**Industrial Pharmacy**

**Lab -1-**

**Introduction**

**Industrial Pharmacy:**

It concerns with the conversion of raw materials into certain dosage form. There different types of dosage forms such as tablets, capsules, ampoules, suspension, emulsion, etc.

The dosage form should be effective, stable, safe, bioavailable. So to formulate the dosage forms in such properties we should have good background and knowledge about the constituents of the dosage form (which are active ingredient and additives). This include the physic-chemical properties of both active ingredient and additives of the dosage form to get effective, stable, safe, bioavailable. For example if we want to prepare dosage form for a drug affected by Oxygen and light such as Ergonovine Maleate we should add antioxidants o replacement of air by inert gas like N2 and protected from light by placing it in a cold dark place.

Other example on physic-chemical properties of active ingredients and additives are color, odor, and taste.

**Department of drug industry: which includes:**

1. **Research and development department:**

It’s responsible for formulation of suitable dosage form and this achieved by certain specification of type and amount of materials that are used in the formulation. The pharmacist should have a good background in some sciences such as pharmacology, biochemistry etc.

In this department the formula will be produced in a small scale while the larger scale will send to the production department. For example if we are asked to prepare 500mg Paracetamol tab the pharmacist should add a proper type and amount of additives that should be added to the active ingredient in order to get the required tab.

When a new compound is discovered it should pass the research department first to check whether the drug has pharmacological effect or not, then if the result is positive it will be passed to the development department to develop as a new drug require preparation of new formula in pilot plant small scale.

1. **Production department:**

The job of this department is the production of dosage form in large scale. This department divided into many subareas:

1. Area for production of **tablets**.
2. Area for production of capsules.
3. Area for production of ampoules.
4. Area for production of solutions.

In this department it’s not necessary to have advanced pharmaceutical science degree, the important thing is to have skilled workers in this department.

1. **Quality control department:**

This department is responsible for:

1. Evaluation of drug dosage form before going to the market (to ensure that there is no differences **between** batches which should be within accepted evaluations)
2. Following up the product from the market to ensure the stability.
3. Evaluation of machine.
4. **Marketing department:**

Responsible for marketing of the drugs to the pharmacies and hospitals.

1. Non-laboratory department:

Finding markets for dispense, also this department responsible for management, payroll, accounting, personnel, and inventory, this department also does not require advanced pharmaceutical degree.

**Some requirements in drug factories:**

1. Should be compatible with the GMP specifications (GMP which is a guidance that outlines the aspects of production and testing that can impact on the quality of the product).
2. Drug factories should be clean, sterile, and all personnel should wear certain protective work outfits.
3. Departments should be separated from each other (for example the Antibiotics department should be separated from other departments).

**Laboratory equipment:**

**1st: Tablet equipment (solid dosage form):**

1. **Mixer: we have many types:**
2. **Cubic mixer:** in which the mixing movement of the product is deflected and interfered with by three mixing rods made of steel.
3. **Double cone mixer.**
4. **V-Shaped mixer.**
5. **Z-Shaped mixer** for powder and granules.
6. **Suppository mixer:** which consist of thermostat to produce suppository, suppository filter and molder used for molding supps, lipsticks, and smaller production.
7. **Ribbon mixer:** can be used for dry and wet mixing procedures, but mainly for wet materials.
8. **Sieves:** to get uniform particle size, we have many types of sieves:
9. **Sub-sieve sizer**: to separate particles according to their size.
10. **Coulter counter**: to measure number of particles and size.
11. **Homogenizer**: or it’s also called granulator we have two types:
12. **Dry granulator** (for dry granules) which is used to granulate slugs and pellets.
13. **Wet granulator** (for wet granules) in which wet mass filled into housing and pressed by pressure plate against cutting knife and rotating discs.
14. **Tablet machine**: which is composed of the following parts:
15. **Hooper** (for storing the materials).
16. **Feeder**.
17. **Die**.
18. **Upper punch** (which determine the thickness of the tablet) and the **lower punch** (which determine the weight of the tablet).
19. **Coating pan**: which is used to produce uniform coating on tablet by either sugar or thin film.
20. **Polishing drum**: which is used to add polishing materials during operating the drum.
21. **Evaluation equipment:**

These equipment are considered within the quality control department and used to determine whether the manufactured tablet fall within required standards or not, and they include:

1. **Flow meter:** to measure the flowability of the tablets.
2. **Flame photometer**: to measure the concentration or amount of ions in the sample, such as K and Na.
3. **Hardness tester**: which used to measure the hardness of the tablet and include two types:
4. **Electrical hardness tester** such as Erweka hardness tester.
5. **Manual hardness tester** such as Monsato hardness tester.
6. **Tablet friabilator**: which measures the tablet friability that means

A very friable tablet will crack rapidly, while a very solid tablet will not crack easily with the given time of the test.

1. **Disintegration apparatus**: which consist of 4 baskets each has 6 cylinders, the tablet is to be placed in the cylinder, which will be immersed in gastric juice (0.1 N HCl) placed in water bath operating at 37° C. The disintegration time is between 15-30 minutes (which is close to the time required for the evacuation of the stomach). The hard tablet with much higher quantity of binder will require more than 30 minutes to disintegrate.
2. **Dissolution rate apparatus**: which measures the dissolution of drugs inside the body in the In-Vitro method. This device consist of a 6 jars filled with gastric juice and 1 tablet is placed in the jar, then a sample is taken every 10 minutes.

**2nd: Semi solid dosage form equipment:**

1. **Ointment agitator.**
2. **Three roller mill.**
3. **Collapsible closer** (to close the tubes).

**3rd: Ampoules equipment:**

1. **Ampoule filling machine** which consist of manual tool that fills the ampoule in every push is 1 ml.
2. **Ampoule filling and sealing machine** which connected with other device that control its operation.
3. **Ampoule sealing machine** which utilize high temperature heat source to seal the tip of the ampoule.
4. **Millipore filter** which is used for sterilization of liquid because it contains small pores (0.3 – 0.5 µ).
5. **Devices for evaluation of ampoules:**
6. **Leaker test apparatus.**
7. **Clarity test device.**
8. **Sterility test.**

**4th: Drying equipment:**

1. **Dry oven** (for dry heat or heat sterilization) which utilize the heat with no presence of any air currents, and usually used for drying processes that require long time (longer than that of autoclave).
2. **Autoclave** (for moist heat sterilization), the autoclave usually operates in the following order:

|  |  |  |
| --- | --- | --- |
| **Temperature** | **Pressure** | **Time for sterilization**  |
| 121° C | 15 PSI | 15 minutes |
| 184° C  | 30 PSI | 3 minutes |

1. **Tray dryer:** which operates by passing hot streams of air.
2. **Freeze dryer:** for substances affected by heat or moisture especially hormones.

**Industrial Pharmacy**

**Lab -2-**

**Effervescent Granules**

**Granule dosage form:**

These are medicinal granules consist of small irregular particles ranging from 4-10 mesh size (mesh= no. of pores per square inch).

**Effervescent granules:**

They are mixtures of medicinal agent with citric acid, tartaric acid, and bicarbonate. They are dissolved in water for purposes of administration and are taken during effervescence or immediately after. They are used for administration of many water-soluble drugs.

Alka seltzer, citrocarbonate and citro soda are examples of such preparations.

Granules may be dietary supplements such as delose granules.

**Notes**:

By using granules or coarse particles of mixed powders rather than small powder particles, the rate of solution is decreased and violent and uncontrollable effervescence is prevented .sudden and rapid effervescence could overflow the glass and leave little residual carbonation in the solution.

By using a combination of citric acid and tartaric acids rather than either acid alone ,certain difficulties are avoided because when tartaric acid is used alone the resulting granules loss their firmness readily and crumble ,while citric acid alone result in a sticky mixture difficult to granulate

**Advantages**:

1. Rapid onset of action (they are prepared as solution so rapid disintegration and dissolution).

2. Pleasant taste, the chemical reaction between the acid and the base lead to librate CO2 which act as local anesthetic effect of oral cavity so mask the undesirable taste.

3. Psychological effect, patient comfort to it.

4. Provide alkaline solution, neutralization of an acidic drugs as aspirin (alkalinization of urine and increase excretion of drug which is acidic).

**Disadvantages**:

1. Unstable, so it may absorb the water (moisture) from the atmosphere.

2. Not accurate dose estimation because the one who estimate the dose is the patient himself.

3. Sodium overload. (These granules are not suitable for hypertensive patients)

4. Have many drug-drug interaction.

**Notes**/ The first 2 disadvantages can be overcome by packaging and compressing into tablet dosage form and put them in aluminum foil (not in plastic foil because it allow the absorption of water from moisture).

Sources of acids

1. Natural (food) acids: e.g. citric acid, tartaric acid, malic acid, fumaric acid,

and others. These are highly soluble in water and thus widely use in preparation of effervescent.

2. Anhydride acids: e.g.anhydrous citric acid and anhydrous tartaric acid.

These when dissolved in water give hydrous acids.

 3. Salts acids: e.g. disodium dihydrogen phosphate, and sodium disulfide

They become soluble at pH 4.5 otherwise they are strong acids.

 4. Effervescent base: which is used mainly in the preparation of effervescent granules.

**Ciric acid 1 part**

**Tartaric acid 2 part**

**NaHCO 3.44 part**

**Total 6.44**

So we usually use a mixture of both acids in a ratio of 1:2 because citric acid alone lead to sticky granules while tartaric acid alone lead to chalky and friable granules. Sometimes we use Na2CO3 instead of NaHCO3 but the last is more effective because it´s more soluble in water.

**Method of effervescent granules production:**

1. Formulation: we should know:

A/ Amount of each material in the formula.

B/ Number of doses: usually we 1 tsp. as ordinary dose which is equal to 5 gm of effervescent.

 No. of doses =total amount /wt .of each dose

C/ The physic-chemical properties of each component.

2. Mixing: to get uniform distribution.

3. Moistening and granulation: here we should use certain solvent to get a required paste through wet granulator. If we use small amount we can use sieve with suitable particle size instead of granulator.

There are 2 methods of moistening and granulation:

1. **Dry method (heat fusion method)**: This method is used in the preparation of drugs which are not affected by heat (e.g.Mg Sulfate), it depend on water of crystallization of citric acid where is each molecule of citric acid liberating with 1 molecule of H2O as water molecule is liberated up on heating (60-80°).This liberated water can be used as a liquid in prepare the moist mass and granulation. (During the heating process, the heat causes the release of water of crystallization from the citric acid, which in turn dissolves a portion of powder mixture, setting of the chemical reaction and the consequent release of some carbon dioxide.
2. **Wet fusion method**: Used for preparation of small amount of effervescent granules and for compounds which are affected by heat.

1st mix the powder together and then add ethanol as moisture to get wet mass.

Water can´t be used as moisture because it reacts directly and end the reaction.

4. Drying: only for heat fusion method, usually we use tray dryer for this purpose.

5. Packaging and storage (cool and dry place):These granules should be stored in a wide mouth bottle with colored glass, should be tightly closed and sealed to exclude air, then the container should be kept in a cool dry place.

These granules may be pressured into tablet dosage form (e.g. Vit. C), so that the dosage is accurate.

**Experimental work:**

Prepare 25 gm of effervescent granules using 1.5 gm of Mg sulfate per dose as laxative. As known that effervescent granules composed of effervescent base and active ingredient (Mg sulfate).

The steps of calculation:

1. Find the no. of doses

No. of doses =total amount of granules /wt. of each dose

 =25/5

 =5

1. Find the amount of active ingredient added to the total amount of effervescent granules (25gm ):

5 × 1.5=7.5 gm of Mg sulfate should be added

3. Find the wt. of each active constituent of effervescent base that should be added to the added to the formula.

25 -7.5=17.5 gm amount of the base.

For Citric acid, for Tartaric acid and for NaHCO3:

|  |  |
| --- | --- |
| Total | gm of citric acid |
| 6.4 |  1 |
| 17.5 |  X |

x =2.7 gm

|  |  |
| --- | --- |
| Total | gm of tartaric acid |
| 6.4 |  2 |
| 17.5 |  x |

X =5.4 gm or 2 x 2.7 = 5.4 gm

|  |  |
| --- | --- |
| Total | gm of NaHCO3 |
| 6.4 |  3.4 |
| 17.5 |  x |

x = 9.3 gm or 2.7 x 3.4=9.3

**Procedure (by heat fusion method):**

1. Mix tartaric acid, NaHCO3, Mg sulfate together.

2. Heat citric acid water 60 -80 c° to release water crystallization till it becomes warm.

3. Immediately and directly add the above mixture to dish of citric acid with rapid mixing by hand till get the wet paste.

4. Sieving.

5. Drying.

**Procedure (by wet fusion method):**

1. Mix all ingredients including Tartaric acid, Citric acid, NaHCO3, and the active ingredient Mg sulfate.
2. Add Alcohol (95%) drop by drop with the continuous mixing till we get a wet paste.
3. Sieving.
4. Drying.

**Industrial Pharmacy**

**Lab -3-**

**Rheology**

Rheology is the flow properties of pharmacological particles.

Rheo = Flow

One of the most popular dosage forms was powder and by time it’s converted to tablets and capsules because the powder dosage form has many **disadvantages** which include:

1. Inaccuracy in weight.
2. Cannot be used for drugs having hygroscopicity because it may absorb moisture.
3. Powders that have bad taste.

Therefore we have to study the rheoology of the powder or granules because during some phase of manufacture the materials are utilized in a particular form especially for industrial pharmacist.

In other words modern tablet machine can produce 5-20 thousands tablets/min and the capsule machine can produce about 150 thousands capsules/min and in order to ensure this type of production we must 1st ensure the integrity of powder flow rate (to ensure flowability of the powder).

**In general we have 2 types of powder flowability:**

1. **Freely flowable powder.**
2. **Non-free (sticky) flowable powder.**

**Factors reducing flow rate:**

1. **Intermolecular forces:** these are weak cohesive forces on the surface of the particles of different charges such as Vander Waals forces, they affect the powder flowability.

When molecules interact both repulsive and attractive forces operate. As two molecules brought close together the opposite charges on both molecules are close together and the molecules will attract to each other leading to bad flowability.

 H $H^{+}$------ $O^{-}$ $H^{+}$

Vander Waals Forces

$$O^{-}$$

$$H^{+}$$

1. **Frictional Forces (electrostatic forces):** these forces present on the surface of the particle and normally they manifest their effect due to friction between particles during movement.

As the surface area increases, the friction increases, the formation of charges increases, and as a result the flowability decreases.

The charges developed depend on:

1. Materials involved.
2. Type of motion produced in it.
3. **Shape of particles:** the spherical shape particle with small surface area have good flowability, while irregular particles or particles with needle and crystalline shape, also flat particles and particles with rough surface, all these types have bad flowability.
4. **Size of the particles:** the small particles have high surface area and high frictional forces and so bad flowability.

So if the size of the particle is too large it may not be able to enter the orifices of the instrument.

Flow rate

Particle size

When performing experiment of the measuring the flow rate of mixture of the same material but with different particle size, it’s clearly as the proportion of the fine particles increases in the mixture there is a fall in the flow rate.

1. **Moisture:** to a certain extent it will help the flow by the absorbed layer of moisture on the particle surface will reduce the chance of any complicating electrostatic effect by producing conduction path of charge dissipation, but the excessive moisture higher than that of 50 % lead to forming moisture bridges between particle which will cause sticky mixture and thus reduce the flow rate.

**Note**: Bad flowable powder may cause the following:

1. Weight variation in the final product.
2. Non uniform particle packing.
3. Air entrapment within the powder which may cause tableting problems.
4. Excessive fine particles which cause lubricating problems.

**Improving flowability:**

1. **Formulation additives** :
2. Talc.
3. Magnesium oxide ( which act by disrupting the continuous film of adsorbed water surrounding the moist particles)
4. Colloidal silicon Dioxide (which act by reducing the balk density of tightly packed powder).
5. **Force feeder** (which push the powder down in the die).
6. **Vibrating Hooper** (provide regular vibration allowing the powder to flow continuously).

**Measurement of flowability by:**

1. **Flow meter** (determine the flow rate and also provide a means of quantifying uniformity of flow).
2. **Angle of repose**: also called funnel and petri dish method is relatively simple method for estimating the flow properties of a powder, which can be determined by allowing the powder to flow through a funnel and fall freely onto a surface, the height and the diameter of the resulting cone will be measured and the angle of repose which is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane, this angle can be calculated from the following equation:

tan θ = h / r

Where θ = angle of repose, h = height of the powder cone, and r = radius of the cone.

Angle of repose range from 0°- 90° depending on type of powder, it is related to density, surface area, shape of particles, coefficient of friction of the material

The value of angle of repose increases if the powder is cohesive.

This table represent the scale of flow determined from Carr’s scale of flowability:

|  |  |
| --- | --- |
| **Angle of repose**  | **Flow property**  |
| 25° -30° | Excellent |
| 31°-35° | Good |
| 36°-40° | Fair ( aid not required) |
| 41°-45° | Passable ( may hang up) |
| 46°-55° | Poor ( must agitate , vibrate ) |
| > 55° | Very poor |

**Industrial Pharmacy**

**Lab -4-**

**Powder Density**

**Powder bulk density**

The [bulk density](http://en.wikipedia.org/wiki/Bulk_density) of a powder simply expresses the amount, usually weight or mass, of a powder in a specified volume. However, since powders are composed of particles and [voids](http://en.wikipedia.org/wiki/Void_ratio), the volume occupied by a given number of particles depends on how closely they are packed. The packing of particles depends on their shape, cohesiveness, short-range motion and external forces.

**Tapped density**

Tapped density is the term used to describe the [bulk density](http://en.wikipedia.org/wiki/Bulk_density) of a [powder](http://en.wikipedia.org/wiki/Powder) (or granular solid) after [consolidation](http://en.wikipedia.org/wiki/Consolidation_%28soil%29)/compression prescribed in terms of "tapping" the container of powder a measured number of times, usually from a predetermined height. The method of "tapping" is best described as lifting and dropping.

**Measuring Bulk density**

Is determined by pouring perceived bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight.

**Measuring tapped density**

In general, any graduated container can serve as a means to determine tapped density. In practice, [graduated glass measuring cylinders](http://en.wikipedia.org/wiki/Graduated_cylinder) are most often used. In the standard methods below, the total capacity of the cylinder to be used, and the readability of its [scale](http://en.wikipedia.org/wiki/Graduation_%28instrument%29) are stated. The cylinder can be tapped manually or by mechanical device.

Manual and mechanical tapping

The raising and lowering of the cylinder by hand is done either without reference to the height traversed and arbitrary acceleration in both upward and downward directions; the hand remaining in contact with the cylinder at all times (hand tapping) .In hand tapping the cylinder containing the powder is tapped by repeatedly striking its base down onto a hard surface.

Tap density analyzers (tap density testers) use an electric motor to turn a cam under a specially constructed cylinder holder. The holder secures the cylinder to a vertical shaft which runs in a low friction [bearing](http://en.wikipedia.org/wiki/Bearing_%28mechanical%29). The tapping rate is normally expressed in taps per minute; the rate being typically a few hundred. The actual rate is determined by the rotational speed of the cam under the shaft/platform.

Digital or electromechanical counters are usually incorporated in the device to automatically stop the cam rotation after a predetermined (yet adjustable) number of taps. The height through which the container falls is known as the drop height or stroke. It is set by the distance between the highest point on the cam and the striking surface.

Once density problem is identified, it is easily corrected by

1. **Milling**
2. **Slugging**
3. **Formulation**

Bulk density is important in the consideration the size of high dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities.

Also knowing the dose and formulation density to determine the appropriate size for a capsule formulation.

Tapped density and powder flowability

The change in tapped powder volume has been related to flow properties of powders and can be determined by compressibility which is computed from powder density using the following equation

% compressibility =$\left(ρt-ρo/ρt\right)$× 100

𝜌t- tapped density

𝜌o- bulk density

The following table shows the link between the compressibility and flowability of powders

|  |  |
| --- | --- |
| % compressibility | Flowability |
| 5-15 | Excellent |
| 12-16 | Good |
| 18-21 | Fair passable |
| 23-35 | Poor |
| 33-38 | Very poor |
|  More than 40 | Very very poor |



**Industrial Pharmacy**

**Lab -5-**

**Drying**

* Drying: - is the removal of liquid from material by application of heat.
* It is accomplished by the transfer of a liquid from a surface into an unsaturated vapor phase.

**Purposes of drying:**

1- Unit of process in pharmaceutical manufacturing

(E.g. preparation of granules then dispense as capsules or tablets).

2- Reduce bulk and weight so lower the cost of transportation and storage.

3- Aid in preservation of animal and vegetable drugs by minimizing mold and bacterial growth in moisture laden material

4- Facilitate comminution by increasing friability.

**Classification of solids on drying behavior:**

1. Granular or crystalline solids (water is held in shallow and open surface pores as well as in interstitial spaces between particles that are easily accessible to the surface).

Ex: calcium sulfate, zinc oxide, magnesium oxide

1. Amorphous, fibrous or gelatinous solids (moisture is an integral part of the molecular structure as well as being physically entrapped in fine capillaries and small interior pores).

Ex: starch, insulin and aluminum hydroxide.

**Note: Amorphous solids are difficult to dry than granular or crystalline solids.**

**Classification of dryers:**

1. **Static-bed dryers- systems:**
2. ***Tray and truck dryers:*** *it consist from cabinet in which the material dried is spread on tiers of trays.*
3. ***Tunnel and conveyor dryer:*** *an adaptation of truck dryer for continuous drying.*
4. ***oven:*** *including autoclave and dry oven*
5. **Moving-bed dryers-systems:** *The drying particles are partially separated so that they flow over each other.**It includes*

***A. turbo-tray dryer***

***B. pan dryer***

**3- Fluidized - bed dryers systems:** *Solid particles are partially suspended in upward moving gas steam.*

***4-*pneumatic dryers system**: *Drying particles are entrained and conveyed in a high velocity gas stream.*

***5*- Specialized drying methods:**

1. ***Freeze dryer:*** *for drying of thermo labile compounds*
2. ***Microwave drying:-*** *here instead of applying heat externally to material, energy in form of microwaves is converted into internal heat by interaction with material itself*

**Solids drying**

* The moisture in a solid can be expressed on a **wet-weight** or **dry-weight** basis.
* **Wet-weight basis: loss on drying**

**%LOD = wt. of water in sample × 100**

 **Total wt. of wet sample**

* **Dry-weight basis: moisture content**

**%MC = wt. of water in sample × 100**

 **Wt. of dry sample**

**Example:**

If exactly 7 g of moist solid is brought to a constant dry weight of 5 g:

MC = $\frac{7-5}{5}$ x 100 = 40%

Whereas

 LOD = $\frac{7-5}{7}$ x 100 = 28.57%

**Industrial Pharmacy**

**Milling**

**Lab -6-**

**Introduction:**

**Milling:** Is a mechanical process of reducing particle size of solids.

Milling also termed synonymously as comminution which represent different expressions like, crushing, disintegration, dispersion, grinding and pulverization.

All of these depend on product, equipment and process.

**Milling equipment:**

Milling equipment classified according to the size of the milled product into:

1. Coarse milling (particles > 20-mesh)
2. Intermediate (particles 200- 20 mesh [74-840 micron])
3. Fine (particles < 200 mesh)

Note: Size expressed in term of mesh (number of openings per linear inch of a screen).

**Pharmaceutical Applications:**

1- Increasing therapeutic efficacy of low solubility drugs due to increasing specific surface area (S.A per unit wt), thus, increasing area of contact with dissolving fluid, e.g. griseofulvin

2- Facilitate drying of wet masses due to increase surface area and reduce the distance the moisture travel within particle to reach outer surface, e.g. granulation of wet mass in tablet preparation.

3- Facilitate easier and uniform mixing or blending the ingredients are approximately of same size.

4- Solid dosage form that is artificially colored are often milled to ensure that the mixture is not mottled and is uniform from batch to batch.

5-Lubricants should be milled to fine powder to ensure their ability to coat surface of powder or granules.

6- Milling in Ointments, creams and pastes provide smooth texture, better appearance and improve physical stability.

**Milling operations:**

A- open-circuit milling: Materials is reduced to the desired size by passing it through the mill.

B- closed-circuit milling: Materials discharge from mill pass through classifier or size-separation device, and the oversize are returned to the grinding chamber for further reduction in size.

**Parts of mills:**

1- Feed part

2- Grinding part (milling chamber)

3-Discharge chamber (receiver)

**Important Note:** The rate of discharge should be equal to the rate of feed.

A- If rate of feed is slow the product discharge readily and the amount of undersize or fines is minimized

B- If rate of feed is fast the material remain in the milling chamber for long time because its discharge is impeded by large amount of material leads to greater size reduction and lower mill capacity.

**Mechanism of size reduction:**

* Cutting: materials cut by sharp blades
* Compression: materials is crushed by pressure.
* Impact: stationary materials hit moving materials at high speed or strikes a stationary surface (case of machine) which shatters of materials to small pieces.
* Attrition: materials subjected to pressure and surfaces are moving relative to each other, so shear forces which breaks particles.

**Hammer mill:**

* Principle: Operates as an impact between rapidly moving hammers mounted on the rotor and the powder material.
* Used for almost any type of size reduction (dry material, wet filter-press cakes, ointment, slurries).
* It is popular in pharmaceutical industry because of versatility

**Ball mill:**

* Principle: Combination of impact and attrition
* A horizontal rotating hollow vessel of cylindrical shape filled with balls of steel or pebbles (grinding medium).

A- Pebble mill

B- Rods or bars mill

**Roller mill:**

* Principle: combination of compression and shearing action.
* Mechanism of action: 2-5 smooth rollers operating at different speed.

**Cutting mill:**

* Principle: cutting and shearing action
* Uses: for fibrous and tough material.
* Types: single and double runner disc mills.

**Size distribution and measurement:**

* In naturally occurring particulate solids and milled solids The shape of particle is irregular, and size varies from largest to smallest size
* Therefore , size distribution used instead of particle size Which represents % frequency of each particle size(i.e what size present in what proportion)

**Methods of measurement of size distribution:**

1- Microscopy

2- Sieving

3-sedimentation

4- Other methods (sorption, electrical conductivity, light and x-ray scattering, permeametry, and particle trajectory).

1. **Microscopy:**
* Direct Method for measuring P.S. distribution.
* Disadvantages: can’t resolve particles if it’s size is close to the wave length of the light source.
1. **Sieving:**
* It is pan with bottom of wire cloth with square openings
* Most widely method for measuring P.S. distribution
* Advantages: Inexpensive, simple, rapid, limited variation between operators
* Measuring diameter of powder bypass series of sieves:
* 30-mesh and retained on 45-mesh (diameter= 590 + 350)/2 or 470 microns.
* Size of distribution effected by:
1. No. of Sieves (by passing powder through series of smaller sieves and weighing portion retained on each sieve).
2. Motion of sieve (vibratory, side-tap, bottom-tap, rotary-tab, rotary).
3. Time of sieving.
4. Load or thickness of powder (proportional to time).

**Industrial Pharmacy**

**Lab-7-**

**Mixing**

**(Solid-Solid)**

* **Definition**: Mixing a process that results in a randomization of dissimilar particles within a system.

**Solid Mixing and their mechanisms**

**The variables effecting solid mixing:**

1- Particle size and particle size distribution (Particles with P.S. <100 Micron is free flowing)

2- Particle density, elasticity, surface roughness and shape.

**Mixing mechanisms:**

**Solid mixing proceeds by the combination of one or more mechanism:**

1. Convective mixing
2. Shear mixing
3. Diffusive mixing

**1. Convective mixing**

Mechanism analogous to bulk transport

Convective (bulk) mixing occurred by: Inversion of powder bed

By the aid of:

A- Blades or peddles

B- Revolving screw

C- Any method of moving large mass of material from one part of powder bed to another.

**2. Shear mixing**

As a result of forces within mass leading to slip planes, depending on the flow characteristic of powder, that can occur in such a way to give rise to [laminar flow]

When shear occurs between regions of different composition and parallel to their interface it reduce the scale of segregation by thinning the dissimilar layers.

**3- Diffusive mixing**

Random motion of particles within a powder bed, leading to change position by single particles relative to one another, causing reduction intensity of segregation.

**Equipment for solid mixing**

In batch mixing Mixers consist of containers of one or several geometric forms (mounted and rotated about an axis). Tumbling motion by baffles or by virtue of shape of container.

**1- twin-shell blender/tumbling mixers
(form V-shape mixers)**

* Effective because it’s mechanism of mixing is:
* Bulk transport and shearing.
* Efficiency is dependent on speed of rotation.
* Optimum rotation (30 - 100 rpm)

**2- Stationary container type:**

Employs stationary container to hold the material and bring mixing by moving screws, peddles or blades.

Useful in mixing solids that have been wetted and therefore are in sticky or plastic state.

Well know mixers include:

1. **Ribbon blender**

(Consist of horizontal cylindrical tank usually opening at the top and fitted with helical blades).

{Blades mounted on the shaft through the long axis of tank and have both right and left hand twist}

1. **Helical flight mixers**

Powders are lifted by a centrally located vertical screw and allowed to cascade to the bottom of the tank.

**Mixer selection:**

* **Mixer selection and evaluation depend on:**
* 1- Measuring degree of mixing
* [according to the function of mixer that indicates the uniformity of powder bed].
* 2- Power requirements
* [power required to produce good mixture with appropriate time]
* Since long mixing time causing un mixing and segregation leading to:
* {1- improper mixing operation or wrong mixer or both}
* {2- after prolong mixing the milling occur because of abrasion of particles}

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**Mixing (2)**

**Fluid mixing and their mechanisms:**

Depending upon relationship between shear rate and the applied shear stress, the fluids may be divided into

* **Newtonian Fluids**
* **Non-Newtonian Fluids**

**Liquid mixing mechanisms**

* Bulk transport
* Turbulent flow
* Laminar flow
* Molecular diffusion
1. **Bulk transport**
* The movement of relatively large portion of material being mixed from one location in the system to another.
* Bulk transport accomplished by means of paddles, revolving blades, or other devices within the mixer arranged so as to move adjacent volumes of fluid in different direction (3D shuffling**).**

**2- Turbulent mixing**

* It is a direct result of turbulent fluid flow which is characterized by a random fluctuation of the fluid velocity at any given point within the system.
* In turbulent flow, the fluid has a different instantaneous velocities at different location at same instant in time.
* Turbulent flow visualized as (eddies) with various sizes [portion of fluid moving as a unit in a direction contrary to that of general flow]. Larger eddies breakup forming smaller and smaller size eddies until are no longer distinguished.

**3. Laminar mixing**

* Streamline or laminar flow is frequently encountered when highly viscous fluid are being processed.
* Occur with gentle stirring and adjacent to stationary surfaces in vessels where turbulent flow is predominant.
* When two dissimilar liquids are mixed through laminar flow, the shear generated stretches the interface between them.

**4. Molecular diffusion**

* Mixing at the molecular level by diffusion resulting from thermal motion of molecules.
* Occurs in conjugation with laminar flow that tends to reduce sharp discontinuities at the interface between the fluid layers which leads to complete mixing after sufficient time.

**Equipment**

**Equipment**

**A-Batch mixing**

* Impellers
* Air stream
* Liquid jet

**B-Continuous mixing**

1. **Batch Mixing:** Mixing is limited in volume contained in suitable mixer
* Parts:
1. Tank or container
2. energy supplier : Also used to direct the flow within vessel like baffles, Vanes or ducts, it includes
* energy supplier
* Air stream
* Liquid jet

**Impeller types**

The type of impeller depends on

1. Type of flow (radial, axial, tangential)
2. Shape and pitch of blades
* There are different types of impellers including
1. Propellers:
* Produce flow parallel to their axis.
* High efficient with low viscosity liquids
1. Turbine:
* Produce axial or tangential flow or combination
* Blades have constant pitch throughout their length and used for very viscous liquids.
1. Paddles:
* Circulation is primarily tangential
* Operate at a very low speed and used to mix viscous liquids and semisolids.

**Factors affecting mixer selection:**

1. Physical properties of material to be mixed (density, viscosity and miscibility).
2. Economic consideration regarding processing (time for mixing and powder expenditure).
3. Cost of equipment and its maintenance.

**Mixing of polyphase systems:**

* **Liquid –liquid mixing:** Mixing of two immiscible liquids requires subdivision of one of the phases into globules which then distributed throughout bulk of fluid forming a stable emulsion.
* **Solid-liquid mixing:** Mixing of Finely divided solid with liquid of low viscosity in the production of suspension depends on separation of aggregates into primary particles and the distribution of these particles throughout the fluid.