Alzahraa University for women
College of pharmacy
Department of pharmaceutics
Industrial pharmacy I /4th stage

Disintegration apparatus

Dissolution apparatus

Friability tester

mixer

Sieves

Tablet machine

oven

Course Description

Course Objectives The course provides an introduction to the essential unit operations used in the manufacture of pharmaceutical products. Unit operations including blending, milling, drying, clarification and sterilization will be addressed.

Students learn to recognize how the output of one process is the input to the next process, and how deviations can cascade along the production sequence until they cause process failures. The course emphasizes design, scale-up, trouble-shooting, and optimization of pharmaceutical unit operations.

Teaching and Learning Strategies

Lecturing

Homework Quiz

Practical laboratory demonstrations

Oral exam and practical tests

References

1. Lachman L., Liberman H. and Kanig J.; The Theory and Practice of Industrial Pharmacy; Third Edition
2. Lachman L., Liberman L. and Schwartz J.; Pharmaceutical Dosage Forms: Tablets; Second Edition : Volume I.
3. Websites

Table of content

Lab 1

Introduction

Pharmaceutical industry, the discovery, development, and manufacture of drugs and medications (pharmaceuticals) by public and private organizations.

Formulation is the process of developing a drug candidate into a drug product. Initially, there may be a number of potential drug candidate molecules, each with a unique set of physicochemical properties and each showing activity towards a particular biological target.

Ultimately, only one (at best) will be developed into a drug product. The decision to select a successful drug candidate to be developed does not depend on pharmacological efficacy alone.

In practice, the physicochemical properties of the molecule affect how a material will be processed pharmaceutically, its stability, its interaction with excipients and how it will transfer to solution and, ultimately, will determine its bioavailability.

It follows that characterizing the physicochemical properties of drug candidates early in the development process will provide the fundamental knowledge base upon which candidate selection, and ultimately dosage form design, can be made, reducing development time and costs.

Preformulation

It is the process during which physical pharmacist should meet the drug development to obtain information on the known properties of the compound.

So, it is the investigation of the physical and chemical properties of drug substance [alone or with additives (excipients) like lubricant, diluent, disintegrants,…..etc.] to formulate stable, safe, effective and bioavailable dosage form and avoid the interaction that may occur between active and non-active ingredients.

• **Note*:*** For powders, the first identification includes: M.P., assay, IR, UV purity, and then study Preformulation.

Preformulation Stages or Factors:

1- Organoleptic Properties (color, odor, taste, …etc.):

a. Color: white, creamy, shiny,….
Some drugs are affected by the light, so if it present in capsule dosage form, we should use colored capsule to protect it from light effect.
If it present in tablet dosage form, coated tablet should be used or adding coloring agents.
Other example is the use of colored glass in manufacturing light sensitive injectable dosage form.

b. Odor: sulfurous, fruity, aromatic and odorless.
Ex: the decay of aspirin after period of time and exposure to moisture lead to liberation of acetic acid odor.
This is due to decay of aspirin **to** acetic acid **+** salicylic acid.

c. Taste: bitter, sweet, acidic, intense, and tasteless.
Ex: clindamycin has a bitter taste, so we use the less soluble form unless unless it affects on the bioavailability.
For acidic drugs we use orange, lemon to mask the undesirable taste especially in the preparation of pediatric dosage form.

2- Purity:

The presence of impurities affects the appearance and stability of the material. More pure drug is better. Sometimes it is important to identify the type of impurities because it may be toxic and carcinogenic. Sometimes impurities contain metals like Cu, Pb, Fe and these may catalyze some reactions like oxidation.

Methods of studying the Purity:

1- Melting point and boiling point.
2- Chromatography (HPLC, TLC & GC).
3- Differential and gravimetric analysis.
4- Colorimetry.

3- Particle Size and Surface area:

Particle size affects the biopharmaceutical behavior of the drug.

a. Solubility: especially for slightly soluble drugs because the dissolution is the rate- limiting step of the absorption process, e.g. when we decrease particle size of griseofulvin, it leads to increase surface area and increase rate of dissolution and then increase rate of diffusion through cell membrane.

So, particle size in this drug is critical for detection of surface area and solubility. Particle size is not always critical, e.g. sometimes particle size doesn't affect on tablet but may affect on suspension dosage form.

b. Flow rate: ↓ particle size → ↑ surface area → ↑ electrostatic charges → ↑ friction → ↓ flowability.

c. Pressure behavior: particle size and shape affect the efficiency of mixing and affect the stability (fine particles more open to atmospheric oxygen, humidity and interacting with excipients).

<u>Particle size can be measured by:</u>

1- Sieving
2- Sedimentation
3- Microscopy

4- Light scattering
5- Coulter Counter.

The surface area with dissolution rate can be determined by (**Noyes-Whitney Equation**).

$$\frac{dC}{dt} = KS(C_s - C_t)$$

dc/ dt = dissolution rate
K = dissolution rate constant
S = surface area
Cs = conc. of solute in the saturated solution
C= conc. of solute at time (t)

$$K = D / hV$$

D = diffusion coefficient
h = thickness of the diffusion layer at the solid- liquid interface.

Surface area can be measured by using adsorption theory:
Each drug substance adsorb monomolecular layer of gas under certain condition of pressure and temperature.

Usually, we use room temperature and partial pressure of nitrogen gas.

• **Note:**Particle size is important in stability like in aerosols because small particles cause dusting.

4- Solubility:

It is important especially for slightly soluble drugs because the dissolution is the rate- limiting step for absorption.
Drugs having limited solubility (< 1%) in the fluids of GIT often exhibit poor absorption.

Terms of approximate solubility:

Term	Parts of solvent required for 1 part of solute
Very soluble	Less than one part
Freely soluble	1-10 parts
Soluble	10-30 parts
Sparingly soluble	30-100 parts
Slightly soluble	100-1000 parts
Very slightly soluble	1000-10000 parts
Practically insoluble	>10000 parts

Methods for improving solubility:

1- Co-solvent
2- Salt formation
3- Complexation
4- Surface active agent (used with limited conc.)
5- Decreasing particle size
6- Polymer formation like PEG-6000
7- Prodrug
8- PH of solution (take physiological PH in concern)

• ***Note:*** Sometimes we need to decrease solubility as in clindamycin (bitter taste) and if the material has an irritant effect on the stomach.

Co-solvent: it is not recommended to use organic solvent alone (it is preferred to mix it with water). Weak electrolyte and non polar molecules frequently have poor water solubility, their solubility can be increased by addition of water-miscible solvent in which the drug has good solubility, this process called co-solvency.
The mechanism responsible for solubility enhancement is by reducing the interfacial tension between the aqueous solution and hydrophobic solute.
Addition of co-solvent should not exceed 10% because of toxic effect of organic solvent.
Examples of co-solvents are: ethanol, propylene glycol and glycerin.

Complexation: adding complexing agent to form more soluble compound and it is important to increase solubility to the wanted limit and also should be safe and specific.

Disadvantages of complexation include that it may increase solubility to unwanted limit and may be attached to essential metals causing certain defect in co-enzyme system, so it should be specific and release drug in the body and not accumulate inside the body.

Examples on complexing agent: caffeine and nicotinamide (Vit B_3).

Lab. (2)

Flowability measurement

The flowability of a powder or granules can be expressed in term of

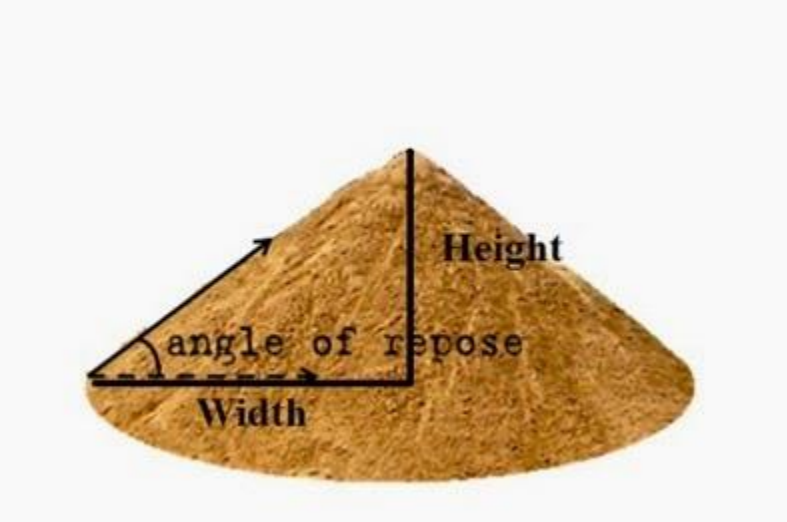
(1) The angle of repose,(2) the flow rate

Angle of repose

If a powder is poured freely onto a plane surface, it forms a cone that has a constant angle between the surface of pile and the horizontal plane. This angle is known as the **angle of repose.** The angle is calculated by simple geometry from the **radius r** of the base of the cone and its **height h**.

$$\text{Tan } Ø = \frac{h}{r} \quad \text{… } \textit{(Tan theta)}$$

100 grams of the powder in a funnel on 15 cm height.



It is possible that different angle of repose could be obtained for the same powder, owing to differences in the way the samples were handled prior to measurement, for this reason angle of repose tend to be variable.

As a general guide ,powder with angle of repose greater than 50º have unsatisfactory flow properties ,while minimum angle close to 25º correspond to very good flow properties.

Flow properties	Repose angle (°)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	> 66

Flow rate

Flow rate can be measured either by:

1- **Flow-meter**: we measure the time required for a certain weight of a powder to be passed through an orifice.

2- **Funnel and petri dish**: we measure the weight of powder required to pass through an orifice at a certain time.

Therefore, from the above methods we can conclude that, the angle of repose is a qualitative test and petridish test is a quantitative test

General scale of flowability for flow through an orifice

No general scale is available because flow rate is critically dependent on the method used to measure it. Comparison between published results is difficult.

(Recording the time required for 100 grams of the powder in a funnel on 15 cm height to pass through the orifice of the funnel). Or the amount of powder passing in 10 sec.

USP: the time it takes for 100 grams of powder to pass through the orifice to the nearest tenth of a second or the amount of powder passing through the orifice in 10 seconds to the nearest tenth of a gram.

Benefits of the quantitative methods:

1- To evaluate rheological properties of powders.
2- The effectiveness of lubricants and glidants used according to the obtained results.
3- Estimation of the proper concentration of lubricant and glidant that should be added to improve the flowability of powders.

(Compressibility measurement)

The packing properties of powders are very important in the production of solid dosage forms such as powders, tablets and capsules. This is of particular relevance during powder mixing, filling of capsules with powders or granules, and filling of dies during tabletting operation**.** Compressibility can be determined by measuring **bulk volume and tapped volume.** Bulk volume represents the true volume of particles and voids while tapped volume represent true volume of powder without voids. Compressibility index or Carr´s index can be calculated by the following equation:

100 grams of the powder 250-mL volumetric cylinder

$$\text{Carr´s index} = \frac{\text{(Bulk volume- Tapped volume)}}{\text{Bulk volume}} \times 100$$

OR

Carr´s index= (Tapped density-Bulk density) x100

Tapped density

V_0 V_f

Carr's Index	State of Flowability
5-15	Excellent
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very Poor
>40	Very, Very Poor

EXPERIMENTAL WORK

Determination of flowability and compressibility of formula.

HOME WORK:

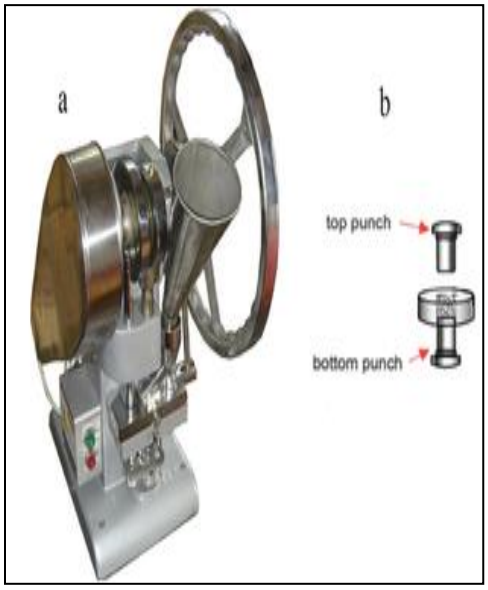
1- What are methods to determination flow ability of powder?
2- What are method available to measure the powder flow ?
3- What are method of improvement of compressibility and flowability?
4- Compressibility and angle of repose value ?
5- Why salts are more soluble than weak acid or weak base ?

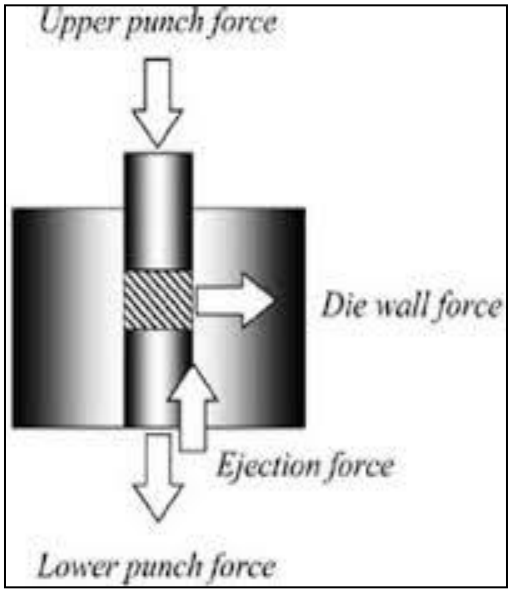
Lab. (3)

Rheology

Rheology is the flow science**.** It is the study of flow properties of materials. The need for proper understanding of rheological properties of pharmaceutical materials is essential during preparation, development and evaluation of pharmaceutical dosage form.

Tablets and capsules are most commonly used dosage forms; an important consideration in manufacturing these dosage forms is the **flow** of solid powder particles from the hopper through feeder. Preparation of such dosage forms required measured filling for the production of each unit; and the uniformity of the final products requires **constant flow rate of particles.**





The die must be filled with the same amount of granules in each compression time; in order to get such amount, constant flow rate of particles should be ensured by having freely flowable powder or granules.

A good flow will lead to constant weight of powder reach die at each compression; as a result, no weight variation, constant content uniformity and good bioavailability.

Good powder flow….Uniform dosage form….Good bioavailability

Powder flowability divided into two types:

1- Freely flowable powder.
2- Non freely (sticky) flowable powder.

Factors reducing flow rate(problems):

1-Intermolecular forces:

These are weak forces on the surface of particles (different charges), like **Van der Waals** forces. Although, these forces are weak but they do affect the flowability of powder .The particles are already **charged.**

Different charges… Particles attraction to each other …Powder clamping…Powder slow movement
…Bad flowability.

2-Frictional (electrostatic) forces:

These forces are generated on the surface of particles due to the friction between them during their movement. The particles are already **uncharged**.

3-Particle shape:

The spherical particles with smooth surface have good and free flowability, while irregular shape particles (needle shape) with flat or rough surfaces have a bad flowability. This is because of the friction

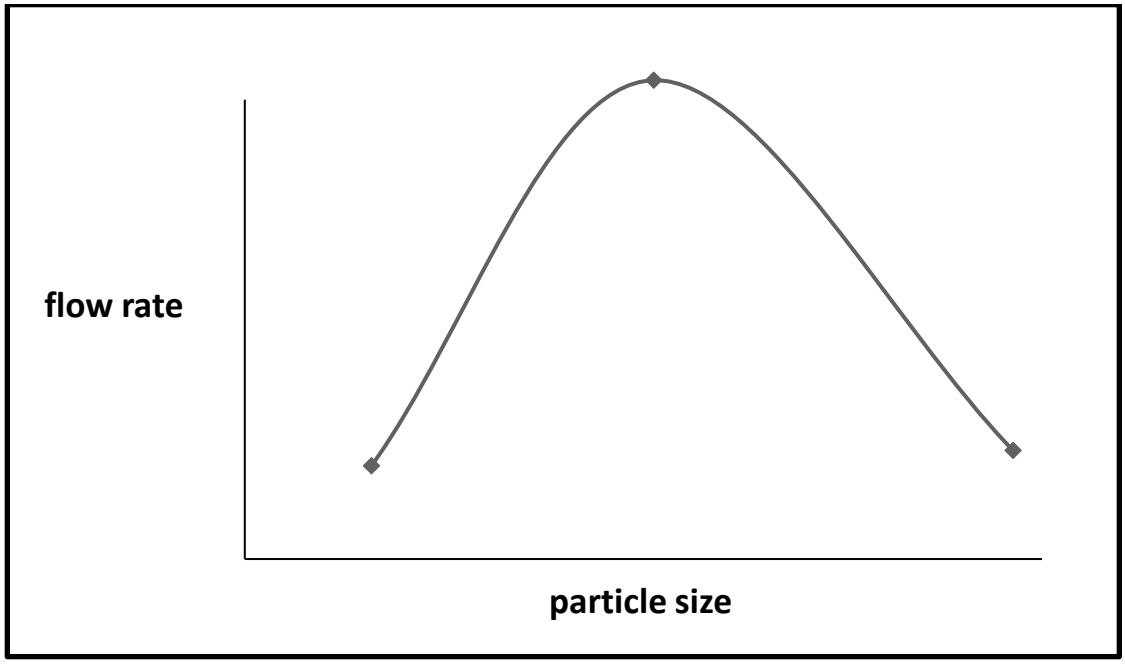
that occurs between particles and irregular shape particles will fill the spaces and hider the flow.

4-Particle size:

Small particle size...Large surface area...Increase frictional forces...Increase charges develop on particle surface…Bad flowability.

Large particle size …Small surface area…Decrease frictional forces…Decrease charges develop on particle surface…Good flowability. But, this is the case to a certain limit above which bad floawability will result and this is due to:

A-Large particle mostly have rough surfaces.
B-Large particles cause blockage of the machine orifice.
The relation between flow rate and particle size can be represented by the following figure.



5-Moisture:

Moisture plays an important role and may act as a binder between particles, but high moisture content leads to formation of sticky particles and result in a bad flowability.

Factors increasing flow rate(solutions):

1- Addition of lubricant or glidants:

The glidant will prevent the friction between particles themselves, while lubricant decreases the friction between particles and walls of machine. Therefore, both will result in a good flowability.
However, glidant and lubricant concentration should be small due to its hydrophobic nature, which can cause stickiness and bad flowability in large concentration, therefore the lubricant and glidant concentration is very critical.

2- Granulation :

Conversion of fine powder into granules with uniform size and spherical shape, can solve the problems resulted from irregular size or shape of particles.

3-Drying:

Drying of particles will lead to remove of excess amount of moisture, but over drying convert the granules into fine powder again, therefore the time of drying is very critical.

Lab. (4)

EFFERVESSENT GRANULES

Effervescent: evolution of CO_2 gas from acid-base reaction.

Granules: aggregation of small irregular particles ranging in size from 4-12 mesh.

Advantages of effervescent dosage form:

To improve the flow ability.
Decrease and increase the stability.
Easy to make solution and avoid flow out of the fluid from the glass.
Take as solution with fast onset of action.
To mask undesirable (by benefit of CO_2 taste)
Patient compliance (psychological effect).
To neutralize acidity of the drug and decrease the acidity of the stomach.

Effervescent granule:

Are granules or coarse to very coarse powder containing a medicinal agent in a dry mixture usually composed of citric acid, tartaric acid and sodium bicarbonate in size range from 4-10mesh. When the water add the acid –based reaction will be formed causing the CO2 liberation which result in effervescent preparation.

Disadvantages of effervescent dosage form:

Unsuitable for the patient with hypertension or any cardiac diseases because the sodium over load. 'To overcome this problem can be use potassium carbonate or calcium carbonate instead of sodium bicarbonate'.
Some drug – drug interaction.
Unstable because moisture absorption from the atmosphere. 'Moisture initiated the reaction so it must be stored in dry place'.
Inquorate dose estimation 'because the dose estimated by the patient '.to avoid this problem must be prepared as tablet or as packets.

Cannot use for potent drug of narrow therapeutic index. ‘because the dose estimate by the patient’

Base use in effervescent:

Sodium bicarbonate: wide use because it is cheap, soluble and available.
b.Calcium bicarbonate.

C.Potassium bicarbonate.

Acid use in effervescent:

Natural acid:
This acid contain many carboxylic groups so it is highly soluble .Ex: citric acid, tartaric acid, fumaric acid, malic acid.

unhydrous acid:
This acid without molecules of water. Ex: unhydrous succinic acid, unhydrous citric acid.

acidic salt:
Disodium dihydrogen phosphate.

Notes:

A-the drug use must be:

water soluble “if water insoluble must be improve the solubility “
Drug must be stable in water.
B-dead granules: during storage of effervescent granules it may absorb moisture from atmosphere and initiate the reaction then liberate CO2leading to loss their effectiveness.

C-use citric acid and tartaric acid in combination because if use citric acid alone lead to form sticky granules and if use tartaric acid alone lead to form brittle or fragile and crumbly granules.

Rx:

Citric acid 1 part
Tartaric acid 2part
Sodium bicarbonate 3.4 part

- _____
- 6.4 parts

When used the ratio of 1-2 citric acid and tartaric acid to produce not sticky and not brittle granules.

$$C_6H_8O_7 + 3NaHCO_3 \rightarrow C_6H_5O_8Na_3 + 3H_2O + 3CO_2 \uparrow$$

Citric acid sodium bicarbonate

'Hydrate'

- $\frac{1}{210} = \frac{x}{3*84}$

210 "m.wt. of citric acid"

84 "m.wt. of sodium bicarbonate"

X=1.2 parts NaHCO3 react with 1 part citric acid.

$$C_4H_6O_6 + 2NaHCO_3 \rightarrow C_4H_4O_6Na_2 + 2H_2O + 2CO_2 \uparrow$$

Tartaric acid sodium bicarbonate

- $\frac{2}{150} = \frac{x}{2*84}$

150 "m.wt. of tartaric acid.

X=2.24 parts of NaHCO3 react with 2 parts of tartaric acid.

1.2 +2.24 =3.4 parts of NaHCO3 used.

Note: 0.04 remain used for pleasant odor and some acidic test in powder

Method of effervescent granules formation:

Fusion (dry method):

Using H2Omolecule present in citric acid and act as binding agent for powder mixture.

The heat cause H2O release from citric acid which then dissolve portion of powder mixture and release CO2then the soften mass pass through sieve to produce granules then drying at temperature not more than 54C then transfer to the closed container .

Note: the drug must not effect by heat.

Wet method:
Crystallization (use unhydrous) but use alcohol as binding agent then soften mass sieving.

Ex: prepare 25 g of effervescent granules each dose contain 1.5 g $MgSO_4$

Sol.\ the stander dose = 5 g

No. of dose =$\frac{25}{5} = 5$ doses

5*1.5 = 7.5 g the active ingredient.

25 – 7.5 = 17.5 g the effervescent base

$\frac{17.5}{6.4} = 2.734375$ g

Citric acid = 1 part 1 * 2.734375 = 2.734375 g

Tartaric acid = 2 parts 2 * $2.734375 = 5.46875$ g

Sodium bicarbonate = 3.4 parts

3.4 * 2.734375 = 9.296875 g

2.734375 + $5.46875 +$ 9.296875 =17.5 g

Procedure:

Study the physicochemical properties of the drug (stable , soluble ,---)
Calculate the number of dose.
Weigh the amount of each drug.
Mixing to insure uniform distribution
Granulation.

Drying.
Packing and storage.

HOME WORK:

Replace $NaHCO_3$ by $KHCO_3$ or $CaCO_3$,what are the parts for each one?
Why the amount of sodium bicarbonate is 3.4 g in preparation of effervescent granule?
What are the therapeutically uses of magnesium sulfate?

Lab.(5)

Drying

Drying is defined as the removal of a liquid from a material by the application of heat and is accomplished by the transfer of a liquid into an unsaturated vapor phase**.**

Drying involves both **heat and mass transfer**, heat must be transferred to the materials to be dried to supply the latent heat required for the vaporization of the moisture. Mass transfer is involved in the diffusion of water through the material to the evaporating surface in the subsequent evaporation of the water from the surface and the diffusion of the resultant vapor into the passing air stream.

A passing air stream (air-water system) should have low moisture content, this **vapor –carrying capacity** is very critical in drying operation because, this capacity determine the **rate and extent of drying**. Also the rate and extent of drying directly proportional to the **surface area** subjected to the heat.

Pharmaceutical importance of drying is:

1- It is important process in preparation of granules, which can be dispensed in bulk or converted into tablet or capsule.
2- Many products are more stable in drying form (aspirin, antibiotics powders for reconstitution.) because drying reduces chemical reactivity of the remaining water.

Types of dryers :

1-Static bed dryer (tray, tunnel dryers)
2-Moving bed dryer (turbo tray dryer)
3- Fluidized bed dryers.
4-Specialized dryers (**freeze dryer) H.W**????

Expression of drying efficiency in drying of solid.

The moisture in a sample can be expressed by two terms

1-**Loss on drying**

$$\textbf{LOD\%} = \frac{\textbf{weight of water in the sample}}{\textbf{total weight of wet sample}} \times 100$$

2-**Moisture content**

$$\textbf{MC\%} = \frac{\textbf{weight of water in the sample}}{\textbf{weight of dry sample}} \times 100$$

Experimental work

1- Prepare granules using gelatin as a binder.

2- Dry the powder using two different dryers for5 and 10 minutes to show the efficiency of the dryer used.

3- Calculate the MC and LOD %

Lab. (6)

Clarification

Clarification is a process that involves the removal of a solid from a fluid.
Clarification can be achieved using either filtration or centrifugation.

Advantages of clarification:

1. To remove unwanted solid particles from a liquid.
2. To collect the solid as the product itself, e.g., following crystallization.

Filtration

Solid/liquid filtration: It is the most common type of filtration encountered in pharmacy.

Advantages:

• Improvement of the appearance of solutions to make them elegant.

• Removal of irritants, e.g. from eye-drop.

• Recovery of desired solid material from a suspension, e.g. to obtain a drug after a crystallization process.

• Sterilization of liquid products when processes involving heat are not appropriate.

Liquid/liquid filtration: Flavouring oils are sometimes added to liquid preparations in the form of a spirit, i.e. dissolved in alcohol.

Factors affecting the rate of filtration

according to Darcy equation:

$$\frac{V}{t} = \frac{KA\Delta P}{\mu L}$$

The rate of filtration (volume of filtered material (V) obtained in unit time (t)) depends on the following factors:

1. The area available for filtration (A), which in this case is the cross-sectional area of the funnel;

2. The pressure difference ($\wedge P$) across the filter medium. This can be increased by drawing a vacuum in the flask.

3. The viscosity (μ) of the filtrate. A viscous fluid will filter more slowly than a less viscous one owing to the greater resistance to movement offered by viscous fluids.

4. The thickness of the filter medium and any deposited cake (L).The cake will increase in thickness as filtration proceeds, so if the cake is not removed the rate of filtration will decrease.

5. Porosity of the of the filtration medium (K) which expresses the permeability of both the filter medium and cake, and will increase as the porosity of the bed increases. It is clearly desirable that the K value should be large in order to maximize the filtration rate.

Methods used to increase filtration rate

1- Increase the area available for filtration

2- Increase the pressure difference

3- Decrease the filtrate viscosity

4- Decrease the thickness of filter cake

5- Increase the permeability of the cake

FILTRATION EQUIPMENT

Equipment selection:

There are a number of product-related factors that should be considered when selecting a filter for a particular process. These include:

1- The chemical nature of the product.

2- The volume to be filtered and the filtration rate required.

3- The operating pressure needed.

4- The amount of material to be removed.

5- The degree of filtration required.

6- The product viscosity and filtration temperature.

Industrial filtration equipment:

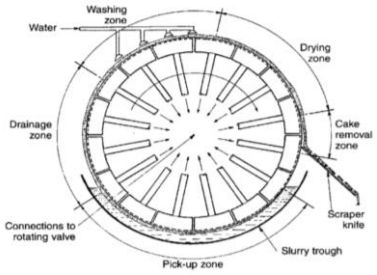
Filters can be organized into three classes:

Gravity filters

Filters that rely on gravity only generate low pressures, and their use on a large scale is limited. Gravity filters are simple and cheap, and are frequently used in *laboratory filtration* where volumes are small and a low filtration rate is relatively unimportant.

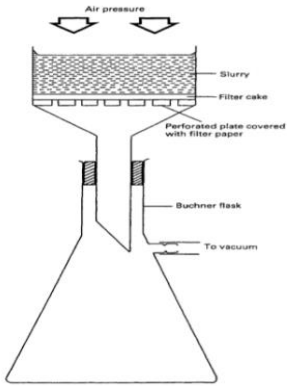
Vacuum filters

The rotary vacuum filter: In large-scale filtration continuous operation is desirable, and this may be difficult when it is necessary to filter slurries containing a high proportion of solids. The rotary vacuum filter is continuous in operation and has a system for removing the cake so that it can be run for long periods handling concentrated slurries



Pressure filters

Pressure filters feed the product to the filter at a pressure greater than that which would arise from gravity alone. This is the most common type of filter used in the processing of pharmaceutical products. Example on such type is the metafilter. It is operated by pumping the slurry under relatively high pressure.



EXPERMENTAL WORK: