IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 2, Issue 1, December 2022
Impact Factor: 6.252

Review On: Lyophilization Process of Pharmaceuticals Manufacturing

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Abstract: *To establish a commertially feasible shelf life, lyophillization (freeze drying) is frequently employed to manufacture dry pharmaceuticals formulations. It is not necessary to refrigerate properly frozen dried products. Also kept at room temperature. Lyophilization is common, but it is expensive intense. Using the right process parameters, we can get the results we want. Compared to standard drying methods, our products are of the highest quality methods. Lyophilization has become increasingly significant in the pharmaceutical industry. It is subject to further growth and expansion. The procedure includes the following steps: Freezing, primary drying, and secondary drying are the three steps. Article focused on how various elements influence the lyophilization process, as well as provides a complete list of excipients used in lyophilized products...*

Keywords: Lyophilization, Freezing, Primary, and Secondary Drying, End point of freeze drying

I. INTRODUCTION

The coining of the term Lyophilization is generally attributed because of porous nature of the dried product & its "lyophilization" characteristics to rapidly reabsorb the solvent &restores the substance to its original state. Lyophilization is the most genaral technique for formulating parenterals producs when stability in aqueous solution is an issue.[1].Freeze drying has used in number of applications from many years in food & pharmaceuticals however there are many other uses for process including stabilization of living materials including microbiological culture & other items damage by water. Freeze drying involve removal of water & other solvents from the frozen matrix by the process known as sublimation 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 proces s to produce a product that "loves the dry state"[2].

II. PRINCIPLE

The main principle involved in freeze drying is a phenomenon call sublimation where water passes directly from Solid state to the vapour state without passing through the liquid state. Sublimation of water can take place at pressure and temperature below triple point I.e. 4.579 mm of Hg and 0.0099 degree Celsius[3].

At temperature and one atmosphere pressure ,Aqueous solution contains dissolved solutes in water and the whole formulation exit as liquid.

The liquid state of aqueous formulation can be altered by increasing the temperature to100°C to form a vapour and decreasing the temperature to 0°C to form an Ice.

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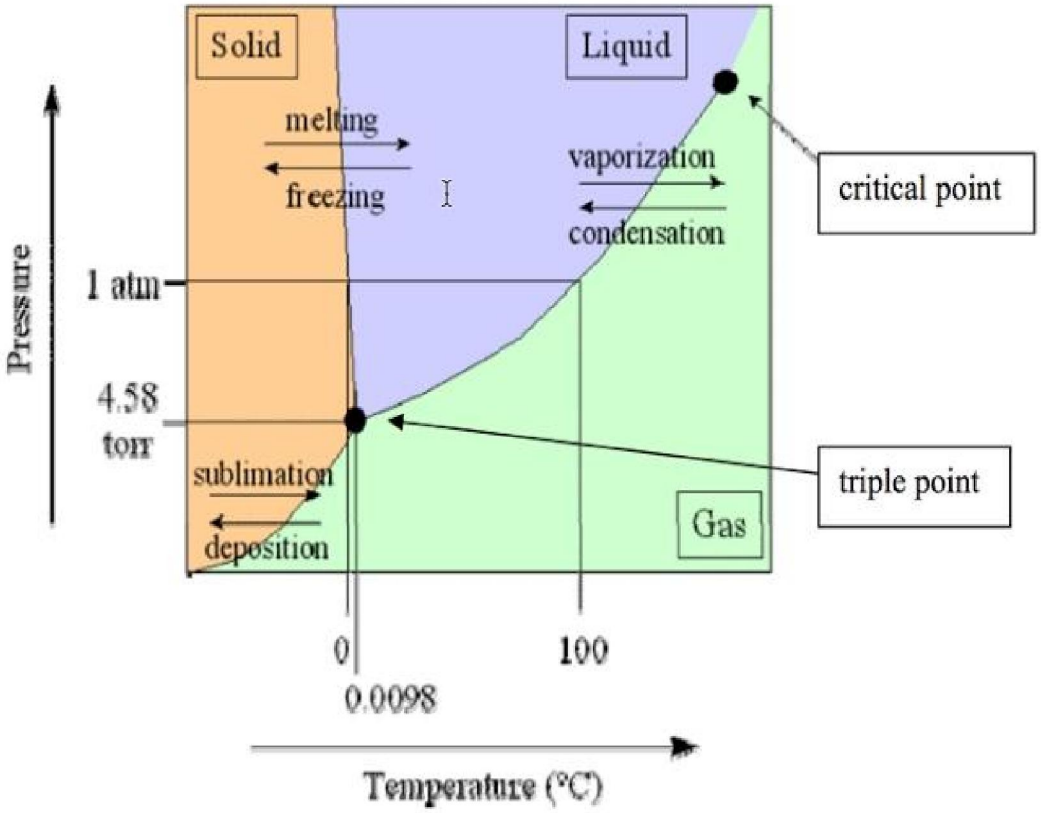

Figure 1: Phase diagram for freeze drying

III. LYOPHILIZATION

Typically, lyophilization occurs in following stages:

1. Pre Freezing
2. Freezing
3. Primary drying
4. Secondary drying
5. Sealing of lyophilization product

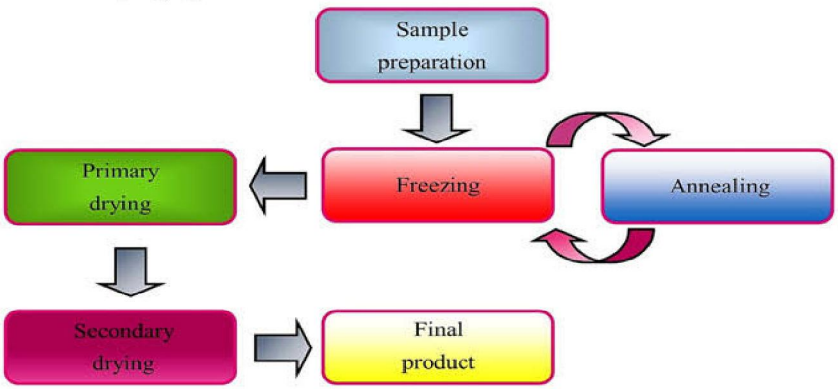

Figure 2: Lyophilization process flow

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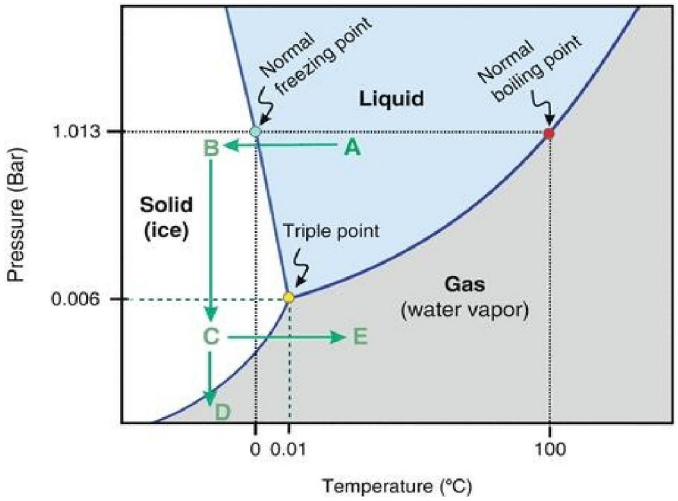
3.1 Pre Freezing

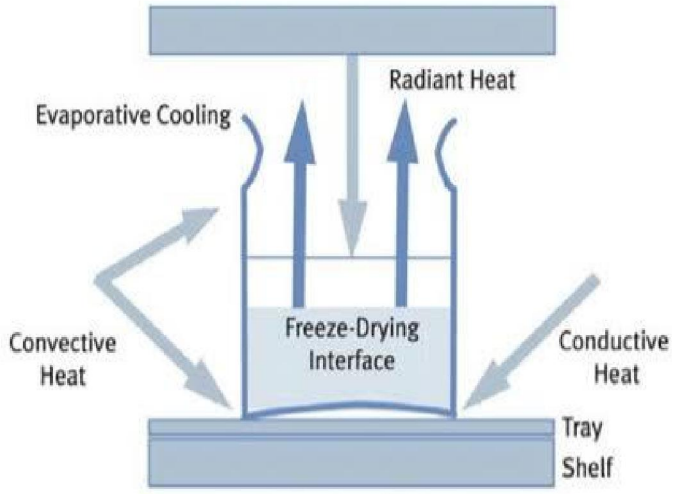
In lyophilisation process and final temperature affect ability to successfully freeze dry the material . in lyophilizaton freezing step mainly affected by cooling rate rapid cooling rate rate mainly used for preserving stature to be examined in the microscopically but product is more is difficult to lyophilized.

3.2 Frezeeing

Most samples that are to be freeze Dried are eutectics which are a mixture of substances that freeze at lower temperatures than The surrounding water. When the aqueous suspension is cooled, changes occur in the solute Concentrations of the product matrix. And as cooling proceeds, the water is separated from The solutes as it changes to ice, creating more concentrated areas of solute. These pockets of Concentrated materials have a lower freezing temperature than the water. Although a product May appear to be frozen because of all the ice present, in actuality it is not completely frozen Until all of the solute in the suspension is frozen.



1. Therotical thermodynamics value
2. Cryo- microscope
3. DSC (Different scanning calorimetry)
4. Measurement of temperature and resistance during the freezing phase.



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3.3 Primary Drying

Primary drying is also known as main drying because in this Phase of Lyophilization sublimation occurs. Sublimation Occurs when a frozen solvent passes to gaseous phase without Passing through liquid phase. The crystals of ice by using a special freezing method will grow extremely uniformly. The ice sublimes and the remaining solids show their original structure after freezing. In the process of sublimation the ice temperature at the sublimation front (Tice) should be done at well below the collapse temperature (Tc)[4]. The end of the sublimation phase corresponds to the decrease in the moisture sensor signal down to a low constant value[5]. The vapour transportation of vapour and supply of heat to the condenser which is shown Fig. 4 is most important parameter during primary drying.

3.4 Secondary Drying

After primary freeze-drying is complete, and all ice has sublimed, bound moisture is still present in the product[6]. 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 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.

Freeze Drying Method

Isothermal is normally continued at a moisture content to optimum values. This process is called „Isothermal Desorption" as the bound water is desorbed from the product.

Freeze Drying Methods

Three methods commonly used:

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

Determination of end point of freeze drying process:

The following are the techniques used for determination of end point of primary drying process,
Techniques based on gas composition in the product chamber:

1. Comparative pressure measurement (i.e., Pirani vs. capacitance manometer)
2. Dew point monitor (electronic moisture sensor)
3. Process H2O concentration from tunable diode laser absorption spectroscopy (TDLAS)
4. Lyotrack (gas plasma spectroscopy) Others:
5. Product thermocouple response
6. Condenser pressure
7. Pressure rise test (manometric temperature measurement (MTM) .

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

During the drying step, the chamber pressure is controlled using a capacitance manometer, Which measures the absolute pressure in the drying chamber. However, the Pirani vacuum Gauge works on the principle of measuring the thermal conductivity of the gas in the drying Chamber.[7]

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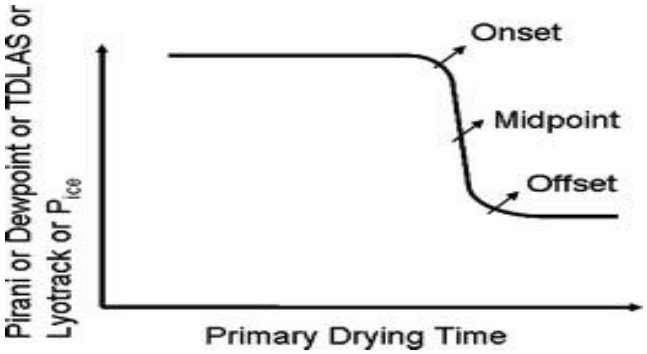

Figure 3: Pressure, dew point, TDLAS (process [H2O]), Lyotrack (gas Composition), and ice(vapor pressure of ice from pressure rise test) profile during Primary drying

Dew Point

The measurement is based on the principle of changes in the capacitance of A thin film of aluminum oxide arising from adsorption of water at a given partial pressure. Similar to the Pirani, the point where "dew point" starts dropping indicates that the Sublimation is "essentially" complete, i.e. gas composition is changing from mostly water Vapor to nitrogen (figure).[8]

V. EVALUATION PARAMETER FOR LYOPHILIZED PRODUCT

5.1 Appearance

The cake should not be collapsed on removal from the lyophilizer chamber. It must occupy the same volume at the of the liquid filled before the lyophilization or freeze-drying process.

5.2 Reconstitution Time and Clarity of Reconstituted Solution

In the lyophilization process when the surface area of the cake increases, resultant solubility also increases. Reconstitution of the product should take a very least time as possible and after reconstitution completion, the solution should be clear, without any visible particles in solution.

5.3 Choosing Excipients for a Lyophilized Formulation

The active pharmaceutical ingredient (API) and method of administration influence the choice of excipients for the lyophilized formulation. A single excipient or a combination of excipients diffrerent functions may be present in the lyophilized formulation. [16,17,18]

Uses for excipients include:

1. Buffers
2. Bulking substances
3. The stabilisers
4. Modifiers of tonicity

A. Buffers

Buffers that stabilise pH are utilised in medicinal formulations. The choice of buffer is important when creating lyophilized formulations since buffers like sodium phosphate and phosphate undergo significant pH changes during freezing. Citrate and histidine buffers, which exhibit minimal pH change during the freezing process, are used in low doses. [19]

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B. Bulking agents

The bulking agent used in the lyophilized product to provide bulk to the formulation. when very low concentrations of the active ingredient (API) are used. The bulking agents those are crystalline in nature provide good mechanical properties with elegant cake structure.

C. Stabilizers

In lyophilization formulation, used as disaccharides form an amorphous sugar to be used for stabilizing products such as proteins and liposomes during the process of lyophilization. Trehalose and Sucrose are inert and have been used in stabilizing protein, liposomes, and various formulations. Glucose, maltose, and lactose are reducing sugars and used in prevent of proteins from the mallard reaction. [20,21]

D.Modifiers of Tonicity

In many circumstances, an isotonic formulation is necessary. The tonicity adjuster needed in a formulation for the bulk solution's stability or in cases where the route of administration is involved. A few examples of excipients are Good tonicity adjusters include PharmaTutor glycerol, sodium chloride, mannitol, glycine, and sucrose. In the amorphous phase, glycine is utilised to reduce the glass transition temperature. [22]

VI. ADVANTAGE AND DISADVANTAGE OF LYOPHILIZATION

6.1 Advantages

1. Processing a liquid with ease (handling thereby simplyfying aseptic handling.
2. Enhancing the stability of dry powder as well as the product stability in a dry state
3. Removing water without having to hear the product excessively.
4. Dissolution of reconstituted product (rapidly or easily)

6.2 Disadvantages

1. Handling and processing time increases.
2. Sterile diluents needed upon reconstitution.
3. Equipment become costly and complex.
4. Expensive
5. Timely

VII. CONCLUSION

In conclusion, the expanding range of pharmaceutical applications and the new approaches to Understand and control the combination of formulation and process highlight the high Importance of the lyophilization process. awareness of the complexity of the freezing process and its consequences on product quality and process performance is essential for successful lyophilization. The knowledge of how to control, or atleast manipulate, the freezing step will help to develop more efficient lyophilization cycles and biopharmaceutical products with an impKudra T., Mujumdar AS., Advanced D

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