8

Mixing

Section I—MIXING OF SOLIDS

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. It is difficult to predict the inter-particle interactions. Therefore, 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 noncohesive. *Noncohesive materials* such as grain, dry sand and plastic chips readily flow out of a bin or silo.

Cohesive materials such as wet clay are characterised by their resistance to flow through openings.

There are significant differences between solid mixing and liquid mixing. 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

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 are added. Therefore mixing of powders becomes an essential part of the process. When the dose of the active substance is high (for example 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 pharmacopoeial 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, the 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 the 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 interparticulate 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—If 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 area of contact—The larger the surface area of contact, greater the exchange of momentum.

(4) Surface roughness—The surface 'roughness' of the particles involved 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 are 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 *micromixing*.

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

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 35 minutes. Once the desired mixture has been achieved, the process should be stopped.

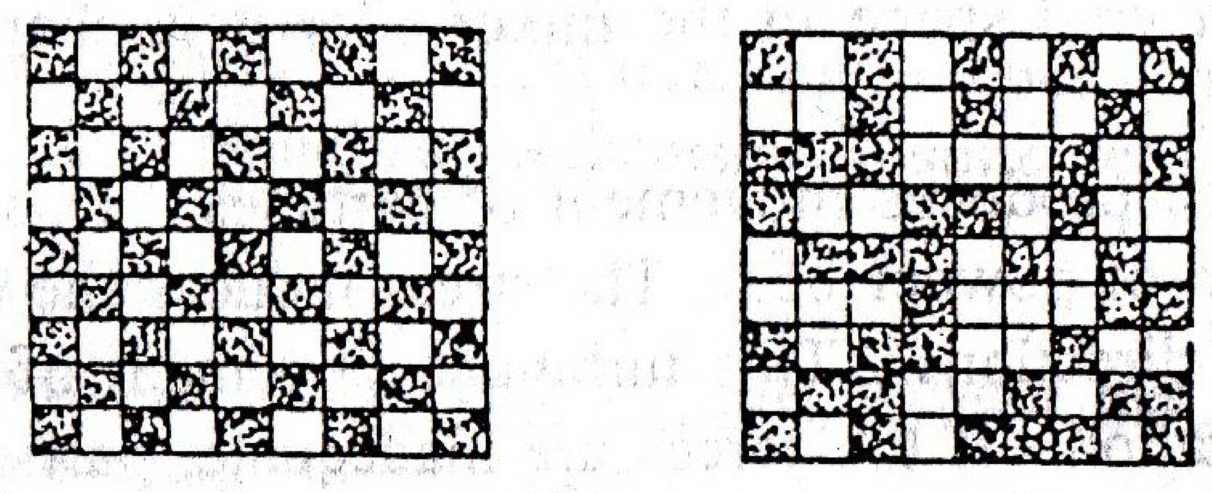
Once mixing is stopped, the blend should exist in static equilibrium. Subsequent handling of the mixture should be so as not to disturb the static equilibrium.

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 8-1a 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.



(a) Perfect mix (b) Randomized mix

Figure 8-1. Types of binary mixtures.

Acceptable Mixing

Since perfect mixing can not 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 8-1b. *Random mixing* means same ratio of components in the entire mixture. Artificial randomization in the Figure 8-1b 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 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 8-2). The smaller the units, the more uniform the mix. Since no particulate adhesion is present, segregation of the mix easily takes place on further handling.

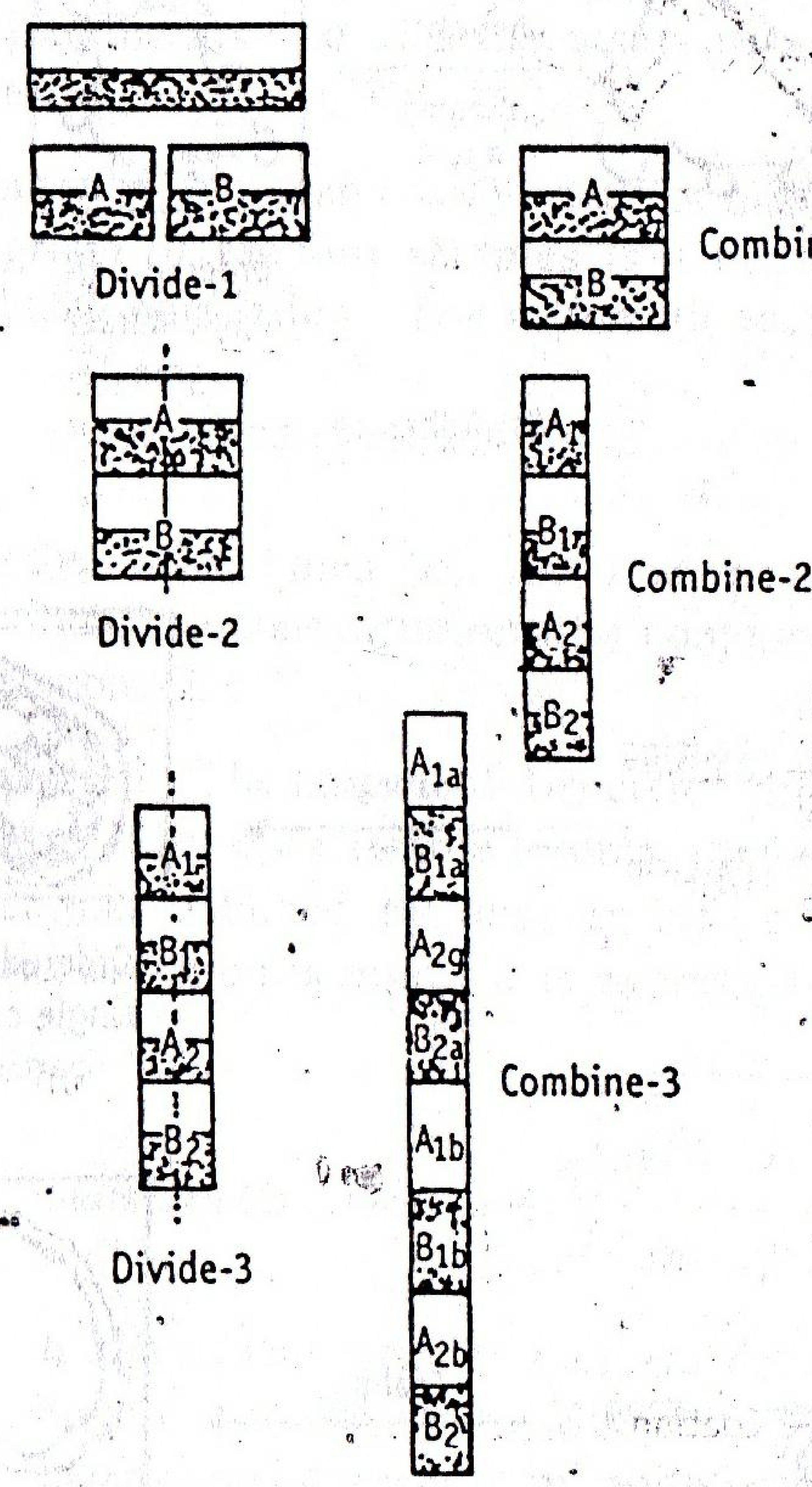


Figure 8-2. Ordered mechanical mixing.

(2) Adhesion means of ordered mixing: These forces of particles may create ordered units of nearly identical composition depending on the process (Figure 8-3a). Partial solubilisation or the use of a binding agent during wet granulation approximates the same effect as shown in Figure 8-3a.

(3) Coating means of ordered mixing: Particles in an assemblage may also be coated with other ingredients to give an ordered mix either as individual or coated particle agglomerates (Figure 8-3b).

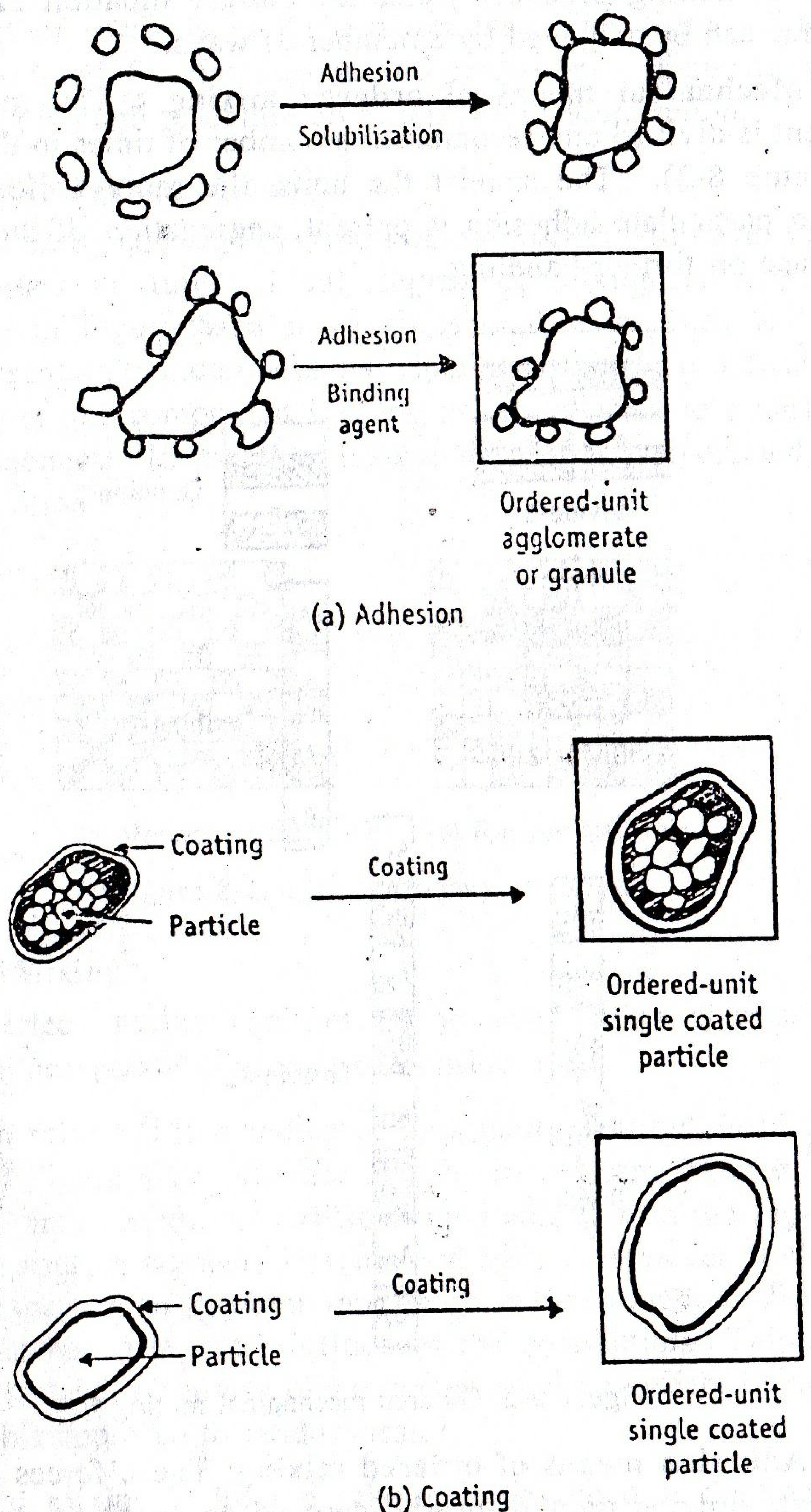


Figure 8-3. Ordered mixing based on the principles of (a) adhesion and (b) coating.

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 determines 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 mean, $\bar{y}$, 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 ± 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:

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

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. Two of them are:

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

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

where σ_0 = standard deviation of unmixed powder.

The ratio will be less than 1. 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:

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

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 8-1.

The objectives have been specified in the Table 8-1. 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, but 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 more 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 of 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.

TABLE 8-1

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).

Sample utilization: (a) Scooping sampling
(b) Thief probing (preferred)

Sampling methods: (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 unmixed 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.

Some times, 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 are 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 can not 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 can not 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 8-1.

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 does not induce 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 aerosil (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. Demixing 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 interlocked 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.

The fundamental aspects of the particles and powders are discussed in the *Textbook of Physical Pharmaceutics* by C.V.S. Subrahmanyam (Vallabh Prakashan, Delhi).

CLASSIFICATION OF EQUIPMENT FOR SOLIDS MIXING

Based on the flow properties of the powders, appropriate mixer should be selected.

Free flowing solids – V cone blender
– Double cone blender

Cohesive solids – Planetary mixer
– Sigma blender

Based on the scale of mixing, mixing equipment may be classified as given in Table 8-2.

TABLE 8-2
Classification of Mixing Equipment

S.No.	*Nature of mixer*	*Examples*	*Mechanism of mixing*
1.	**Batch type** Small scale	Mortar and pestle	Trituration
2.	Tumbling mixers or cylindrical mixers without mixing blade	Double cone blender, V cone mixers without baffles Cube blender	Tumbling action
3.	Tumbling mixer with a mixing blade	V cone blender with a mixing blade Double cone blender with a mixing blade	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	Fluidised mixer	Air supported blending
6.	**Continuous type** Large scale	Barrel type Zigzag type	Rotating shell with rotating blade

EQUIPMENT

A mixer that promotes the randomness in mixing should be selected. It should also prevent the conditions responsible for segregation. Therefore, optimization of operational conditions is critical.

Mixing Equipment—Criteria

1. The powder bed may expand sufficiently, therefore, equipment should never be filled for more than about 60% so as to leave sufficient mixing volume.
2. The particles should be subjected to movement in three directions.
3. The shearing force should be sufficient to prevent aggregation. Appropriate mixing mechanism should be selected and allowed to continue for optimum time.
4. There should be no centrifugal effect, so that the powder does not get separated according to their weights.
5. The forces should not cause breakage of the particles, which may bring about demixing due to differences in particle size.
6. The mixing process should be stopped abruptly, because slow or diminishing forces in one direction might cause demixing. Therefore handling of powder blend after mixing is equally important.

Some mixing equipment are discussed below.

TUMBLERS OR CYLINDRICAL BLENDERS WITH NO MIXING BLADE

This is a general class of equipment meant for blending of dry powders. The equipment consists of a container of one of the several geometric form. These are mounted so that it can be rotated about an axis. These do not have packing glands (seals) round the shaft. Cubes or hexagonal cylinders may be rotated in any axis depending on the manufacture (Figure 8-4). Such a cylindrical vessel is not suitable for mixing since one-dimensional movement would be obtained.

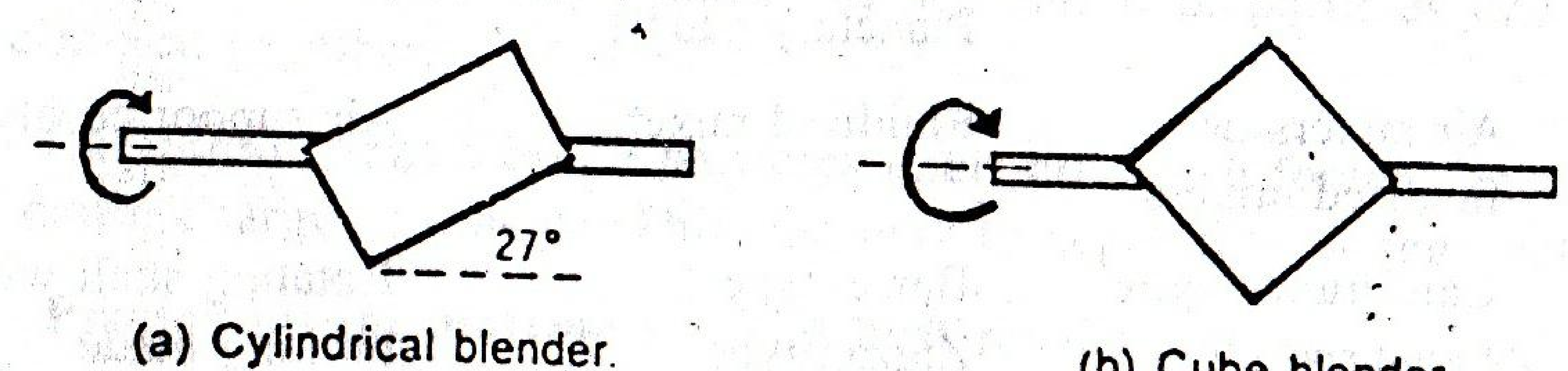


Figure 8-4. Tumbler blenders without agitator blade.

Edge of 27 degrees is good for mixing. Special rollers are available so that any vessel can be placed on it at the optimal condition. It is very handy since the vessel can be used every where in the process. When mixed, cohesive powders tend to ball up and aggregate. Therefore, tumbler type is not suitable.

The efficiency of a tumbling mixer highly depends on the speed of rotation. It should be critical.

(1) Slow rotation – No intense tumbling, no cascade motion. Not enough shear rates is applied.

(2) Rapid rotation – Sufficient centrifugal action to hold the powder to the sides of the mixer, more dusting and segregation of fines is possible.

Therefore, the rate of rotation should be optimal, which depends on the size, shape of the tumbler and the nature of material to be mixed. Common range is 30 to 100 rpm.

Neither cylindrical nor cube mixers are used to a great extent in the industry. For simple blending of dry mixers, V cone and double cone blenders without baffles are used. The tumbling motion is accentuated by means of baffles or simply by virtue of the shape of the container.

TWIN SHELL BLENDER OR V CONE BLENDER

The construction of a twin shell blender is shown in Figure 8-5. 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 15 revolutions per minute. The material is loaded through either of the shell hatches. Emptying of the blend is normally done through an apex port.

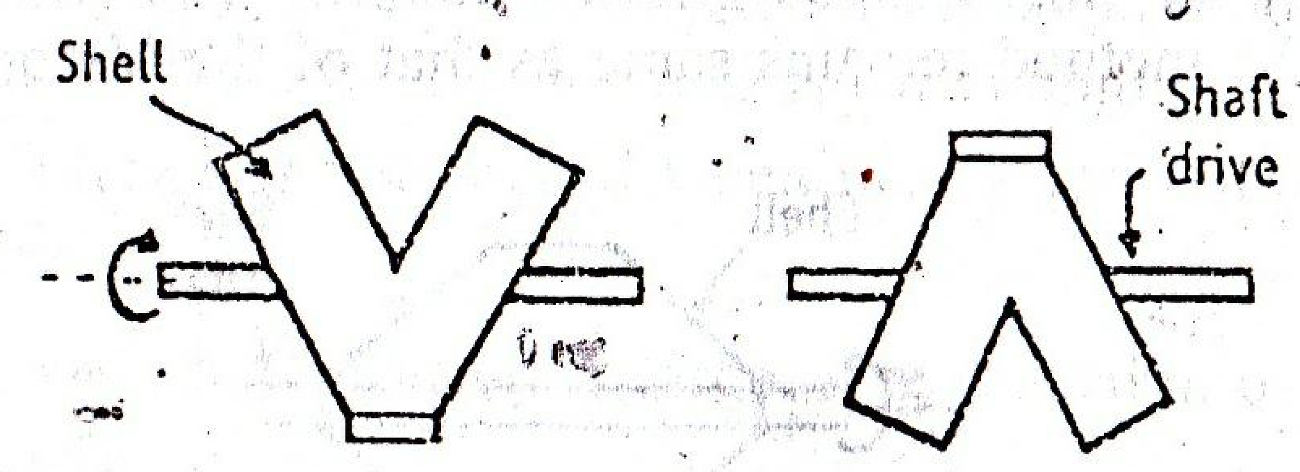


Figure 8-5. V cone blender. Rotating shell without baffles.

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 shockwise, so that no demixing 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 fine 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 8-6. 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.

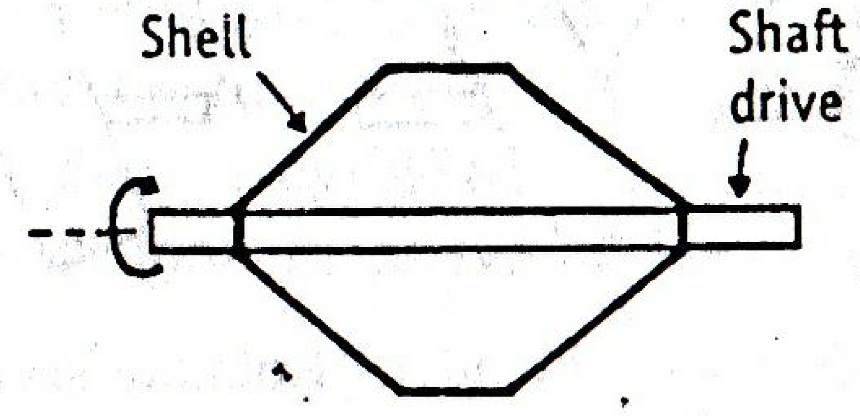


Figure 8-6. Double cone blender.
Rotating shell without baffles.

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

The V-cone blender and double cone blender with agitator blade (baffles) are shown in Figures 8-7 and 8-8, respectively. The general construction and working is same as mentioned above. Agitator blades are added which have several advantages.

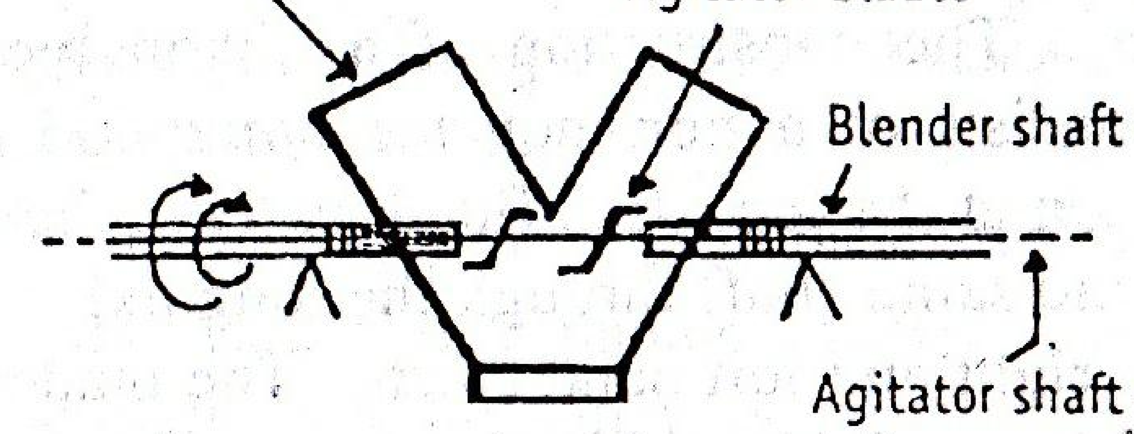


Figure 8-7. V cone blender.
Rotating shell with rotating baffles.

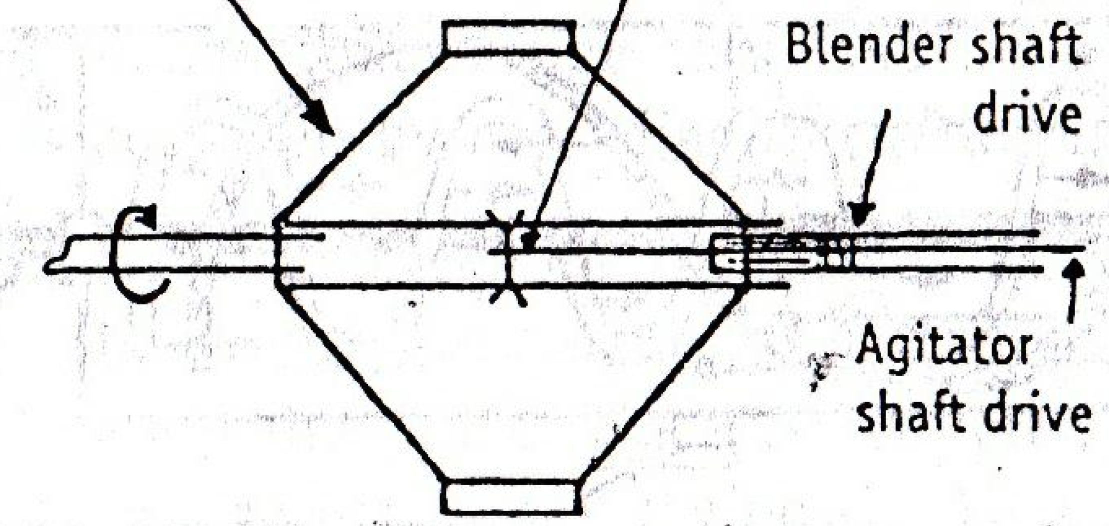


Figure 8-8. Double cone blender.
Rotating shell with rotating baffles.

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 of 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 lifted 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 8-9. 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 are connected to a fixed speed drive. Ribbon blender is top loading with a bottom discharge port. The trough can be closed with a lid.

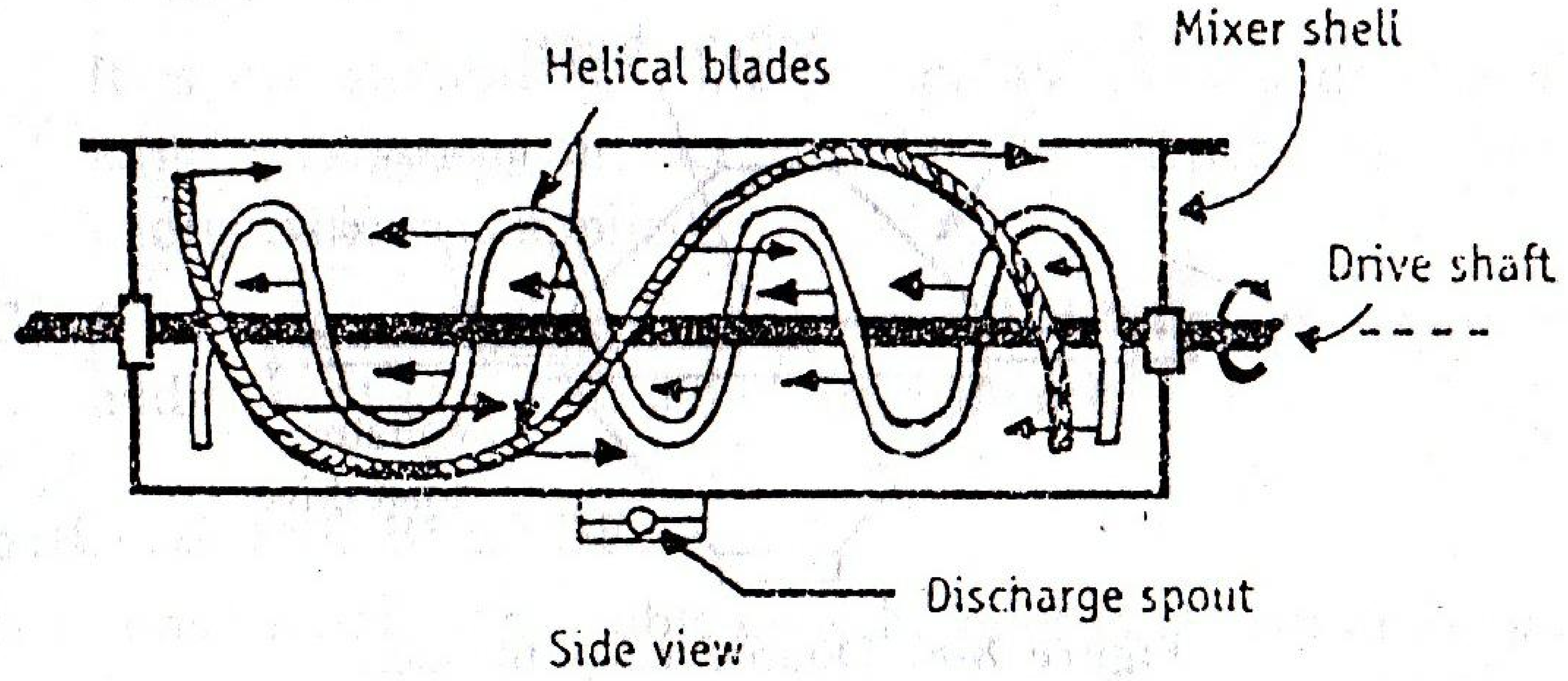


Figure 8-9. Ribbon mixer. Stationary shell and rotating blades.

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 are 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 effect 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, which 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 mixer, though they are minimum.

(4) It is having fixed speed drive.

SIGMA BLADE MIXER

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

Construction : The construction of a sigma blade blender is shown in Figure 8-10. 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.

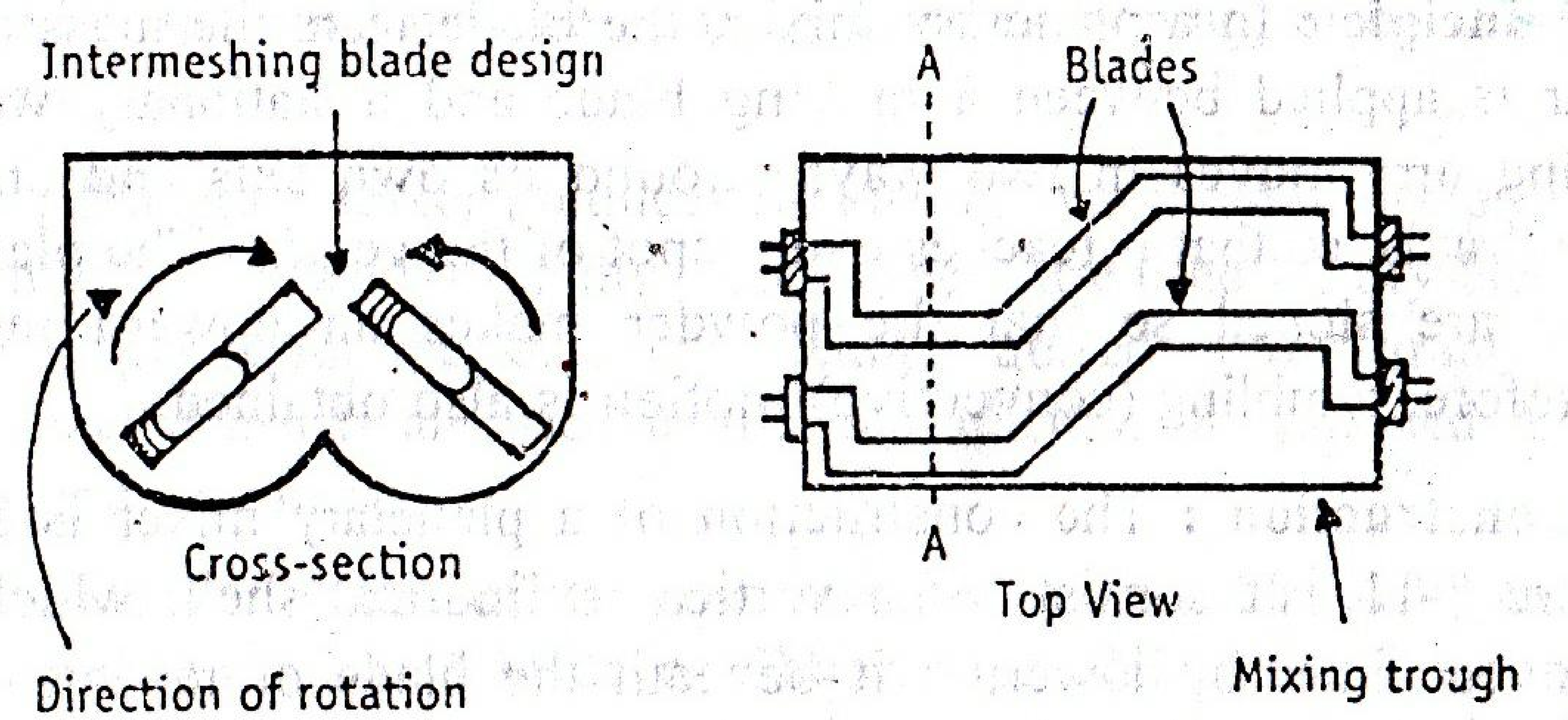


Figure 8-10. Sigma blade mixer. Stationary shell and rotating blades.

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 effect 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) It has close tolerances between the blades and the side-walls as well as bottom of the mixer shell.

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 mixing 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 8-11. It consists of a vertical cylindrical shell, which can be removed either 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 8-11. It rotates around the ring gear, which further rotates round the mixer blade. It is normally built with a variable speed drive.

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.

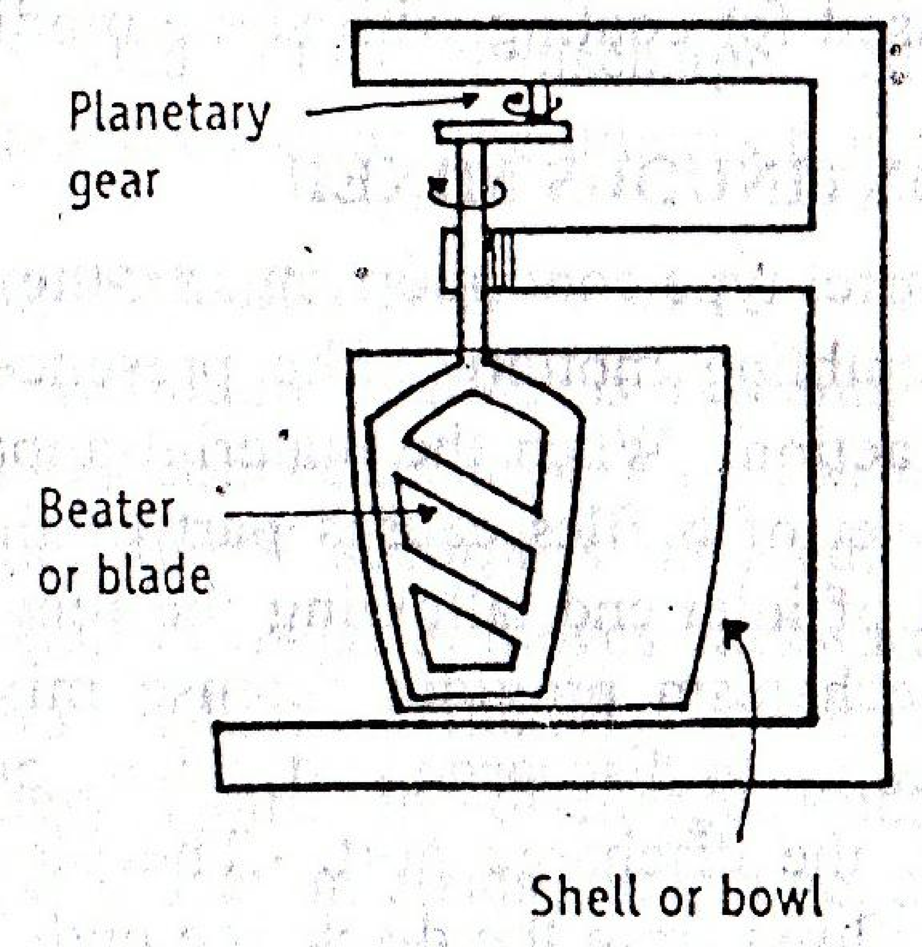


Figure 8-11. Planetary mixer.

Emptying the 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.

AIR MIXER OR FLUIDIZED MIXER

Principle : The air movement is used for mixing powders. The powders are mixed in a stationary cylindrical vessel. Air is admitted at its base at an angle. This gives tumbling action and spiral movements to the powder. Thus mixing is achieved.

The construction and working of an air mixer or fluidised mixer remains same as shown in fluidised bed dryer in the Chapter Drying.

Advantages : Air mixer shortens the mixing time. It is useful as a through-output. Mixing is intimate and efficient. It is also used for wet granulation in tablets. With additional attachments, this equipment is useful for mixing, wet massing and drying in the wet granulation method. This method is also used for coating with some modifications.

BARREL TYPE CONTINUOUS MIXER

Principle : In a barrel type continuous mixer, the rotating shell keeps the material under tumbling motion. The presence of baffles further enhances the mixing action. When the material approach the mid-point of the shell, another set of baffles causes part of the material to move towards the direction of inlet end, allowing the remaining part to move forward. Such a mechanism provides intense mixing of ingredients. This process continues up to discharge end, where another set of baffles guide the material to the discharge port. The blended material at an equilibrium state overflows from the discharge end.

Construction : The construction of a barrel type mixer is shown in Figure 8-12. It resembles a large cement mixer. Baffles are fitted to the inner surface of the shell. The shell is fixed to a shaft, which is allowed

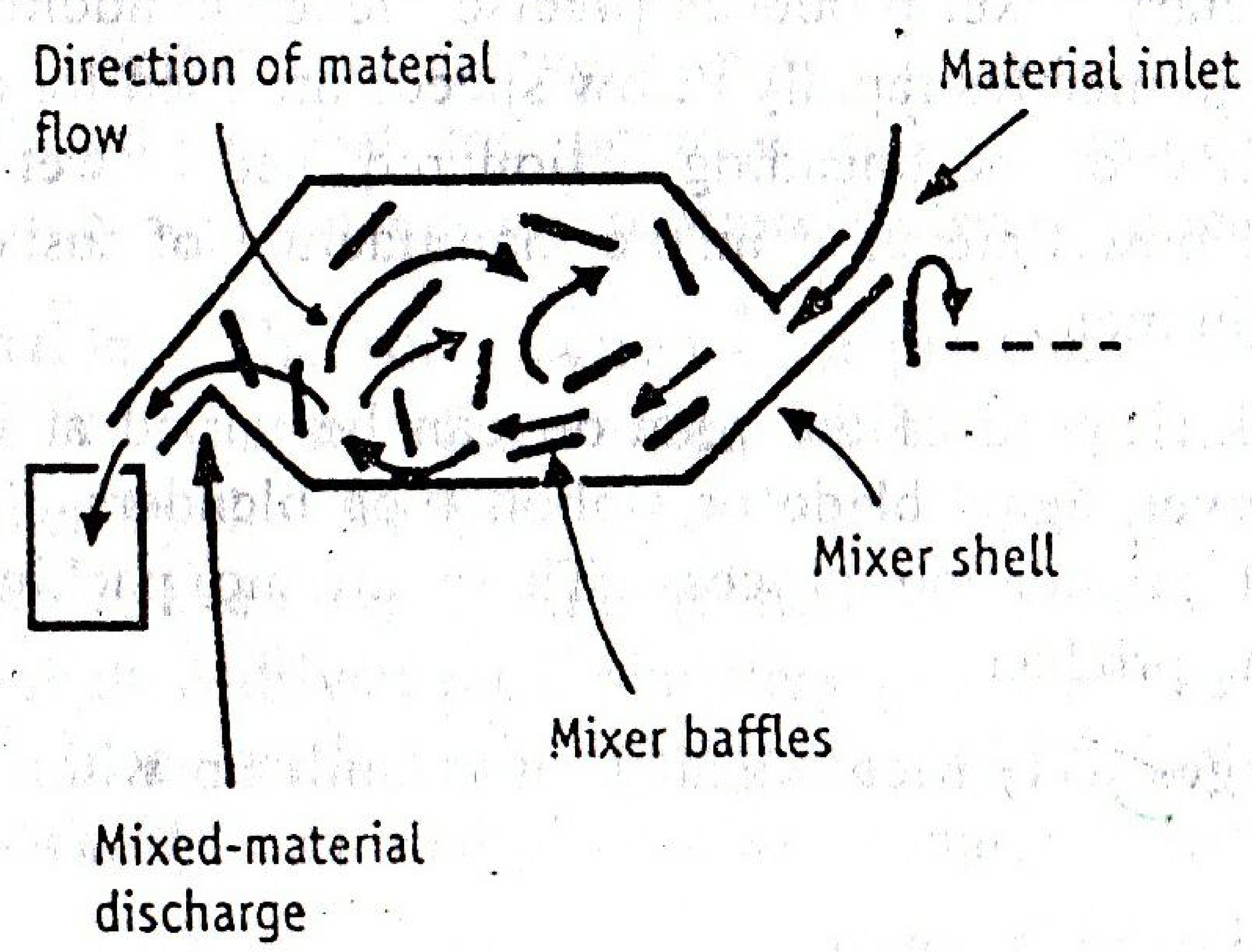


Figure 8-12. Construction of barrel type continuous mixer.

to rotate using electric power. Side openings are provided on each side for charging and discharging of materials.

Working : The mixer is allowed to rotate. Along with it the baffles also rotate. The ingredients are introduced into the shell through the inlet. They begin moving towards the opposite end of the blender due to tumbling action. Baffles further enhance the mixing. As the material approaches the mid-point of the mixer shell, the baffles are so positioned to cause the feedback of part of the material in the direction of the inlet end. The movements are shown in Figure 8-12 using arrow markings. The feedback action continues up to the discharge end where another set of baffles guides the material to the discharge port. The overflow of material causes the blended solids to discharge. Since charging and discharging are simultaneously done, the process becomes continuous.

ZIGZAG CONTINUOUS BLENDER

Principle : Zigzag continuous blender is a rotating shell type having several V shaped blenders connected in series. The material undergoes tumbling motion. When the V section is inverted, the material splits into two portions; one-half of material moves backward (into the preceding section), while another-half of material moves forward. Due to inclined axis of the shell towards the discharged end, the material gets discharged. As the first V section clears the charge, a fresh feed enters. Thus, it is used for continuous blending of solids.

Construction : The construction of a zigzag continuous blender is shown in Figure 8-13. The shell takes the shape of several V shaped

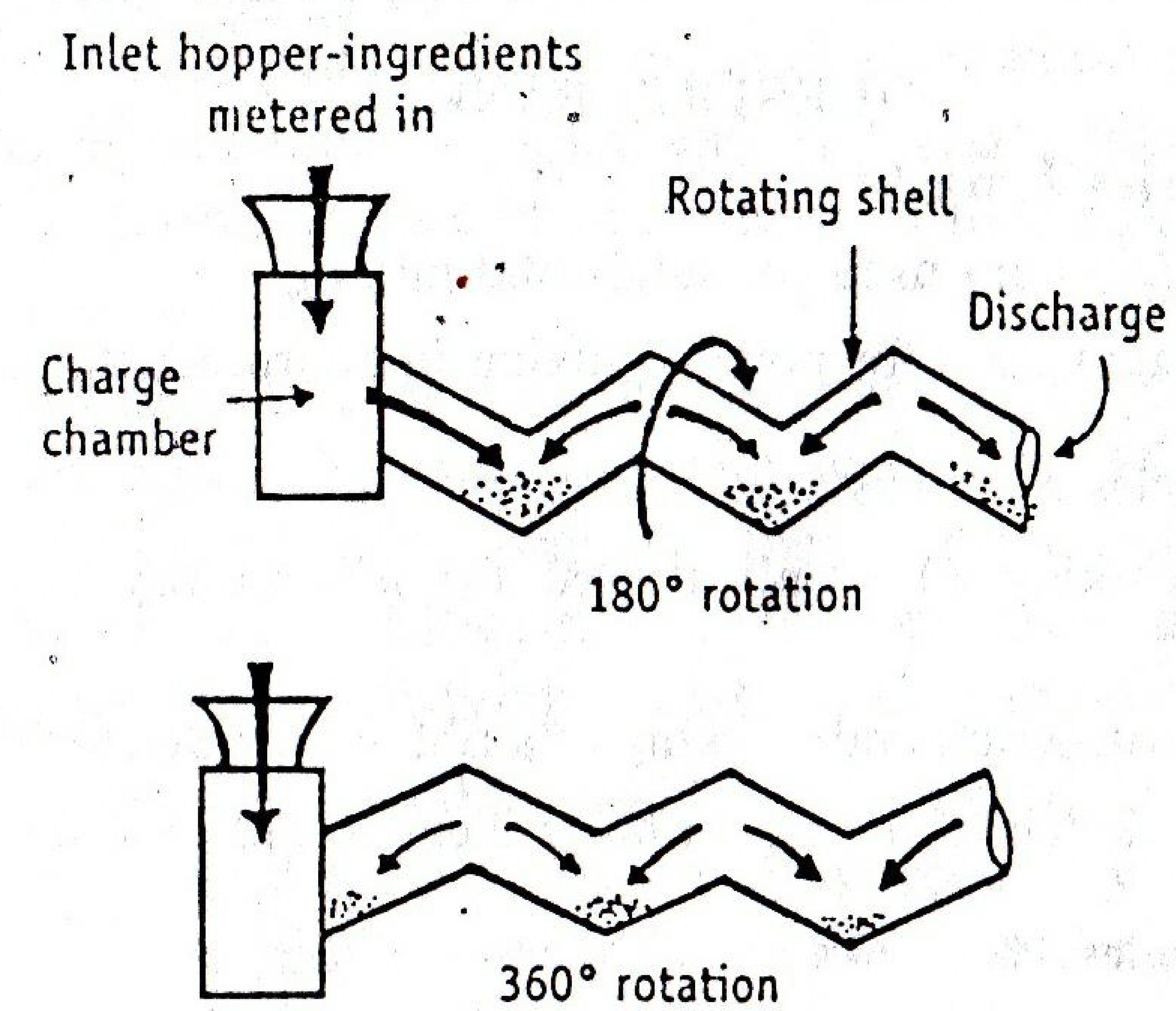


Figure 8-13. Construction of zigzag continuous blender.

blenders connected in series. A chamber for charging is attached to one end of the shell. The other end allows the discharge of material. The shell is inclined towards the discharge end.

Working : A single pre-weighed charge is introduced into the charge chamber. As the shell rotates, at one particular angle (Figure 8-13) a metered material enters the V-shaped section by gravity. With each rotation, one-half of the blend material moves downward back to the preceding leg and another-half of the material moves forward to the next leg of the blender. In each rotation, a part of the material moves towards the discharge end.

As the first charge clears the first V section, which may take only a few minutes, the next charge is added. The uniformity of blending depends on the flow properties of the ingredients.

Glossary of Symbols

A = Constant.
a = Overall fraction of tracer in the mixture.
t = Time, min.
k = Constant.
M = Degree of mixing or mixing index at time, t.
n = Number of samples.
RSD = Relative standard deviation.
σ = Standard deviation
σ_0 = Standard deviation of unmixed powder.
σ_R = Standard deviation of random blend.
y = Arithmetic mean (particle size or concentration).
$\bar{y}$ = True mean of the standard.
y_i = The value of a given sample.

QUESTION BANK

Each question carries 2 marks

1. Mention the equipment used for solid-solid mixing.
2. List the equipment used for powder mixing in pharmaceutical industry.

Each question carries 5 marks

1. Explain the working of a mixer used for mixing dry powders before granulation.
2. Explain the construction and working of a ribbon blender for mixing solids.
3. Draw the neat sketch of the sigma blade blender and give its working.

Each question carries 10 marks

1. Describe the equipment for solid-solid mixing of pharmaceutical materials.

Section II—MIXING OF LIQUIDS

Mechanisms of Mixing
Mixing Vessels or Tanks
Mixing Devices – Flow Pattern
Mixing Equipment

Liquid-liquid mixing is considered as a simple operation compared to that of solid-liquid mixing. It 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 be 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. The general flow characteristics of the fluids have been discussed in the *Textbook of Physical Pharmaceutics*, by C.V.S. Subrahmanyam (Vallabh Prakashan, Delhi).

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 system.

In 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 time.

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 VESSELS

The mixing apparatus consists of a container (tank) and a mixing device. These are assembled and used for a batch process. The general construction of the mixing tank or container is shown in Figure 8-14 along with other accessories required for mixing. A mixing device is called impeller, which is mounted with the help of a shaft. The shaft is driven by a motor.

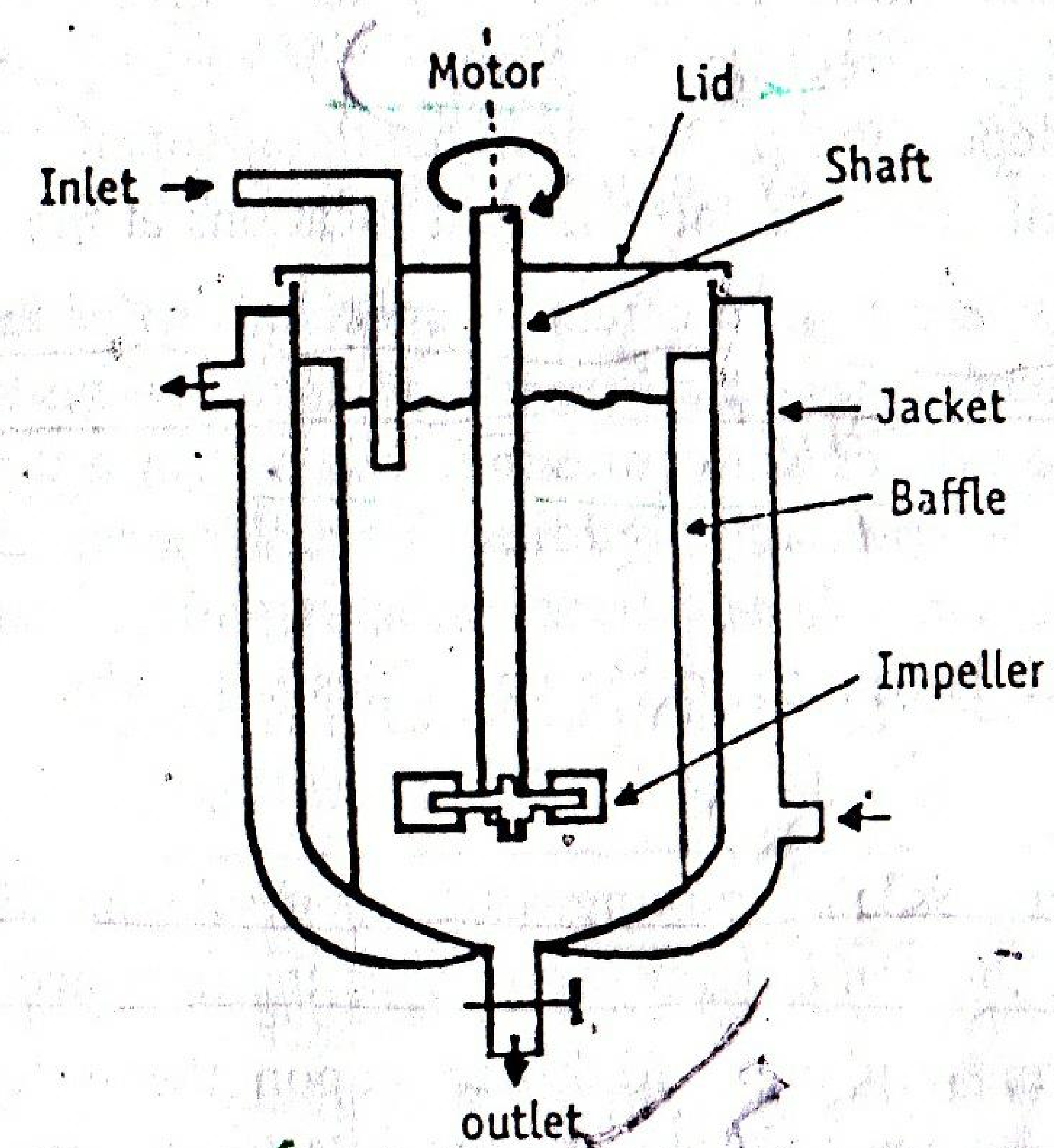


Figure 8-14. Mixing vessel or tank.

The tank is made up of stainless steel. The top of the tank may be open or closed. It is constructed with tank diameter to liquid height ratio of 1:1. The size of the tank depends on the nature of the agitation method. The tank bottom is rounded (not flat) to eliminate sharp corners or regions into which fluid would penetrate. It also carries an outlet, coils, jackets, temperature measuring device etc., wherever necessary.

Baffles : Containers can be either baffled or unbaffled. Baffled containers are those in which metal strips (baffles) are placed vertically to the internal surface. When bulk transport is important in mixing, baffles are used. These are particularly desirable in the initial stages of mixing when segregation is present on a large scale. Baffles facilitate intermingling of the liquids even from remote regions of the mixer.

In most of the cases four baffles are sufficient. Even one or two baffles provide a strong effect on mixing. The width of the baffle may be from $1/10^{th}$ to $1/18^{th}$ of the tank diameter. If solids are present in the liquid to be mixed, the baffles are fixed with a gap of about 25 millimetres between the baffle and the tank surface.

The above discussion includes containers in which the liquids move. In some cases, the container itself moves to mix the liquids. One example is *shaker mixer*. Oscillatory movement is applicable on a small scale whereas rotary movement is applicable on a large scale. Shaker mixers are rarely used in pharmacy.

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 and pitch of the blades that are attached to the central shaft. Three main types of impellers are used namely, propellers, turbines and paddles. These are discussed below.

Propellers

A propeller normally contains a number of blades (Figure 8-15). 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.

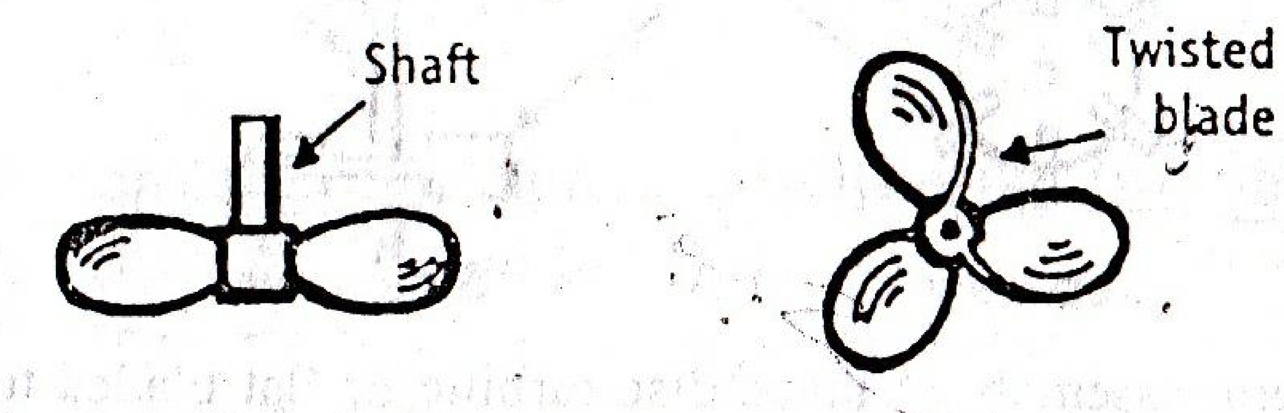


Figure 8-15. Propeller type of mixing devices. A three bladed design.

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 of 20 is sufficient for low viscous liquids. However, for large tanks the maximum size of 0.5 metres propeller is used. Small propellers turn at full motor speed up to 8000 revolutions per minute.

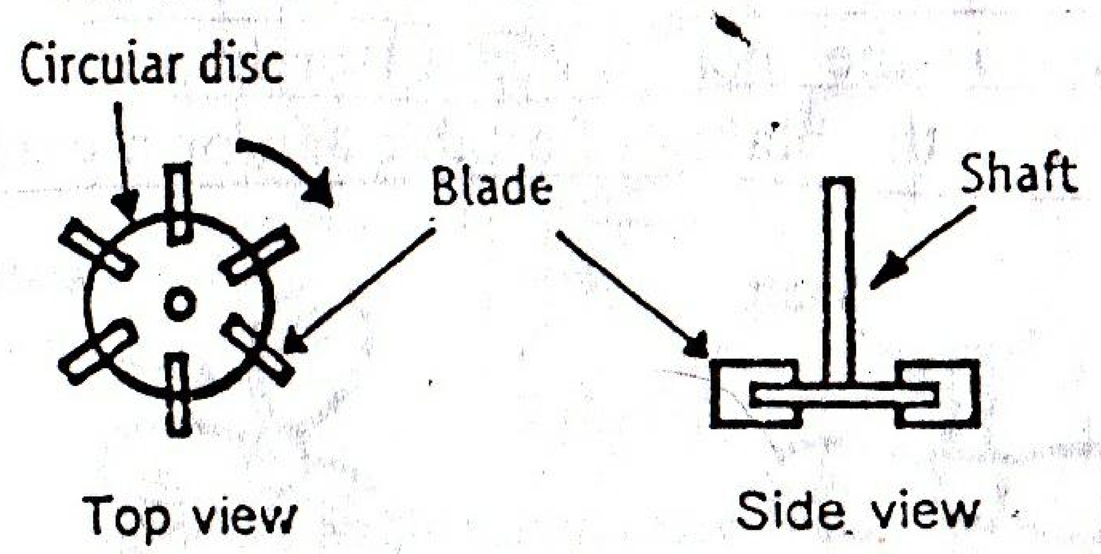
The propeller produces axial (longitudinal) movement of the liquid. The flow currents leaving the propeller continue through the liquid in a given direction until deflected by the floor or wall of the tank.

Uses : Propellers are used when high mixing capacity is needed. These are effective in handling liquids having a maximum viscosity of about 2.0 pascals·second and slurries up to 10% solids of fine mesh size. They can be used upto 3.5 metre cube (or 3500 litres). Effective gas-liquid dispersion is possible at the laboratory scale. Multivitamin elixir, disinfectant solutions are manufactured using propellers.

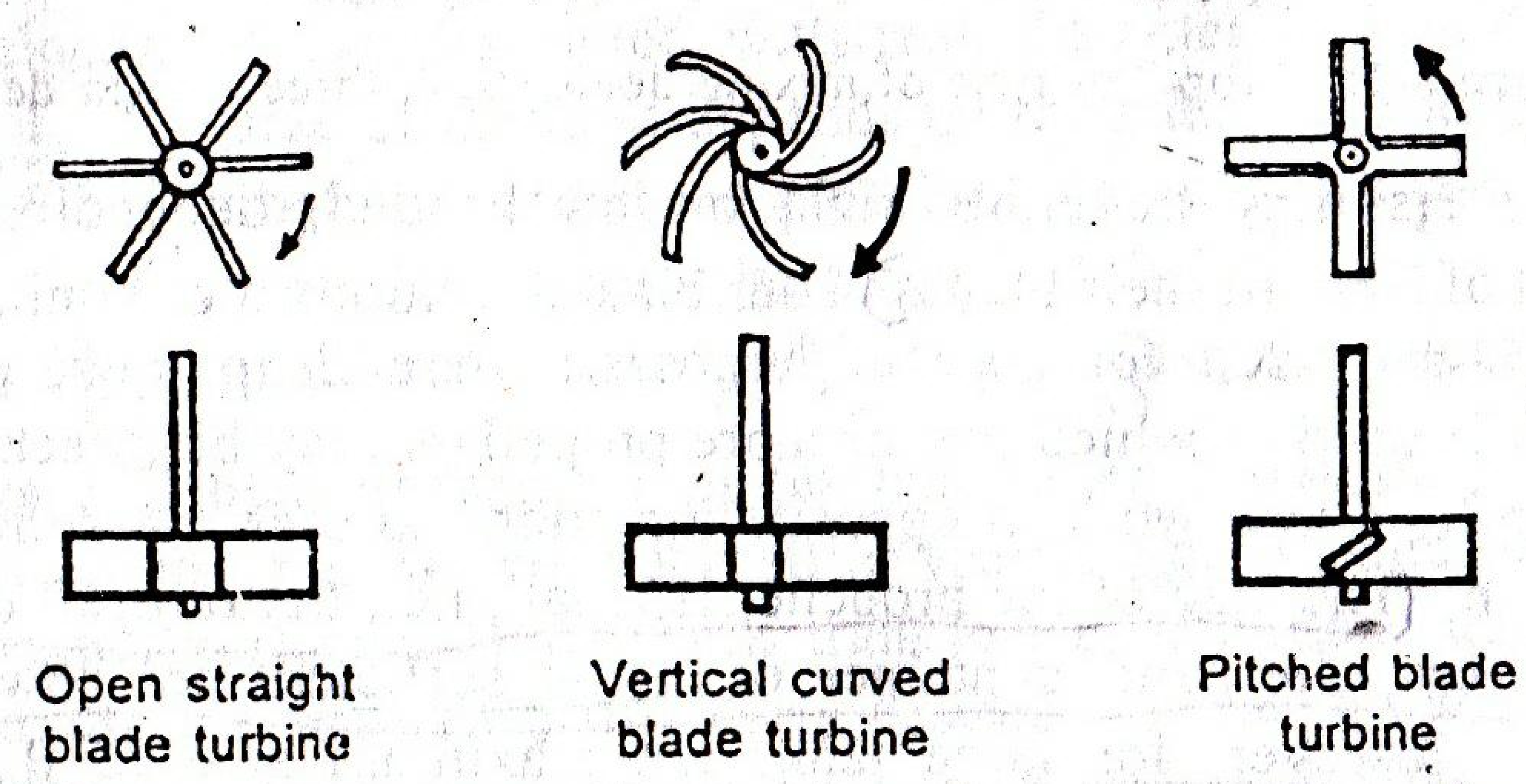
Disadvantage : Propellers are not normally effective with liquids of viscosity greater than 5 pascal·second, for example, glycerin, castor oil etc.

Turbines

A turbine consists of a circular disc to which a number of short blades are attached. (Figure 8-16a). The diameter of the turbine ranges from 30-50 percent of the diameter of the vessel. It rotates at a lower speed than propeller (50-200 revolutions per minute). Different forms of terbines are shown in Figure 8-16. The blades may be straight, curved, pitched or vertical.



(a) General assembly of blade disc turbine or flat bladed turbine.



(b) Various types of turbines

Figure 8-16. Turbine impeller (or mixing element).

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

Pitch is defined as the distance the impeller would move through the fluid 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 vortexing.

Uses : Turbines are effective for high viscous solutions with a very wide range of viscosities upto 7.00 pascal·seconds. A few examples are syrups, liquid paraffin, glycerin etc. In low viscosity materials of large volumes, turbines generate 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 (Figure 8-17).

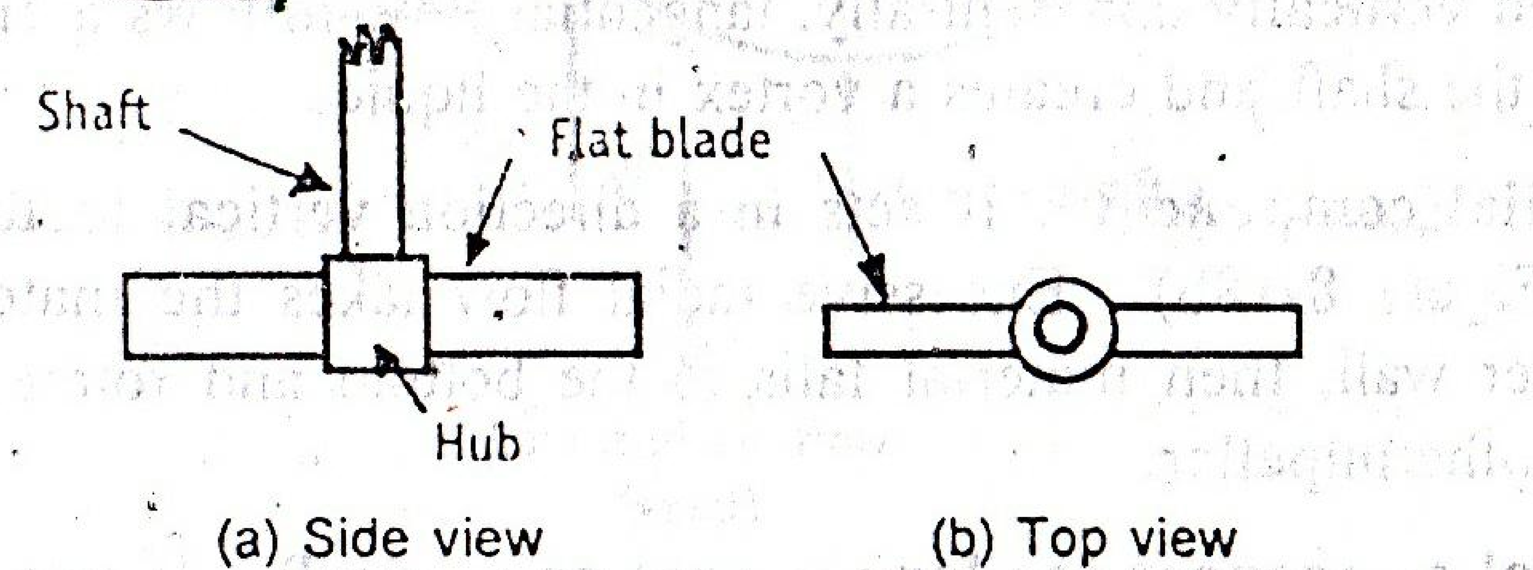


Figure 8-17. Paddle type of agitator or impeller.

Paddles with two blades or four blades are common. Sometimes, the blades are pitched. In some paddles, the blades are dished or hemispherical 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 shaft carrying hub-blades rotates at a low speed of the order of 100 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, where as 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, antidiarroheal 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.

Flow Pattern During Mixing

Liquids are mixed usually by impellers, which produce shear forces, for inducing necessary flow pattern in the container. Mixing takes place due to the resultant effect of three components acting on the liquid. These are radial component, longitudinal component and tangential component (Figure 8-18).

Tangential component (or circular) : It acts in a direction tangent to the circle of rotation around the impeller shaft (Figure 8-18a). If shaft is placed vertically and centrally, tangential flow follows a circular path around the shaft and creates a vortex in the liquid.

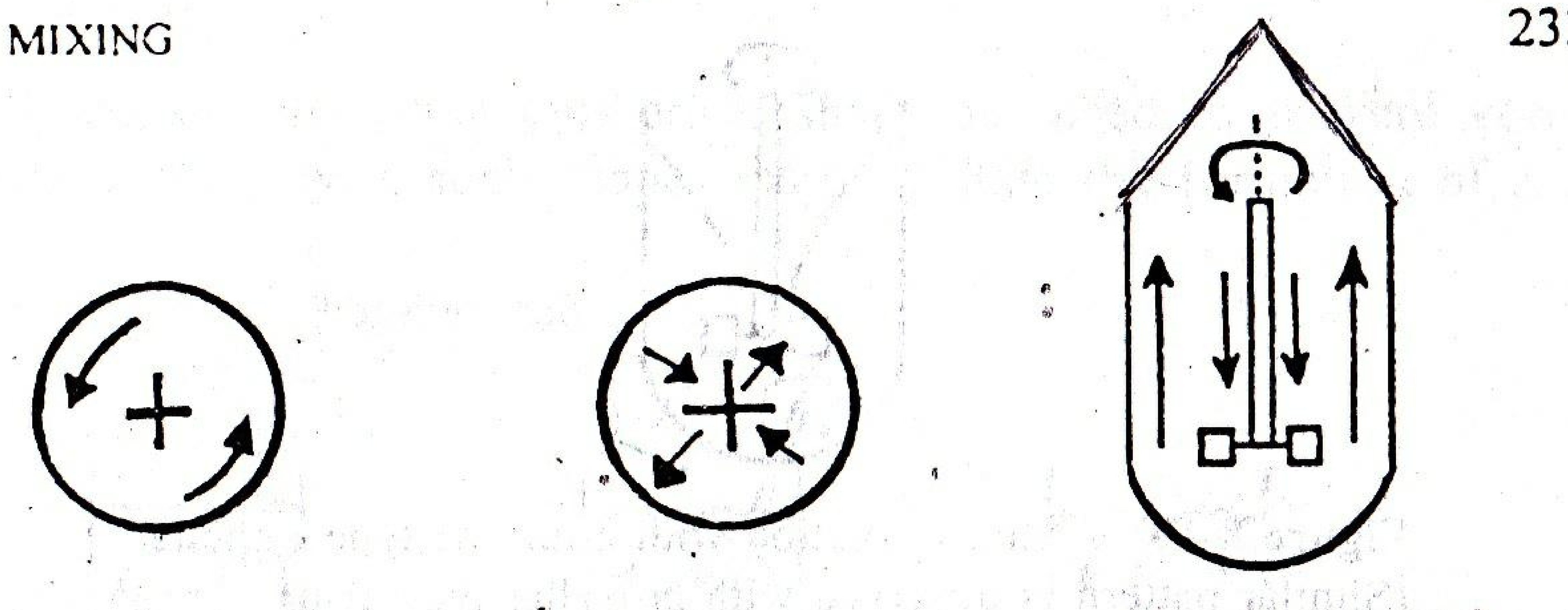
Radial component : It acts in a direction vertical to the impeller shaft (Figure 8-18b). Excessive radial flow takes the material to the container wall, then material falls to the bottom and rotate as a mass beneath the impeller.

Axial component (or longitudinal or vertical) : It acts in a direction parallel to the impeller shaft (Figure 8-18c). Inadequate longitudinal component causes the liquid and solid to rotate in layers without mixing. Adequate longitudinal pattern is best used to generate strong vertical currents particularly when suspending solids are present in a liquid.

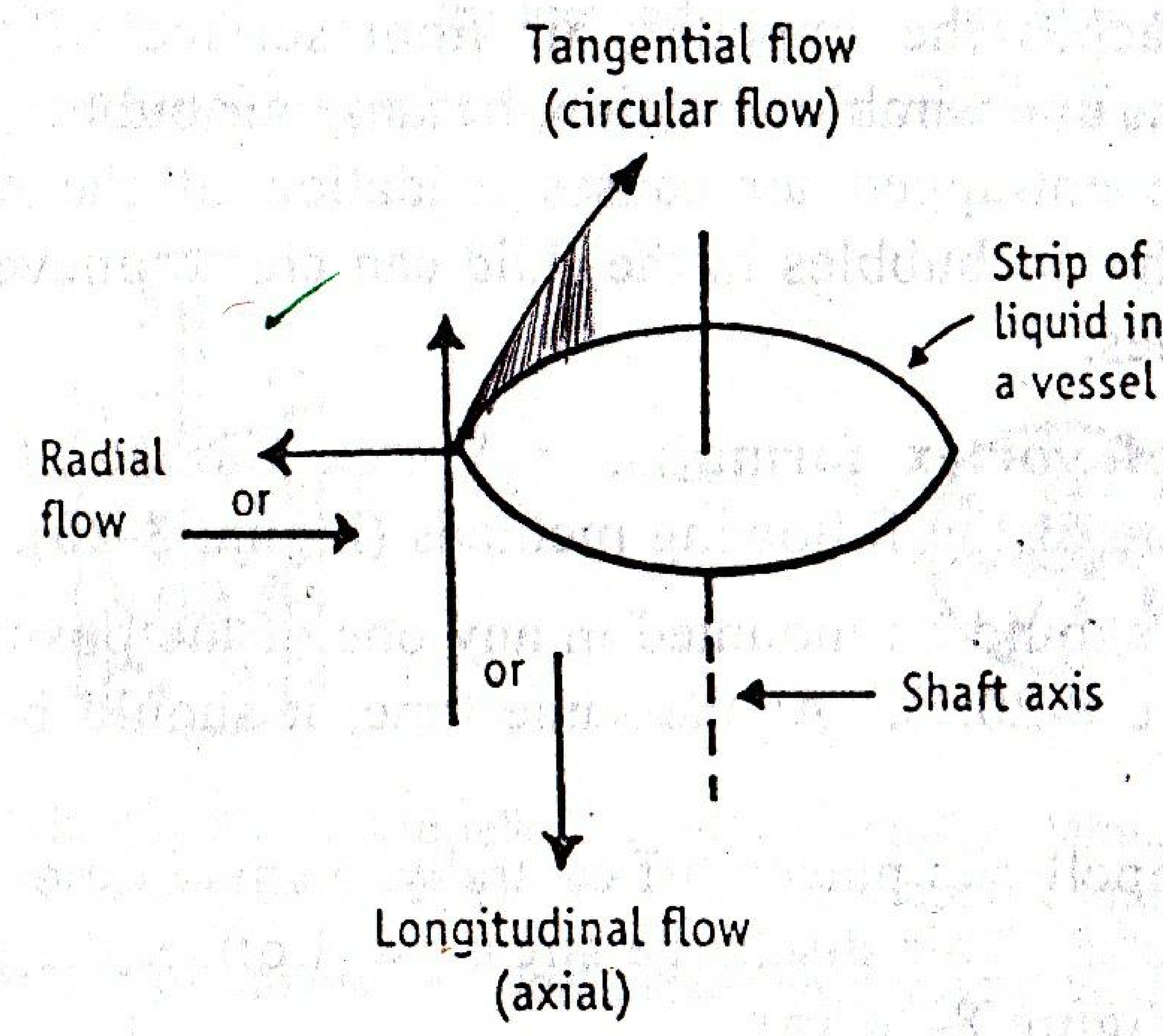
These may occur singly or in various combinations. A satisfactory flow pattern depends on the balance of the components. The flow patterns of different impellers are given in Table 8-3.

TABLE 8-3
Flow Patterns of Impellers

Impeller type	*Flow component*
Propellers	axial
Turbines	axial or tangential or both
Paddles	radial and tangential not axial
Paddles with pitch	radial, tangential and axial



(a) Tangential or circular flow (top view)   (b) Radial flow (top view)   (c) Axial or longitudinal flow (side view).



(d) Different components of flow at a horizontal strip of liquid section.

Figure 8-18. Diagrammatic representation of a cylindrical tank with tangential, radial and axial flow. Each diagram represents one type of flow (a, b, and c). In usual situations, one or more or a combination of these flow patterns occur simultaneously (d).

Vortex Formation

A strong circulatory flow pattern sometimes manifests into formation of a vortex near the impeller shaft (Figure 8-19).

Vortex can be formed when:

- The shaft is mounted vertically in the centre of the tank, i.e., symmetry. Such a mounting tend to induce tangential flow.
- Blades in the turbines are arranged perpendicular to the central shaft.
- At high impeller speeds.
- In unbaffled tanks.

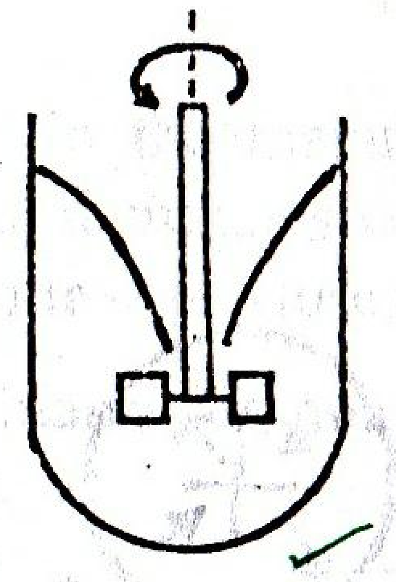


Figure 8-19. Vortex formation with a turbine type impeller (Similar pattern is observed with propeller type also).

Disadvantages : Vortex formation reduces the mixing intensity by reducing the velocity of the impeller relative to the surrounding fluid. When vortex reaches the impeller, air from surface of the liquid is drawn. This is an undesirable situation, because air bubbles are difficult to remove. The entrapped air causes oxidation of the substances in certain cases. The air bubbles in the fluid can create uneven loading of the impeller blades.

Prevention of vortex formation : Vortex formation can be prevented by any one of the following methods (Figure 8-20).

(1) Impeller should be mounted in any one of the positions to avoid symmetry (Figure 8-20.1). At the same time, it should be deep in the liquid.

When the propeller is placed off centrally, a small amount of tangential flow is induced. This discharge stream will offset the swirl induced by its rotation (Figure 8-20.1a).

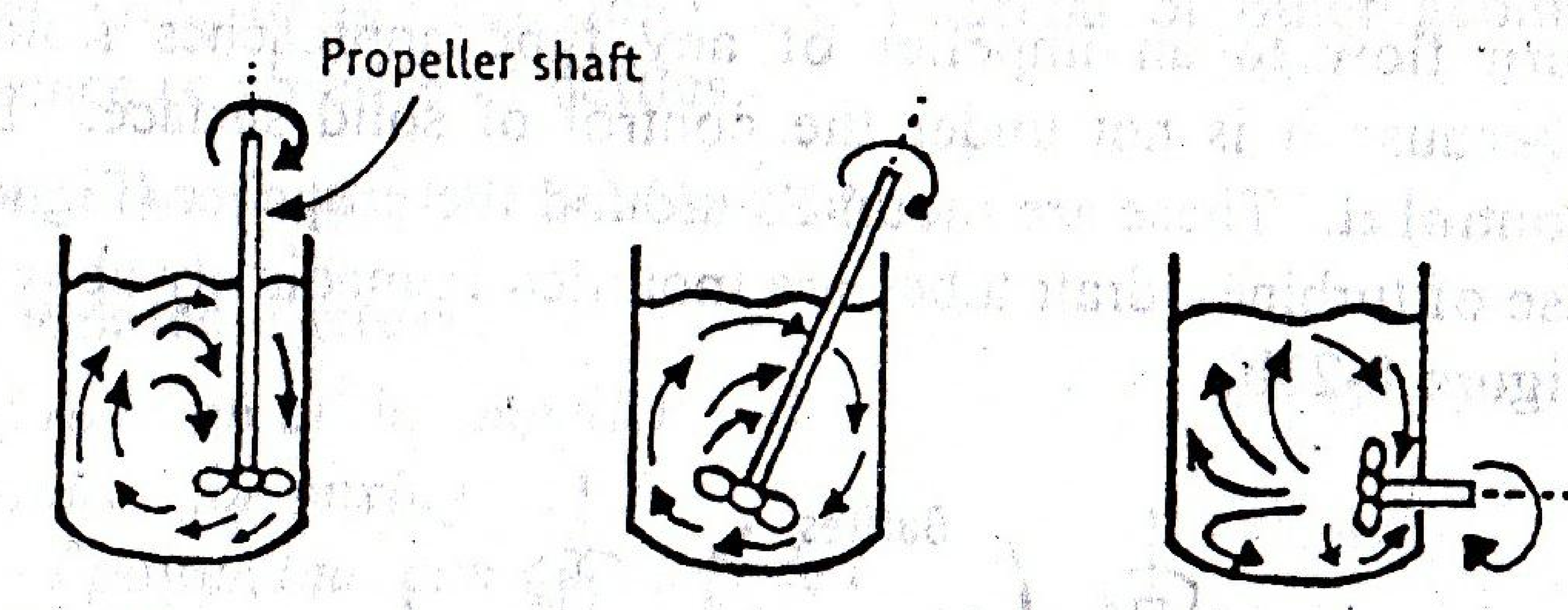
A similar effect can be observed by placing the impeller in an inclined position (Figure 8-20.1b).

In side entering propeller, swirl is seldom a problem. This geometry provides a baffling effect and results in circulation of material from the top to bottom in a vessel (Figure 8-20.1c). The disadvantage for this position is leakage, therefore, the packing round the shaft must be secured. Side entry is also a source of contamination, which is difficult to clean.

(2) Baffled containers should be used (Figure 8-20.2i). In such a case, impeller can be mounted vertically at the center.

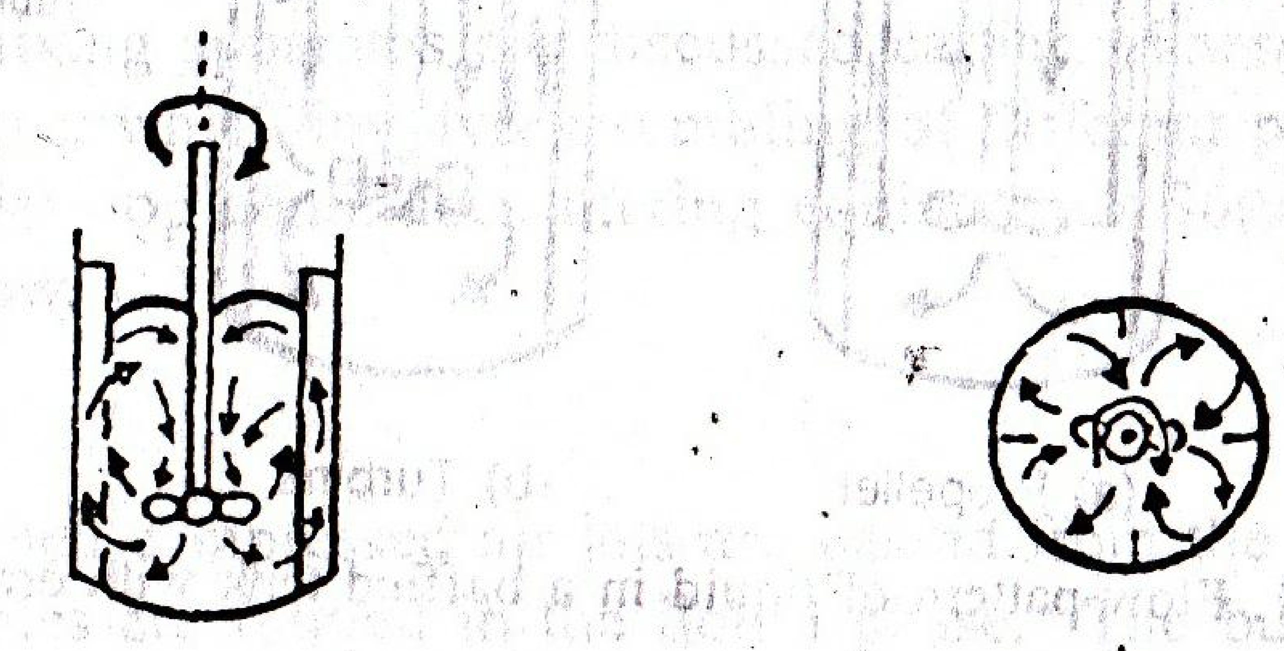
(3) Two or more impellers are mounted on same shaft in a tank where greater depth is desired. This system is known as *push-pull mechanism*. With such an arrangement each impeller acts as a separate mixer. Two types of flow are produced from impellers. The bottom impeller is placed about one impeller diameter above the bottom of the tank (Figure 8-20.3a and b). It creates a zone of high turbulence.

(4) Tanks other than cylindrical shape are used to prevent vortex formation. However, such shapes may facilitate the formation of dead spots.



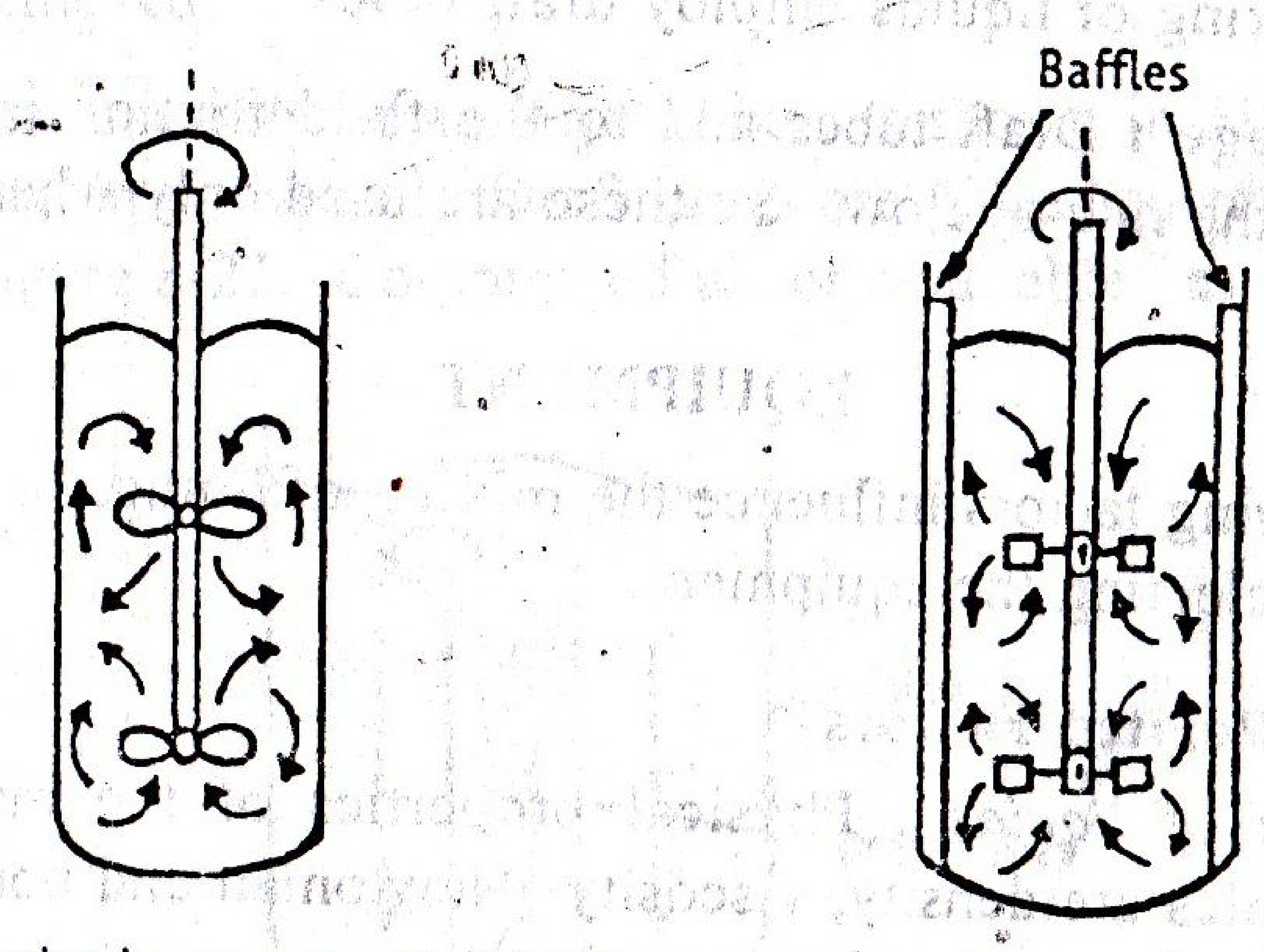
(a) Off center (b) Inclined (c) Side entry

1. Positions of propellers with flow pattern in a vessel to prevent vortex.



(i) Centrally placed propeller in a baffled tank, side view (ii) Centrally placed propeller in a baffled tank, top view

2. Arrangement of baffles and flow pattern in a vessel to prevent vortex.



(a) Propeller in an unbaffled tank (b) Turbine in a baffled tank

3. Arrangement of push-pull mechanism with flow patterns in a tank to prevent vortex.

Figure 8-20. Positions of impellers with flow pattern in a vessel to prevent vortex formation and gas entrapment.

Return Flow with Draft Tubes

Draft tubes are placed to control the direction and velocity of the flow to the impeller.

The return flow to an impeller of any type approaches from all directions, because it is not under the control of solid surface. Draft tubes can control it. These are mounted around the propeller (Figure 8-21a). In case of turbines, draft tubes are mounted immediately above the impeller (Figure 8-21b).

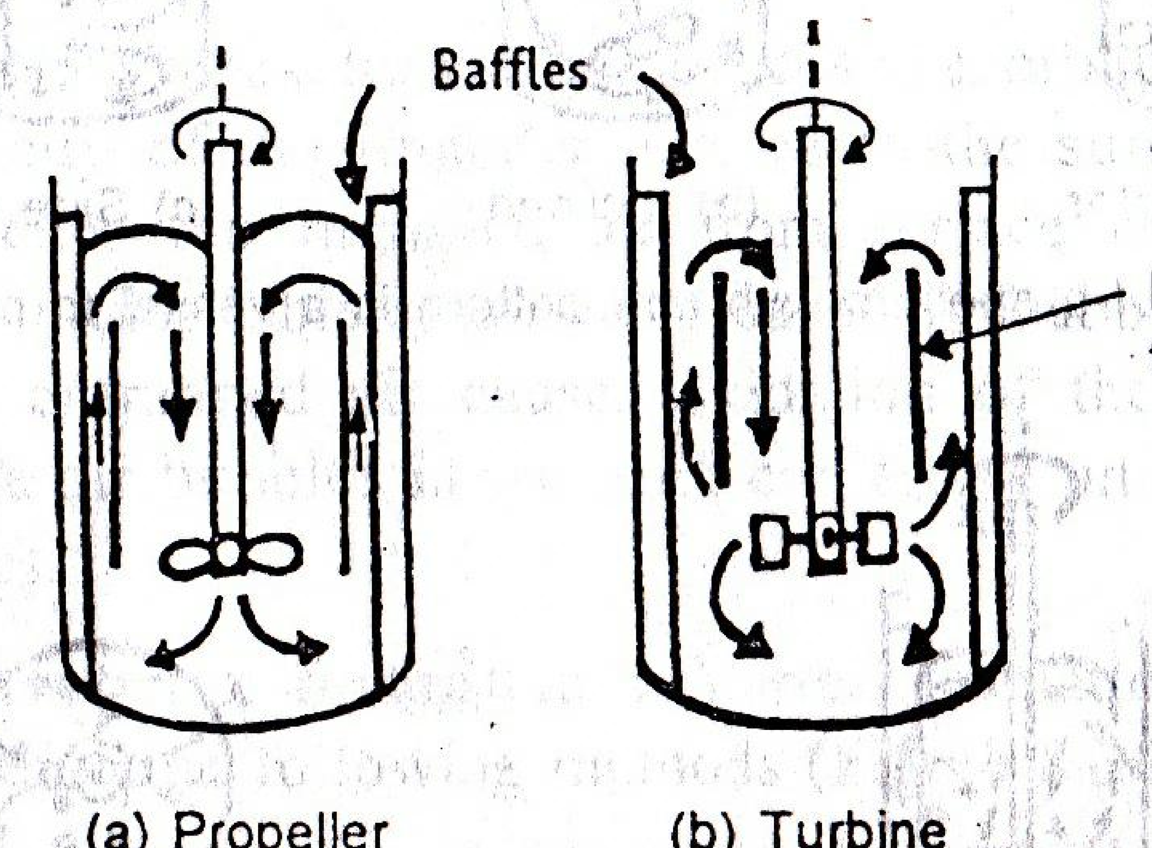


Figure 8-21. Flow pattern of liquid in a baffled tank with draft tubes

Uses : Draft tubes are fitted to equipment used in the manufacture of certain emulsions. When solid particles tend to float on the surface of the liquid, they are dispersed using draft tubes. Airjet mixers for continuous mixing of liquids employ draft tubes.

Disadvantage : Draft tubes add to the fluid friction in the system. These reduce the rate of flow. So these are used only when required.

EQUIPMENT

The following factors influence the mixing of liquids in tanks. These also help in selecting the equipment.

A. Material Related Factors

Properties of liquids : Physical properties of the materials to be mixed. Examples are density, viscosity (Newtonian and non-Newtonian) and miscibility (intermolecular attractions).

B. Equipment Related Factors

Shape of the impeller : Propeller type, straight, vertical, curved or pitched.

Position of the 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.

C. 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

The general mixing apparatus are discussed earlier. These are used for batch operations, which involve assembling of different parts. It is also possible to develop continuous mixing equipment. Some of them are discussed below.

AIRJET MIXER

Principle : When compressed air jets are passed from the bottom of a vessel, air bubbles are formed in the liquid phase. The buoyancy of the bubbles lifts the liquids, which are confined to the central portion due to the presence of draft tubes. The liquids flow down from the periphery of the vessel and enter from the bottom due to suction effect. Thus mixing is achieved.

Working : The assembly of an airjet mixer is shown in Figure 8-22. The liquid is placed in the vessel. Draft tubes are placed surrounding air jet as shown in Figure 8-22. Compressed air or a suitable gas is allowed

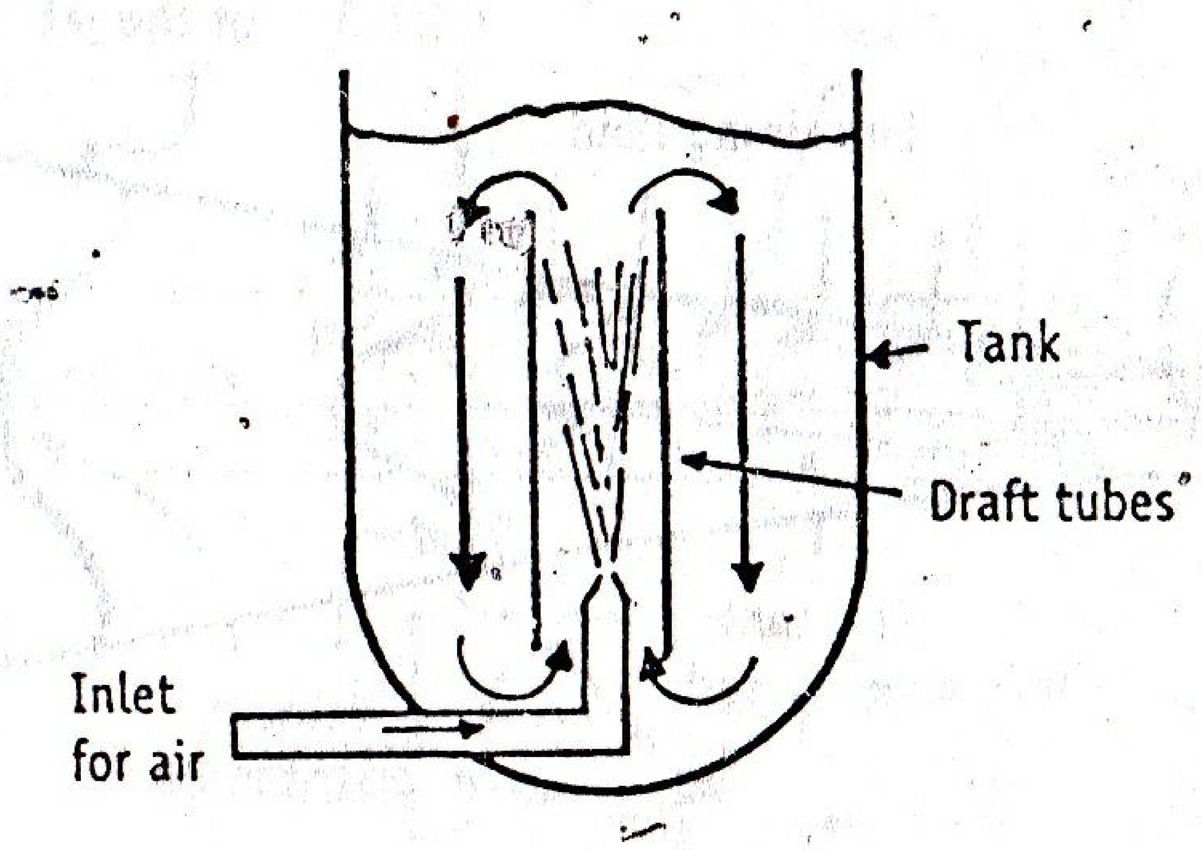


Figure 8-22. Vertical tank with centrally located airjet and draft tube. Mechanism of mixing.

to pass at high pressure from the inlet provided at the bottom of the tank. This causes buoyancy of the bubbles, which lifts the liquids from bottom to the top of the vessel.

Draft tubes serve to confine the expanding bubbles, and entrained liquids to the central portion. This results in a more efficient lifting action by the bubbles. The liquid mixture flows down from the periphery of the vessel. The overall circulation brings liquids from all parts of the vessel to the region of the jet itself. Thus mixing is achieved.

Uses : Liquids of low viscosity, non-foaming, non-reactive with gas are mixed by using airjet mixer.

JET MIXER

Principle : The liquids to be mixed are pumped separately into a jet mixer at different velocities. The high velocity fluid has a lower static pressure than surrounding liquid (higher static pressure). During mixing, the slow moving liquid will be drawn into the high velocity jet. This increases the volume of the jet and decreases velocity, which causes the jet to expand. Thus shear is developed and aids in mixing.

Working : The construction of a jet mixer is shown in Figure 8-23. Two liquids are introduced into the mixing tank at different velocities. One liquid is pumped through a small nozzle at uniform high velocity. The second liquid enters the tank at a low velocity. The fast moving liquid impinges on the slow moving liquid at high velocity. As the jet moves away from the orifice, the area of its influence decreases. The core of the jet is surrounded by an expanding turbulent jet, in which the radial velocity decreases with distance from the center-line of the jet.

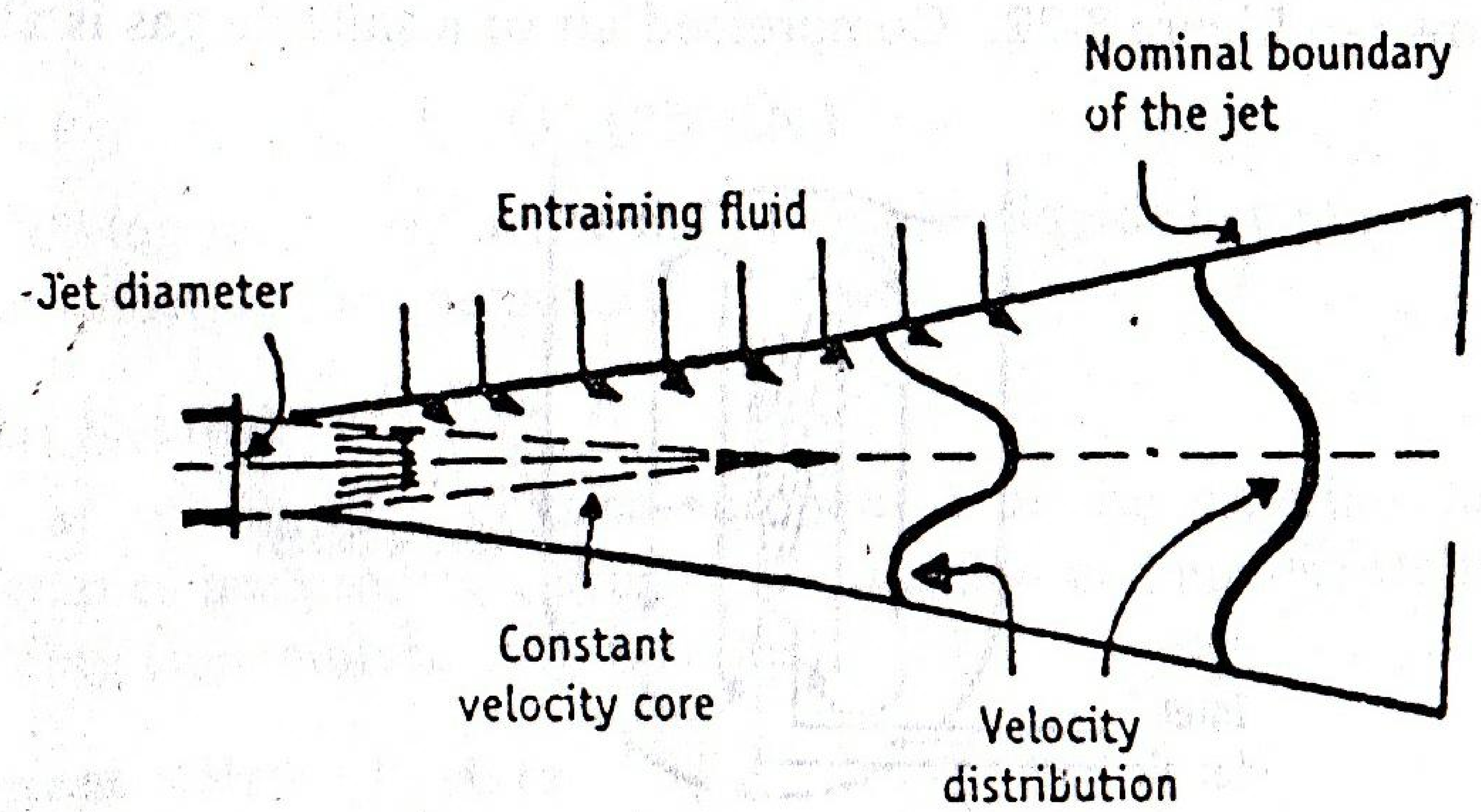


Figure 8-23. Mechanism of mixing in submerged circular jet mixer.

When a rapidly moving liquid comes in contact with slow moving (or almost stationary) liquid, high velocity gradient will be developed at the boundary. As a result, strong shear stresses exist at the boundary, which induce mixing in two ways.

(1) The stresses tear off portions of the fast moving stream and send it off into the slower moving areas as vortexes or eddies. The shear stresses tear off eddies and generates considerable turbulence, which contributes to the mixing action.

(2) When a slow moving liquid enters the jet, the volume of jet increases and velocity decreases. This decreasing velocity causes the jet to expand. Thus shear develops which aids in mixing.

Enough time and space must be provided for the stream to blend thoroughly into the mass of fluid by the mechanism of entrainment.

Advantage : The power required for pumping is often sufficient to accomplish the mixing operation.

FLOW MIXER OR LINE MIXER OR PIPE MIXER

The constructions of a baffled pipe mixer and a chamber mixer are shown in Figure 8-24a and b, respectively. Liquids to be mixed are passed through the pipe. Mixing takes place mainly through bulk transport in the direction of flow. Placing certain devices, such as vanes, baffles, screws, grids and a combination of them, enhances the mixing efficiency. Little additional power supplied to pump the liquid itself accomplishes mixing.

For an effective mixing, controlling the feed rate is essential. Suitable metering devices are employed. If input rate is difficult to control

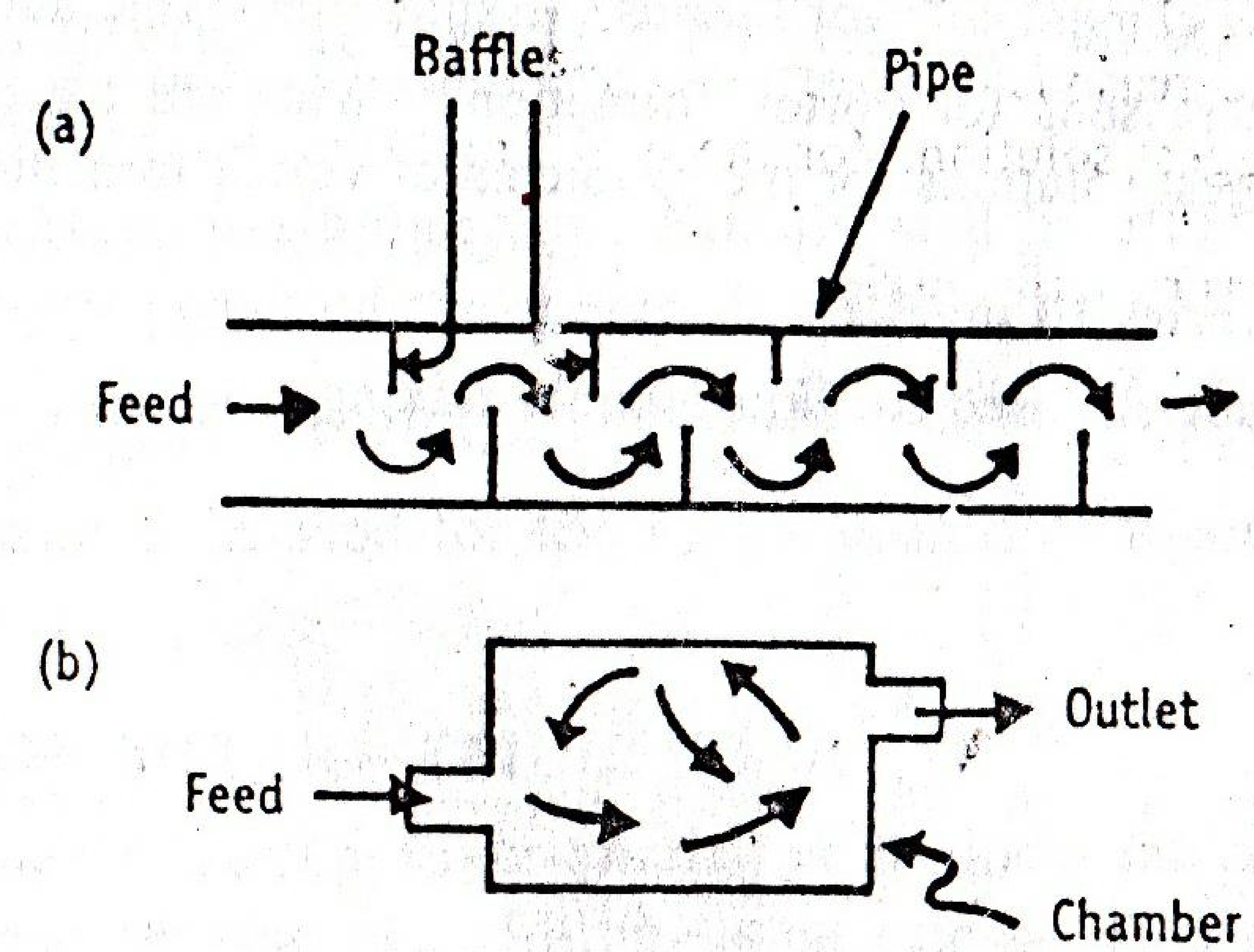


Figure 8-24. Flow pattern of continuous mixer or line mixer.

and fluctuations in the added proportions of the liquids are unavoidable, continuous mixing equipment of tank type is preferable, because hold-up of the liquids and back flow or recirculation is possible.

Uses : When large volume of liquids are to be mixed, flow mixers are used.

(a) Baffled pipe mixer with little back flow.

(b) Chamber mixer with flow induced recirculation and hold up.

QUESTION BANK

Each question carries 2 marks

1. Define and differentiate mixing and agitation.
2. Classify liquids based on their miscibility. Give one example in each case.
3. Enumerate the applications of liquid mixing.
4. Describe the mechanisms for liquid mixing.
5. What are the factors affecting selection of a mixer?
6. How are pipe mixers advantageous in liquid mixing?
7. What do you mean by vortex? How is it prevented?

Each question carries 5 marks

1. Give the characteristics of mixing impellers.
2. Describe the operation of agitator mixers.
3. Describe the turbine mixer with flow pattern.
4. Suggest a suitable mixer and its operation for mixing of viscous liquids.
5. Draw a neat-labeled diagram of mixing tank with accessories for efficient liquid mixing.
6. Describe the principle, working and advantages of jet mixer.
7. What are flow components for liquids? Explain their role during mixing.
8. What are the reasons for vortex formation? What are the drawbacks of vortex? Suggest solutions for the problems of vortex formation.

Each question carries 10 marks

1. Discuss the devices used for liquid-liquid mixing.

Section III—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 these equipment are 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.

Some equipment used for the preparation of emulsions are described below.

SILVERSON MIXER—EMULSIFIER

Principle : Silverson mixer-emulsifier produces intense shearing forces and turbulence by the use of high-speed 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 Silverson emulsifier is shown in the Figure 8-25. 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 and 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.

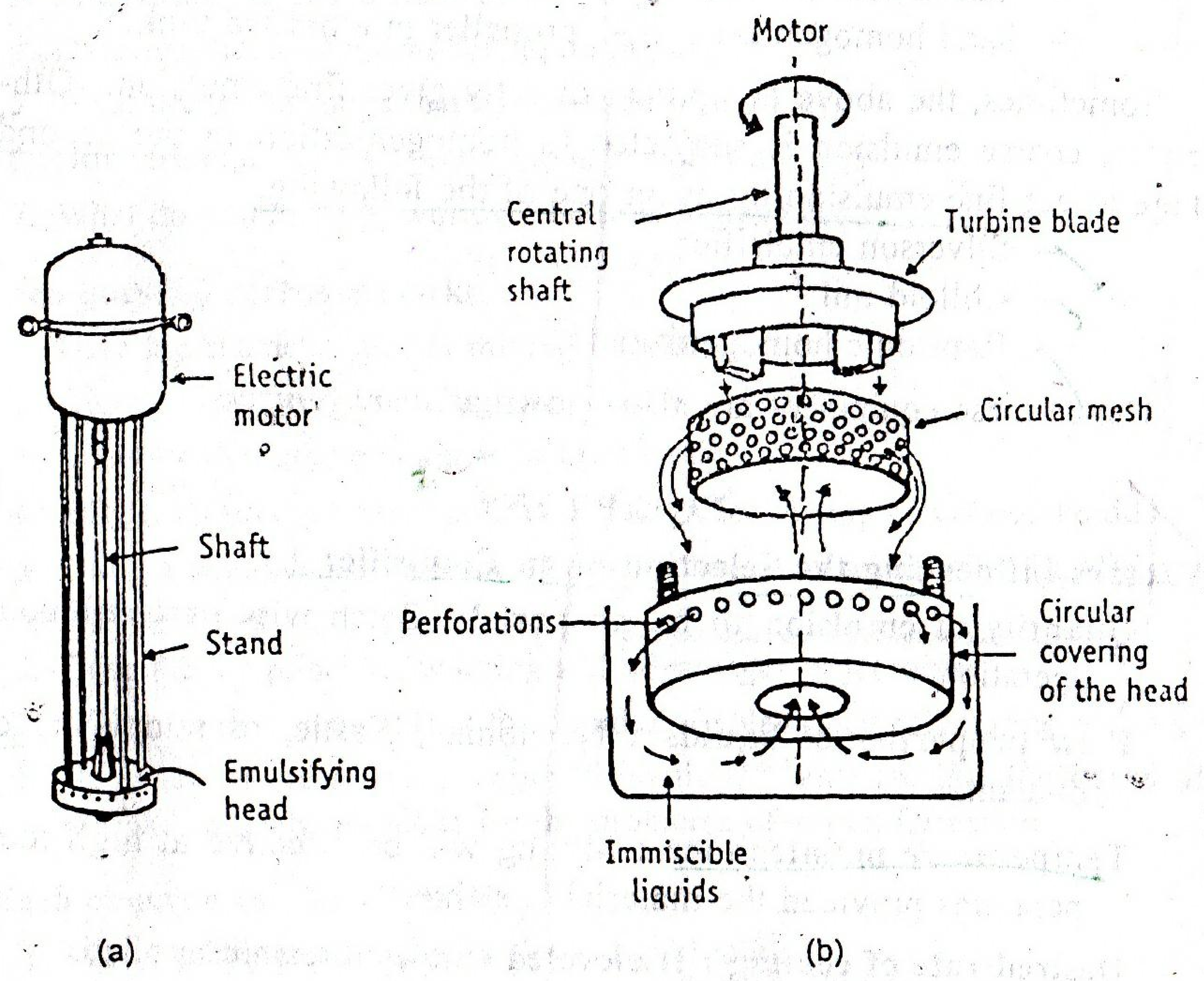


Figure 8-25. Construction of Silverson emulsifier.

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 central 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 center of the base and subjected to

intense mixing action. Centrifugal forces expel the contents of the head with great force through the mesh and onto the cover (Figure 8-25b). 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.

COLLOID MILL

Principle : Colloid mill is based on the principle that the coarse emulsion is intensely sheared in a narrow space between the fast moving rotor and stator for a short period to get a very fine emulsion.

Colloid mill is a mixer as well as milling equipment because size reduction is also simultaneously involved. The construction, working, advantages and disadvantages are discussed in the Chapter 6, Size Reduction.

ULTRASONIC EMULSIFIERS—RAPISONIC HOMOGENIZER

Principle : When a liquid is subjected to ultrasonic vibrations, alternate regions of compression and rarefaction are produced in the liquid. Cavities are formed in the regions of rarefaction, which subsequently collapse in the regions of compression. This results in the generation of great forces for emulsification.

Construction : The construction of a Rapisonic homogenizer is shown in Figure 8-26. It consists of a pump driven by a motor. It is connected with an inlet tube and outlet tube for the discharge of a fine emulsion. The homogenizer head consists of a flat jet for liquid inlet. Facing the jet, a thin blade is present with edges facing each other. This blade vibrates at its natural frequency of about 30 kilohertz.

Working : Coarse emulsion is pumped into Rapisonic homogenizer through one end of a tube. A powerful stream of liquid is forced through the jet. Liquid impinges on the blade causing it to vibrate. The streaming liquid deflects on either side alternatively with the result that oscillations above the sonic range are produced in the liquid. During this process, the emulsion experiences alternate regions of compression and rarefaction. In the regions of rarefaction, cavities are formed. Because of external pressure, the cavities collapse violently afterwards. Thus sufficient turbulence is created which is capable of causing dispersion of phases. Thus a coarse emulsion is converted into a fine emulsion.

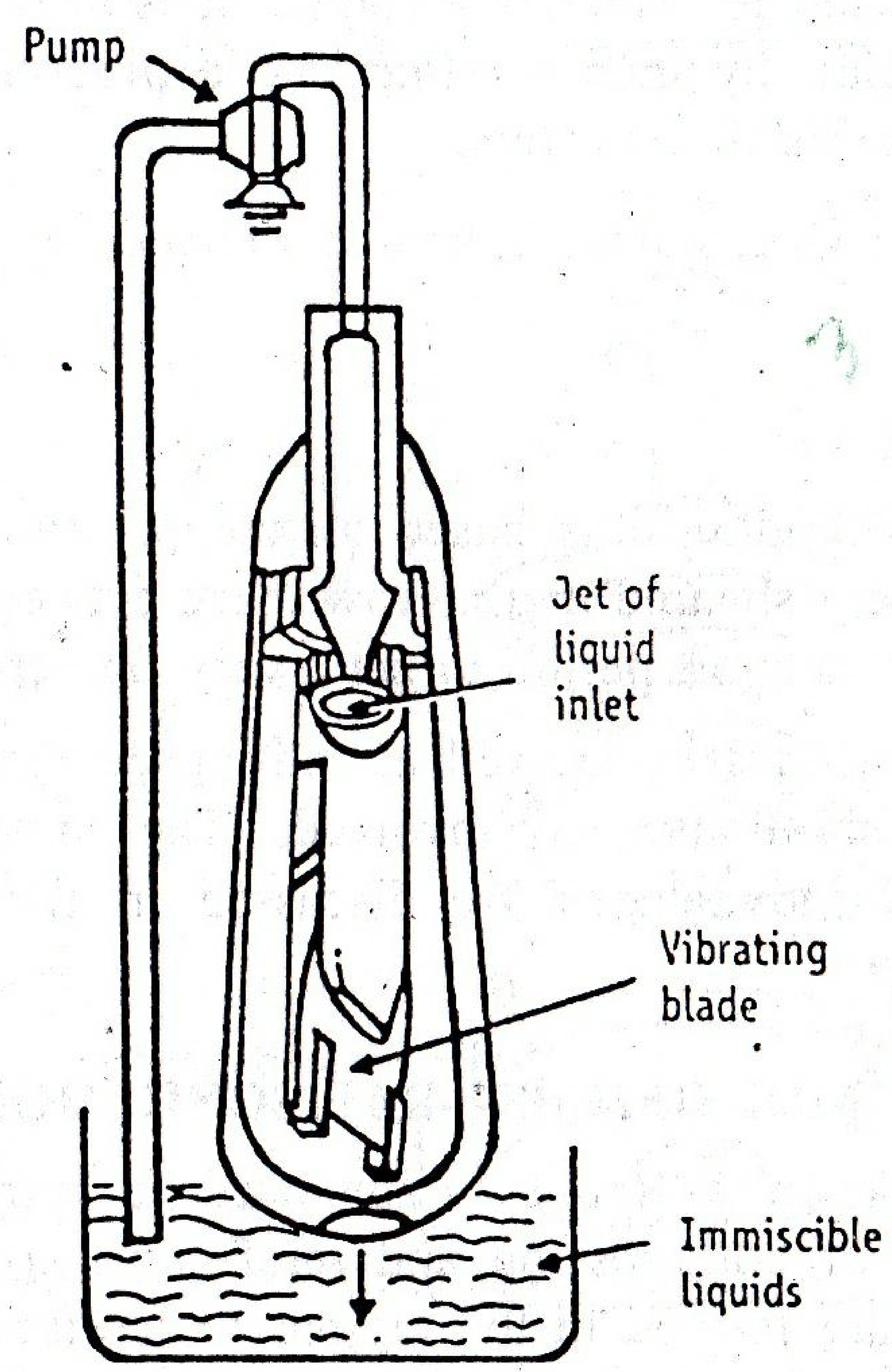


Figure 8-26. Construction of Rapisonic homogenizer.

Advantages : (1) Rapisonic homogenizer can be used either for batch process by placing it in a tank or for continuous process by keeping in a pipeline. In a pipeline, the time of exposure is less for a given sample of liquid in one pass. So, mixing may be incomplete. To ensure complete mixing, liquids must be recirculated.

(2) It has the capacity to produce dispersed globules of one micron size.

(3) As this method is highly efficient to decrease globule size. reduced concentration of emulgents is sufficient.

(4) Its capacity of mixing liquids ranges from 20 to 500 litres per minute.

(5) In Rapisonic homogenizer, heat is not generated during mixing unlike colloid mill. Hence this is suitable for thermolabile substances.

Disadvantage : Rapisonic homogenizer is useful only with liquids of low viscosity.

Section IV—MIXING OF SEMISOLIDS

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.

EQUIPMENT

Classification of Equipment

Agitator mixers : Examples are sigma mixer and planetary mixer.

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

Sigma blade mixer and planetary mixer are discussed in the solid-solid mixing. Colloidal mill is discussed in the Chapter 'Size Reduction'. Triple roller mill is discussed here.

Selection of Mixing Equipment for Semisolids

(1) Physical properties of the materials - density, viscosity and miscibility.

(2) Economic considerations regarding processing - time required for mixing and power consumption.

(3) The cost of equipment and its maintenance.

TRIPLE ROLLER MILL

Principle : The differential speed and the narrow space between the rollers develop high shear over the material. This shear causes crushing of aggregates, particles and also distributes the drug uniformly through out the semisolid base.

Construction : The construction of a triple roller mill is shown in Figure 8-27. It consists of three parallel rollers of equal diameters. These are made up of hard abrasion resistant material, normally stainless steel. The rollers are mounted in a rigid framework horizontally. The pressure and gap between the rollers are independently adjustable. A hopper is arranged between the first two rollers. A scrapper is attached to the last roller.

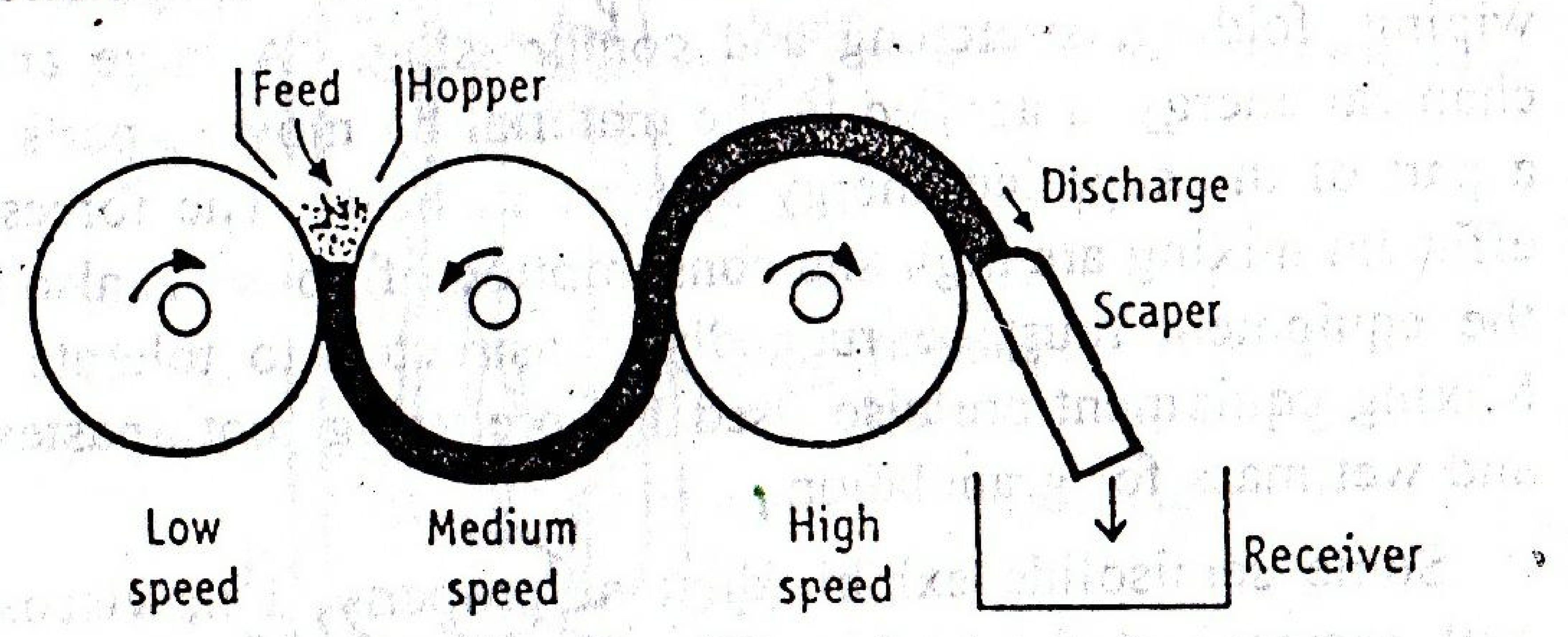


Figure 8-27. Construction of triple roller mill.

Working : The gap between the last two rollers is adjusted to be less than the gap between the first two rollers. The rollers are rotated at different speeds. In practice, the first roller (receiving-roller) rotates at a slower speed compared to the second roller. Similarly second roller speed is less than that of third roller (discharge roller).

The feed is passed through the gap between the first and second rollers. The aggregates and particles are crushed and then abraded by the rubbing action of the rollers, which is developed due to different speeds of rotation. A film of appreciable thickness of the feed is produced. The material passes from slow rotating to fast rotating roller.

Between second and third roller, the gap is small and produces a thinner film of feed. The speed of the third roller is increased to compensate the reduction of cross sectional area. In the thinning film, more crushing and more abrasion are developed.

Finally the scrapper removes the material completely from the last roller which can be collected immediately into the receiver or transported through a suitable conveyor.

Advantage : Triple roller mill is suitable for continuous processes. Extremely uniform dispersion is obtained.

QUESTION BANK

Each question carries 2 marks

1. Suggest suitable mixing equipment for semisolids.
2. Describe the different factors influencing the selection of an emulsifier.

Each question carries 5 marks

1. Describe the construction and working of a Silverson mixer-emulsifier with the help of a neat diagram.

Each question carries 10 marks

1. With a neat sketch, describe the construction and working of equipment for mixing pastes and plastic masses. What are their pharmaceutical applications?