Drying

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Credit: Prof. Nizar Al-Zoubi

Drying

Drying is an important operation in pharmaceutical industry in:

1. the synthesis of active drugs and raw materials (usually the last step before packaging)
2. wet granulation process

Drying can be:

1. Thermal: the removal of a liquid from a material by application of heat. This is achieved by the transfer of liquid from a surface onto an unsaturated vapor phase.
2. Non-thermal: There are other methods for drying which are non-thermal like expression (squeezing of a wetted sponge) or centrifugation (such as domestic spin dryer)

The drying of wet solids

Moisture content of wet solids:

It is the weight of water in sample divided by the weight of dry sample. Therefore it is calculated on a dry-weight basis as follows:

W1---------→ W2

$$\%MC = \frac{\text{wt. of water in sample}}{\text{wt. of dry sample}} \times 100\%$$

Loss on drying:

$$\%LOD = \frac{\text{wt. of water in sample}}{\text{total wt. of wet sample}} \times 100\%$$

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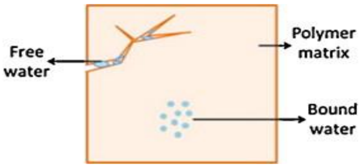
The drying of wet solids

Total moisture content:

- This is the total amount of water associated with a wet solid. Part of the water can be easily removed by the evaporative drying processes and is known as ***unbound water.***
- The content of unbound water is known as ***Free moisture content***



Equilibrium moisture content (EMC)

- Evaporative drying process will not remove all the possible moisture present in a wet product because the solid equilibrates with the moisture present in the air.
- This moisture content is termed ***Equilibrium moisture content*** **(EMC).**
- Its value changes with temperature humidity and the nature of the solid.
- The part of moisture that is practically more difficult to remove is known as ***bound water.***

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The drying of wet solids

Relative humidity (RH) of air

Air at a given temperature is capable of taking up water vapor until it is saturated (100% RH).

Relative humidity (% RH) may be defined as:

*vapor pressure of water vapor in the air / vapor pressure of water vapor in air **saturated** at same temperature*

This is approximately equal to the percentage saturation, which is the ratio:

Mass of vapor present per kg of dry air / Mass of vapor required to saturate 1 kg of air at the same temperature

The relationship shows that relative humidity is dependent on temperature.

If the temperature is raised then the air will be able to take more moisture and the relative humidity falls.

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Relationship between EMC and RH

- The equilibrium moisture content (EMC) of a solid exposed to air varies with the relative humidity (RH).
- Lower EMC and therefore further drying can be achieved by reducing the RH values of the ambient air.
- This can be done mechanically on a large scale using air conditioning systems, or on small scale using dissectors with moisture absorbing materials (like silica gel and phosphorous pentoxide).

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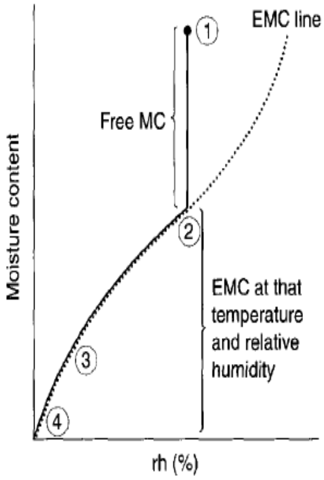

Fig. 26.3 Loss of water from a drying solid. The wet solid prior to drying is at condition (1). It can lose water by evaporation to position (2), its equilibrium moisture content at that RH. The only way the solid can lose more water is to reduce the RH of the ambient or storage atmosphere, to (3) with silica gel or to (4) with phosphorus pentoxide.

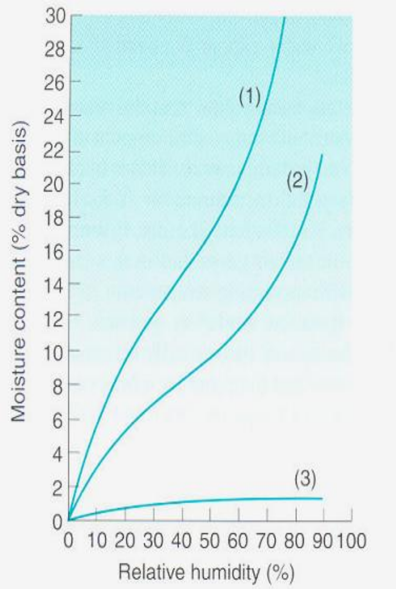

Fig. 30.1 Typical equilibrium moisture contents at 20°C. (1) Starch-based materials. (2) Textiles and fibrous materials. (3) Inorganic substance, such as kaolin.

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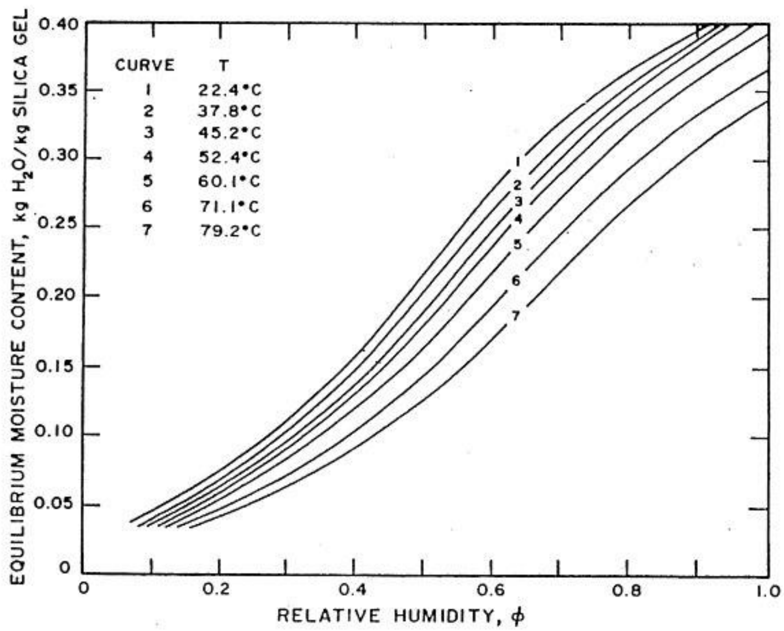

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Relationship between EMC and RH

- Materials exposed to humid conditions will regain moisture and therefore drying to a moisture content lower than that which the material will have under the conditions of use has no advantage.
- Tablet granules have superior compaction properties with small amount (1 - 2 %) of moisture.

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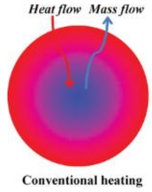
Types of drying method

The general principles for efficient drying can be summarized as follows:

- Large surface area for heat transfer
- Efficient heat transfer per unit area (to supply sufficient latent heat of vaporization or, in case of freeze drying, heat of sublimation.
- Efficient mass transfer of evaporated water through any surrounding boundary layers (i.e. sufficient turbulence to minimize the thickness of boundary layers)
- Efficient vapor removal (i.e. low relative humidity air at adequate velocity).



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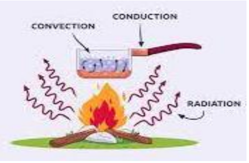
Types of drying method

Points considering the selection of drying method

1. Heat sensitivity of the material being dried
2. Physical characteristics of the material
3. The necessity for asepsis
4. Nature of the liquid to be removed
5. The scale of operation
6. Available sources of heat (steam, electrical)



➢ Pharmaceutical dryers may be classified according to the heat transfer method used (i.e. convective, conductive or radiant)

<u>Fixed (static) bed convective drying</u>

Tray and truck dryers

The wet material is spread on shallow trays resting on shelves and heating is accomplished by the forced circulation of large volumes of heated air.

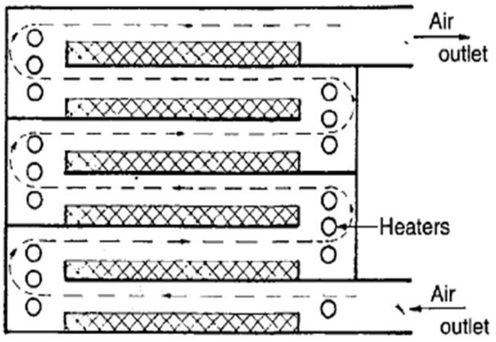


Fig. 26.4 Directed-circulation tray drier.

Convective drying

Fixed (static) bed convective drying

Tray and truck dryers

- Electrical elements or steam-heated pipes are positioned so that air is periodically reheated after it has cooled by passage over the wet material on one shelf before it passes over the material on the next.
- The required latent heat for vaporization is transferred convectionally from the air.

Rate of heat transfer, $dH/dt = h_c A \Delta T$

hc is a heat transfer coefficient for convective heat transfer

A: Area

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Convective drying

Fixed (static) bed convective drying

Tray and truck dryers

- Heat transfer coefficient for convective drying (h_c) is commonly around only 10 - 20 $Wm^{-2}K^{-1}$.
- Therefore, heat transfer from air is relatively inefficient and so convective drying is slow and can take up to 24 hours.
- Relative humidity of the air must be kept well below the saturation level
- These conditions are achieved by having brisk turbulent air flow over the surface and by periodic reheating as the temperature falls.

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Rate of drying in fixed beds

- The rate of drying of a sample can be determined by suspending the wet material on a scale or balance in a drying cabinet and measuring the weight of sample during drying as a function of time.

1-Initial Adjustment Period (A-B):

- Also called the "**Heating up" period**.
- In this period the substance gets heat and increases in temperature.
- Drying has not yet started.

2) Constant rate period (B-C)

- For given conditions of temperature and humidity, most substances dry at a similar rate in the constant rate period.
- It is found that evaporation rate from the drying bed is equal to that of solvent alone from a free liquid surface under the same condition.
- The surface remains wet in this period as the liquid evaporating from the surface is replaced from below at a rate equal to the rate of evaporation.
- The rate of drying is constant

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Rate of drying in fixed beds

3) First falling rate period (C-D)

- the surface of water is no longer replaced at a rate enough to maintain a continuous film. Dry spots begin to appear and the rate of drying fall.
- The moisture content at which this occurs is called critical moisture content.

4) Second falling rate period(D-E)

- Any moisture that remains at the end of the first falling rate period is unable to move and drying can not take place on the surface
- The drying rate depends on the movement of vapor through the pores of the bed.

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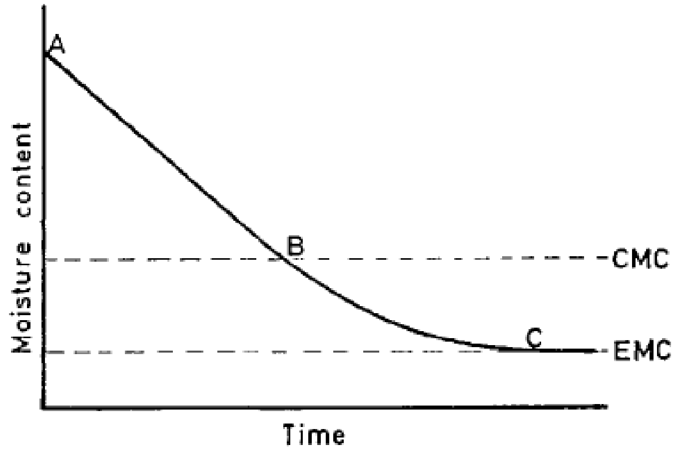

Fig. 26.5 Drying curve. CMC, critical moisture content, EMC, equilibrium moisture content.

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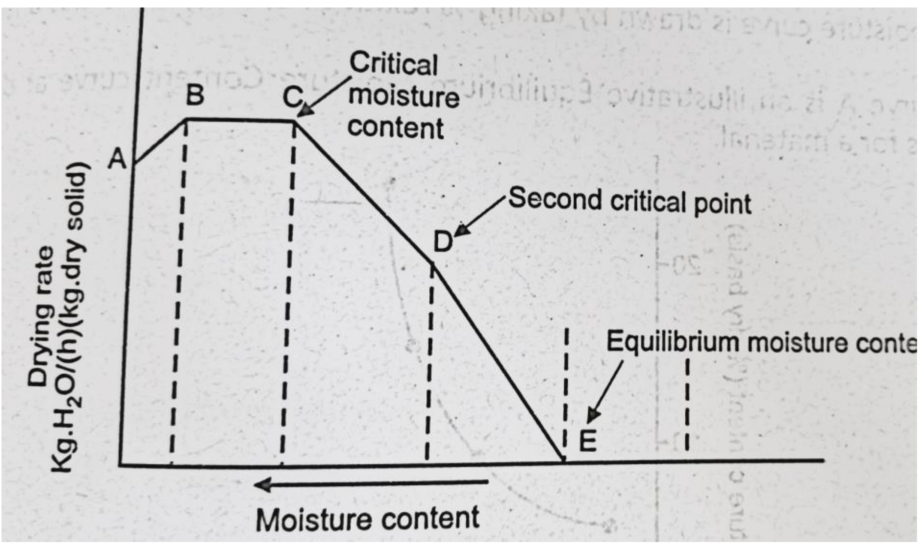

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Dynamic convective drying

Fluidized-bed dryer

- If a gas is allowed to flow up through a bed of particulate at a velocity higher than the settling velocity of particles, the solids become partially suspended in the gas stream. The resultant mixture of solid and gas behaves like a liquid and the solids are said to be fluidized.

- If hot air is used the turbulent conditions lead to high heat and mass transfer rates.

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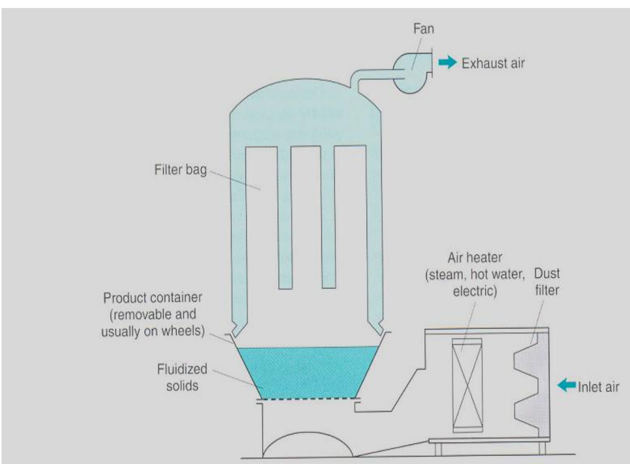

Fig. 30.4 Fluidized bed dryer.

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Dynamic convective drying

Fluidized-bed dryer

Advantages

1. Higher drying rate and shorter drying times than those with static-bed convection dryers.
2. Drying occurs from the surface of all the individual particles. Hence, most of the drying will be at the constant rate, while the falling rate period is very short.
3. The temperature of a fluidized bed is uniform and can be controlled precisely.
4. The turbulence in fluidized bed causes some attrition to the surface of the granule producing a more spherical free-flowing product.
5. The free movement of particles eliminates the risk of intergranular solute migration.
6. The containers can be mobile for simple movement around the production area.

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Dynamic convective drying

Fluidized-bed dryer

Disadvantages

1. The turbulence may cause excessive attrition and damage to some granules and the production of too much dust.
2. Fine particles may become entrained in the air and must be collected by bag filters, with care to avoid segregation
3. The vigorous movement of particles in hot dry air can lead to the generation of electrostatic charges and danger of explosion (Adequate electrical earthing is essential).

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Conductive drying

Vacuum oven

- Vacuum oven consists of a jacketed vessel constructed to withstand vacuum within the oven and steam pressure in the jacket.
- The supports for the shelves form part of the jacket, giving a large area for conduction heat transfer.
- The oven can be closed by a door to give an air tight seal and it is connected through a condenser to a vacuum pump.
- Operating pressures can be as low as 0.03-0.06 bar, at which pressures water boils at 25-35 ^{o}C.
- The main advantage is that drying takes place at a low temperature, and as there is little air present the risk of oxidation is minimized.

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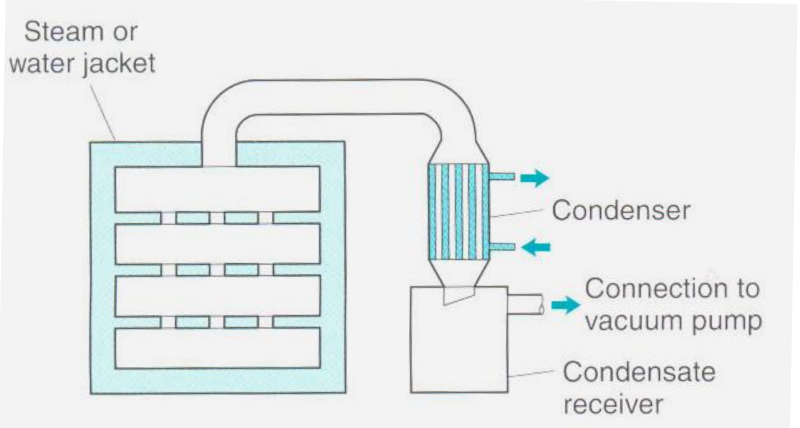

Fig. 30.5 Vacuum oven (schematic).

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Conductive drying

Vacuum tumbling dryer

- One design of vacuum tumbling dryer resembles a large Y-cone mixer.
- The vessel is steam jacketed and is connected to a vacuum.
- It can be used for drying tablet granules, which tumble over the heated surface as the vessel slowly revolves.
- Heat transfer rates are much higher than can be attained in a conventional vacuum oven, where the material is static.

Radiation drying

Microwave radiation

- The penetration of microwaves into the wet solid is very good so that heat is generated uniformly within the solid.

Generation and action

- Microwaves are produced by an electronic device called magnetron
- Heating is due to molecular friction caused by electronic resonance in the molecules when exposed to radiation.
- The absorption of microwave radiation differs according to the molecules and the ratio of the absorbed energy is indicated by loss factor.
- Dry solids do not resonate as well as water, so further heating may be avoided once the water is removed.

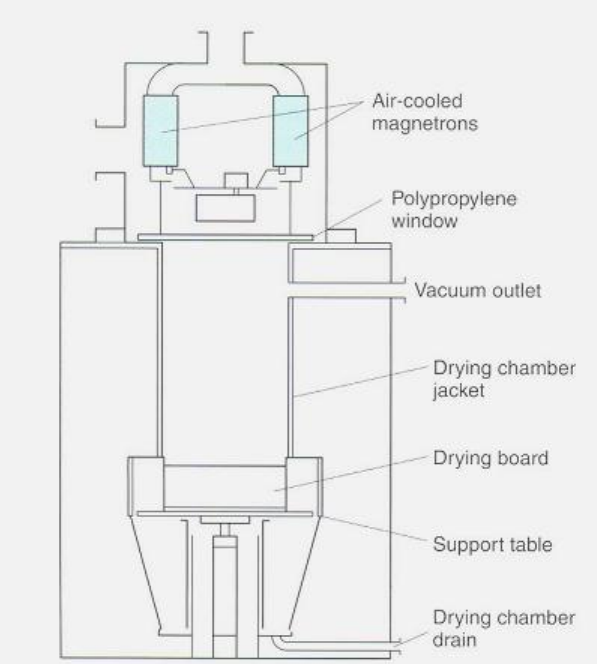

Fig. 30.6 Microwave dryer (courtesy of T K Fielder).

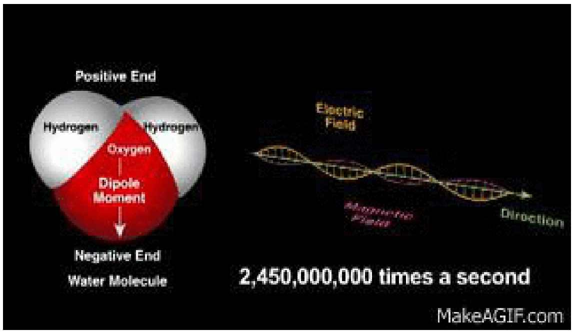

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Table 30.1 Microwave energy loss factors for some pharmaceutical solvents and excipients

Material	Loss factor
Methanol	13.6
Ethanol	8.6
Water	6.1
Isopropanol	2.9
Acetone	1.25
Maize starch	0.41
Magnesium carbonate	0.08
Lactose	0.02

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Radiation drying

Microwave drying of granules

Advantages

A. It provides rapid drying at fairly low temperatures.
B. The thermal efficiency is high.
C. Vacuum can be applied.
D. The bed is stationary avoiding the problem of dust and attrition.
E. Solute migration is reduced as there is uniform heating of the wet mass.
F. Drying end point is possible by measuring the residual microwave energy, which rises rapidly when there is little solvent left to evaporate.

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Radiation drying

Microwave drying of granules

Disadvantages

- The batch size of commercial production microwave dryers is smaller than those available for fluidized bed dryers.

- Microwave radiations are harmful to the operators and therefore care must be taken to shield them from these radiations.

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Dryers for dilute solutions and suspensions

The objective of these dryers is to spread the liquid to a large surface area for heat and mass transfer and to provide an effective means of collecting the dry solid.

Drum dryer

- The drum dryer consists of a drum 0.75-1.5 m in diameter and 2-4 m in length, heated internally by steam or hot water, and rotated on its longitudinal axis.
- The liquid is applied on the surface of drum and spread to a film, simply by dipping into a feed pan.
- Drying rate is controlled by manipulating the speed of rotation of the drum and its temperature.
- The product is scraped from the surface by means of a knife.

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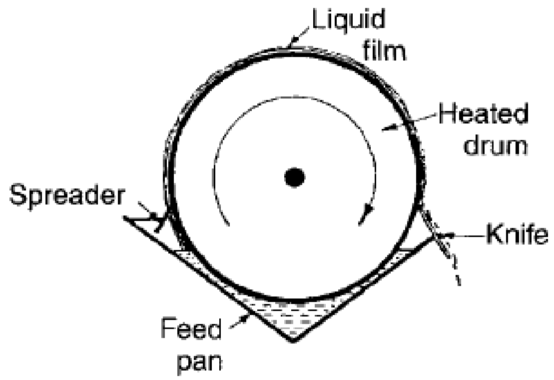

Fig. 26.10 Drum drier.

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Dryers for dilute solutions and suspensions

Drum dryer

Advantages

a) The method gives rapid drying, the thin film spread over a large area resulting in rapid heat and mass transfer.
b) The equipment is compact, occupying much less space than spray dryer.
c) Heating time is short (few seconds).
d) The drum can be enclosed in a vacuum jacket.
e) The product is obtained in flake form, which is convenient for many purposes .

Disadvantage

The only disadvantage is that operating conditions are critical and its necessary to make careful control on feeding rate, film thickness, speed of drum rotation and drum temperature.

Dryers for dilute solutions and suspensions

Spray dryer

- The spray dryers provide a large surface area for heat and mass transfer by spraying the liquid as small droplets into a stream of hot air.
- There are many forms of spray dryers.
- The character of the particles is controlled by the droplet size.
- Spray-dried products are uniform in appearance.
- The particles are in the form of hollow spheres.

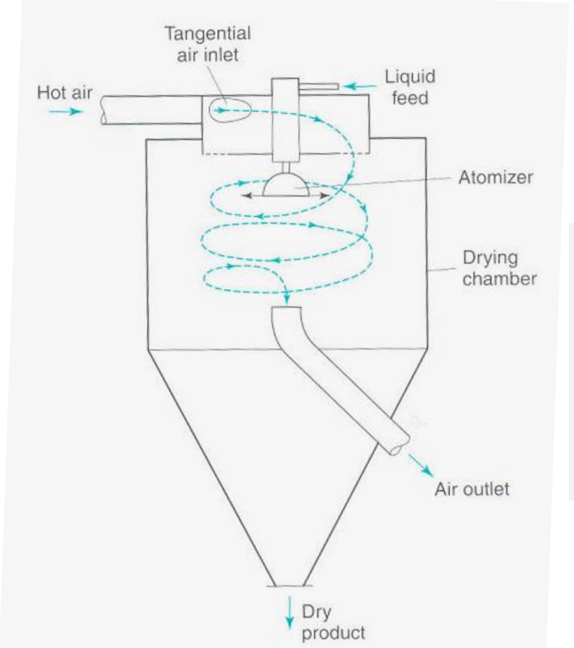

Fig. 30.7 Spray dryer.

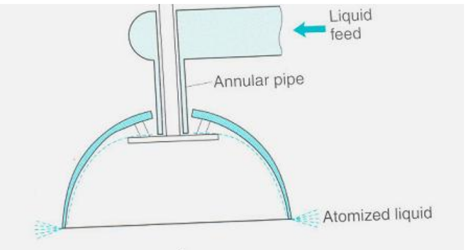

Fig. 30.8 Rotary atomizer.

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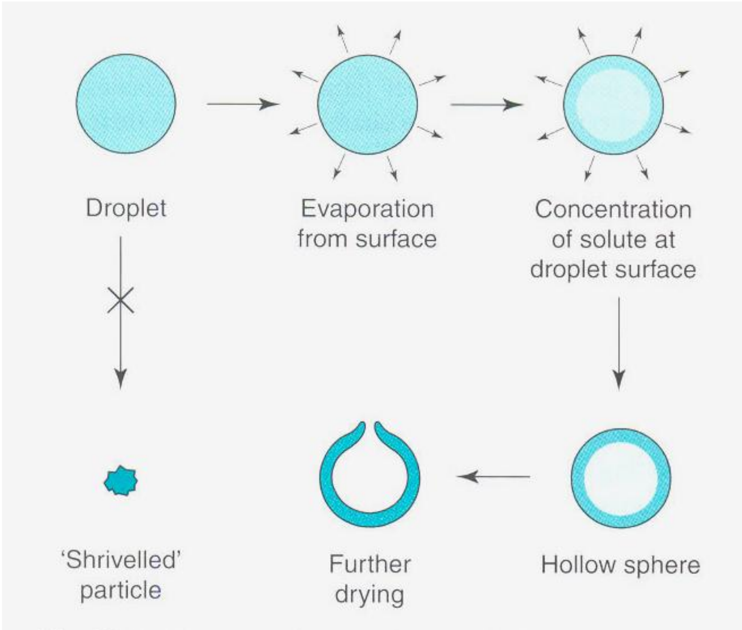

Fig. 30.9 Formation of product in spray drying.

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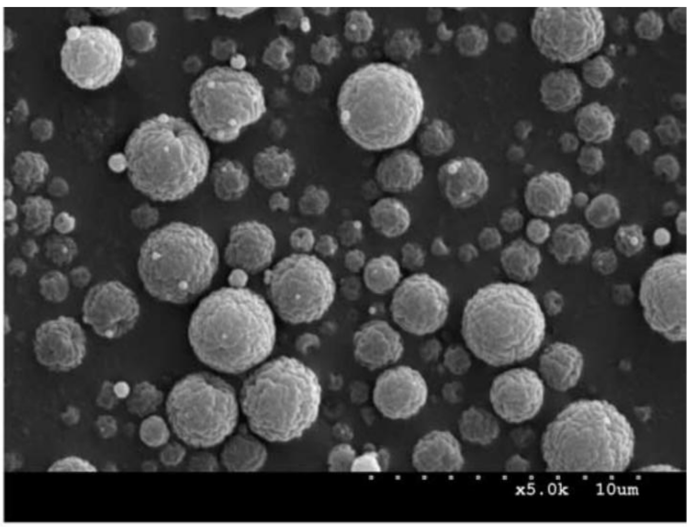

Scanning electron micrograph (SEM) for spray dried particles

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Dryers for dilute solutions and suspensions

Spray dryer

Advantages

- Millions of small droplets are formed and so evaporation is very rapid (The overall time in the dryer is a few seconds).
- The characteristic particles have large surface area and so rapid dissolution.
- The powder has a uniform and controllable particle size.
- The product formed has excellent flow and compaction properties.
- Labor costs are low.

Dryers for dilute solutions and suspensions

Spray dryer

Disadvantages

- The equipment is very bulky and expensive (may be as much as 15 m in height and 6 m in diameter).
- The overall thermal efficiency is low, as the air must still be hot enough when it leaves the dryer to avoid condensation of moisture. Also a large volume of heated air pass through the chamber without contacting a particle.

Dryers for dilute solutions and suspensions

Pharmaceutical uses of spray drying

- The spray drying can be used for drying almost any substance, in solution or in suspension.
- It is possible to operate spray dryers aseptically using heated filtered air to dry sterile products.
- There are three major uses for spray drying

1) Drying heat sensitive materials
2) Changing the physical form of the materials for better properties (flowability and compressibility)
3) Encapsulating solid and liquid particles

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Freeze drying (lyophilization)

- Freeze drying is a process used to dry extremely heat-sensitive materials (proteins, blood products and microorganisms).

- In this process, the initial liquid solution or suspension is frozen, the pressure is reduced and the water is removed by sublimation (liquid to solid then solid to vapor).

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Freeze drying (lyophilization)

- The theory and practice of freeze drying is based on understanding of the phase diagram of water and the following practical problems:
  - The depression of the freezing point caused by the presence of dissolved materials.
  - Sublimation can only occur at the frozen surface and is a slow process.
  - At low pressure large volumes of water vapor are produced which must be rapidly removed to prevent pressure rising above the triple point.
  - The dry material often needs to be sterile, and it must also be prevented from regaining moisture prior to final packing.

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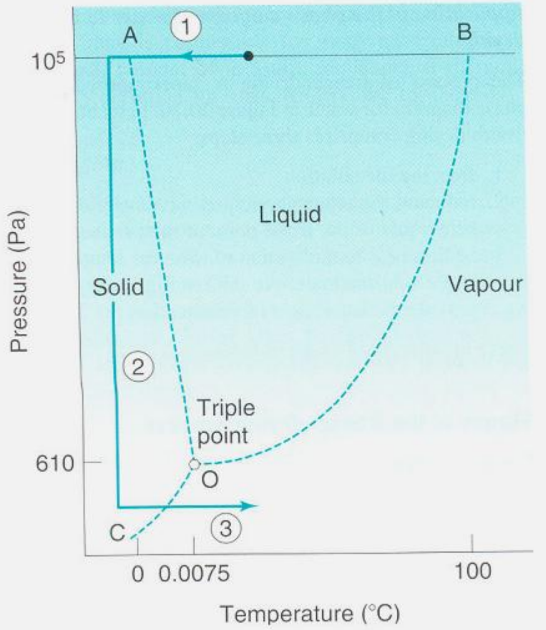

Fig. 30.10 The phase diagram for water (not to scale) with freeze-drying process superimposed (see text for explanation).

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Stages of the freeze drying process

1. Freezing stage
2. Vacuum application stag
3. Sublimation stage
4. Secondary drying
5. Packaging

A benchtop manifold freeze-dryer

Stages of the freeze drying process

Freezing stage

- To avoid frothing, the liquid material is frozen before the application of vacuum and to increase the rate of sublimation, several methods are used to produce a large frozen surface.
- Two common techniques are used:
  - Shell freezing
  - Centrifugal evaporative freezing

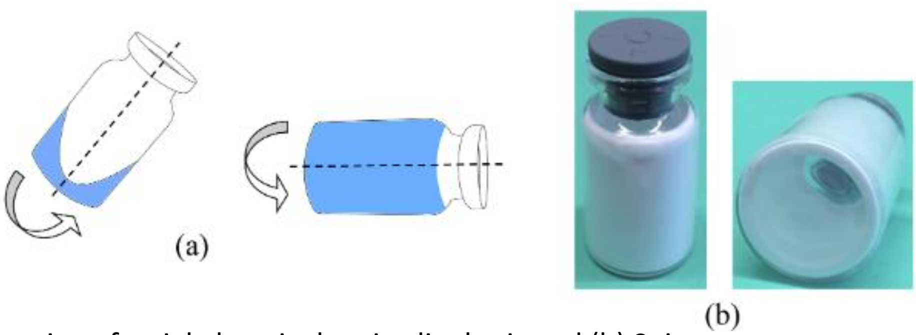
Stages of the freeze drying process

Shell freezing

- This is applied for fairly large volumes such as blood products.
- The bottles are rotated slowly and almost horizontally in a refrigerated bath. The liquid freezes in a shell around the inner circumference of the bottle

Disadvantages:

- Freezing is slow
- large ice crystals form which may damage blood cells and reduce the viability of microbial cultures



(a) Spin-freezing of a vial along its longitudinal axis and (b) Spin-freeze-dried vials. Reprinted from (De Meyer et al., 2017).

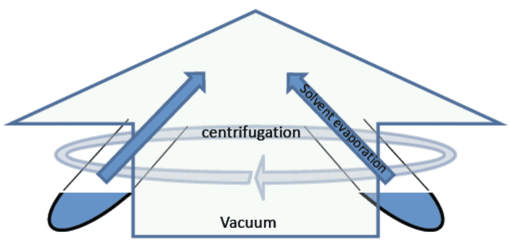


Figure 1

Stages of the freeze drying process

Centrifugal evaporative freezing

- The solution is spun in small container within a centrifuge. This prevents foaming when vacuum is applied.
- The vacuum causes boiling at room temperature and this removes so much latent heat so that the solution cools quickly and snap freezes.
- About 20 % of the water is removed prior to freeze drying and there is no need for refrigeration.
- Ampoules are usually frozen in this way.

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Stages of the freeze drying process

Vacuum application stage

- The containers and the frozen material must be connected to a vacuum source sufficient to drop the pressure below the triple point and remove the large volumes of low-pressure vapors formed during drying.
- An excess vacuum is normal in practice to ensure that the product in question is below its triple point.
- Commonly a number of bottles or vials are attached to individual outlets of a manifold, which is connected to a vacuum.

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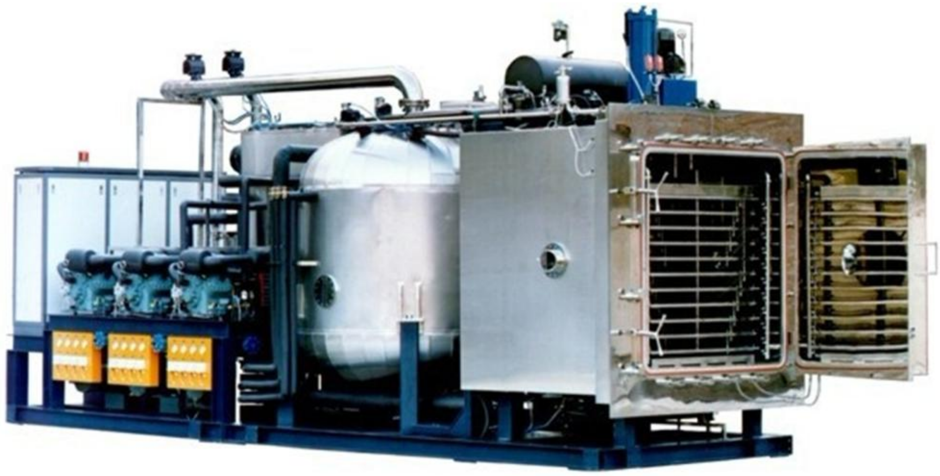

Industrial-scale lyophilizer

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Stages of the freeze drying process

Sublimation stage (primary drying)

- Heat of sublimation must be supplied. Under these conditions the ice slowly sublimes leaving a porous solid which still contains about 0.5 % moisture.
- Heat transfer is critical insufficient heat input prolongs the process, which is already slow, and excess heat will cause melting.
- The vapor formed must be removed continually and efficiently to prevent the pressure within the container rising above the triple point pressure.
- The drying rate is very slow (1 mm depth per hour) which is at constant rate during most of the time.

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Stages of the freeze drying process

Secondary drying

- The removal of residual moisture at the end of primary drying is performed by raising the temperature of the solid as high as 50 or 60 ^{o}C.

Packaging

- Attention should be paid to packaging freeze-dried products to ensure protection from moisture

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Advantages of freeze drying

- Drying takes place at very low temperatures, so that enzyme action is inhibited and chemical decomposition is minimized.
- The final dry product occupies the same volume as the original solution. Thus the product is light and porous which enhances dissolution.
- Oxidation is minimized as there is little contact with air.

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Disadvantages of freeze drying

- The porosity, ready solubility and complete dryness yield a very hygroscopic product.
- The process is very slow and uses complicated and expensive plant.

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Uses of freeze drying

- Freeze drying is used mainly for products that cannot be dried by any other heat method. These include biological products such as:
  - Blood products
  - Vaccines
  - Enzyme preparations
  - Microbial cultures

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Solute migration during drying

- Solute migration is a phenomenon which can occur during drying and results from the movement of a solution within the wet system. The solvent moves towards the surface of a solid, taking any dissolved solute with it.

- Migration associated with the drying of granules can be of two types, ***intergranular*** (between granules) and ***intragranular*** (within individual granule).

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Solute migration during drying

Intergranular migration

- Intergranular migration can occur during the drying of static beds of granules (e.g. tray drying), when the solvent and accompanying solute(s) move from granule to granule towards the top surface of the bed where evaporation takes place.

- This results in variation in drug content between granules at surface and those in the bottom

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Solute migration during drying

Intragranular migration

- Drying methods based on fluidization and vacuum tumbling keep the granules separate during drying and so prevent the intergranular migration that may occur in fixed beds.
- However, intragranular migration may occur in fluidized bed systems, where the solute moves towards the periphery of each granule.

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Consequences of solute migration

1) Bad distribution or loss of active drug

- In case of intragranular migration,, the periphery of each granule may become enriched with the interior suffering a depletion.
- If the outer layer is abraded(scraped) and lost as may happen in fluid bed dryers, the granules will suffer a net loss of drug.
- In case of intergranular migration, the surface will be rich in drug and therefore mixing is important after drying.

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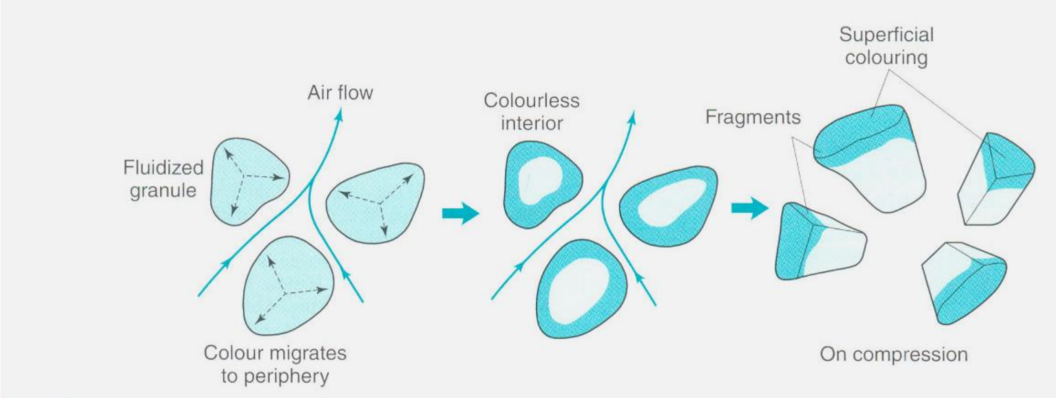

Fig. 30.12 Diagram of mottling caused by intragranular migration.

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Consequences of solute migration

2) Mottling of colored tablets

- Colored tablets may be made by adding soluble colors during wet granulation.

In case of intergranular color migration, the granules at the surface will be highly colored.

- Intragranular migration of colors may lead to dry granules with a highly colored outer zone and a colorless interior.

During compaction, granules are fractured and the interior is exposed. The eye then sees the colored fragments against a colorless background and the tablets appear mottled.

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Consequences of solute migration

3) Migration of soluble binders

- Intragranular migration may deposit a soluble binder at the periphery of the granules which is sometimes beneficial due to:
  - making the granules harder and more resistant to abrasion.
  - increase the bonding process between granules during compression as a result of binder-binder contact,

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The influence of formulation on solute migration

Nature of the substrate

- If the granule substrate has an affinity to the solute then migration will be impeded.
- It is likely that the presence of adsorbent materials such as starch and microcrystalline cellulose will minimize solute migration.
- The use of water insoluble aluminum lakes (pigments) reduces mottling compared with water soluble dyes

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The influence of formulation on solute migration

Viscosity of granulating liquid

- The viscosity impedes the movement of moisture by increasing fluid friction.

- Increasing the viscosity of PVP solution has been shown to slow the migration of drugs in fixed beds of wet granules.

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The influence of process factors on solute migration

Drying method

- Intergranular solute migration will occur whenever a particular method of drying creates a temperature gradient which results in greater evaporation from hotter zones.
- In slow fixed-bed convective drying, the maximum concentration of migrated solute will occur in the surface of the drying bed.
- Drying by microwave radiation results in uniform heating and so minimizes solute migration.
- Fluid-bed drying reduces intergranular migration but intragranular migration can still occur. Vacuum tumbling methods remarkably reduce migration

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The influence of process factors on solute migration

Initial moisture content

- The greater the initial moisture content the greater will be the moisture movement and the greater the migration

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Practical means of reducing solute migration

- Use the minimum quantity of granulating liquid and ensure that it is well distributed.
- Prepare the smallest satisfactory granules to reduce mottling.
- Avoid tray drying if there is a better alternative method.
- If tray drying is used, the dry granules should be remixed before compression.
- If intragranular migration is likely to be troublesome use vacuum or microwave drying instead of fluid-bed drying.

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