Freeze Drying

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1. Freeze drying, also called lyophilization, is a process in which water is frozen, followed by its removal from the sample, initially by sublimation followed by desorption.
2. The equipment used to dry solutions or suspensions at or below freezing points of liquids is called as freeze dryer or lyophilizer.
3. Freeze drying is used in the manufacture of pharmaceuticals and biologicals that are thermolabile or otherwise unstable in water or moisture for prolonged storage periods, but that are stable in the dry state.

Principle:

1. The principle involved in freeze drying is sublimation, where water passes directly from solid state (ice) to the vapour state without passing through the liquid state.
2. Sublimation of water can take place at pressures and temperature below triple point of water.
   - (The temperature and pressure at which a substance can exist in equilibrium in the liquid, solid, and gaseous states. The triple point of pure water is at 0.01°C and 4.58 mm Hg.)
3. The material to be dried is first frozen and then subjected under a high vacuum to heat (by conduction or radiation or by both) so that frozen liquid sublimes leaving only non-volatile solid, dried components of the original liquid.

Construction:

1. Generally, there are three types of freeze dryers, for example, manifold freeze-dryer, the rotary freeze dryer and the tray style freeze-dryer.
2. These freeze-dryers differ in the method by which the dried substance is interfaced with a condenser.
3. The components common to all of them are a vacuum pump to reduce the ambient gas pressure and a condenser to remove the moisture by condensation on a surface cooled to -20 to -80 °C.
4. A freeze dryer consists of a vacuum chamber wherein products to be dried are kept on shelves and capable of cooling and heating containers and their contents.
5. A vacuum pump, a refrigeration unit, and associated controls are connected to the vacuum chamber.

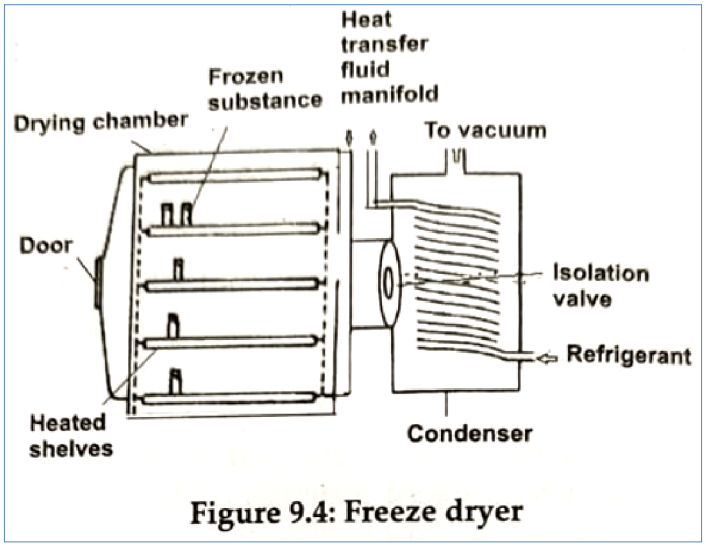


Figure 9.4: Freeze dryer

Working:

1. Traditional freeze drying is a complex process that requires a careful balancing of sample, equipment and processing techniques.
2. In this process, water is removed from a sample after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapour without passing through a liquid phase.
3. It is performed at temperature and pressure conditions below the triple point of liquid, to enable sublimation of frozen material.
4. The entire process is performed at low temperature and pressure. Steps involved in lyophilization start from sample preparation followed by freezing, primary drying and secondary drying, to obtain the final dried product.

5. The vapour pressure of water increases with an increase in temperature during the primary drying.
6. Therefore, primary drying temperature should be kept as high as possible, but below the critical process temperature, to avoid a loss of cake structure.
7. There are four important stages in the complete freeze drying process namely pretreatment, freezing, primary drying and secondary drying.

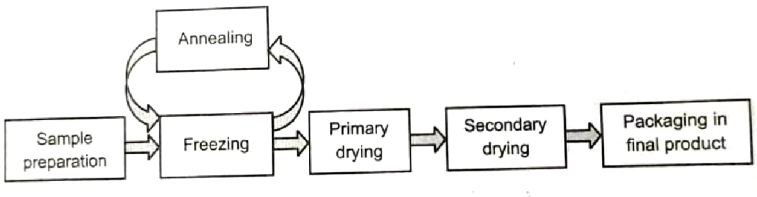
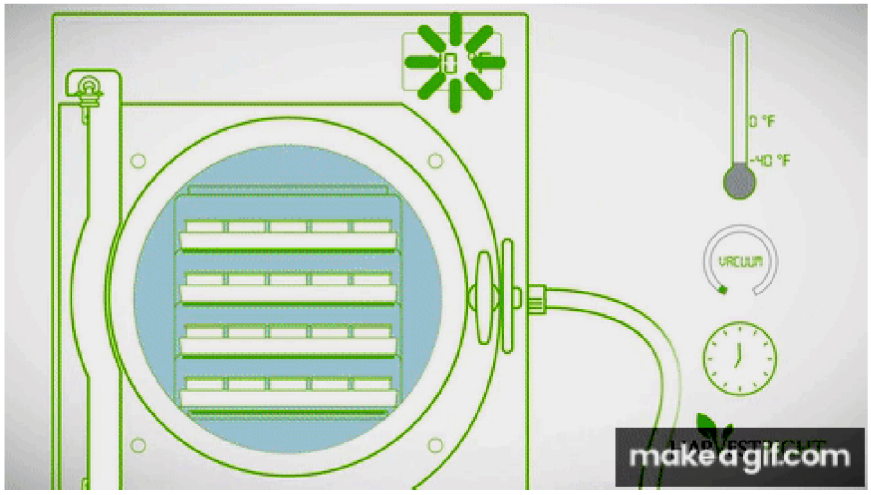


Fig. 4.18: Freeze Drying Cycle- Sequence of Operational Steps



1. **Pretreatment:**

   In this stage product is treated for freeze concentration, solution phase concentration, preserve product appearance, stabilize reactive products, prior to freezing increase surface area, and decrease high vapour pressure solvents concentration.

2. **Freezing:**

   During freezing stage usually the liquid sample is cooled down to -40 to -60 °C until pure crystalline ice forms from part of the liquid and the remainder of the sample is freeze-concentrated into a glassy state where the viscosity is too high to allow further crystallization.

3. **Primary drying:**

   In primary drying the ice formed during the freezing is removed by sublimation under vacuum at low temperatures, leaving a highly porous structure in the remaining amorphous solute, that is typically 10% water. This step is carried out at pressures of 104 to 109 atmospheres, and a product temperature of -45 to -20 °C. The sublimation during primary drying is the result of coupled heat- and mass-transfer processes.

4. **Secondary drying:**

   This is last step wherein most of the remaining water is desorbed from the glass as the temperature of the sample is gradually increased up to 10 - 15 °C while maintaining low pressures. Ideally, the final product is a dry cake with a high surface area and low moisture content (<3% w/w) which can be easily reconstituted.

Steps in Freeze Drying Process

Advantages:

1. This is suitable for drying heat sensitive products.
2. Freeze dried product is porous and easy to be rehydrated and instantly dissolved.
3. Drying takes place at very low temperature, so that enzyme action is inhibited and chemical decomposition, particularly hydrolysis is minimized.
4. Denaturation of protein does not occur.
5. Loss of volatile materials is less.
6. Sterility can be minimized.

Disadvantages:

1. The process is very slow.
2. Expensive process.
3. The period of drying is high.
4. The product is prone to oxidation, it must be vacuum packed.

Applications:

1. Freeze-drying is used to increase the shelf life of thermolabile products, such as vaccines and other injectable.
2. It is used to enhance stability of products during storage, shipping, and transportation.
3. Freeze-drying is used to reduce weight of products.
4. It is used to preserve blood products in freeze-dried form.
5. It is used in chemical synthesis to make products more stable and easier to dissolve in water.
6. Freeze-drying can effectively be used in bio-separations in purification procedures.
7. It can be used to concentrate low molecular weight substances that are too small to be removed by a membrane filtration.