages and improve the stability of the lyophilized product during storage.

The choice of solvent used in the formulation can also impact lyophilization outcomes. Solvents with low freezing points, such as water or organic solvents are commonly used for lyophilization. Water-based formulations are preferred for biological products due to their compatibility with biological molecules and ease of removal during drying. However, organic solvents may be used for lipophilic compounds or formulations requiring rapid drying rates.[22]

Furthermore, the pH and buffer concentration of the formulation can influence the stability of the active ingredients and pH of the final lyophilized product. Maintaining the appropriate pH range and buffer capacity is essential for preserving the integrity and bioactivity of sensitive compounds, like proteins or enzymes, during the lyophilization process.[23]

Stabilizers, such as antioxidants or chelating agents, may also be added to lyophilization formulations to protect against degradation reactions, such as oxidation or hydrolysis. These stabilizers help maintain the stability and efficacy of the active ingredients throughout the lyophilization process and during storage.[24]

## Container Design and Configuration

Container design and configuration play a crucial role in lyophilization processes, significantly influencing heat transfer, drying efficiency, and product uniformity. The choice of vial size,

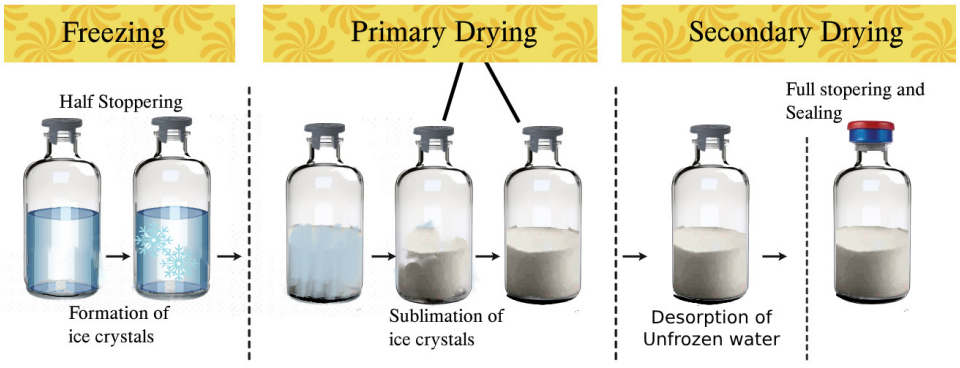


**Figure 1:** Steps in lyophilization.


**Figure 2:** Mass Transfer during primary drying.

shape, and material can have a profound impact on the outcome of the lyophilization process.[25]

When considering container design, factors such as surface area to volume ratio and geometry of the vial are critical. Vials with larger surface area-to-volume ratios promote more efficient heat transfer, allowing for faster freezing and drying rates. Additionally, the shape of the vial can affect ice nucleation and the distribution of ice crystals within the product. For example, cylindrical vials are often preferred over other shapes due to their uniform heat distribution and ease of handling during lyophilization process.[26]

Furthermore, the material of the vial is a crucial consideration in container design. Glass vials are commonly used in lyophilization due to their inert nature, transparency, and resistance to thermal shock. However, glass vials may not be suitable for all applications, as they can be fragile and may not provide adequate protection for sensitive products.[26] In such cases, polymer vials, such as those made from Cyclic Olefin Polymers (COP) or Polyethylene Terephthalate (PET), may be preferred for their durability and flexibility.[27]

Proper vial configuration, including the arrangement of vials within the lyophilization chamber, is also essential for achieving uniform drying and product consistency. Vials should be arranged to allow for adequate airflow and heat distribution throughout the chamber. Additionally, considerations should be made for vial spacing and orientation to minimize heat gradients and ensure uniform freezing and drying rates across all vials.[28,29]

Several studies have investigated the impact of container design and configuration on lyophilization outcomes. For example, research by Pikal *et al.*, (1984) examined the influence of vial design on heat transfer during the lyophilization process. The study found that vials with larger surface area-to-volume ratios exhibited more rapid heat transfer and shorter drying times compared to vials with smaller ratios. Similarly, studies by Costantino *et al.*, (2000) and Lu *et al.*, (2015) explored the effects of vial material and configuration on product stability and drying kinetics in pharmaceutical lyophilization processes.[28]

In summary, it's evident that container design and configuration wield substantial influence, profoundly affecting both the quality and efficiency of lyophilization processes. By carefully selecting vial size, shape, and material, and optimizing vial configuration within the lyophilization chamber, manufacturers can achieve more consistent and reproducible lyophilization outcomes, resulting in high-quality lyophilized products.

## Process Parameters and Control

Precise control and monitoring of process parameters are essential for ensuring reproducible lyophilization outcomes and maintaining product quality. Various parameters, including temperature, pressure, and vacuum levels, must be carefully regulated throughout the lyophilization process to achieve optimal drying rates, minimize product degradation, and ensure uniformity. Advanced control systems and monitoring techniques are employed to monitor these parameters in real-time and make necessary adjustments to maintain desired conditions. For example, temperature sensors are used to monitor the temperature of the product and the surrounding environment, while pressure sensors measure the pressure within the lyophilization chamber. Vacuum gauges are also utilized to monitor the level of vacuum within the chamber, which affects the rate of sublimation and drying efficiency.[30,31]

Inadequate process parameters and controls such as slow freezing rate and fast evaporation rate may leads to absence of cake in vial.

In case of fast evaporation rate the solid content in the formulation have chance to get evaporated from the container.

## Material Properties

The properties of the material being lyophilized play a important role in determining success and quality of lyophilization process. These properties encompass a range of characteristics, including particle size, morphology, concentration, and composition, all of which can influence drying kinetics, product stability, and reconstitution properties. Understanding the material properties is essential for selecting appropriate lyophilization protocols and optimizing process parameters to achieve desired product quality.[32]

Particle size is a significant material property that affects lyophilization. Smaller particles have a higher surface area to volume ratio, which can accelerate drying rates by promoting faster vapor diffusion and sublimation. Conversely, larger particles may require longer drying times due to slower vapor transport within the material.

Morphology, or the shape and structure of the material particles, also influences lyophilization outcomes. Irregularly shaped particles may have greater surface roughness, leading to increased surface area available for ice nucleation and drying. However, irregular shapes can also result in heterogeneous drying and variations in product quality. Studies have shown that controlling particle morphology through techniques such as milling or particle engineering can enhance the uniformity and stability of lyophilized products.[33]

Concentration of the solute or active ingredient in the formulation is another critical material property affecting lyophilization. Higher solute concentrations can increase solution viscosity, affecting ice crystal formation and drying kinetics. Moreover, concentrated solutions may exhibit higher osmotic pressures, leading to changes in ice nucleation and growth behavior. Optimization of solute concentration is essential to attain desired product characteristics and reconstitution properties.[34]

In some cases using of strong acid as component of product; it lowers the freezing point of Solution due to its ionic nature hence when acid used in more quantity, the solution may not freeze properly. Leading to various defects in cake or in some cases also responsible for absence of cake. Likely it can also occurs due to use of materials with low melting points, solution containing organic solvents or low levels of total dissolved solids.

Composition, including presence of excipients, stabilizers, or additives, can significantly impact lyophilization outcomes. Excipients such as cryoprotectants or bulking agents play vital roles in protecting the product during freezing and drying, reducing collapse or shrinkage, and maintaining product stability. Additionally, the choice of stabilizers can impact protein conformation and activity during lyophilization. Studies have demonstrated the importance of selecting appropriate excipients and stabilizers to enhance the stability and efficacy of lyophilized biopharmaceuticals.[35]

Ultimately, material properties such as particle size, morphology, concentration, and composition profoundly impact lyophilization processes and product quality. By understanding the influence of these properties and employing appropriate formulation and process optimization strategies, manufacturers can produce high-quality lyophilized products with desired characteristics and stability.

## Environmental Factors

Environmental factors, such as humidity and airflow, play a crucial role in lyophilization processes and can notably influence quality of the final lyophilized product. The lyophilization chamber's environment directly influences drying rates, product uniformity, and overall process efficiency. Proper control and management of these environmental factors are essential for achieving consistent and reproducible drying outcomes.

Humidity levels within the lyophilization chamber are particularly critical, as they affect the rate of water vapor removal from the frozen material. High humidity can impede sublimation by reducing the vapor pressure gradient between the frozen product and the chamber atmosphere. This can prolong drying times and lead to incomplete drying or collapse of the dried product. On the other hand, excessively low humidity levels can result in rapid drying, potentially causing product shrinkage or brittleness.[17]

Airflow patterns within the lyophilization chamber also influence drying kinetics and product uniformity. Proper airflow helps distribute heat and vapor evenly throughout the chamber, promoting uniform drying and preventing localized drying effects. Inadequate airflow can lead to uneven drying rates and variations in product moisture content, compromising product quality and consistency.

Environmental control systems, such as humidity and temperature sensors, are employed to monitor and regulate these factors during the lyophilization process. Advanced lyophilization equipment may also feature airflow control mechanisms to ensure optimal airflow patterns within the chamber. By maintaining precise control over environmental conditions, manufacturers can achieve consistent drying outcomes and produce lyophilized products with desired characteristics.[31]

# CONCLUSION

Temperature control, pressure levels, ramp rate and duration, formulation and composition, container design and configuration, process parameters and control, material properties, and environmental factors all play crucial roles in the lyophilization process. These factors collectively influence the quality and efficiency of the final lyophilized product. Precise temperature

control ensures uniform freezing and efficient sublimation, while optimal pressure levels enhance drying kinetics and product stability. The ramp rate and duration affect ice crystal formation and drying rates, impacting product characteristics. Formulation components such as excipients and stabilizers are vital for product stability and drying behavior. Container design and configuration influence heat transfer and drying efficiency. Real-time monitoring and control of process parameters are essential for achieving consistent outcomes. Material properties like particle size and composition significantly affect the drying process. Lastly, environmental factors such as humidity and airflow within the lyophilization chamber determine drying rates and product uniformity. By optimizing these factors, manufacturers can produce high-quality lyophilized products with enhanced stability and shelf life.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**COP:** Cyclic Olefin Polymers; **PET:** Polyethylene Terephthalate.

## SUMMARY

The article explored important factors that affect the lyophilization process and how these factors influence the quality of the final product. First, maintaining the right temperature is crucial for even freezing and effective drying. Proper pressure levels also help improve drying speed and stability of the product. The ramp rate and duration are key as they impact the formation of ice crystals and how quickly drying happens, which affects the product's features.

Moreover, the ingredients used, like excipients and stabilizers, are essential for keeping the product stable during drying. The design of the container matters too, as it influences how heat is transferred and how efficiently drying occurs. It's also important to monitor and control the process in real time to ensure consistent results. Additionally, characteristics like particle size and composition significantly affect the drying process. Finally, environmental factors such as humidity and airflow in the drying chamber play a role in how quickly and uniformly the product dries. By optimizing all these factors, manufacturers can create high-quality lyophilized products with better stability and longer shelf life.

## REFERENCES

1. Nowak D, Jakubczyk E. The Freeze-Drying of Foods-The Characteristic of the Process Course and the Effect of Its Parameters on the Physical Properties of Food Materials. Foods. 2020; 9(10): 1488; doi: 10.3390/FOODS9101488.
2. Ohori R, Yamashita C. Effects of temperature ramp rate during the primary drying process on the properties of amorphous-based lyophilized cake, Part 1: Cake characterization, collapse temperature and drying behavior. J Drug Deliv Sci Technol. 2017; 39: 131-9; doi: 10.1016/J.JDDST.2017.03.013.
3. Pardeshi SR, Deshmukh NS, Telange DR, *et al.* Process development and quality attributes for the freeze-drying process in pharmaceuticals, biopharmaceuticals and nanomedicine delivery: a state-of-the-art review. Future Journal of Pharmaceutical Sciences. 2023; 9(1): 1-31; doi: 10.1186/S43094-023-00551-8.
4. Kasper JC, Friess W. The freezing step in lyophilization: Physico-chemical fundamentals, freezing methods and consequences on process performance and quality attributes of biopharmaceuticals. European Journal of Pharmaceutics and Biopharmaceutics. 2011; 78(2): 248-63; doi: 10.1016/J.EJPB.2011.03.010.
5. Khandagale PM, Bhairav B, Saudagar RB. Lyophilization Technique: A Review. Asian Journal of Research in Pharmaceutical Sciences. 2016; 6(4): 269-76; doi: 10.5958/2231-5659.2016.00038.2.
6. Doran PM. Unit Operations. Bioprocess Engineering Principles. 2013; 445-595; doi: 10.1016/B978-0-12-220851-5.00011-3.
7. Doran PM. Unit Operations. Bioprocess Engineering Principles. 2013; 445-595; doi: 10.1016/B978-0-12-220851-5.00011-3.
8. Liapis AI, Bruttini R. A theory for the primary and secondary drying stages of the freeze-drying of pharmaceutical crystalline and amorphous solutes: comparison between experimental data and theory. Separations Technology. 1994; 4(3): 144-55; doi: 10.1016/0956-9618(94)80017-0.
9. Anonymous. Basic Principles of Freeze-Drying-Scientific Products. n.d. Available from: https://scientificproducts.com/basic-principles-of-freeze-drying/ [Last accessed: 10/4/2024].
10. Yoon K, Narsimhan V. Understanding Heat Transfer During the Secondary Drying Stage of Freeze Drying: Current Practice and Knowledge Gaps. J Pharm Sci. 2022; 111(2): 368-81; doi: 10.1016/j.xphs.2021.09.032.
11. Tan M, Mei J, Xie J. The Formation and Control of Ice Crystal and Its Impact on the Quality of Frozen Aquatic Products: A Review. Crystals. 2021; 11(1): 68; doi: 10.3390/CRYST11010068.
12. Pikal MJ, Shah S. The collapse temperature in freeze drying: Dependence on measurement methodology and rate of water removal from the glassy phase. Int J Pharm. 1990; 62(2-3): 165-86; doi: 10.1016/0378-5173(90)90231-R.
13. Nail SL, Jiang S, Chongprasert S, *et al.* Fundamentals of freeze-drying. Pharm Biotechnol. 2002; 14: 281-360; doi: 10.1007/978-1-4615-0549-5_6/COVER.
14. Passot S, Fonseca F, Barbouche N, *et al.* Effect of Product Temperature During Primary Drying on the Long-Term Stability of Lyophilized Proteins. Pharm Dev Technol. 2007; 12(6): 543-53; doi: 10.1080/10837450701563459.
15. Li P, shen T, Li L, *et al.* Optimization of the selection of suitable harvesting periods for medicinal plants: taking Dendrobium officinale as an example. Plant Methods. 2024; 20(1): 1-16; doi: 10.1186/S13007-024-01172-9/TABLES/4.
16. Li P, shen T, Li L, *et al.* Optimization of the selection of suitable harvesting periods for medicinal plants: taking Dendrobium officinale as an example. Plant Methods. 2024; 20(1): 1-16; doi: 10.1186/S13007-024-01172-9/TABLES/4.
17. Nowak D, Jakubczyk E. The Freeze-Drying of Foods-The Characteristic of the Process Course and the Effect of Its Parameters on the Physical Properties of Food Materials. Foods. 2020; 9(10); doi: 10.3390/FOODS9101488.
18. Mahiuddin M, Khan MIH, Kumar C, *et al.* Shrinkage of Food Materials During Drying: Current Status and Challenges. Compr Rev Food Sci Food Saf. 2018; 17(5): 1113-26; doi: 10.1111/1541-4337.12375.
19. Juckers A, Knerr P, Harms F, *et al.* Emerging PAT for Freeze-Drying Processes for Advanced Process Control. Processes. 2022; 10(10): 2059; doi: 10.3390/PR10102059.
20. Kawasaki H, Shimanouchi T, Kimura Y. Recent Development of Optimization of Lyophilization Process. J Chem. 2019; 2019; doi: 10.1155/2019/9502856.
21. Kasper JC, Friess W. The freezing step in lyophilization: Physico-chemical fundamentals, freezing methods and consequences on process performance and quality attributes of biopharmaceuticals. European Journal of Pharmaceutics and Biopharmaceutics. 2011; 78(2): 248-63; doi: 10.1016/J.EJPB.2011.03.010.
22. Kunz C, Schuldt-Lieb S, Gieseler H. Freeze-Drying from Organic Co-Solvent Systems, Part 2: Process Modifications to Reduce Residual Solvent Levels and Improve Product Quality Attributes. J Pharm Sci. 2019; 108(1): 399-415; doi: 10.1016/J.XPHS.2018.07.002.
23. Wu C, Shamblin S, Varshney D, *et al.* Advance Understanding of Buffer Behavior during Lyophilization. Lyophilized Biologics and Vaccines. 2015; 25-41; doi: 10.1007/978-1-4939-2383-0_3.
24. Molina MDC, Anchordoquy TJ. Formulation strategies to minimize oxidative damage in lyophilized lipid/DNA complexes during storage. J Pharm Sci. 2008; 97(12): 5089-105; doi: 10.1002/JPS.21365.
25. Sarmadi M, Holmes S, Agha R, *et al.* A comparative study of freeze-drying heat transfer in polymeric vials and glass vials. Scientific Reports. 2023; 13(1): 1-18; doi: 10.1038/s41598-023-40777-3.

26. Kullmann D, Martinez CL, Lümkemann J, *et al.* Part I: Significant reduction of lyophilization process times by using novel matrix based scaffolds. European Journal of Pharmaceutics and Biopharmaceutics. 2023; 184: 248-61; doi: 10.1016/J.EJPB.2022.12.008.
27. Sarmadi M, Holmes S, Agha R, *et al.* A comparative study of freeze-drying heat transfer in polymeric vials and glass vials. Scientific Reports. 2023; 13(1): 1-18; doi: 10.1038/s41598-023-40777-3.
28. Jin X, O'Grady D, Affleck RP, et al. Freeze Drying and Vial Breakage: Misconceptions, Root Causes and Mitigation Strategies for the Pharmaceutical Industry. J Pharm Sci. 2024; 113(5): 1306-18; doi: 10.1016/j.xphs.2023.12.010.
29. Daller S, Friess W, Schroeder R. Energy Transfer in Vials Nested in a Rack System During Lyophilization. Pharmaceutics. 2020; 12(1); doi: 10.3390/PHARMACEUTICS12010061.
30. Kawasaki H, Shimanouchi T, Kimura Y. Recent Development of Optimization of Lyophilization Process. J Chem. 2019; 2019; doi: 10.1155/2019/9502856.
31. Juckers A, Knerr P, Harms F, *et al.* Emerging PAT for Freeze-Drying Processes for Advanced Process Control. Processes. 2022; 10(10): 2059; doi: 10.3390/PR10102059.
32. Luo WC, O'Reilly Beringhs A, Kim R, *et al.* Impact of formulation on the quality and stability of freeze-dried nanoparticles. European Journal of Pharmaceutics and Biopharmaceutics. 2021; 169: 256-67; doi: 10.1016/J.EJPB.2021.10.014.
33. Gatto MS, Najahi-Missaoui W. Lyophilization of Nanoparticles, Does It Really Work? Overview of the Current Status and Challenges. Int J Mol Sci. 2023; 24(18); doi: 10.3390/IJMS241814041.
34. Merivaara A, Zini J, Koivunotko E, *et al.* Preservation of biomaterials and cells by freeze-drying: Change of paradigm. Journal of Controlled Release. 2021; 336: 480-98; doi: 10.1016/J.JCONREL.2021.06.042.
35. Emami F, Vatanara A, Park EJ, *et al.* Drying Technologies for the Stability and Bioavailability of Biopharmaceuticals. Pharmaceutics. 2018; 10(3); doi: 10.3390/PHARMACEUTICS10030131.


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