

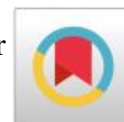


Science

LYOPHILIZATION: AN IMPORTANT FORMULATION TECHNIQUE

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Abstract

Lyophilization, is an important development for medicament formulation because of its ability to safely dry heat-sensitive vaccines, antibiotics, and protein-based formulations. The lyophilization process results in long shelf lives powder formulation which can be reconstituted at the point of use. As Injectable biopharmaceuticals become a more prominent part of the overall drug market the value of lyophilized product is has increased significantly. In 1998, lyophilized pharmaceuticals accounted for 11.9% of all new Injectable or infusible drugs, but, by 2015, they made up half of all such new drug introductions (Ratti et al 2001, Bubnovich et al 2012).

Keywords: Lyophilization; Formulation; Technique.

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1. Introduction

Principle: The principle involved in Lyophilization is the transition of a solid (ice) to the gas phase, without first becoming liquid phase. It works on the principle that solids have a weak intermolecular force hence a higher vapor pressure which converts it into directly vapor state. Sublimation of liquid can take place at temperature and pressures below triple point i.e. 0.0099 degree Celsius and 4.579 mm of Hg. The material to be dried is frozen first and then treated under a high vacuum to heat (by radiation or conduction or by both methods) so that frozen liquid sublimates leaving only dried and solid components of the original liquid. The driving force for the removal of water during Lyophilization is the concentration gradient of water vapor between the drying front and condenser (**Sheena et al 2018**).

Process: A low pressure environment is pre-requisite to allow Lyophilization process to take place. In order to start the removal of water, the pressure inside the freeze dryer must be below the “triple point value” for the product, whilst also maintaining the temperature of the sample below its freeze point in the lyophilization process which is suitable for drying of thermo-labile materials (**Nail et al, 1992**). The steps involved in lyophilization begins with preparation of sample followed by Pre-freezing, primary drying and secondary drying, to obtain the final dried product with

desired moisture content (**Dalgleish et al, 2007**). The concentration gradient of water vapor between the drying front and condenser is the driving force for removal of water during lyophilization. During the primary drying vapor pressure of water increases with an increase in the temperature. Hence, primary drying temperature should be maintained 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. The ice crystals start separating out until the solution becomes fully concentrated during freezing process. On further cooling, phase separation of the solute and ice takes place (**Adams et al, 1993**). Annealing is an optional step, sometime 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 (T_g). The determination of this critical temperature is important aspect for development of an optimized lyophilization process cycle. During the primary drying, temperature should not cross the critical temperature, which otherwise leads to 'meltback' or 'collapse' phenomenon. In most of the lyophilized formulations, excipients are included to improve the functional properties and stability of the lyophilized product (**Nireesha et al, 2013**).

2. The Fundamental Process Steps

- 1) **Freezing:** The product is frozen to provide a necessary condition for low temperature drying.
- 2) **Vacuum:** After freezing, the product is placed under vacuum to 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 removes the vaporized solvent from the vacuum chamber by converting it back to a solid.

3. Advantages of Lyophilization (Gannu Et Al, 2011)

Lyophilization Techniques has various important advantages compared to other drying and preserving techniques.

- 1) It is an ideal drying technique for heat sensitive products
- 2) Easy reconstitution significantly reduces weight and makes the products easier to transport, maintains food/biochemical and chemical reagent quality
- 3) It can enhance product stability in a dry state.
- 4) Reconstitution of the dried product facilitates use in emergency medicine and safe application in hospitals.
- 5) Lyophilized products sensitive to oxidation can be stopper and sealed within an inert atmosphere (i.e. nitrogen) to minimize detrimental effects.
- 6) It is not limited to products for parenteral use but can also be used for fast dissolving sublingual tablets. Tablets can have very low disintegration time and have great mouth feel due to fast melting effect.
- 7) It is much easier to achieve sterility of the product and freedom of foreign particles than using other drying methods.

4. Disadvantages of Lyophilization (Gannu et al, 2011)

Although lyophilization has many advantages compared to other drying and preserving techniques it has a few disadvantages as well.

- 1) It is a time consuming process.
- 2) It requires heavy cost which intern increases the coast of the product.
- 3) It requires sterile diluents for reconstitution.

5. Applications of Lyophilization Technology (Gannu et al, 2011)

The main application of this dynamic Lyophilization technology is found in the Industries (Table 1).

- 1) Pharmaceutical Industry
 - Antibiotics macromolecules and electrolytes are being produced by freeze-drying.
 - Used for drying of heat sensitive products for example: antibiotics, blood products and vaccine.
 - Development of solid protein pharmaceuticals (for long term storage).
 - Lyophilized nasal inserts.
 - Drying of micro and nano particles and lysosphere.
- 2) Food industry: Lyophilization is used to preserve food and make it very lightweight. The process has been known in the forms of freeze-dried ice-cream for example of astronaut food. It is also convenient for hikers because the reduced weight help them to carry more food and reconstitute with available water.
- 3) Other industries: In chemical synthesis, products are often lyophilized to make them more stable and easier to dissolve in water for subsequent use.
- 4) Miscellaneous applications: Agencies 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. Recent ceramics processes sometimes use Lyophilization to create a formable powder from a sprayed slurry mist. It gives softer particles with a more uniform chemical composition than traditional hot spray drying. Recently, some taxidermists have begun using freeze-drying to preserve animals, such as pets. Lyophilization can also be used for floral preservation.

6. Conclusion

Currently about 50% of the biopharmaceuticals are lyophilized, representing the most popular formulation strategy. In the freeze dried solid state, chemical or physical degradation reactions are constrained or sufficiently slow down, resulting in improved long term stability. In addition to the advantage of good stability, lyophilized formulations also provide easy handling during shipping and storage. The understanding of the complexity of the freezing process and its consequences on product quality and process performance is important for successful lyophilization. The cognizance of how to control, or at least manipulate, the freezing step will help to develop more efficient lyophilization cycles and biopharmaceutical products with an better stability.

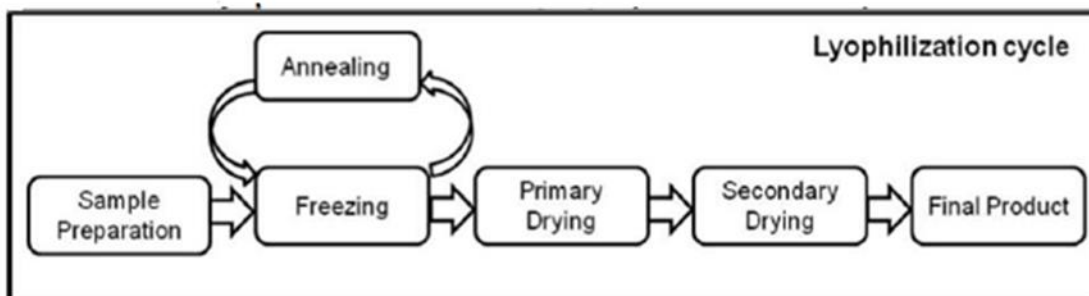


Figure 1: Steps involve in Lyophilization from sample preparation to final product formulation

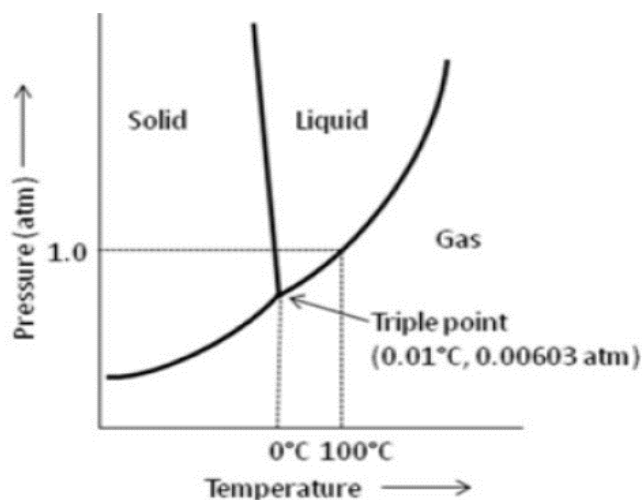


Figure 2: Phase Diagram showing the triple point of water at 0.01 °C at 0.00603 atm.

Table 1: Lyophilized products available in the market in powder form

S. No	Drug Name	Company Name
1	Cefaxone	Lupin Pharmaceuticals Pvt Ltd
2	Cefogram	Orchid Pharmaceuticals Pvt Ltd
3	Fortum	Glaxo Smithkline
4	Pantoprazole	Zenon Health Care, Aristo Pharmaceuticals
5	Rebolac I V	Cadila Pharmaceuticals
6	Omez	Dr.Reddys Laboratories
7	Reflin	Ranbaxy
8	Rabeprazole I V	Dr.Reddys Laboratories
9	Omeprazole	Neon Antibiotics
10	Tigecycline	Natco Pharma Ltd
11	Cilastatin	Natco Pharma Ltd
12	Ganciclovir	Natco Pharma Ltd
13	Omeprazole	Natco Pharma Ltd
14	Bortezomib	Natco Pharma Ltd
15	Pemetrexed	Natco Pharma Ltd
16	Zoledronic acid	Natco Pharma Ltd
17	Docetaxel	Natco Pharma Ltd

7. Future Prospect

One major area of lyophilization technology that require attention is control of the process. Indeed, it is questionable whether existing techniques actually “control” the process at all, since they are neither scalable nor transferable, and rely on the ability of a specific piece of equipment to replicate a set of condition which are known to produce the desired result. Initiative such as (Process Analytical Technology) from the FDA only serve exacerbate this observation. As a result, is ongoing in to method by which the process of Lyophilization can be more directly controlled, for example by observing the mass flow of vapor (**Kessier, 2004**).

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