UNIT: III **(MIXING)**

CLASS:25

TOPIC: OBJECTIVES, APPLICATIONS AND FACTORS EFFECTING MIXING, DIFFERENCE BETWEEN SOLID AND LIQUID MIXING, MECHANISM OF MIXING

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 or assemblage with more or less thorough diffusion of the constituent elements, among one another. The term blending means to mix smoothly and inseparably together. During blending a minimum energy is imparted to the bed. These terms are commonly used interchangeably in the industry.

Some of the mixing operations in the dispensing practice are spatulation, trituration, tumbling, geometric dilution etc. However, industrial pharmaceutical mixing involves large-scale equipment. A major complication in the intimate mixing of particles is the segregation of particulate solids that results from gravitational effect on the agitated bed. Mixing can also be achieved by milling, kneading etc.

The diverse characteristics of particles, such as size, shape, volume, surface area, density, porosity, flow and charge, contribute to the solid mixing. T is difficult to predict, the inter-particle interactions. There fore. Some empirical correlations are possible. In practice, optimum mixing is considered satisfactory.

Depending on their flow properties, solids are divided into two classes; cohesive and non-cohesive. *Non-cohesive materials* such as grain, dry sand and plasti chips readily flow out of a bin or soil. Cohesive materials such as wet clay are characterised by their resistance to flow through openings.

There are significant differences between solid mixing and liquid These are given below

Liquid mixing	*Solid mixing*
Flow currents are responsible for transporting unmixed material to the mixing zone adjacent to impeller.	Flow currents are not possible.
Truly homogeneous liquid phase can be observed.	Product often consists of two or more easily identifiable phases.
Small sample size is sufficient to study degree of mixing.	Large sample size is required.
Mixing requires low power.	Mixing requires high power.

Liquid mixing	Solid mixing
(i) Fluid mixing is generally associated with liquid-liquid mixing and liquid gas mixing.	(i) Mixing of solids to some extent resembles the mixing of low-viscosity liquids.
(ii) Liquid mixing depends on the creation of flow currents, which transport unmixed material to the mixing zone adjacent to the impeller.	(ii) In heavy masses of particulate solids there are no such currents possible and mixing is accomplished by some other means.
(iii) Power required for mixing and the blending of liquids is less.	(iii) Power required for mixing of dry solids is comparatively higher.
(iv) In liquid mixing, a well-mixed product is usually a truly homogenous liquid phase.	(iv) In solid mixing the product often consists of two or more easily identifiable phases, each of which may contain individual particles of considerable size.
(v) A "well-mixed" liquid product samples are homogenous in nature.	(v) A "well-mixed" solid product samples differ markedly in composition.
(vi) Design, construction, and operation of fluid mixing equipment are specific and are termed as liquid agitators.	(vi) Design, construction, and operation of solid mixing equipment are different than liquids and are commonly referred to as mixers and blenders.
(vii) The liquid mixing technology has been extensively studied and understood.	(vii) The understanding of solid mixing, and the design of solid mixers is an art rather than a science.
(viii) The liquid mixing technology is simple.	viii) Solid mixing is more complex.

Objectives of mixing in Pharmacy

The aim of mixing is to ensure that there is uniformity of composition between the mixed ingredients that represent the overall composition of the mixture. The primary objective of mixing is to make a homogeneous product using the minimum amount of energy and time.

The other objectives are as follows:

(i) To produce a single physical mixture

This may be simply the production of a blend of two or more miscible liquids or two or more uniformly divided solids. In pharmaceutical practice, the degree of mixing must commonly be of a high order as many of such mixtures are dilutions of active substances and must be in accurate amount for dose uniformity in dosage forms.

(ii) To produce physical change: Mixing can be performed to produce physical as well as chemical change, for example, solution of a soluble substance. In such cases, a the lower efficiency of mixing is often acceptable because mixing merely accelerates a dissolution and diffusion process that could occur by simply agitation.

(iii) To produce dispersion:

Mixing is also aimed to include the dispersion of two immiscible liquids to form an emulsion or dispersion of a solid in liquid to give a suspension or paste. Usually, good mixing is required to ensure stability and effectiveness.

(iv) To promote chemical reaction

Mixing encourages and at the same time control a chemical reaction. Mixing ensures a uniform product such as reactions where accurate adjustment to pH is required and the degree of mixing will decide the possibility of reaction.

Mixing fulfils many objectives beyond a simple combination of raw ingredients. These include preparing fine emulsions, reducing particle size, carrying out chemical reactions, manipulating rheology, dissolving components, facilitating heat transfer, etc. So even within a single pharmaceutical product line, it is a common practice to employ a number of different style mixers to process raw ingredients, handle intermediates and prepare the finished product.

Applications

Mixing is one of the most common pharmaceutical operations. It is involved in the preparation of many types of formulations. Mixing 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 (insufflations).
- Production of pellets for capsules.

In the manufacture of tablets, normally a number of additives arc added. Therefore mixing of powders becomes an essential part of the process. When the dose of the active substance is high (for ex ample paracetamol tablets) mixing is not a problem. But in case of potent drugs and low dose drugs, high amounts of adjuvants (for example lactose) are added. Therefore, mixing is considered as a critical factor. Otherwise, content uniformity of tablets does not confirm to the pharmacopeial specifications. Similarly, weight variation increases.

Mixing of cohesive materials is even more difficult due to formation of aggregates and lumps. Wet mixing is also encountered in pharmacy as an individual operation or as a subsequent step after dry blending. In several situations, these operations are carried out in a vessel and by some mixing element. Hence, this section describes some aspects of theoretical considerations and equipment for dry as well as wet mixing.

INTERPARTICLE INTERACTIONS-SEGREGATION

The particle characteristics such as size, Size distribution, shape and Surface influence the interparticle interactions in a powder bed.

Inertial Forces

Inertial forces tend to hold neighbouring particles in a fixed relative position. These are van der Waals, electrostatic and surface forces. A special mention of surface forces is relevant.

Surface (or interface) forces: The cohesive forces prevent intimate mixing owing to interaction of their surfaces (or interfaces). Frictional Forces also resist the movement of particles so that they tend to form lumps. These depend on surface area, surface roughness, surface polarity. Surface charge and adsorbed substances' such as moisture. During mixing, 1he particles develop surface charges. Surface charges produce particle-particle repulsions. Which make random mixing impossible. For effective mixing, surface to surface interactions should be minimal, which can be achieved by surface treatment.

Segregation occurs due to the following reasons.

1. Poor flow properties of the powder bed inside a blender.
2. Wide differences in particle sizes in a dry mixture.
3. Differences in the mobilities of individual. Ingredients.
4. Differences in particle density and shape to a lesser extent.
5. Transporting stage, pouring the powder from one container to another (hopper or drums), or emptying the container.
6. Dusting stage, fine particles become air borne and separate from bulk of the powder.

Segregation may occur even after the mixing.

Gravitational Forces

Gravitational forces tend to improve the movement of two adjacent particles or groups of particles. Tumbling action promotes the. Inter particulate movement due to gravitational forces.

Motion of particles can result from direct contact with the mixer surface or/and from contact with one another. These processes accelerate the movement of translational and rotational modes of single particle or groups of particles. When particle-particle collisions occur, exchange (transfer) of momentum is achieved. Continuous exchange or distribution of momentum between translational and rotational modes is necessary for effective mixing. The efficiency of momentum transfer depends on:

1. Elasticity of the collisions---1f collisions are elastic, effective transfer of momentum does not take place. The loss due to Inelasticity should be minimal.
2. Coefficient of friction---Particles with high coefficient of friction will be likely to exchange rotational momentum more readily.
3. Surface arca of contact-The larger the surface area of contact, greater the exchange of momentum.
4. Surface roughness-The surface 'roughness' of the particles in- volved in collisions determines the distribution of the transferred momentum between translational and rotational modes.
5. Centrifugal forces---These act on rotating aggregates to break them into smaller units and aid in mixing process.

MECHANISMS OF MIXING IN SOLIDS

Segregation of particles occurs due to a number of reasons. Mixing can prevent it. The principal mechanisms in solid-solid mixing are:

Convective Mixing

It is achieved by the inversion of the powder bed using blades or paddles or screw element.

A large mass of material moves from one part to another. Convective mixing is referred to as *macromixing.*

Shear Mixing

In this type, the forces of attraction arc broken down so that each particle moves on its own between regions of different composition and parallel to their surfaces

In a particulate mass, the forces of attraction are predominating. Which make the layers slip over one another. Such types of attraction forces are predominant among same type of particles. Shear forces reduce these attractions and reduce the scale of segregation

Diffusive Mixing

It involves the random motion of. Particles within the powder bed. Thereby particles change their positions relative to one another.

Diffusive mixing occurs at the interfaces of dissimilar regions. Diffusion is sometimes referred to as *micro mixing*.

The motion of particles to achieve random distribution assumes that no other factor influences the distribution. This is rarely the case. Instead. A number of properties of the powders influence the approach to randomness. Flow characteristics of powders largely determine the ease with which the primary particles can be mixed.

MIXING PROCESS-STEPS

In the solid-solid mixing operation four steps are involved. These are:

1. Expansion of the bed of solids
2. Application of three-dimensional shear forces to the powder bed.
3. Mix long enough to permit true randomization of particles.
4. Maintain randomization (no segregation after mixing).

When dry materials are loaded into a mixer. They, form a static bed. This bed expands sufficiently. When mixing is initiated. Therefore, there should be enough void space in the mixer after it is charged with the ingredients.

The shear force produces movement of particles. This is accompanied by expansion of powder bed. The stress induces the movement of particles in three directions. This turbulent movement of particles can achieve randomization. If the forces are inadequate, particle agglomerates move together leading to poor mixing.

Mixing is expected to produce random distribution of particles. It depends on the probability that an event happens in a given time. The law of mixing appears to follow a first order.

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

Where M = degree of mixing after time

T = time, min

A and k = constants

The constants a and k depend on the mixer geometry, physical characteristics of the powders and proportion of the material being mixed. Initially the rate of mixing is rapid. At a later stage the rate decreases. Since the rate process is first order (asymptotic), perfect mixing is not attainable. i.e., it takes infinite time. Empirically the best mixing time would be 30 to 3S minutes. Once the desired mixture has been achieved, the process should be stopped.

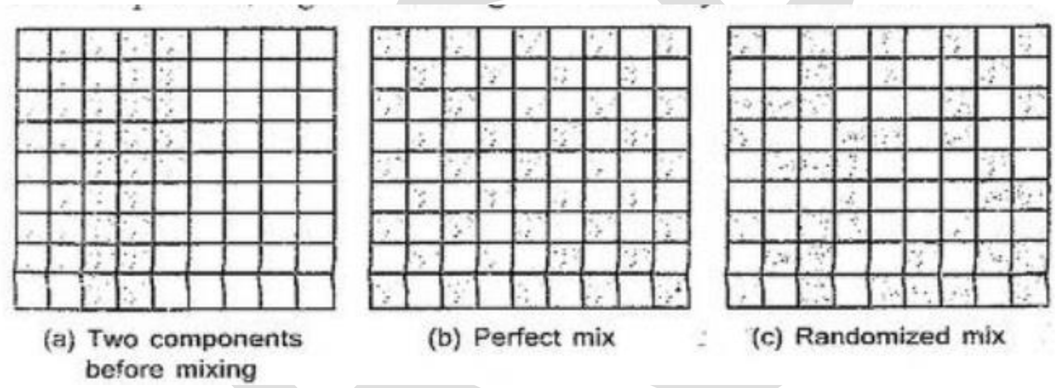
Once mixing is stopped, the blend should exist in static equilibrium. Subsequent handling of the mixture should be so as not to disturb the static equilibrium.

DEGREE OF MIXING AND STATISTICAL EVALUATION

Degree of mixing is also known as degree of homogeneity. After mixing, the best possible degree of mixing can be achieved provided each particle moves freely to every spot of the equipment. It requires the movement of particles in three directions. The degree of mixing must be considered for the purpose of economics. Time of mixing should be long enough to obtain an acceptable randomisation.

Ideal Mixing or Perfect Mixing

As illustrated by equation (1), the mixing process will never yield an ideal or perfect mixture. Ideal degree of mixing is represented schematically in Figure a by a chessboard with black and white squares representing two components (equal quantities). It indicates that each particle of one component is lying nearly adjacent to a particle of another component. In practice, degree of mixing is indicated by its standard deviation.



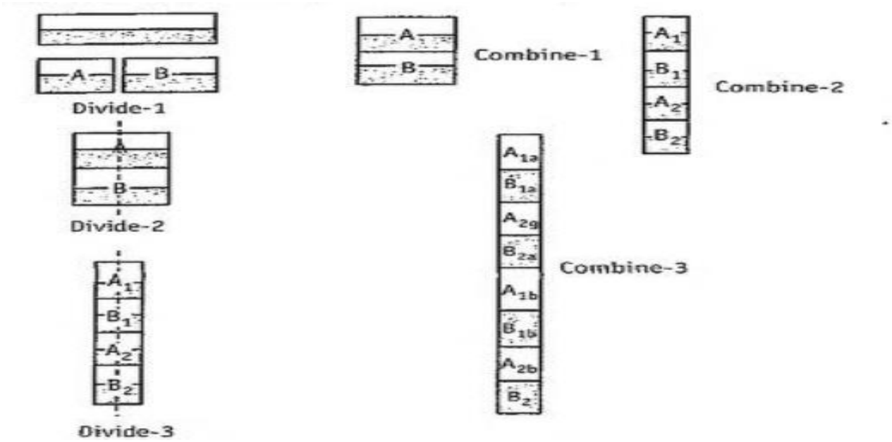
Types of binary mixtures.

Acceptable Mixing

Since perfect mixing cannot be achieved, other alternatives for obtaining an acceptable mix must be considered.

Random mixing: It is indicated by random distribution of particles as shown in Figure b. Random mixing means same ratio of components in. the entire mixture. Artificial randomization in the Figure b is based on random numbers in statistical Tables. However, it should be noted that the use of random motion to achieve random distribution assumes that no other factor influences the distribution. This is rarely the case. Instead, a number of properties of the powders being mixed influence this approach to randomness

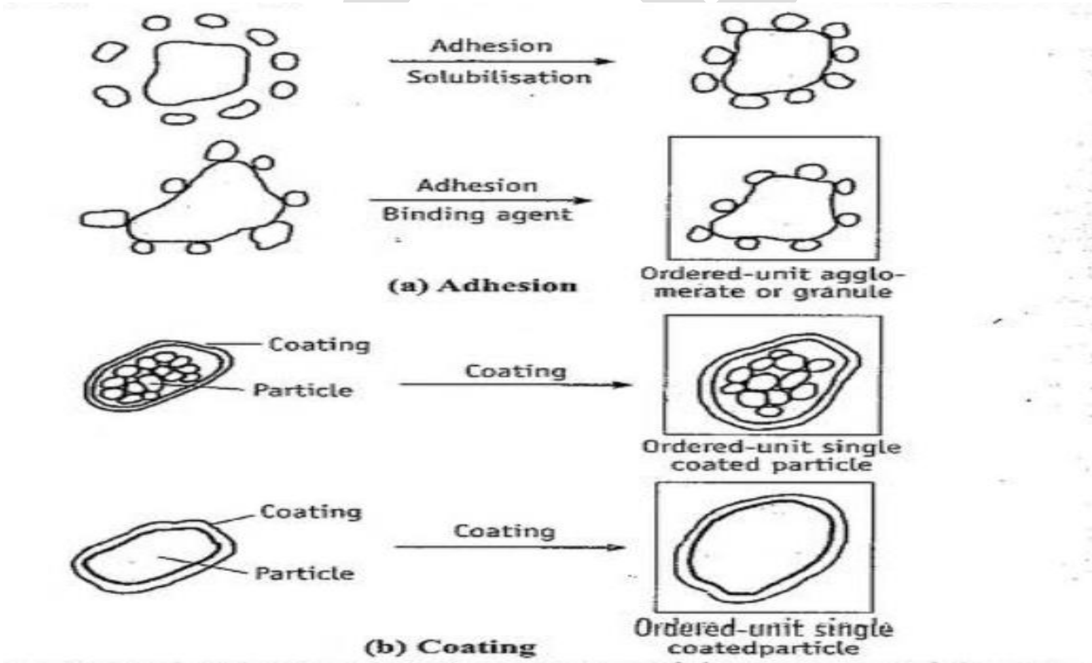
Ordered mixing Ordered mixing is described as the use of mechanical, adhesional and coating forces. Ordered units in the mix should be such that ordered unit will be the smallest possible sample to the mix. It will be nearly identical in composition to all other ordered units in the mix.



Ordered mechanical mixing.

Ordered mixing probably yields the closest situation of the perfect mix. This can be achieved by a number of ways.

(1) **Mechanical means of ordered mixing**: The mass of each ingredient is divided and recombined a number of times in the powdered bed (Figure). The smaller the units, the more uniform the mix. Since no particulate adhesion is present, segregation of the mix easily takes place on further hand



Ordered mixing based on the principles of (a) adhesion and (b) coating.

(2) **Adhesion means of ordered mixing**: These forces of particles may create ordered units of nearly identical composition depending on the process (Figure a). Partial solubilisation or the use of a binding agent during wet granulation approximates the same effect as shown in Figure a.
(3) **Coating means of ordered mixing**: Particles in an assemblage may also be coaled with other ingredients to give an ordered mix either as individual or coated particle agglomerates (Figure b).

Ideally, the degree of mixing begins rapidly up to a particular level and slows down gradually. Uniform degree of mixing can be resulted by continuing mixing for. Some more time. The practical definition of mixing uniformity is selected to relate as closely as ‘possible to the desired properties of the mix. The sampling technique largely deter- mines the validity and interpretation of the derived mix.

Statistical Parameters

The analysis of samples before and after mixing provides information about the degree of mixing. Solid mixing with some kind of tracer material is used for easy analysis. Some important methods of analysis are the particle size distribution and the assay procedures for different ingredients in the sample.

Arithmetic mean: The mean (assay value or size distribution analysis) value of a group of random samples is a measure of the central tendency of the batch population. The arithmetic mean is expressed as:

$$\text{Arithmetic mean, } \bar{Y} = \sum_{i}^{n} \frac{y_i}{n} \qquad (2)$$

Taking a number of samples (n), the true men. Y, is estimated. Mean may be attributed to concentration of a component or particle size of a particular component.

Standard deviation: The spread of dispersion of individual samples is important, because it is impracticable to obtain the same true mean for the same product mix obtained by another lot or by another mixer. Therefore, standard deviation is used. It is expressed as:

$$\text{Standard deviation, } \sigma = \sqrt{\frac{\sum_{i}^{n}(y_i - \bar{Y})^2}{(n-1)}} \qquad (3)$$

Variance, which is a square term of standard deviation, can also be used for characterisation of powder mix. Standard deviation is applicable for a specific material and a specific mixer.

Mixing of pharmaceutical powders, should be continued until the amount of the active drug that is required in a dose is within $\pm$ 3 SD units of that found by assay in a representative number of sample doses. To achieve this objective, n should be large. This is possible by milling the ingredients to fineness.

Relative standard deviation: One may follow the mixing operation in a given process by plotting the standard deviations as a function of time. The relative standard deviation (RSD) should replace the standard deviation as a measure of sample uniformity, which is expressed as:

$$\text{Percent relative standard standard deviation (RSD)} = \frac{standard\ deviation\ (\sigma)}{mean\ (y)} \times 100 \qquad (4)$$

Equation (4) is useful for comparing the efficiency of two or more mixing operations or different sample sizes or different compositions.

Mixing Indices

The selection of a mixer depends on the mixing index or degree of mixing. The above-mentioned statistical parameters are useful for evaluating the mixing indices.

Mixing index involves the comparison of standard deviation of sample of a mixture under study with the estimated standard deviation of a, completely random mixture.

Mixing index is expressed by Lacey.

$$\text{Mixing index, M} = \frac{standard\ deviation\ of\ random\ blend}{standard\ deviation\ of\ the\ sample\ blend} = \frac{\sigma_R}{\sigma} \qquad (5)$$

$$\text{Mixing index, } M = \frac{\sigma_0 - \sigma}{\sigma_0 - \sigma_R} \qquad (6)$$

Where σ_0 = standard deviation of unmixed powder.

The ratio will be less than I. The higher the M value, the greater the homogeneity. Equations (5) and (6) are used to determine homogeneity in a mixture depending on the objectives at hand. The selection of a particular equation is essential when the mechanism of mixing is being Results of practical use can be achieved by using statistical analysis.

The differences may indicate poor or inadequate sampling, inappropriate mixing operation, improper handling of the powder sample, unsuitability of the mixer, operational conditions etc

Before mixing has begun, the material in the mixer exists in two layers, one of which contains no tracer material and one of which is tracer only. Under these conditions, the standard deviation at zero time (σ_0) may be expressed as

$$\sigma_0 = \sqrt{a\,(1-a)} \qquad (7)$$

Where a = overall fraction of tracer in the mixture.

Statistical Evaluation

Mixer selection depends on the degree of mixing of the powder in the final product. The procedure involves sampling and analysis. The sequence of steps involved in the evaluation of the degree of mixing or degree of homogeneity is given in the Table.

The objectives have been specified in the Table. The sampling technique largely determines the validity and interpretation of the derived mix.

Criteria of sampling: While sampling a bed of powder, there should be assurance that the bed is sampled uniformly. It is assumed that the powder bed consists of a number of zones. Within each zone the composition is uniform, bat among zones, the composition is different Therefore Method of sampling is very important. For this purpose, two concepts are important.

Scale of segregation: It is a function of size of the zone. It assumes that zones are having uniform bed, but differing in composition. Good mixing should yield a greater number of zones with small size. Then, the sample reflects the true character of the powder bed.

Intensity of segregation: It is a function of composition differences among zones. Generally, the process of mixing tends to reduce the intensity of segregation.

Sample size guidelines: The number of samples required should be not less than 20. Preferably 30 and more ideally 100. Analysis »f these samples is time consuming and tedious. Therefore, economic considerations suggest 20 samples.,

Random sampling is the method of choice for studies. Sample size. In most cases, should approximate the unit dose size of the final product.

Collection of samples: Some golden rules of sampling are:

1. A powder should be sampled when it is in motion.
2. The whole of the stream of powder should be taken for many short increments of time in preference to a part of the stream taken for the whole time.

3. Sampling after completion of the mixing.

Statistical Evaluation Procedure for the Blending or Mixing of Powders

---

Objectives

1. To compare the efficiency of two or more mixing operations.
2. To compare the efficiency of two or more equipment.
3. To follow the mixing process with time.
4. To optimise processing parameters.
5. To investigate the mechanism of mixing in a given piece of equipment.

Sample size guidelines: (a) Random sampling (b) Number of samples

Number of samples: Required- 30;

Ideal- 100;

Economical sampling—20 (preferred).

Sample size – approximately a unit dose of the final product.

Sample collection: (a) At different intervals when the blend is in motion.

(b) After blending is completed (preferred).

Sampling methods: (a) Scooping sampling

(b) Thief probing (preferred)

Sample utilization: (a) Returning the sample to the bulk, for example, after completion of particle size analysis (non- Destructive evaluation).

(b) Not returning the sample to the bulk, for example, due to solubilisation for assay procedure (destructive method).

Statistical Analysis

- Determination of arithmetic mean and standard deviation of the randomly mixed sample (standard).
- Determination of arithmetic mean and standard deviation of the un- mixed blend of sample (initial stage).
- Determination of arithmetic mean and standard deviation of the sample after blending (test sample).
- Comparing mean values (sample) with target value (true mean).
- If they are comparable, standard deviation should be calculated (indicates uniformity of the sample): High standard deviation indicates less uniformity.
- Determination of mixing indices
- Scattering of sample about mean or standard deviation (plot of standard Deviation vs. time).
- Accuracy and precision assessments of these estimates.

Sometimes, powder sample cannot be sampled from a moving stream, because:

(1) configuration of the mixer- for example the shape of the bowl does not lend itself to dumping.

(2) size of the batch large volumes is not conducive to routine transfer from the blender to drum or larger collectors.

(3) possibility of mixture segregation biasing the sample. Therefore, it is always preferable to collect the sample once mixing is completed.

Method of collecting samples: Samples should be collected at selected points or serially as the powder is discharged from the mixer. Two types of sampling methods are adopted.

(1) Scoop sampling of the bulk mixture
(2) Thief probing of the bulk mixture

Scoop sample: This method has some drawbacks. (A) Surface layer sample may represent segregated mixture (B) Samples cannot be removed from the bottom and middle of the blender or container.

Thief probe: This method has some drawbacks. (i) During sampling, some compaction takes place around the thief. (ii) As the thief is inserted in the powder bed, it carries material from the surface of the mixture down into the mixture.

Thief probe is preferred over the scoop, because samples can be taken from deep within the, powder bed and a fair degree of random sampling can be achieved.

Sample utilization: If the method of analysis is non-destructive, for example, particle size analysis, the sample can be returned to the mixture after analysis. If the method is destructive, for example assay, the sample cannot be returned.

Analysis of data: Several statistical parameters and mixing indices are calculated. The comparison of the mean value of the sample under analysis and the target value. If the mean value of the sample under analysis is on or near the target value, calculation of the standard deviation (and or variance) will give an indication of the uniformity of the sample. Other details are given in the Table

FACTORS INFLUENCING MIXING

Particle and powder characteristics influence the mixing process. Aggregation inhibits proper mixing. Therefore, higher shearing forces are applied. Hence, correct mixing of one component does not imply good mixing of other components. Therefore, Adding dye to the mixture is often misleading. The dye may not aggregate. But active substance may aggregate.

A single factor can in no way be considered as a unique indication of mixing. However, flow properties of the components is the most important consideration which is again influenced by a number of factors

Nature of the, surface: rough surface of one of the components docs not in use satisfactory mixing. This can be due to the entry of active substance into the pores of the other ingredients.

Adding a substance, which will be adsorbed on its surface, can decrease aggregation. Example is the addition of aerosol (colloidal silicon dioxide) to zinc oxide. Thus, a strongly aggregating zinc oxide becomes a fine dusting powder. Which can be mixed easily.

Density of the particles: It is of minor importance. De-mixing is accelerated when the density of the smaller particles is higher or when the mixing process is stopped abruptly. This is due to the fact that dense material always moves downward and settles at the bottom.

Particle size: It is easy to mix two powders having approximately the same particle size. The variation of particle size can lead to separation, because the small particles move downward through the spaces between the bigger particles. As the particle size increases, flow properties also increase due to the influence of gravitational force on the size. Beyond a particular point, flow property decreases. The powders with a mean particle size of less than 100 µm are free flowing, which facilitates mixing.

Particle Shape: The ideal particle is spherical in shape for the purpose of uniform mixing. The irregular shapes can become inter. Locked and there are less chances of separation of particles once these are mixed together.

Particle charge: Some particles exert attractive forces due to electrostatic charges on them. This can lead to separation or segregation.

Proportion of materials: The best results can be obtained if two powders are mixed in equal proportion by weight and by volume. If there is a large difference in the proportion of two powders, mixing is always done in the ascending order of their weights.

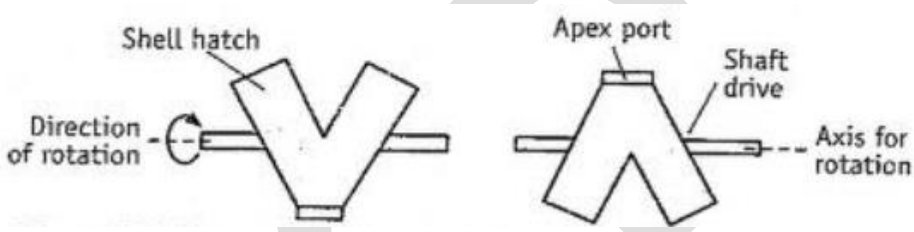
UNIT: III **(MIXING)**

CLASS:26

TOPIC: PRINCIPAL, CONSTRUCTION, WORKING, USES, MERITS AND DEMERITS OF TWIN SHELL BLENDER, DOUBLE CONE BLENDER, RIBBON BLENDER

TWIN SHELL BLENDER OR V CONE BLENDER

The construction of a twin shell blender is shown in Figure. It is made of either stainless steel or transparent plastic. Smaller models take a charge of 20 kg and rotate at 35 revolutions per minute, while larger ones take a charge of about 1 tonne and rotate at l5 revolutions per minute. The material is loaded through either of the shell hatches. Emptying of the blend is normally done through an apex port.



V cone blender. Rotating shell without baffles.

The material (to be blended), is loaded approximately 50 to 60 % of its total volume. As the blender rotates, the material undergoes tumbling motion. When the V is inverted, the material splits into two portions. This process of dividing and recombining continuously yields ordered mixing by mechanical means. The powder mass Is converted shock-wise, so that no de-mixing due to density differences will occur. It is rotated so that the material alternatively is collected in the bottom of the V

Blender speed is the key for mixing efficiency At high speeds. More dusting or segregation of fines is possible. While at low speeds. Not enough shear may be applied.

Advantages:

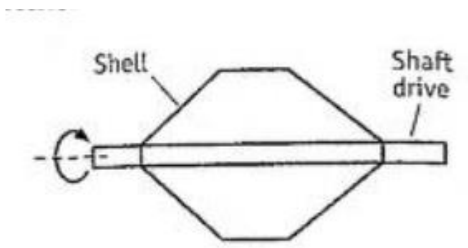
1. If fragile granules are to be blended, twin shell blender is suitable because of minimum attrition.
2. They handle large capacities
3. Easy to clean. Load and unload.
4. This equipment requires minimum maintenance.

Disadvantages

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

DOUBLE CONE BLENDER

The construction of a double cone blender is shown in Figure. It is usually charged and discharged through the same port. It is an efficient design for mixing powders of different densities. These are used mostly for small amounts of powders. The rate of rotation should be optimum depending on the size and shape of the tumbler, nature of material to be mixed. Commonly the range is 30 to 100 revolutions per minute. The method remains same as that of the V-cone blender.



Double cone blender. Rotating shell without baffles.

The advantages and disadvantages for double cone blender are same as given in Twin shell blender (or V cone blender).

TUMBLING BLENDERS WITH AGITATOR MIXING BLADE

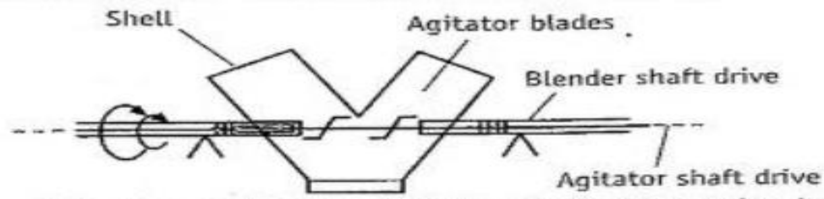
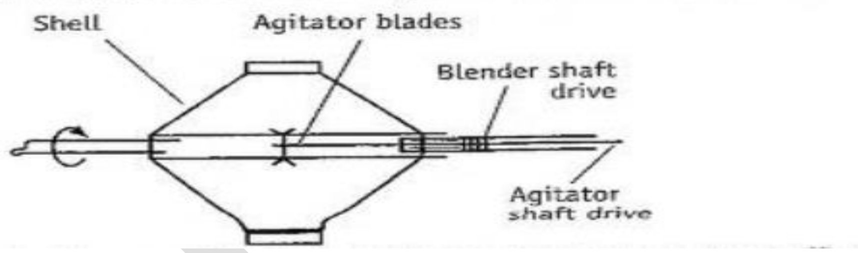


Figure 9-9. V cone blender. Rotating shell with rotating baffles.



Double cone blender. Rotating shell with rotating baffles

The V-cone blender and double cone blender with agitator blade (baffles) are shown in Figures The general construction and working is same as mentioned above. Agitator blades are added which have several advantages.

Advantages:

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

Disadvantages:

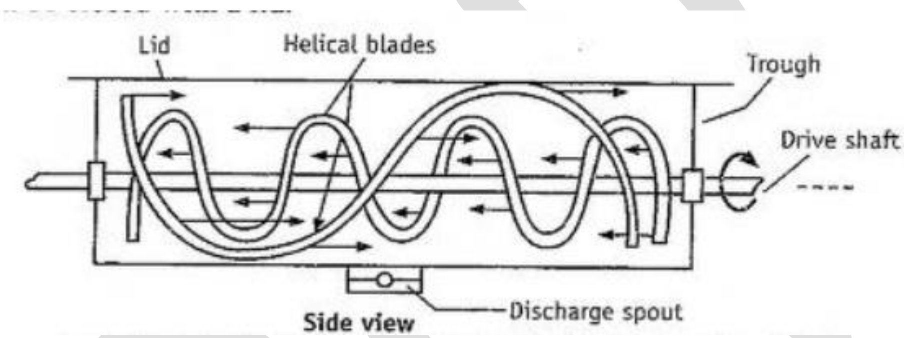
1. Attrition is large. Size reduction of friable particles results.
2. Scale-up can prove a problem, because general principles off Scale up do not work.

3. Cleaning may be a problem, because the agitator assembly must be removed and the packing should be replaced for a product changeover
4. Potential packing (sealing) problems.

RIBBON BLENDER

Principle: The mechanism of mixing is shear. Shear is transferred to the powder bed by moving blades (ribbon shaped) in a fixed (non- movable) shell. High shear rates are effective in breaking lumps and aggregates. Convective mixing also occurs as the powder bed is listed. And allowed to cascade to the bottom of the container. An equilibrium state of mixing can be achieved.

Construction: The construction of a ribbon blender is shown in Figure. It consists of a non-movable horizontal cylindrical trough (shell) 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. The blades have both right and left hand twists. The blades arc connected to a fixed speed drive. Ribbon blender is top loading with a bottom discharge port. The trough can be closed with a lid.



Ribbon mixer. Stationary shell and rotating blades.

Working: Through the fixed speed drive, ribbons are allowed to rotate. One blade moves the solids slowly in one direction and the other moves them quickly in opposite direction. Different powders are introduced from the top of the trough. The body is covered because considerable dust may be evolved during dry blending and granulating solution may evaporate during wet granulation.

The powders are lifted by a centrally located vertical screw. And allowed to cascade to the bottom of the container (tumbling action). The counteracting blades set up high shear and arc effective in breaking up lumps or aggregates. Helical blades move the powders. From one end to another as shown in Figure 8-9. The final stage of mix represents an equilibrium state. The: operating conditions of a given mixer can markedly affect the steady state and thus the quality of the mixing. The blend is discharged from the bottom opening.

Uses: Ribbon blender is used to mix finely divided solids, wet solid mass, sticky and plastic solids. Uniform size and density material can be easily mixed. It is used for liquid-solid and solid-solid mixing.

Advantages: High shear can be applied by using perforated baffles, high bring about a rubbing and break down aggregates. Headroom requirement is less.

Disadvantages:

1. It is a poor mixer, because movement of particles is two-dimensional.
2. Shearing action is less than in planetary mixer.
3. Dead spots (areas that remain unmixed) are observed in the miser. Though they are minimum.
4. It is having fixed speed drive.

UNIT: III **(MIXING)**

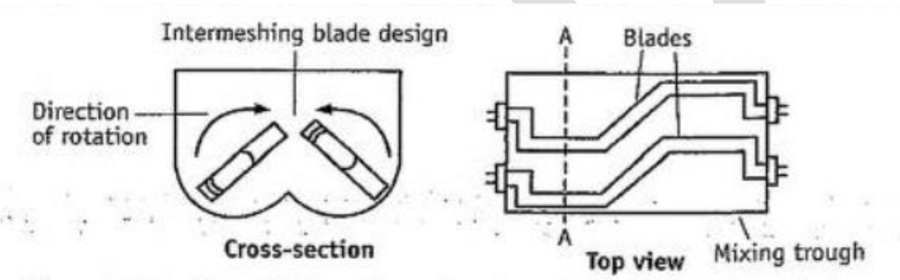
CLASS:27

TOPIC: PRINCIPAL, CONSTRUCTION, WORKING, USES, MERITS AND DEMERITS OF SIGMA BLADE MIXERS, PLANATERY MIXERS

SIGMA BLADE MIXER

Principle: The mechanism of mixing is shearing. The inter-meshing of sigma shaped blades creates high shear and kneading actions. Convective mining is achieved by cascading the material.

Construction: The construction of a sigma blade blender is shown in Figure It consists of double trough shaped stationary bowl. Two sigma (indicating the shape of the Greek letter) shaped blades are fitted horizontally in each trough of, the bowl. These are connected to a fixed speed drive. The mixer is loaded from the top and unloaded by tilting the entire bowl by means of a rack-and-pinion drive.



Sigma blade mixer. Stationary shell and rotating blades.

Working: Different powders are introduced from the top of the trough. The body is covered because considerable dust may be evolved during dry blending and granulating solution may evaporate during wet granulation.

Through the fixed speed drive. The sigma blades are allowed to rotate. The blades move at different speeds. One usually about twice the speed of other, resulting in lateral pulling of the material. They turn towards each other so that the powders move from the sides to the centre of the bowl. The material further moves from the top to downwards over the point and then sheared between the blades and the wall of the trough. Thus, cascading action (convective) as well as shear action can be achieved. The perforated blades help in breaking lumps and aggregates. Thus, high shear forces are set up. The final stage of mix represents an equilibrium state. The operating conditions of a given mixer can markedly affect the steady state and thus the quality of the mixing. By means of a rack-and-pinion drive the bowl is tilted to empty the blend.

Uses: Sigma blade mixer is commonly used for mixing of dough ingredients in the baking industry. It is used in 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:

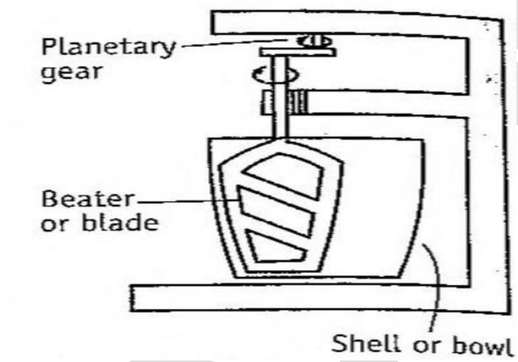
1. Sigma blade mixer creates a minimum dead space during mixing
2. At has close tolerances between the blades and the side-walls as, well as bottom of the mixer shell.

3. **Disadvantage**: Sigma blade mixer works at a fixed speed.

PLANETARY MIXER

Principle: In a planetary mixer. The blade tears the mass apart and shear, is applied between a moving blade and a stationary wall. The missing arm moves in two ways, around its own axis and around. The central axis, so that it reaches every spot of the vessel. The plates in the blade are sloped so that the powder makes an upward movement. Therefore: tumbling (convective). Motion is also obtained.

Construction: The construction of a planetary mixer is shown in figure. It consists of a vertical cylindrical shell, which can be removed ither by lowering it beneath the blade or raising the blade above the bowl. The mixing blade is mounted from the top of the bowl. The mixing shaft is driven by a planetary gear train. As indicated in the Figure. It rotates around the ring gear, which further rotates round the mixer blade. It is normally built with a variable speed drive.



planetary mixer

Working: In the planetary mixer. The agitator has a planetary motion. It rotates on its own, and around the central axis so that it reaches all parts of the vessel. Beater is shaped to pass with close clearance over the side and bottom of the mixing bowl. Therefore, literally there are no dead spaces in the mixing bowl. The blade tears the mass apart and. Shear is applied between the moving blade and the stationary wall. The plates in the blade are sloped so that the. Powder makes an upward movement. Therefore. Tumbling (convective) motion -is also obtained. Since it is a variable speed driven. Initially the blade moves slowly for premixing and finally at increased speed for active mixing. Thus, high shear can be applied for mixing. Emptying he bowl may be done by hand (scooping) or by dumping mechanism.

Uses: Planetary mixer produces precise blends in addition to breaking down of agglomerates rapidly. Low speeds are used for dry blending and faster speeds for the kneading action required in wet granulation. Steam jacketed bowls are used in. the manufacture of sustained release products and ointments.

Advantages: Speed of the rotation can be varied at will. So, it is advantageous over sigma blade or ribbon type blenders. This is more useful for wet granulation process. There are no packing glands in contact with the product.

Disadvantages:

(1) Mechanical heat is built up within the powder mix.
(2) It requires high power.
(3) It has limited size and is useful for batch work only

UNIT: III **(MIXING)**

CLASS:27

TOPIC: LIQUID MIXING AND SEMISOLIDS MIXING, PROPELLERS, TURBINES, PADDLES & SILVERSON EMULSIFIER

MIXING OF LIQUIDS

Liquid-liquid mixing is considered as a simple operation compared to that of solid-liquid mixing. At involves the formation of a homogeneous system. Similar to solid-solid mixing, fluid (or liquid) mixing also involves the application of shear. Agitation and mixing are not synonymous.

Agitation refers to the induced motion of a material in a specified way. Usually in a circulatory pattern. Inside a container.

Mixing refers to the random distribution into or through one another of two or more separate phases

The nature of liquids mainly determines the ease of mixing According to theories of solutions, liquid mixtures are classified as follows.,

1. **Miscible liquids** These are miscible in all proportions. For example, ethyl alcohol and water. Are miscible in all proportions. These liquids can be mixed easily by employing the mechanisms of bulk transport and shear. Cosmetics (after-shave lotion). Elixirs etc., belong to this class.

2. **Partially miscible liquids**: These are miscible in. one-another at one particular proportion. Their miscibility depends on temperature and pressure: For example, p-cresol and water. are miscible in a certain proportion. Mixing poses certain difficulties in the preparation of disinfectant solutions.

3. Immiscible liquids: As the name indicates, these are not miscible. For example, vegetable oils and water are not miscible or their miscibility is very- low. Normally, they form emulsions. Mixing of these liquids is very difficult. A homogeneous dispersion may b obtained by adding emulsifying agents. Mixing them requires high shear.

The mixing of immiscible liquids is discussed as a separate section. In pharmacy, one of the liquids normally used is water. A number of solid and liquid ingredients are added in the formulation of dosage forms. Based on the shear stress-shear rate relationship, fluids are classified as Newtonian and non-Newtonian systems.

Applications 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. For example, agitated batch crystallizer works on this principle. Liquid mixing process is essential in the manufacture of a number of dosage forms. Some of them are listed below.

Preparations	*Phases mixing*	*Examples*
Suspensions	Solid-liquid	Calamine lotion
Emulsions	Liquid-liquid (immiscible)	Benzyl benzoate emulsion
Solutions	Soluble solid-liquid	B Complex elixir
Solutions	Soluble liquid-liquid	Alcohol-water (elixir) Chloroform-water (preservative)
Aerosols	Liquid-gas	Salbutamol inhaler

MECHANISMS OF MIXING

The mechanisms of liquid mixing can be studied under four classes. They are

Bulk transport

Turbulent mixing

Laminar mixing

Molecular diffusion

Bulk Transport

Bulk transport is defined as the movement of a large portion of a material from one location to another location in a given system.

For this purpose, mixing devices such as rotating blades and paddles are used, which moves the material in different directions.

Turbulent Mixing

Turbulent mixing is defined as mixing due to turbulent flow, which results in random fluctuation of the fluid velocity at any, given point within the systemin the turbulent flow, fluid velocity at a given point fluctuates continuously in three directions, x, y and z However, the Liquid moves in one direction depending on the dominant component. In general, the liquid has different velocities at different locations at the same tine.

Turbulent flow is a highly effective mechanism for mixing. Turbulent flow can be seen as a composite of eddies of various sizes. An **eddy** is defined as a portion of fluid moving as a unit in a direction. Large eddies tend to break up forming eddies of smaller size, until they are no longer distinguishable. An additional characteristic of turbulent flow is its intensity, which is related to the velocities with which eddies move.

Laminar Mixing

Laminar mixing is the mixing of two dissimilar liquids through laminar flow, i.e., the applied shear stretches the interface between them. In this mechanism, layers fold back upon themselves. Thus, the number of layers Increases Hence, the interfacial area between them also increases exponentially with time. Mixing may also result in simple stretching of the fluid layers without any significant folding action. This Is also suitable for liquids, which require moderate mixing.

Molecular Diffusion

Molecular diffusion is the mixing at molecular level in which molecules diffuse due to thermal motion.

Molecular diffusion is explained by the Fick's law, which depends on the concentration gradient at different regions. The concentration gradient decreases with time and it reaches zero when mixing is completed i.e., equilibrium condition. When molecular diffusion and laminar flow occur simultaneously, molecular diffusion reduces the sharp discontinuities at the interface between the two layers

Simultaneously more than one mechanism may operate during mixing.

MIXING DEVICES-FLOW PATTERN

Mixing devices are used to supply energy to the system so long as to bring about reasonably rapid mixing. Flow currents are responsible for transporting unmixed materials to the mixing zone.

Mixing devices are technically called-as impellers. Impellers are classified on the basis of the shape arid pitch of the blades that are attached to the central shaft. Three main types of impellers are used namely. Propellers, turbines and paddles.

Propellers

Propeller normally contains a number of blades (Figure). A three bladed design is the most common for liquids. The marine type Propeller is similar to the blades of a table fan or a ceiling fan.

(a) Side view (b) Top view (Propeller type of mixing devices. A three bladed design.)

Propellers may be either right or left-handed, depending on the direction of slant of their blades) Four bladed or toothed or similar design propellers are used for special. Purposes. In a deep tank, push-pull propeller is used in which two or more propellers may be attached to the same shaft. These work in opposite directions to create a zone of high turbulence. (The size of the propeller. Is small, i.e., the ratio of diameters between propeller and container o 20 is Sufficient to low viscous liquids. However, for large tanks the maximum size of 0.5 meters propeller is used. Small propellers turn at full motor speed up to 8000 revolutions per minute

The propeller produces axial(longitudinal) movement of the liquid. The flow Currents leaving the propeller continue through the liquid in a given direction until deflected by the floor or wall of the tank.

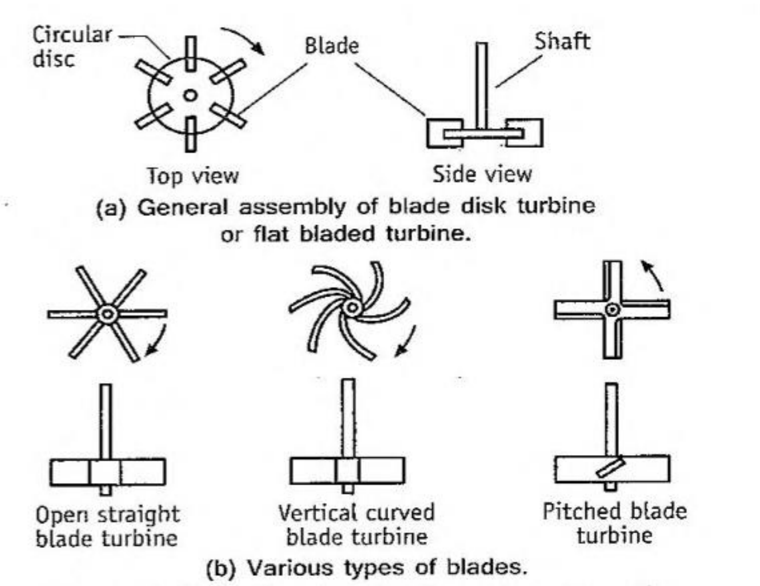
Uses: Propellers are used when high mixing capacity is needed. These are effective in handling liquids having a maximum viscosity of about 2.0pascals second and slurries up to 10% solids of fine mesh size. They can be used upte3.5 metre cube (or 3500 litres). Effective gas- liquid dispersion is possible at the laboratory scale. Multivitamin elixir, disinfectant solutions are manufactured using propellers.

Disadvantage: Propellers are not normally effective with liquids of viscosity greater than 5 pascal-second, for example, glycerine, castor oil etc.

Turbines

A turbine consists of a circular disc to which a number of short blades are attached. The diameter of the turbine ranges from 30-S0 percent of the diameter of the vessel. It rotates at a lower speed than propeller (50-200 revolutions. Per minute). Different forms of turbines are shown in Figure. The blades may be straight, curved, pitched or vertical.

A flat bladed turbine produces radial and tangential low, but as speed increases, radial flow dominates. A pitched blade turbine produces axial flow



Turbine impeller (or mixing clement).

Pitch is defined as the distance the impeller would move through the uid per revolution, if slippage does not occur.

Near the impeller, the zone of rapid currents, high turbulence and intense shear is observed. The shear produced by turbines can be further enhanced using a diffuser ring. A diffuser ring is a stationary perforated

Or slotted ring, which surrounds the turbine. It increases shear forces. The liquid passes through the perforations reducing rotational swirling and vertexing.

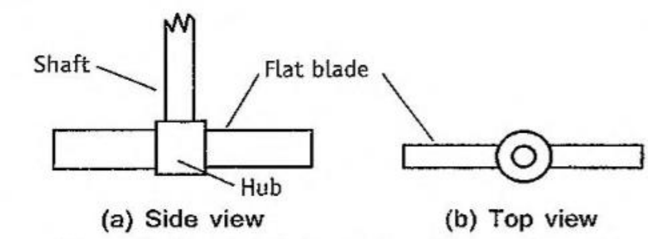
Uses: Turbines are effective for high viscous solutions with a very wide range of viscosities up to 7000-pascal seconds. A few examples are syrups, liquid paraffin. Glycerine et. In low viscosity materials of large volumes. Turbines gene rate strong currents (intense shear) which spread throughout the 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.

Advantages: Turbines give greater shearing forces than propellers, though the pumping rate is less. Therefore, turbines are suitable for emulsification.

Paddles

A paddle consists of a hub centrally with two long flat blades attached to it vertically

Paddles with two blades or four blades are common. Sometimes, the blades arc pitched. In some paddles, the blades are dished or hemi- spherical in shape and have a large surface area in relation to the tank in which they are used. Because of this shape, paddles pass close to the tank walls and effectively mix viscous liquids, avoiding dead spots and deposited solids.



(a) Side view (b) Top view. Paddle type of agitator or impeller

A shaft carry Ing hub-blades rotates at a low speed of the order of I00 revolutions-per minute. They Push the liquid radially and tangentially with almost no axial motion unless the 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 an unbaffled tank, whereas for higher speeds baffles are necessary. Otherwise, the liquid is swirled around the vessel with little mixing.

Uses: Paddles are, used in the manufacture of antacid suspensions (aluminium hydroxide gel and magnesium hydroxide), agar and pectin Related purgatives, antidiarrheal mixtures such as bismuth-kaolin.

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

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

MIXING OF IMMISCIBLE LIQUIDS

Equipment

Mixing of immiscible liquids is carried in pharmacy mainly in the manufacturing of emulsions. The equipment used for the preparation of an emulsion is Known as emulsifier Generally a fine emulsion can be obtained and, therefore, equipment is also known.as homogenizer

Fine emulsion is prepared in two stages. In the first stage, coarse emulsion is prepared by using one of the following.

- Wedge wood
- porcelain mortar and pestle
- mechanical blender
- milk-shake mixer
- Hand homogenizer
- propeller in a baffled tank.

Sometimes, the above equipment directly gives fine emulsion. Otherwise, coarse emulsion is subjected to homogenization in the second stage to get fine emulsion by using one of the following

- Silverson emulsifier
- Colloid mil
- Rapisonic homogenizer

Hence this equipment is also known as *homogenizers*.

EQUIPMENT

Factors Influencing the Selection of an Emulsifier

Quantity of emulsion to be Prepared: Batch wise. Or continuous operation.

Flow properties of liquids: Newtonian, plastic, pseudoplastic or Dilatant.

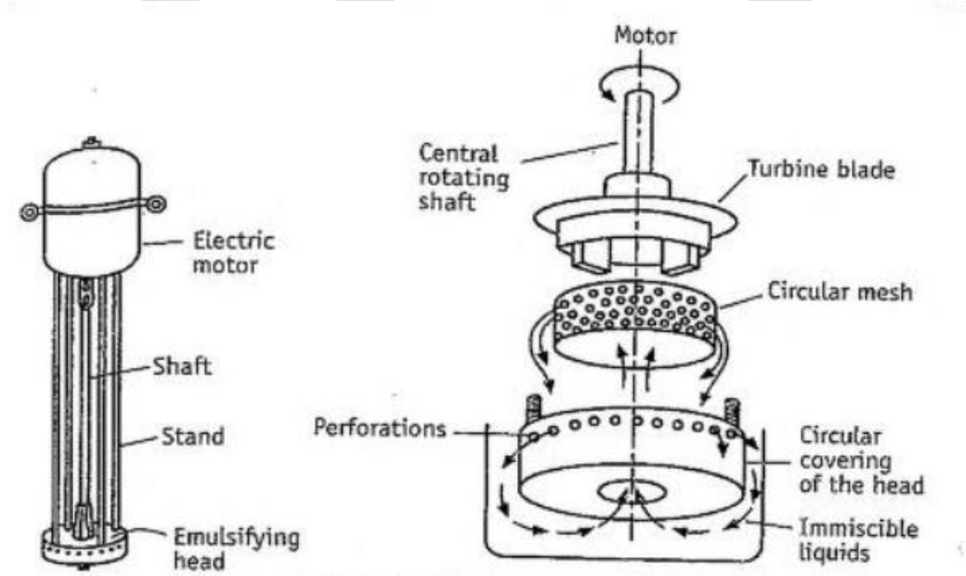
Temperature maintenance: Mixing will be effective at high temperatures provided the material is stable.

Desired rate of cooling: if elevated temperatures are applied.

SILVERSON MIXER—EMULSIFIER

Principle: Silverson mixer-emulsifier produces intense shearing forces and turbulence by the use of high speed5 rotors. This turbulence causes the liquids to pass through fine interstices formed by closely placed perforated metal sheets. 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

Construction The construction of a Severson emulsifier is shown in the Figure. It consists of long supporting columns connected to a motor which give support to the head. The central portion contains a shaft. One end of which is connected to the motor aid the other end is connected to the head. The head carries turbine blades. The blades are surrounded by a mesh, which is further enclosed by a cover having openings:



Construction of Silverson emulsifier.

Working: The emulsifier head is placed in the vessel containing immiscible liquids (or coarse emulsion) in such a way that it should get completely dipped in the liquid. When the motor is started, the centra rotating shaft rotates the head, which in turn rotates turbine blades at a very high speed. This creates a pressure difference. As a result, liquids are sucked into the head from the centre of the base and subjected to intense mixing action. Centrifugal forces expect the contents of the head with great force through the mesh and onto the cover (Figure b). As a result, a fine emulsion emerges through the openings of the outer cover The intake and expulsion of the mixture set up a pattern of circulation to ensure rapid breakdown of the bigger globules into smaller globules.

Uses: Silverson mixer is used for the preparation of emulsions and creams of fine particle size.

Advantages: (1) Silverson mixer is available in different sizes to handle the liquids ranging from a few millilitres to several thousand litres.

(2) It can be used for batch operations. It is also used for continuous operation by incorporating into a pipeline, through which the immiscible liquids flow.

Disadvantage: Occasionally. There is a chance of clogging of pores of the mesh.

MIXING OF SEMISOLIDSs

Equipment

Semisolid dosage forms include ointments, pastes, creams, jellies etc. While mixing such dosage forms, the material must be brought to the agitator or the agitator must move the material throughout the mixer. The mixing action includes-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 ruggedly constructed to tolerate these forces. Mixing equipment are. Also used for preparing tooth-pastes, pill masses and wet mass for granulation.

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 pseudoplastic materials.

Classification of Equipment

Agitator mixers: Examples are sigma mixer and planetary mixer.

Shear mixers: Examples are triple roller mill and colloidal mill.

Selection of Mixing Equipment, for Semisolids (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.

Mechanism of Semisolids Mixing

The mechanisms involved in mixing semi-solids depend on the properties of the material which generally may show considerable variations. Many semi-solids form neutral mixtures having no tendency to segregate although sedimentation may occur. The three most commonly used semi-solid mixers are:

(i) Sigma blade mixer: This mixer has two blades that operate in a mixing vessel that has a double trough shape. These blades move at different speeds towards each other. It can be used for products like granulation of wet masses and ointments.

(ii) Triple-roller mill: The triple roller has differential speed and narrow clearance between the rollers which develops a high shear over small volumes of semi-solid material. This type of mill is generally used to grind semisolids to achieve complete homogeneity in the material, for example, ointments.

(iii) Planetary mixer: In the mixer, the mixing arm rotates around its own axis and around a common axis typically the mixing wheel itself. Kneading is provided by the blades, while shearing is accomplished by the narrow passage between them and the wall of the can