MIXING –THEORY AND EQUIPMENTS

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Introduction

Mixing is defined as a process that tends to result in a randomization of dissimilar particles within a system.

- The term **MIX** means to put together in one mass.
- The term **BLENDING** means to mix smoothly and inseparably together during which a minimum energy is imparted to the bed.
- The terms **MIXING** and **BLENDING** are commonly used interchangeable in the pharmaceutical industry.

Classification of mixing

A. Mixing of solids
B. Mixing of liquids
C. Mixing of immiscible liquids
D. Mixing of semisolids

A. Mixing of solids

- In the manufacture of tablets or granules normally a number of additives are added. Therefore mixing of powder becomes essential part of the process.
- Mixing is considered as a critical factor, especially in case of potent drugs and low dose drugs where high amounts of adjuvants are added.
- The diverse characteristics of particles such as size shape volume surface area density porosity flow charge contribute to the solid mixing.
- Depending on their flow properties solids are divided into two classes as cohesive and non cohesive.

Interparticle interactions & segregation

1.Inertial forces:

These forces hold neighboring particles in fixed relative position.

E.g.: Vander Waal forces, electrostatic forces, surface forces.

Surface forces:

Cohesive forces and frictional forces results in surface-surface interactions which resist the movement of particles, hence they should be minimal.

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These depend on surface area, surface roughness, polarity, charge, moisture.

Segregation

- Poor flow properties.
- Particle size difference.
- Difference in mobilities.
- Differences in particle density and shape.
- Transporting stage.
- Dusting stage.

❖ It may occur even after mixing.

2 Gravitational forces

- Improve the movement of two adjacent particles or groups of particles
- When particle-particle collisions occur , exchange of momentum is achieved continuous exchange or distribution of momentum between transitional and rotational modes is necessary for effective mixing
- Efficiency of momentum transfer depends on
    - Elasticity of the collisions
    - Coefficient of friction
    - Surface area of contact
    - Centrifugal forces

Mechanism of mixing of solids

1. Convective mixing/Macro mixing:

Inversion of the powder bed using blades or paddles or screw element, in which large mass of material moves from one place to another.

2. Shear mixing:

In this type, forces of attraction are broken down so that each particle moves on its own between regions of different components and parallel to their surface.

3. Diffusion mixing/Micro mixing:

Involves the random motion of particle within the powder bed, thereby particles change their position relative to one another.

- In the solid-solid mixing operations , four steps are involves. These are:

1. Expansion of the bed of solids
2. Application of 3-dimensional shear forces to the powder bed.
3. Mix long enough to permit true randomization of particles.
4. Maintain randomization.

The law of mixing appears to follow first order,

$$M = A\left(1 - e^{-kt}\right)$$

Where M = degree of mixing after time t,

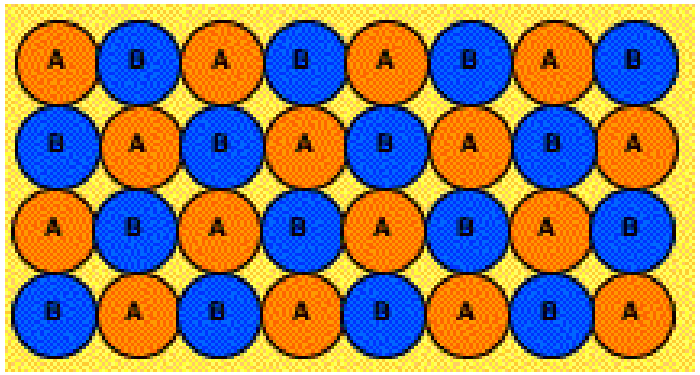
T = time

A and k = constants

- A and k depends on the
  - ✓ Mixer geometry
  - ✓ Physical characteristics of the powders and
  - ✓ Proportion of the material being mixed.

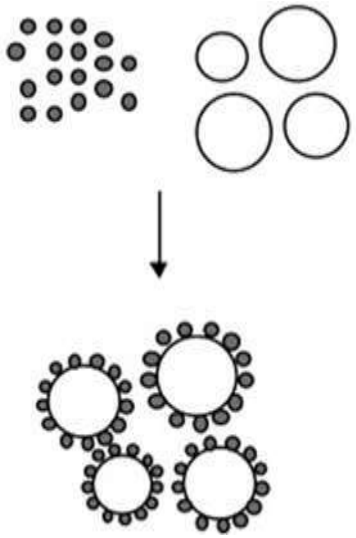
Degree of mixing

- Ideal mixing or perfect mixing:



- Acceptable mixing:
  1. Random mixing
  2. Ordered mixing
     - Mechanical means of ordered mixing
     - Adhesion means of ordered mixing
     - Coating means of ordered mixing

Adhesion means of ordered mixing:



Coating means of ordered mixing:

Statistical parameters

Arithmetic mean:

Size distribution is calculated

$$\text{Arithmetic mean } \bar{y} = \frac{\sum_{i}^{n} y}{n}$$

Standard deviation:

Used to know the spread of dispersion.

$$\text{Standard deviation } \sigma = \sqrt{\frac{\sum^{n}(y_i - \bar{y})^2}{(n-1)}}$$

- Mixing should be continued until the amount of the active drug that is required is with in ± 3 SD units that of found by assay in a representative number of sample dose.

Relative standard deviation:

- It replace the S.D as a measure of sample uniformity.
- Useful for comparing the efficiency of two or more mixing operations or different sample size or different composition.

$$percent\ relative\ S.D = \frac{standard\ deviation(\sigma)}{mean(\bar{y})} X\ 100$$

Mixing indices

- Involves the comparison of SD of sample of a mixture under study with the estimated standard deviation of a completely random mixture.
- It can be expressed -

$$M = \frac{\sigma_R}{\sigma} \quad \text{or} \quad M = \frac{\sigma_o - \sigma}{\sigma_o - \sigma_R}$$

Where,

M = *mixing index*

σ_R = *standard deviation of the random blend*

σ = *standard deviation of the sample blend*

σ_o = *standard deviation of the unmixed powder*

Factors influencing mixing

- Nature of the surface
- Density of the particles
- Particle size
- Particle shape
- Particle charge
- Proportion of materials

EQUIPMENT

Criteria:

1. Powder bed should not be filled for more than 60%
2. Particles should be subjected to movement in three directions
3. Shearing force should be sufficient to prevent aggregation.
4. There should be no centrifugal effect
5. Forces should not cause breakage of the particles.
6. The mixing process should be stopped abruptly.

Classification of equipment for solid mixing

- Based on **flow properties**:
  1. Free flowing solids:

     e.g.: V cone blend , Double cone blender
  2. Cohesive solids:

     e.g.: Sigma blender, Planetary mixer
- Based on **scale of mixing**:
  1. Batch type(small scale):

     e.g.: Mortar and pestle, V cone blender, Double cone blender, Ribbon blender, Sigma blender, Planetary paddle, Fluidized mixer
  2. Continuous type(large scale):

     e.g.: barrel type, zigzag type

S.no.	Nature of mixer	Examples	Mechanism of mixing
1	Batch type	Mortar pestle	Trituration
2	Tumbling mixers or cylindrical mixers with no mixing blade	Double cone blender V cone blender	Tumbling action
3	Tumbling mixer with a mixing blade	V cone blender double cone blender	Tumbling action as well as shearing with blade
4	Static mixers	Ribbon blender Sigma blender Planetary paddle	Stationary shell and rotating blade
5	Air mixers or fluidized mixers	Fluidized mixer	Air supported blending
6	Continuous type	Barrel type Zigzag type	Rotating shell with rotating blade

Tumblers or cylindrical blenders with no mixing blade

- Meant for dry powders
- Equipment consists of a container of any geometric form.
- Container is mounted on special roller so that it can be rotated about any axis.
- Edge of 27 degrees is good for mixing.
- Efficiency of a tumbler mixer highly depends on the speed of rotation. It should be critical and optimum.
- Slow rotation- no intense tumbling, No cascade motion, Not enough shear rates are applied.
- Rapid rotation-sufficient centrifugal action to the powder to the side of the mixer, more dusting and segregation of fines is possible.
- Rate of rotation depends upon size , shape of the tumbler and nature of the material to be mixed. Common range is 30-100rpm.
- Mixing is done by tumbling motion, which is accentuated by virtue of the shape of the container.

Twin shell blender or V cone blender

- It is V shaped and made up of stainless steel or transparent plastic.
- Material is loaded through shell hatches and emptying is normally done through and apex port.
- The material is loaded approximately 50-60% of the total volume.
- Small models – 20 kg , rotate at 35rpm
- Large models – 1 ton, rotate at 15rpm
- As the blender rotates , the material undergoes tumbling motion.
- When V is inverted, the material splits into two portions. This process of dividing and recombining continuously yields ordered mixing by mechanical means.

Double cone blender

- It consists of double cone on rotating shaft.
- It is usually used for small amount of powders.
- It is efficient for mixing powders of different densities.
- Material is loaded and emptying is done through the same port.
- The rate of rotation should be optimum depending upon the size, shape of the tumbler and nature of the material to be mixed.
- The rate of rotation commonly ranges from 30-100rpm.
- Mixing occurs due to tumbling motion.

Double cone blender

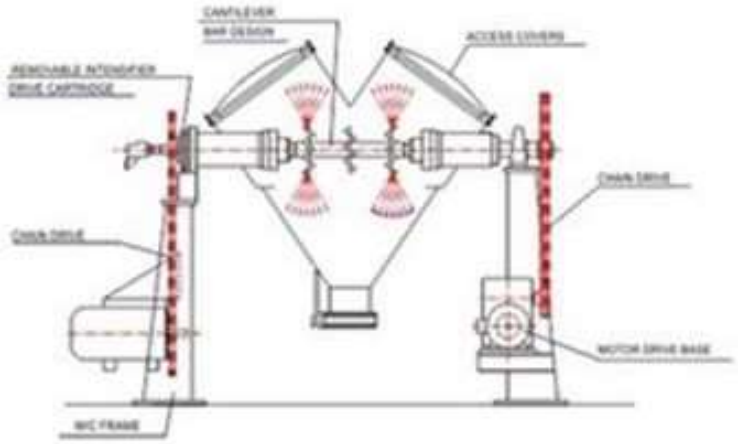
Advantages of V cone blender and double cone blenders:

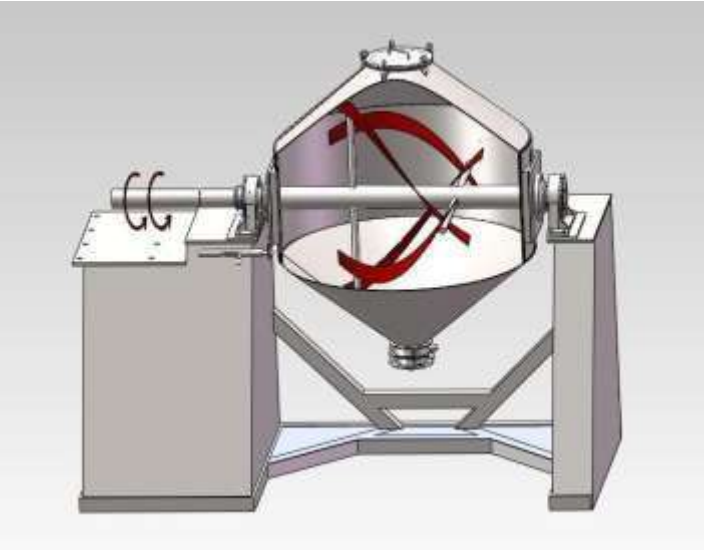
- If fragile granules are to be blended, twin shell blender is suitable because of minimum attrition.
- They handle large capacities.
- Easy to clean , load, and unload.
- This equipment requires minimum maintenance.

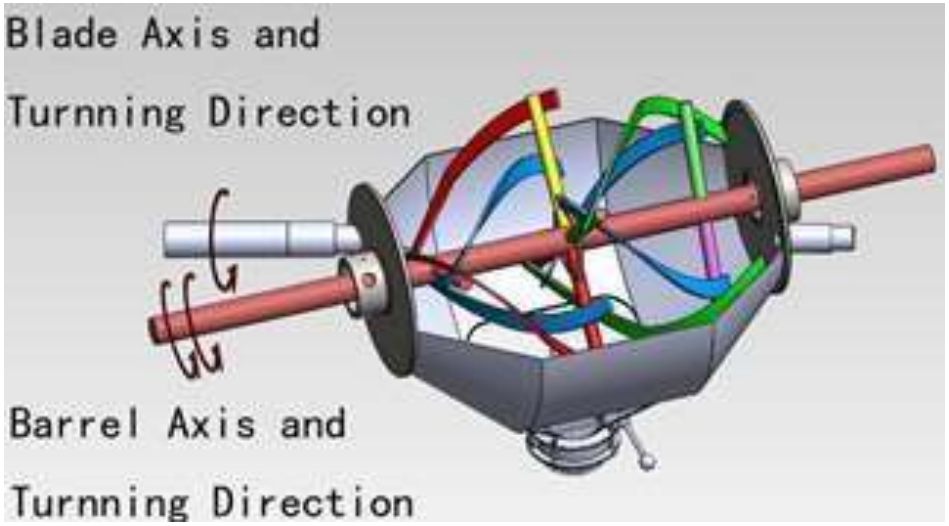
Disadvantages of V cone blender and double cone blenders:

- Twin shell blender needs high headspace for installation.
- It is not suitable for fine particulate system or ingredients of large differences in the particle size distribution, because not enough shear is applied.
- If powders are free flowing, serial dilution is required for the addition of low dose active ingredients.

Tumbling blenders with agitator mixing blades







Advantages of tumblers with blades:

- Baffles are useful for both wet and dry mixing.
- Wide range of shearing force can be applied with agitator bars permitting the intimate mixing of very fine as well as coarse powders.
- Serial dilution is not needed when incorporating low–dose active ingredients.

Disadvantages of tumblers with blades:

- Attrition is large, size reduction of friable particles results.
- Scale–up can prove a problem, because general principles of scale–up do not work
- Cleaning may be a problem, because agitator assembly must be removed and the packing should be replaced for a product changeover
- Potential packing (sealing) problems occur.

Ribbon blender

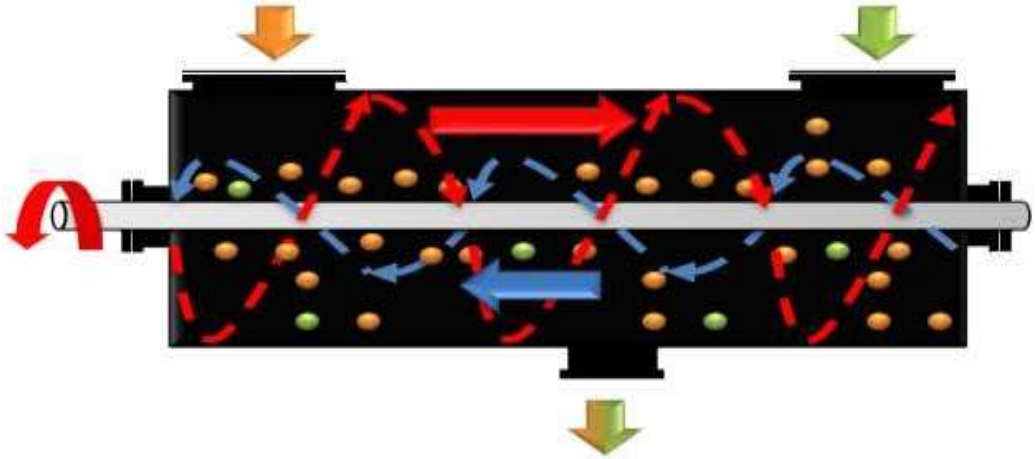
Principle:

Mechanism of mixing is shear. Shear is transferred by moving blades. High shear rates are effective in breaking lumps and aggregates. Convective mixing also occurs as the powder bed is lifted and allowed to cascade to the bottom of the container. An equilibrium state of mixing can be achieved.

Construction:

- Consists of horizontal cylindrical trough usually open at the top. It is fitted with two helical blades, which are mounted on the same shaft through the long axis of the trough.
- Blades have both right and left hand twists.
- Blades are connected to fixed speed drive.
- It can be loaded by top loading and emptying is done through bottom port.

Working:



Uses:

- Used for mixing of finely divided solids, wet solid mass, and plastic solids.
- Uniform size and density materials can be easily mixed.
- Used for solid – solid and liquid – solid mixing.

Advantages of ribbon blender:

- High shear can be applied by using perforated baffles, which bring about a rubbing and breakdown aggregates.
- Headroom requires less space.

Disadvantages of ribbon blender:

- It is a poor mixer, because movement of particles is two dimensional..
- Shearing action is less than in planetary mixer.
- Dead spots are observed in the mixer, though they are minimum.
- It has fixed speed drive.

Sigma blade mixer

Principle – shear. Inter meshing of sigma blades creates high shear and kneading action.

Construction and working:

- It consists of double tough shaped stationary bowl.
- Two sigma shaped blades are fitted horizontally in each tough of the bowl.
- These blades are connected to a fixed speed drive.
- Mixer is loaded from top and unloaded by tilting the entire bowl.
- The blades move at different speeds , one about twice than the other, which allows movement of powder from sides to centers.
- The material also moves top to downwards and gets sheared between the blades and the wall of the tough resulting cascading action.
- Perforated blades can be used to break lumps and aggregates which creates high shear forces.
- The final stage of mix represents an equilibrium state.

Sigma blade mixer

Uses of sigma blade mixer:

- Used in the wet granulation process in the manufacture of tablets, pill masses and ointments,
- It is primarily used for liquid – solid mixing, although it can be used for solid – solid mixing.

Advantages of sigma blade mixer:

- Sigma blade mixer creates a minimum dead space during mixing.
- It has close tolerances between the blades and the sidewalls as well as bottom of the mixer shell.

Disadvantages of sigma blade mixer:

- Sigma blade mixer works at a fixed speed.

Principle:

Mechanism of mixing is shear. Shear is applied between moving blade and stationary wall. Mixing arm moves around its own axis and around the central axis so that it reaches every spot of the vessel. The plates in the blades are sloped so that powder makes an upward movement to achieve tumbling action also.

Construction:

- Consists of vertical cylinder shell which can be removed.
- The blade is mounted from the top of the bowl.
- Mixing shaft is driven by planetary gear and it is normally built with variable speed drive.

Uses :

- Break down agglomerates rapidly.
- Low speeds are used for dry blending and fast for wet granulation.

Advantages:

- Speed of rotation can be varied at will.
- More useful for wet granulation process.

Disadvantages:

- Mechanical heat is buildup within the powder mix.
- It requires high power.
- It has limited size and is useful for batch work only.

Applications of solid mixing

- Involved in the preparation of many types of formulations.
- It is also an intermediate stage in the production of several dosage forms.
  - Wet mixing in the granulation step in the production of tablets and capsules.
  - Dry mixing of several ingredients ready for direct compression as in tablets.
  - Dry blending of powders in capsules, dry syrups and compound powders.
  - Production of pellets for capsules.

B. Mixing of Fluids

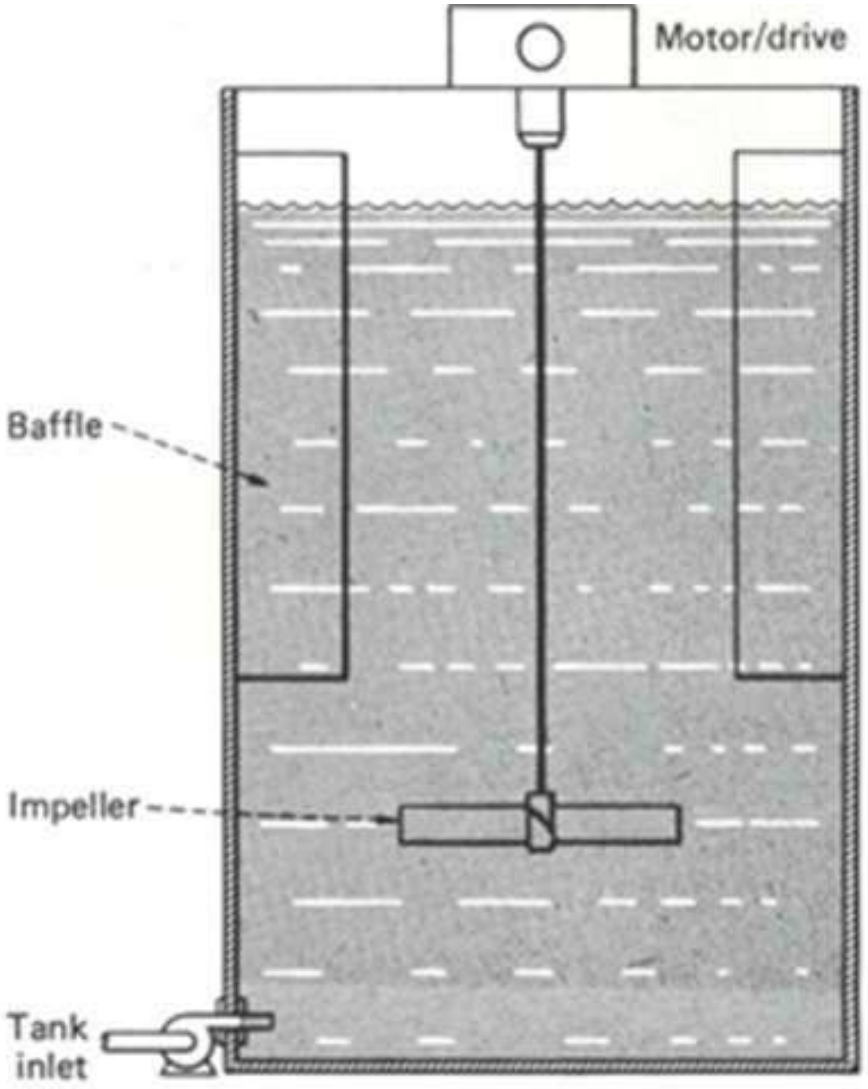
Mechanism:

- **Bulk transport:** Movement of large portion o a material from one location to another location in a give system. Rotating blades and paddles are used.
- **Turbulent mixing:** Highly effective, mixing is due to turbulent flow which results in random fluctuation of the fluid velocity at any given point within the system. Fluid velocity at a given point changes in 3 directions (X, Y and Z).
- **Laminar mixing:** Mixing of two dissimilar liquids through laminar flow, i.e., applied shear stretches the interface between them. Suitable for liquids which require moderate mixing.
- **Molecular diffusion:** Mixing at molecular level in which molecules diffuse due to thermal motion.

Mixing Apparatus for fluids

- A Container and
- A Mixing Device or

  Impeller

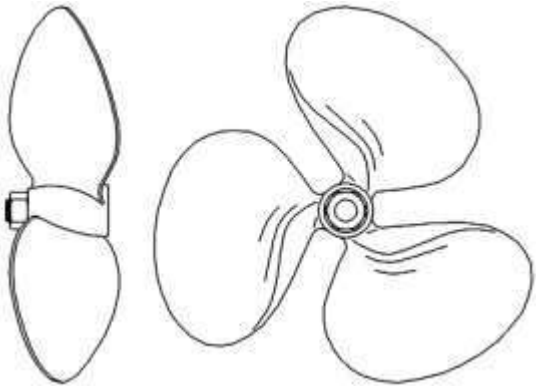


Mixing Device

- Based on shape and pitch , the are classified into 3 types,
  - »Propellers
  - »Turbines
  - »Paddles

Propellers

- It consists of number of blades, generally 3 bladed design is most common for liquids. Blades may be right or left handed depending upon the slant of their blades.
- Two are more propellers are used for deep tank.
- Size of propeller is small and may increased up to 0.5metres depending upon the size of the tank.
- Small size propellers can rotate up to 8000rpm and produce longitudinal movement.

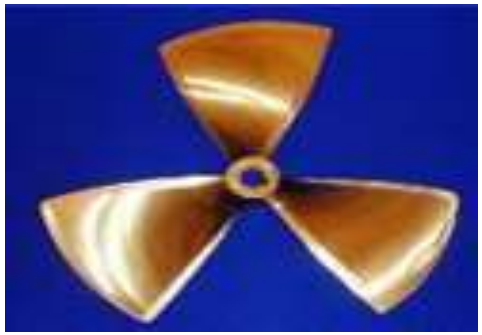


Advantages of propellers:

Used when high mixing capacity is required.

Effective for liquids which have maximum viscosity of 2.0pascals.sec or slurry up to 10% solids of fine mesh size.

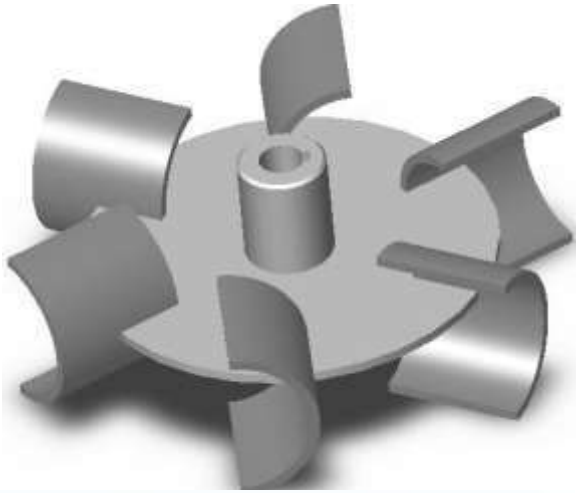
Effective gas-liquid dispersion is possible at laboratory scale.



Disadvantages of propellers:

Propellers are not normally effective with liquids of viscosity greater than 5pascal.second, such as glycerin castor oil, etc.,

Turbines



- A turbine consists of a circular disc to which a number of short blades are attached. Blades may be straight or curved.
- The diameter of the turbine ranges from 30-50% of the diameter of the vessel.
- Turbines rotates at a lower speed than the propellers (50-200rpm).
- Flat blade turbines produce radial and tangential flow but as the speed increases radial flow dominates. Pitched blade turbine produces axial flow.

Near the impeller zone of rapid currents, high turbulence and intense shear is observed. Shear produced by turbines can be further enhanced using a diffuser ring (stationary perforated ring which surrounds the turbine).

Diffuser ring increase the shear forces and liquid passes through the perforations reducing rotational swirling and vortexing.

Advantages of Turbines:

- Turbines give greater shearing forces than propellers through the pumping rate is less. Therefore suitable for emulsification.
- Effective for high viscous solutions with a wide range of viscosities up to 7.0 Pascal. Second.

- In low viscous materials of large volumes turbine create a strong currents which spread throughout the tank destroying stagnant pockets.
- They can handle slurries with 60% solids.
- Turbines are suitable for liquids of large volume and high viscosity, if the tank is baffled.

Paddles

- A paddle consists of a central hub with long flat blades attached to it vertically.
- Two blades or four blades are common. sometimes the blades are pitched and may be dished or hemispherical in shape and have a large surface area in relation to the tank in which they are used.
- Paddles rotates at a low speed of 100rpm.
- They push the liquid radially and tangentially with almost no axial action unless blades are pitched.
- In deep tanks several paddles are attached one above the other on the same shaft.
- At very low speeds it gives mild agitation in unbaffled tank but as for high speeds baffles are necessary.

Paddles are used in the manufacture of antacid suspensions, agar and pectin related purgatives, antidiarrheal mixtures such as bismuth-kaolin.

Advantages of paddles:

Vortex formation is not possible with paddle impellers because of low speed mixing.

Disadvantages of paddles:

Mixing of the suspension is poor therefore baffled tanks are required.

Factors influencing mixing of liquids in tanks

➢ Material related factors-

- Properties of liquids: physical properties of materials to be mixed. e.g.: Density, Viscosity and miscibility.

➢ Equipment related factors-

- Shape of impeller: Propeller type, straight, vertical, curved, or pitched.
- Position of impeller: Central, off-center, side entry, vertical or inclined etc.,
- Shape and size of the container: cylindrical or other geometric forms. Presence or absence of baffles.
- Cost of equipment and its maintenance.

➢ Process related factors-

- Speed of rotation of the impeller.
- Time required for mixing.
- Amount of power that can be expended.
- Ease of operation.
- Batch size.

Advantages of liquid mixing

- Liquid mixing promotes heat transfer between liquid and a heating source. This step is essential in the crystallization of drug substances. Uniform heat transfer in the solution yields crystals of same size.
- Liquid mixing is essential in the manufacture of number of dosageforms.

E.g.:

  - Suspensions
  - Emulsions
  - Solutions
  - Aerosols

C. Mixing of immiscible Liquids

Carried mainly in the manufacture of emulsions, and the equipment used for the preparation of an emulsion is known as emulsifier. Also known as homogenizer as it results in fine emulsion.

Fine emulsion is prepared in 2 stages.

In 1st stage coarse emulsion is prepared by using one of the following process:-

- Wedge wood
- Mechanical blender
- Hand homogenizer
- Porcelain mortar and pestle
- Milk shake mixer
- Propeller in a baffled tank

Some times the above equipment directly gives fine emulsion.

Otherwise coarse emulsion is subjected to homogenizer in the 2nd stage to get fine emulsion by using following process:-

- Silverson emulsifier
- Colloidal mill
- Rapisonic homogenizer

1. Quantity of emulsion to be prepared: batch wise or continuous operation
2. Flow properties of liquids: Newtonian, plastic, pseudo plastic or dilatant.
3. Temperature maintenance: mixing will be effective at high temperatures provided the material is stable.
4. Desired rate of cooling: if elevated temperatures are applied

Equipment

- Silverson emulsifier
- Colloidal mill
- Rapisonic homogenizer

Silverson mixer -Emulsifier

Principle:

- It produces intense shearing forces and turbulence by use of high speed rotors.
- Circulation of material takes place through the head by the suction produced in the inlet at the bottom of the head.
- Circulation of the material ensures rapid breakdown of the dispersed liquid into smaller globules.
- It consists of long supporting columns and a central portion. Central portion consists of a shaft which is connected to motor at one end and other to the head.
- Head carries turbine blades.
- Blades are surrounded by a mesh, which is further enclosed by a cover having openings.

Uses:

- Used for the preparation of emulsions and creams of fine particle size.

Advantages:

- Silver son mixer is available in different sizes to handle the liquids ranging from a few milli liters to several thousand liters.
- Can be used for batch operations as well as for continuous operations by incorporating into a pipeline, through which the immiscible liquids flow.

Disadvantages:

- Occasionally, there is a chance is clogging of pores of the mesh.

D. Mixing of semisolids

- Semi solids dosageforms include ointments, pastes, creams, jellies, etc., while mixing such dosageforms , the material must be brought to the agitator or the agitator must move the material throughout the mixer.
- The mixing action include combination of low speed shear, smearing, wiping, folding, stretching and compressing.
- A large amount of mechanical energy is applied to the material by moving parts. Sometimes a part of the supplied energy appears as heat.
- The forces required for efficient mixing are high and consumption of power is also high. Hence the equipment must be rugged constructed to tolerate these forces.
- Some semisolids exhibit dilatant property i.e., viscosity increases with increase in shear rates. Therefore, mixing must be done at lower speeds.
- The speed must be changed accordingly to thixotropic, plastic and pseudo plastic materials.

Classification of equipment

- Agitator mixers:

e.g.:- Sigma mixers and Planetary mixer.

- Shear mixers:

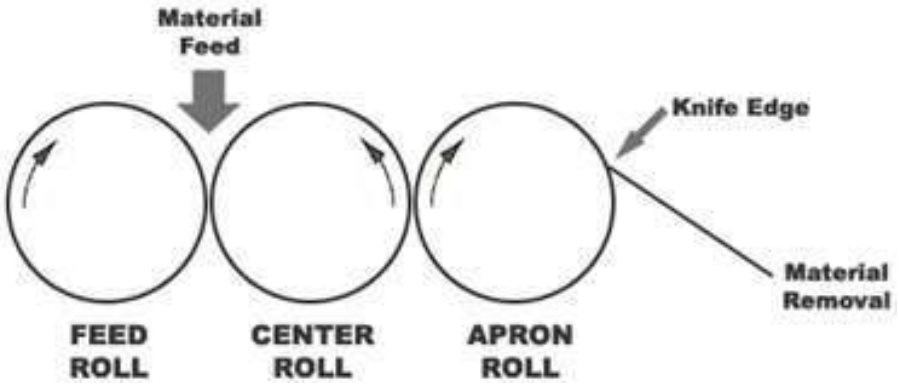
e.g.:- Triple roller mill and Colloidal mill.

Selection of mixing equipment for semi solids

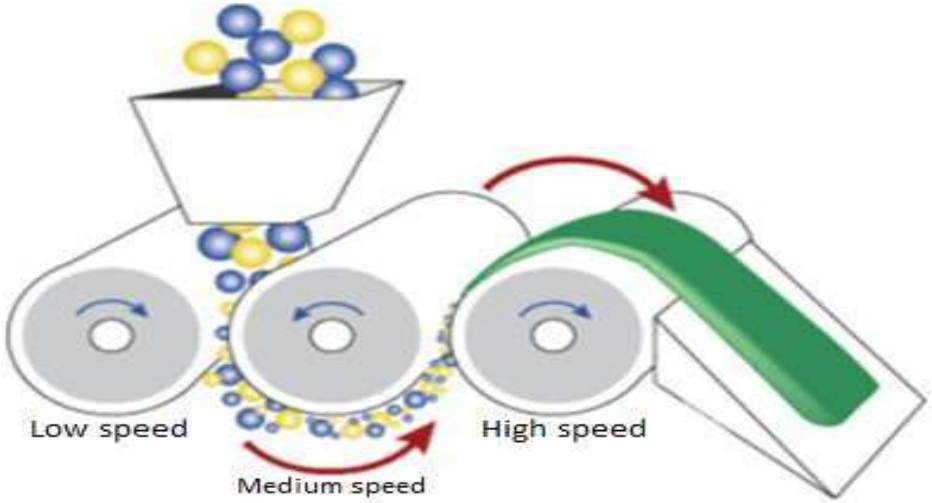
- Physical properties of the materials – density viscosity and miscibility.
- Economic considerations regarding processing – time required for mixing and power consumption.
- The cost of equipment and its maintenance.

Triple roller mill

Principle:- High shear , which causes crushing of aggregates, particles and also distributes the drug uniformly throughout the semi solid base.



- It consists of 3 parallel rollers of equal diameters made up of stainless steel.
- These are mounted on rigid frame work horizontally.
- The gap between the first 2 rollers is more than that of the gap between the last two.
- A hopper is placed in between the first two rollers.
- A scrapper is attached to the last roller.
- First roller rotates at lower speed compared to the 2nd similarly 2nd roller speed is less than the 3rd roller.



- **From the small to the large batch -** Three roll mills are ideally suited for processing the smallest and also very large quantities.
- **Excellent temperature control -** Three roll mills enable excellent control of the product temperature, since the product is processed as a thin film on the roller. This way, the product can be warmed or cooled off depending on your requirements.
- **Avoid contamination -** Through the selection of materials for the rollers and scraper knives, which are available in a broad spectrum of chrome-plated steel, aluminium oxide, zirconium oxide, and silicon carbide, it is possible to avoid product contamination due to metal abrasion.
- Extremely **uniform dispersion** is obtained.
- low material loss.
- easy cleaning.


Thank You