Chapter 1
Drying

Majeedullah and Asad Shareef

Abstract Drying is one of the most common unit operations in pharmaceutical manufacturing. Selection of dryers for pharmaceutical manufacturing is not simple, since different existing dryers can dry the material to the desired level. Selection of efficient dryer and drying parameters requires basic knowledge about drying process. This chapter explains the basic concepts of drying, including its importance and application in pharmaceutical processes. The theory of drying and the parameters affecting the drying process are discussed in detail. It also briefly outlines the several types of dryers used in pharmaceutical industries.

Keywords Theory of drying · Drying curve · Types of dryers · Dryer selection · Classification of dryers

1.1 Introduction

Drying is normally referred to the process of thermally eliminating moisture to obtain solid product. Drying is typically intended for adjustment of moisture levels in solid materials. In practice this liquid refers to the water, but at times certain volatile substances may need to be removed [1]. Drying and vaporization can be distinguished by the relative moisture content removed from the solid.

Drying is one of the most important steps in primary and secondary pharmaceutical processes:

– For recovery of drug during synthesis
– For adjustment of moisture content in powder and granules

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S. A. Khan (ed.), *Essentials of Industrial Pharmacy*, AAPS Advances in the Pharmaceutical Sciences Series 46, https://doi.org/10.1007/978-3-030-84977-1_1

- Impart special properties to material, e.g., spray-dried lactose for better flow
- Reduce weight of material
- Improve stability by reducing hydrolysis of drug
- Improve shelf life by reducing microbial growth

Drying can be attained by many ways: using adsorbent, such as calcium chloride to adsorb moisture, using desiccant in a sealed container such as silica gel that remove water from the air, or exposing material to heat. Heating is the most common mode of drying in pharmaceutical processes.

Moisture held in the microstructure of solid that cannot be easily removed called *Bound water*, has a vapor pressure lower than that of pure water. Moisture other than the bound water is called *Unbound water* [2]. Removal of bound water requires more energy as compared to the unbound water.

When a moist material is heated, two phenomena take place simultaneously:

1. Transfer of energy to the material from surrounding to vaporize the surface moisture
2. Transfer of internal moisture to the surface and ultimately to the surrounding

Therefore, the rate of drying is controlled by the rate at which both these steps take place. The heat transfer from the surrounding to the material can occur as a result of *convection*, *conduction*, or *radiation*, and in many cases combination of all these.

For understanding it can be simplistically represented by combining heat transfer and mass transfer equations [3]:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{qc + qk + qr}{Lv} = K'A\Delta C \tag{1.1}$$

where $\mathrm{d}m/\mathrm{d}t$ is the rate of vapors transferred per unit time; qc, qk and qr are the rate of heat transfer by *convection*, *conduction*, and *radiation*, respectively; Lv is the latent heat of vaporization; K' is mass transfer coefficient; and ΔC is the difference in moisture content between material and environment.

It is evident from the above equation that rate of evaporation can be increased by:

- Increasing q_c = by rising the flow rate of air (i.e., *convection*)
- Increasing q_k= by prolonging contact time with the heating surface (i.e., *conduction*)
- Increasing q_r = by introducing high temperature radiating heat source, such as heating coils (i.e., *radiation*)
- Increasing A = by increasing the surface area
- Increasing ΔC = by dehumidifying the inlet air

1.2 Important Terms Used in Drying Process

Proper understanding of drying process requires the explanation of following related terms.

Total Moisture Content It is the total amount of liquid present in the material. Not all the moisture can be removed by simple evaporation [4]. The amount of easily removable moisture (unbound) is known as free moisture content, and the remaining moisture is termed as equilibrium moisture content.

Equilibrium Moisture Content It is the amount of moisture present in a material at ambient conditions, and it is dependent on the humidity, temperature, and nature of material.

Bound Water It is the moisture trapped in the microstructure of the solid that cannot be easily removed. Bound water has vapor pressure lower than that of pure water.

Percent Loss on Drying (% LOD) It is the term used to express moisture in a wet substance on the basis of wet weight [5]. It is calculated as:

$$\%LOD = \frac{\text{Weight of water in a solid}}{\text{Total weight of the wet solid}} \times 100 \tag{1.2}$$

The LOD of the wet solid can be determined using a balance which has calibrated scale. A weighed sample is placed in the pan and dried until constant weight. The moisture lost by evaporation is read directly from the % LOD scale.

Percent Moisture Content (% MC) It is the term used to express moisture content of a substance on dry-weight basis. It can be calculated as:

$$\%MC = \frac{\text{Weight of water in a sample}}{\text{Weight of the dry sample}} \times 100 \tag{1.3}$$

For example, if 8 g of moist solid is brought to a constant dry weight of 5 g then:

$$\%MC = \frac{8-5}{5} \times 100 = 60\% \tag{1.4}$$

while,

$$\%LOD = \frac{8-5}{8} \times 100 = 37.5\% \tag{1.5}$$

LOD values may vary from 0% to slightly below 100%, but MC values may vary from above 0% to infinity. A small change in LOD value represents an increase in

MC value. Thus %MC is more realistic value than %LOD in evaluation of drying process.

Dry-Bulb Temperature It is simply the ambient condition, i.e., the temperature of dry air, and is typically measured with a conventional thermometer.

Wet-Bulb temperature It gets its name because a wet permeable membrane, such as wet gauze, is used in conjunction with a regular thermometer for temperature measurement [6]. The air temperature is measured while a wet gauze is wrapped around the thermometer bulb. Since water is evaporated from the gauze, it leaves evaporative cooling on the thermometer. Consequently wet-bulb temperature is lower than dry-bulb temperature [7]. However, at 100% relative humidity dry-bulb temperature is equal to wet-bulb temperature, since no evaporation of water takes place from wet gauze.

1.3 The Drying Curve

Each material has a representative *drying curve* that describes its drying behavior. This curve is obtained by plotting moisture content vs time. The changes during drying process can also be understood by plotting drying rate vs moisture content [8]. As shown in Fig. 1.1, the drying curve can be divided into four stages:

(a) Initial adjustment period
(b) Constant rate period
(c) First falling rate period
(d) Second falling rate period

The stage A–B in Fig. 1.1 represents the initial adjustment period. The drying surface is equilibrated with drying air. This stage is very short and often ignored in predicting the drying time. The stage B–C shows a constant rate period. A moisture film continuously exists on the solid surface, and solvent is evaporated continuously

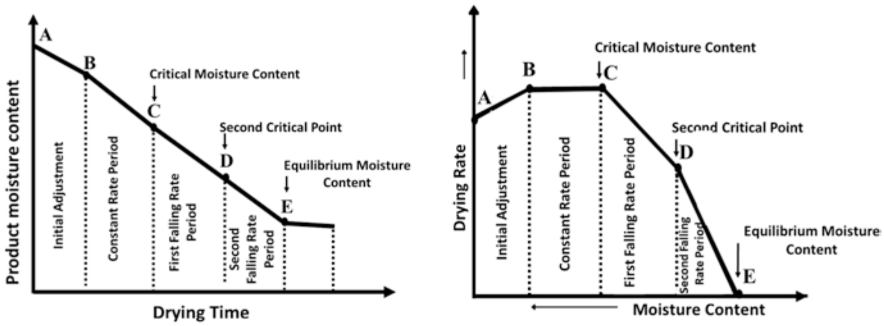

Fig. 1.1 Typical drying curves

from this moisture film. The moisture content at the end of constant rate period (point C) is called critical moisture content (CMC). From this point onward the first falling rate period starts, i.e., the rate of drying slows down, since the moisture film on the solid surface starts to vanish. The second falling rate period begins from point D, where the surface is completely dried. The moisture diffuses from within the material to the surface and gets evaporated. Most of the drying occurs in second falling rate period [9].

1.4 End Point Detection in Drying Process

The drying end point is one of the key factors that affect quality of final product. For batch dryers, end point is typically measured by monitoring moisture content periodically. Then constructing a "*drying curve*" by plotting residual moisture content in the product over time. The end point is the point where the desired level of residual moisture in the product is attained.

To minimize sampling, inline end point testing is preferred, which relies on secondary factors, such as airflow, air pressure, inlet or outlet air temperature, and product temperature. Recently, the inline near infrared spectroscopy (NIR) for determination of product moisture is more common. Moreover, inline mass spectrometry (MS) has also been used for continuous monitoring of headspace solvent concentration.

1.5 Selection of Industrial Dryers

Selection of dryers for pharmaceutical manufacturing is not simple, since different existing dryers can dry the material to the desired level. The choice of dryer depends on the nature of the material being handled and the cost to attain required end point while complying all safety and environmental standards. A more structural approach in selection of dryer may follow the following steps [10].

(a) Process specifications are selected.
(b) A few of the dryers in the available options are selected.
(c) Bench-scale operation and quality tests are performed.
(d) Economic feasibility of the selected dryer is evaluated.
(e) Pilot-scale trials are performed.
(f) The most appropriate dryer is selected.

However, most recently, in many advance setups, dryers are selected on the basis of algorithms that assign a certain score to each dryer, based on the information available for different dryers, the properties of material to be dried, the quantity to be dried, and the required moisture content, etc. [11].

1.6 Classification of Dryers

1.6.1 Classification on the Basis of Mode of Energy Input

Certain features of dryers might vary with the mode of energy input that may affect the feasibility of dryer for certain applications. The mode of energy input may be direct or indirect; hence the corresponding dryers are called direct dryers or indirect dryers.

1.6.1.1 Direct Dryers

These are the most common type of dryers often referred to as *convective dryers*. Most of the industrial dryers are of this type. As the name indicates, the drying medium directly contacts the content to be dried. Typically, hot air or gas is used as drying medium that provides heat for drying and carries the evaporated moisture away. The temperatures of air/gas may vary from 50 to 400 °C. Sometimes, dehumidified air/gas might be required for drying of very heat-sensitive contents. An inert gas like nitrogen may possibly be suitable while drying explosive or flammable materials. Solvents recovered must be extracted by condensation from the exhaust so that they can be reused.

1.6.1.2 Indirect Dryers

In these dryers the drying medium does not directly contact the material to be dried, i.e., heat is transferred by *conduction*. However, it is essential to either use vacuum/ or gentle air current to get rid of the vaporized moisture to avoid chamber saturation with vapors. Heat transfer shelves could range in temperature from −40 °C (as in freeze-dryer) to nearly 300 °C (combustion of waste sludges). Application of vacuum is also helpful for the retrieval of solvents through direct condensation. Additionally, vacuum setup drops the boiling point of the liquid withdrawn and thus permits drying of heat-sensitive materials at fairly faster rates. These types of dryers are applicable for drying of toxic, dusty products. In addition, heat may also be delivered by radiation (electric or natural gas-fired radiators) or dielectric fields in the microwave/or radio-frequency range.

1.6.2 Classification on the Basis of Solid Handling

Dryers can also be classified on the basis of how the solid is handled during drying, for instance:

(a) Static bed dryers
(b) Moving bed dryers
(c) Fluidized bed dryers
(d) Pneumatic dryers
(e) Specialized dryers

1.6.2.1 Static Bed Dryers

In static bed dryers the individual solid particles are kept static; however, the entire bed of drying powder is moved. Consequently, only a fraction of surface material is exposed to the heat. Reduction in thickness of powder bed will result in increased exposure of the surface. Examples are tray dryer and truck dryer.

Tray Dryer

Tray dryer also called shelf dryer is one of the most commonly used dryers for small-scale drying. It comprises a central cabinet for placement of trays, as shown in Fig. 1.2a. The number of trays held in cabinet is based on the size and shape of the dryer. The heat supply is either direct or indirect. In direct heat supply, hot air is distributed inside the chamber. Indirect heating is provided either by heated shelves or by radiant heat source inside the chamber. The base of trays may be solid or perforated. The trays with solid base utilize heat from top and bottom of the tray, while in perforated base trays, air passes through each tray and the solid. The perforated trays need to be lined with papers as a disposable tray liner to reduce cleaning time and prevent product contamination. For uniform drying a well-insulated cabinet with placed fans and heating coils inside the cabinet is preferred.

Truck Dryer

It is very similar to tray dryer; however, the trays are loaded on truck (wheeled racks), which can roll into and out of the drying cabinet, as shown in Fig. 1.2b. This offers more convenience in loading and unloading of trays. A wheeled rack can house around 18 trays, with about 4–8 ft^2 placement area. The trays are generally loaded 0.5–4.0 inches deep with at least 1.5 inches between the surface and above trays. A control panel is fixed outdoor to monitor the temperature and other features.

Tunnel Dryer

It is an adaptation of the truck dryer and is suitable for large-scale production. It consists of a long tunnel (drying chamber), as shown in Fig. 1.2c. The solid is placed on the trays that are loaded on truck [3]. Air current enters from one end, and trucks

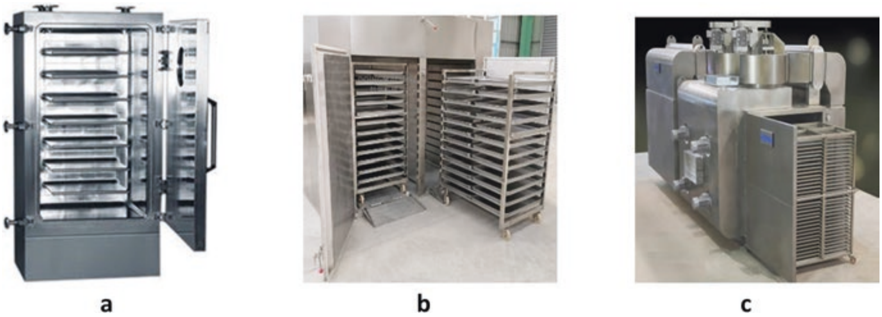

Fig. 1.2 Tray dryer (**a**), truck dryer (**b**), and tunnel dryer (**c**). (Courtesy: Bigtem machines, Turkey)

are slowly moved from the other end with the help of moving chain. The trucks reside in the drying chamber for sufficient time to achieve adequate drying. Tunnel dryers are classified as semicontinuous dryers, since they involve manual handling of material in the drying cycle. However, the drying achieved is not uniform, as the top exposed layer is dried fast compared to the lower layer.

Conveyor Dryer

It is a continuous dryer and is adaptation of tunnel dryer, where individual trucks are replaced with a conveyor belt or panel that carries the wet mass via the tunnel, as shown in Fig. 1.3. In some conveyor design, the partially dried mass rolls onto adjacent conveyor heading in the opposite direction. The wet mass can have a number of serial passages along the chamber before it is discharged from the conveyor.

1.6.2.2 Moving-Bed Dryers

In moving-bed dryers, the particles flow over each other by gravity or due to mechanical agitation. Hence, new surface is regularly exposed to heat that facilitates rapid heat transfer to the particles and improves evaporation of moisture from the particles. Examples of moving-bed dryers are given in coming section.

Rotary Dryer

It consists of a slightly inclined horizontal tube with a feed inlet at one end. The material enters at feed inlet and passes in the revolving cylinder, as shown in Fig. 1.4. The rotation and slope of the revolving cylinder are responsible for the material to slide down [12]. Heating is directly provided using hot air or indirectly by an external jacketed steam tube. Rotary dryers provide continuous and faster

Fig. 1.3 Conveyor dryer. (Courtesy: Bigtem machines, Turkey)

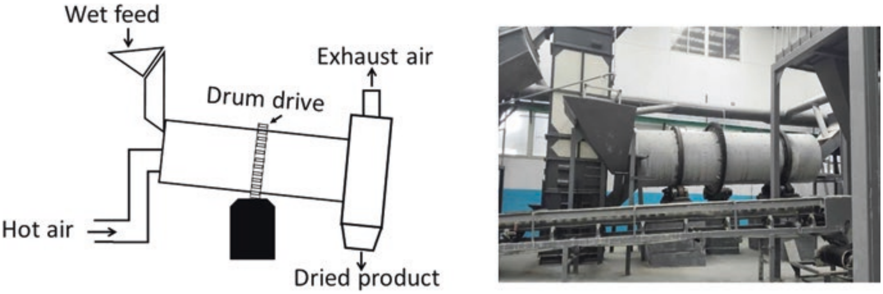

Fig. 1.4 Rotary drum dryer. (Courtesy: Changzhou Fuyi Equipment Co., Ltd. China)

drying. Moreover, the drying achieved is uniform, since all parts get similar exposure to hot air.

1.6.2.3 Fluidized Bed Dryer

In fluidized bed dryer (FBD), individual particles are lifted and then fall back in a random manner, called *fluidization* of particles. FBD generally offers better heat and mass transfer than static and moving-bed dryer. There are two subtypes of FBD, vertical FBD and horizontal FBD.

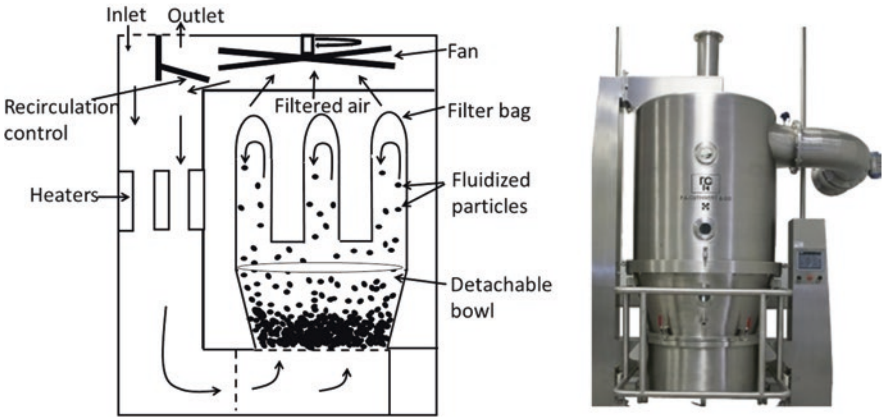

Fig. 1.5 Vertical fluidized bed dryer. (Courtesy: PA Cuthbert & Co. (Pvt) Ltd, South Africa)

Vertical FBD

In vertical FBD, hot air is blown through the wet mass held in drying chamber having a wire mesh support at the bottom. A bag collector filter is mounted at the top of the drying chamber to stop particles from being carried over [13]. A typical vertical FBD is given in Fig. 1.5.

It is a batch-type dryer and typically has the capacity of 5–200 kg, with average drying time in between 20 to 40 min. It offers efficient, fast, and uniform drying with reduced labor cost [3].

Horizontal FBD

Horizontal FBD comprises a vibrating conveying deck passing over a perforated surface; hot air is blown up through perforated conveying surface. The vibration of conveying deck fluidizes the particles. Air stream passes over the fluidized bed into the exhaust hood, as shown in Fig. 1.6.

Horizontal FBD offers continuous drying; however it is not suitable for friable materials.

1.6.2.4 Pneumatic Systems

In pneumatic systems, particles slurry is introduced to the drying chamber in the form of a fine mist. Individual particles are entirely exposed to drying gas as a result heat and mass transfer is very rapid. One of the most common examples of pneumatic systems is spray dryer.

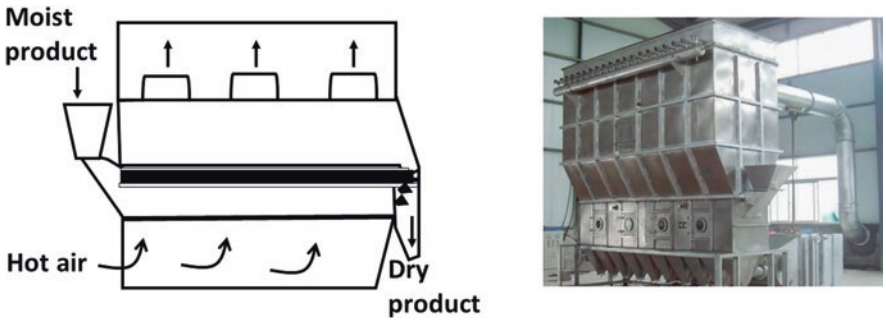

Fig. 1.6 Horizontal fluidized bed dryer. (Courtesy: Tianjin HSD Separation Envitech Co., Ltd, China)

Spray Dryer

Contrary to previously discussed dryers, spray dryer can handle only fluids, such as solutions, slurries, and thin pastes. It comprises of a drying chamber, an atomizer and a hot air source and exhaust. The fluid is converted into a fine mist in a moving stream of hot air, where liquid from the droplet is evaporated before touching the wall of drying chamber. Fine dried particles are moved by the gas and gravity flow into the main collector by a cyclone separator (cyclone product), as shown in Fig. 1.7. Some of the dried powder remains in drying chamber, called "chamber product," and is collected from the bottom of the chamber. Particles in chamber product are usually coarser and are subjected to heat for longer time. Final product is a mixture of cyclone product and chamber products [14].

The spray dryer atomizer is of three types:

Pneumatic atomizers: Droplets are formed by a high-velocity jet of air or gas.

Pressure nozzle: Liquid feed is supplied by high-pressure nozzles (upto7000 lb/In^2) and splits by impact of a fixed plate placed in front of the stream.

Spinning disc atomizers: Liquid is split into droplets by a rapidly rotating disc (3000–50,000 rpm).

Spray drying offers three major advantages;

Drying heat-sensitive material. It is suitable for drying of thermolabile materials without degrading them, as evaporation of the liquid keeps the temperature of material lower.

Changing the physical form of material. It changes the shape, size, and bulk density of dried product. It promotes flowability as same size and shape particles are formed with rare sharp edges. The process also reduces air trap in spherical particles making them preferable for usage in the solid dosage forms.

Coating and encapsulation of both solids and liquids. Particles suspended in a solution of the coating agent can be spray-dried into coated particles. As the solvent is evaporated, the coating material covers the suspended particles.

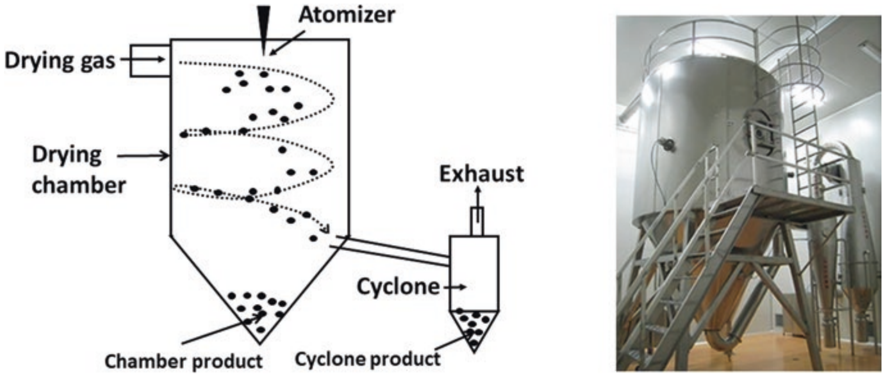

Fig. 1.7 Spray dryer. (JY Drying Engineering Co., Ltd, China)

1.6.2.5 Specialized Dryers

Specialized dryers are designed to dry sensitive pharmaceutical and chemicals, e.g., vacuum dryer and freeze dryer.

Freeze Dryer

Freeze dryer uses the principle of *sublimation*, the conversion of a substance from solid state directly to gas state, without converting into liquid state, as shown in Fig. 1.8.

The liquid contained in material is frozen and evaporated at low temperature under high vacuum. This makes freeze dryer suitable for thermolabile products.

The boiling point of liquid is governed by temperature-pressure relationship. For instance, at normal atmospheric pressure (1 atm or 760 mmHg), water evaporates at 100 °C. The boiling point can be reduced by reducing the pressure and vice versa. At *triple point* (i.e., temperature = 0.0098 °C and pressure = 4.58 mmHg), pure water starts exhibiting the process of sublimation [15]. However, in pharmaceutical dosage forms, certain dissolved components may affect temperature-pressure relationship for each solution. The point at which these solutions are sublimed is called *eutectic point* [16].

Freeze drying is typically carried out at temperature range of −10 to −40 °C under 2.0 to 0.1 mmHg pressure [17].

Advantages of freeze drying

– Freeze drying provides minimum damage to heat-labile materials.
– In freeze drying, minimal structural changes or shrinkage occurs.
– Drying takes place at very low temperature, so that enzyme action is inhibited.
– The dried powder is fluffy and fibrous and has better solubility.
– Freeze drying may increase the shelf life of some drugs.

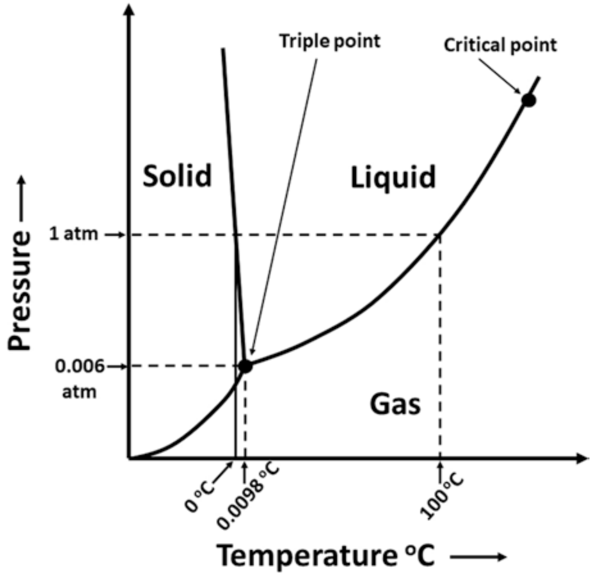

Fig. 1.8 Schematic pressure-temperature diagram for water

– Sterility can be maintained during drying process.

Disadvantages of freeze drying

– Freeze drying system needs vacuum and refrigeration equipment. The initial costs are four times higher than conventional drying. Moreover, energy costs are also higher than the other methods.
– Drying rate is very slow.
– Packaging of freeze-dried product requires special attention/conditions.

Uses of freeze drying

– Freeze drying is used in preparation of hormones, blood products, antibiotics, bacterial culture, and vaccines.
– It is used for food products such as freeze-dried ice cream and instant coffee.
– Recently, some taxidermies have begun using freeze drying to preserve animals.

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