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Mixing

Almost every pharmaceutical product contains more than one component, and this necessitates mixing or blending stages in their manufacturing process. Perry and Chilton (1973) defined *mixing* as a process "in which two or more ingredients in separate or roughly mixed condition are treated so that each particle of any one ingredient is as nearly as possible adjacent to a particle of each of the other ingredients." The term *blending* is synonymous with mixing, and *demixing* or *segregation* is the opposite.

Mixing tends to result in a randomization of dissimilar particles within a system. This is to be distinguished from an ordered system in which the particles are arranged according to some iterative rule and thus follow a repetitive pattern. It is possible to consider the mixing of particles differing only by some vector quantity, such as spatial orientation or translational velocity.

Mixing is a fundamental step in most process sequences, and is normally carried out:

1. To control heat and mass transfer
2. To secure uniformity of composition so that small samples withdrawn from a bulk material represent the overall composition of the mixture
3. To improve single phase and multi-phase systems
4. To promote physical and chemical reactions, such as dissolution, in which natural diffusion is supplemented by agitation

Mixing can be classified as positive, negative, or neutral. Positive mixing applies to the systems where spontaneous, irreversible and complete mixing would take place, by diffusion, without the expenditure of energy, provided time is unlimited, although the input of energy by using mixing apparatus will shorten the time required to obtain the desired degree of mixing. In general, positive mixtures, such as a mixture of two gases or two miscible liquids do not present any problems during mixing. Negative mixing is demonstrated by biphasic systems, in which the phases differ in density. Any two-phase systems such as suspensions of solids in liquids, emulsions and creams tend to separate out quickly, unless energy is continually expended on them. Negative mixtures are generally more difficult to form and maintain, and require a higher degree of mixing as compared to positive mixtures. Neutral mixing occurs when neither mixing nor demixing takes place unless the system is acted upon by an external energy input. Neutral mixtures are static in behavior, have no tendency to mix spontaneously or segregate spontaneously and include mixture of powders, pastes and ointments. The following text deals with the fundamental concepts and equipment employed in the pharmaceutical industries to obtain satisfactory mixing and focuses on practical considerations involved in the evaluation of mixing efficiency. The equipments used for mixing liquids, semisolids and solids are depicted in Fig. 1.1.

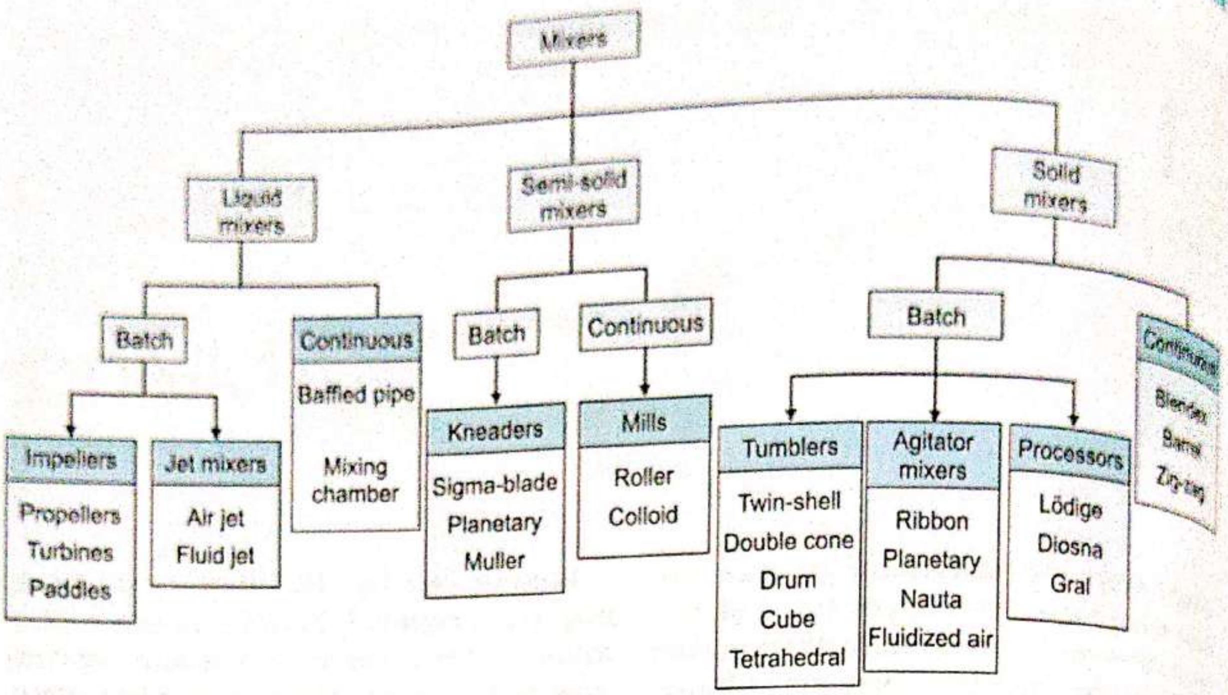


Fig. 1.1: Classification tree of mixing equipments

LIQUID MIXING

Mixing Mechanisms

Mixing mechanisms for fluids fall essentially into four categories: bulk transport, turbulent flow, laminar flow, and molecular diffusion. Usually, more than one of these mechanisms is operative in practical mixing situations.

Bulk Transport

The movement of a relatively large portion of the material being mixed from one location in a system to another constitutes bulk transport. A simple circulation of material in a mixer, however, does not necessarily result in efficient mixing. For bulk transport to be effective, it must result in a rearrangement or permutation of the various portions of the materials to be mixed. This is usually accomplished by means of paddles, revolving blades, or other devices, within the mixer, arranged so as to move adjacent volumes of the fluid in different directions, thereby shuffling the system in three dimensions.

Turbulent Mixing

The phenomenon of turbulent mixing is the direct result of turbulent fluid flow, which is characterized by a random fluctuation of the fluid velocity at any given point within the system. The fluid velocity at any given instant may be expressed as the vector sum of its components in the x, y, and z directions. With turbulence, these directional components fluctuate randomly about their individual mean values, as does the velocity itself.

In general, with turbulence, the fluid has different instantaneous velocities at different locations and such velocity differences within the body of fluid produce a randomization of the fluid molecules. For this reason, turbulence is a highly effective mechanism of mixing.

Turbulent flow can be conveniently visualized as a composite of eddies of various sizes. An eddy is defined as a portion of a fluid moving as a unit in a direction often contrary to that of the general flow. Large eddies tend to break up, forming eddies of smaller size until they are no longer distinguishable. The size distribution of eddies within a turbulent region is referred to as the *scale of turbulence*. Thus, when small eddies are predominant, the *scale of turbulence* is low.

An additional characteristic of turbulent flow is its *intensity*, which is related to the velocities with which the eddies move. A composite picture of eddy size versus the velocity distribution of each size eddy may be described as a complex spectrum. Such a spectrum is the characteristic of a turbulent flow and is used in its analysis.

Laminar Mixing

Streamline or laminar flow is frequently encountered when highly viscous fluids are being processed. It can also occur if stirring is relatively gentle and may exist adjacent to stationary surfaces in the vessels in which the flow is predominantly turbulent. When two dissimilar liquids are mixed through laminar flow, the shear that is generated stretches the interface between them. If the mixer employed folds the layers back upon themselves, the number of layers, and hence the interfacial area between them, increases exponentially with time. This relationship is observed because the rate of increase in interfacial area with time is proportional to the instantaneous interfacial area.

Mixers may also operate by simply stretching the fluid layers without any significant folding action. This mechanism does not have the stretch compounding effect produced by folding, but may be satisfactory for some purposes in which only a moderate reduction in *mixing scale* (defined in detail later) is required. It should be pointed out, however, that by this process alone, an exceedingly long time is required for the layers of the different fluids to reach molecular dimensions. Therefore, good mixing at the molecular level requires a significant contribution by molecular diffusion after the layers have been reduced to a reasonable thickness (several hundred molecules) by laminar flow.

Molecular Diffusion

The primary mechanism responsible for mixing at the molecular level is diffusion, resulting from the thermal motion of the molecules. When it occurs in conjunction with laminar flow, molecular diffusion tends to reduce the sharp discontinuities at the interface between the fluid layers, and if allowed to proceed for sufficient time, results in complete mixing.

The process is described quantitatively in terms of Fick's first law of diffusion:

$$\frac{dm}{dt} = -DA\frac{dc}{dx} \quad \text{... (1)}$$

where the rate of transport of mass, dm/dt, across an interface of area, A, is proportional to the concentration gradient, dc/dx, across the interface. The rate of intermingling is governed also by the diffusion coefficient, D, which is a function of the variables, i.e. fluid viscosity and size of the diffusing molecules. The sharp interface between dissimilar fluids, which has been generated by laminar flow, may be rather quickly eliminated by the resulting diffusion. Considerable time may be required, however, for the entire system to become homogeneous.

Equipments

A system for liquid mixing commonly consists of two primary components: (1) a tank or other container suitable for holding the material being mixed, and (2) a means of supplying energy to the system so as to bring about reasonably rapid mixing. Power may be supplied to the fluid mass by means of an impeller, air stream, or liquid jet. Besides supplying power, these also serve to direct the flow of material within the vessel. Baffles, vanes, and ducts are also used to direct the bulk movement of material in such mixers, thereby increasing their efficiency. When the material to be mixed is limited in volume so that it may be conveniently contained in a suitable mixer, *batch mixing* is usually more feasible, however, for larger volumes *continuous mixing* is preferred.

Impellers

Liquids are most commonly mixed by impellers rotating in tanks. These impellers are classified as (i) propellers, (ii) turbines and (iii) paddles. The distinction between impeller types is often made on the basis of the type of flow pattern they produce, or on the basis of the shape and pitch of the blades. The turbulent flow imposed by impeller causes mixing by projecting eddies into, and entraining liquid from the neighboring zone, thereby preventing the formation of dead zones. The flow pattern may be analyzed in terms of three components: radial (perpendicular to the impeller shaft), axial or longitudinal (parallel to the impeller shaft), and tangential (tangential to the circle of rotation around the impeller shaft). These may occur singly or in various combinations. Figure 1.2 illustrates these patterns as they occur in vertical cylindrical tanks.

Propellers

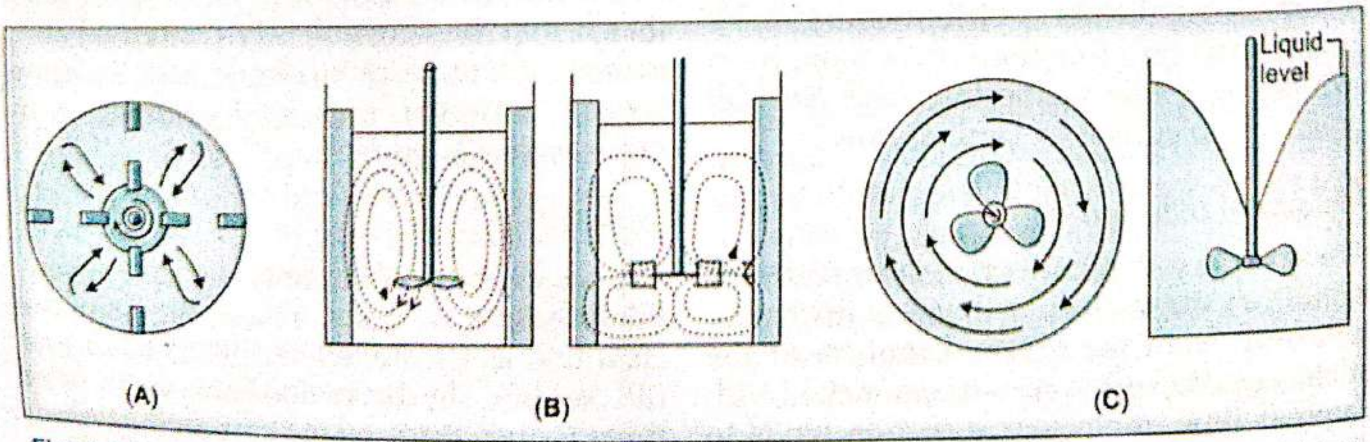
Propellers of various types and forms are used, but all are essentially a segment of a multithreaded screw, that is, a screw with as many threads as the propeller blades (Fig. 1.3A). Also, like the machine screws, propellers may be either right- or left-handed depending on the direction of slant of their blades. As with screws, the propeller pitch is defined as the distance of axial movement per revolution, if no slippage occurs. Although any number of blades may be used, the three-blade design is most commonly used with fluids. The blades may be set at any angle or pitch, but for most applications, the pitch is approximately equal to the propeller diameter. Propellers are most efficient when they run at high speeds in liquids of relatively low viscosity. Although some tangential flow does occur, the primary effect of a propeller is due to axial flow. Also, intense turbulence usually occurs in the immediate vicinity of the propeller. Consider, for example, a downdraft propeller vertically mounted midway to the bottom of the tank. Moderate radial and tangential flow occurs above and below the blade, which acts in conjunction with the axial flow near the shaft, brings portions of fluid together from all regions of the tank, and passes them through the intense turbulence near the blades.

Turbines

They are usually distinguished from propellers in that the blades of the latter do not have a constant pitch throughout their length. When radial-tangential flow is desired, turbines with blades set at a 90-degree angle to their shaft are employed. With these type of impellers, a radial flow is induced by the centrifugal action of the revolving blades. The drag of the blades on the liquid also results in tangential flow, which in many cases is undesirable. Turbines having tilted blades produce an axial discharge quite similar to that of propellers. Because they lend themselves to a simple and rugged design, these turbines can be operated satisfactorily in fluids 1000 times more viscous than fluids in which a propeller of comparable size can be used. Various types of turbines are depicted in Figs 1.3B to D.

Paddles

Paddles are also employed as impellers and are normally operated at low speeds of 50 rpm



Figs 1.2A to C: Diagrammatic representation of flow patterns induced by impellers: (A) Radial flow, (B) Axial flow, (C) Tangential flow

or less. Their blades have a large surface area as compared to the tank in which they are employed, a feature that permits them to pass close to the tank walls and effectively mix viscous liquids and semisolids, which tend to cling to these surfaces. Circulation is primarily tangential, and consequently, concentration gradients in the axial and radial directions may persist in this type of mixer even after prolonged operation. Operating procedures should take these characteristics into account, so as to minimize their undesirable effects. With such mixers, for example, ingredients should not be layered when they are added to the mixing tank. Such vertical stratification can persist even after very long mixing times. The mainstays of high viscosity mixing systems have been gate paddle, anchor paddle and helix (Figs 1.3E to H). These continue to rule the roost, albeit with some interesting hybridization. One of the promising hybrids of paddle mixer is dispertron (Fig. 1.4). It has coaxial blades one for macro mixing and the other for micromixing. Counter rotation of macro- and micromixing elements with variable speed is useful for mixing extremely viscous materials, materials with high solid content and for emulsification and homogenization. The equipment generates maximum shear without vortex formation and minimal air entrapment.

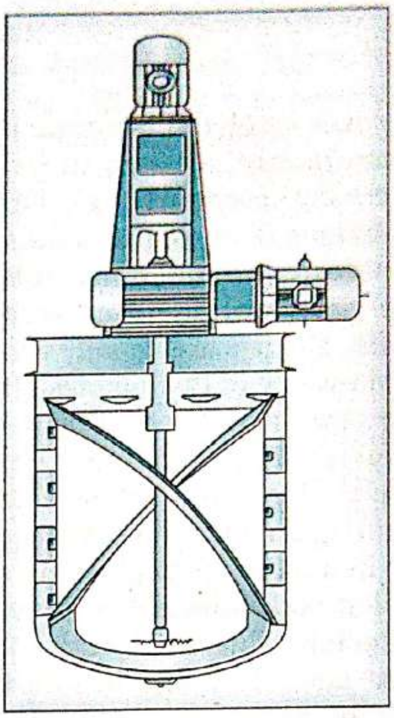
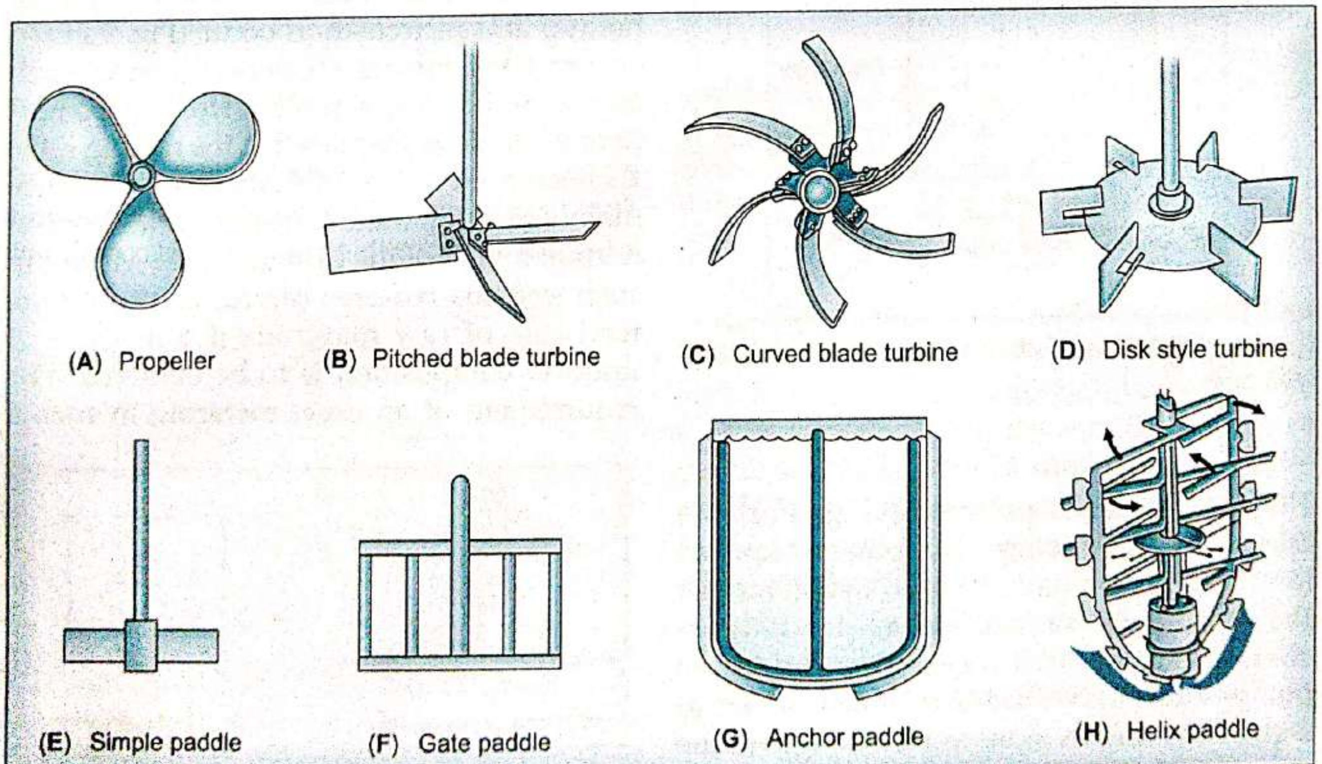


Fig. 1.4: Dispertron: Hybrid of paddle mixer



Figs 1.3A to H: Impeller blade types: (A) Propeller; (B-D) Turbines; (E-H) Paddles

Jet Mixers

Air Jets

Air jet devices involve sub-surface jets of air, or less commonly of some other gas, for effective mixing of certain liquids. Of necessity and for obvious reasons, the liquids must be of low viscosity, nonfoaming, nonreactive with the gas employed, and reasonably nonvolatile. The jets are usually arranged so that the buoyancy of the bubbles lifts liquids from the bottom to the top of the mixing vessel. This is often accomplished with the aid of draft tubes (Fig. 1.5). These serve to confine the expanding bubbles and entrained liquids, resulting in a more efficient lifting action by the bubbles, and inducing an upward fluid flow in the tube. This flow tends to circulate fluid in the tank, bringing it into the turbulent region in the vicinity of the jet. The overall circulation in the mixing vessel brings fluid from all parts of the tank to the region of the jet itself. Here, the intense turbulence generated by the jet produces intimate mixing.

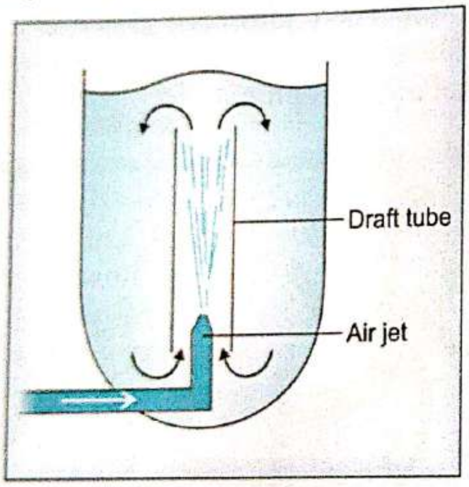


Fig. 1.5: Vertical tank with centrally located air jet and draft tube

Fluid Jets

They utilize liquids pumped at high pressure into a tank for mixing. The power required for pumping can often be used to accomplish the mixing operation, either partially or completely. In such a case, the fluids are pumped through nozzles arranged to permit a good circulation of material throughout the tank (Fig. 1.6). In operation, fluid jets behave somewhat like propellers and they generate turbulent flow axially. However, they do not themselves generate tangential flow, like propellers. Jets also may be operated simply by pumping liquid from the tank through the jet back into the tank.

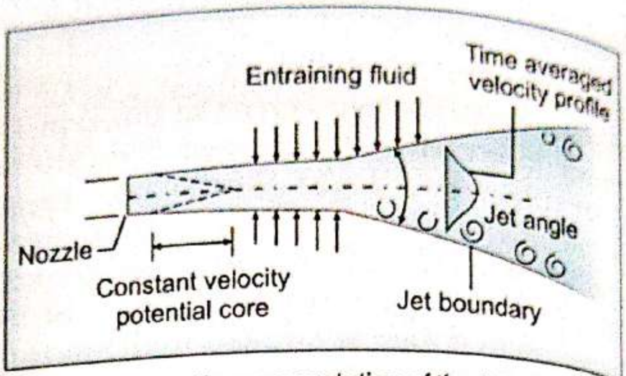
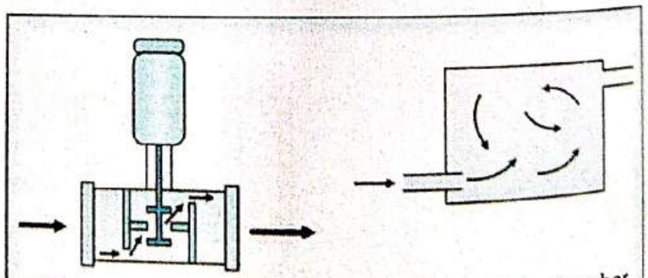


Fig. 1.6: Schematic representation of the fluid jet entering a mass of stationary liquid

Continuous or In-line Mixers

The process of continuous mixing produces an uninterrupted supply of freshly mixed material, and is often desirable when very large volumes of materials are to be handled. It can be accomplished essentially in two ways: in a *tube or pipe* through which the material flows and in which there is very little back flow or recirculation, or in a *mixing chamber* in which a considerable amount of holdup and recirculation occur (Fig. 1.7). To ensure good mixing efficiency, devices such as vanes, baffles, screws, grids, or combinations of these are placed in the mixing tube. As illustrated in Fig. 1.7A, mixing takes place mainly through mass transport in a direction normal to that of the primary flow. Mixing in such systems requires careful control of the feed rate of raw materials if a mixture of uniform composition is to be obtained. The requirement of an exact metering in such a



Figs 1.7A and B: Continuous fluid mixing devices: (A) Baffled pipe mixer; (B) Mixing chamber

device results from the lack of recirculation, which would otherwise tend to average out concentration gradients along the pipe. Where suitable metering devices are available, this method of mixing is very efficient. Little additional power input over that required for simple transfer through a pipe is necessary to accomplish mixing.

When input rate is difficult to control and fluctuations in the ratio of added ingredients are unavoidable, continuous mixing equipment of the tank-type is preferred. Fluctuations in composition of the mixture are greatly reduced by the dilution effect of the material contained in the tank. For example, consider a tank of volume V, which is stirred so as to be perfectly mixed at all times, as illustrated in Fig. 1.8. If each increment of added material is instantaneously distributed evenly throughout the vessel, and the concentrations of equal volumes entering and leaving the mixer are designated as C_i and C_o respectively, conservation of mass requires that:

$$V\frac{dC_o}{d_t} = (C_i - C_o)\frac{dv}{dt} \quad \text{... (2)}$$

where, dv/dt is the rate of flow of material through the tank. For a given concentration difference $(C_i - C_o)$ and flow rate dv/dt, the rate of change of concentration of the effluent with time, dC_o/dt, is inversely proportional to the tank volume. Two tanks in series, each having a volume $V/2$ or half that of the single tank just discussed, would be even more effective

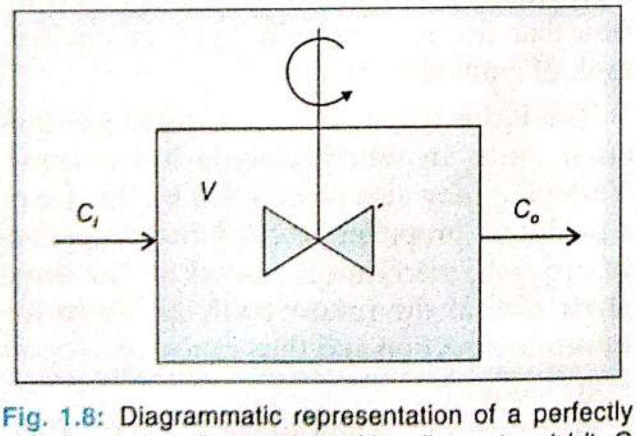


Fig. 1.8: Diagrammatic representation of a perfectly mixed tank in a flow stream with a flow rate, dv/dt. C_i and C_o represent the concentrations entering and leaving the tank at any given instant, respectively

in reducing concentration fluctuations while having the same hold-up. This is true when random fluctuations in concentration occur over small volume increments compared with the tank volumes. This is essentially a serial dilution effect.

Example: When integrated, equation (2) yields the expression:

$$C_o = C_i(1 - e^{-kt}) \quad \text{... (3)}$$

where, $k = dv/Vdt$. When two identical tanks, each of volume $V/2$, are connected in series, the relationship between input and output concentrations becomes:

$$C_o = C_i\,(1 - e^{-2kt} - 2kte^{-2kt}) \quad \text{... (4)}$$

For comparison purposes, let us set k equal to 0.1 min^{-1}, and examine the ratio of C_o to C_i after 5 min of operation, with the mixing tank(s) at an initial concentration of C_o and with a constant inlet concentration of C_i. When a single tank is used, C_o/C_i equals 0.393, whereas with two tanks in series, each having one-half of the volume, C_o/C_i is 0.264. This effect appears more pronounced at shorter times and less so over longer periods in relation to k, when C_o closely approaches C_i.

$$\frac{C_o}{C_i} = 1 - e^{-1/2} = 0.393$$

$$\frac{C_o}{C_i} = 1 - e^{-1} - e^{-1} = 0.264$$

An effect similar to that obtained with two tanks can be observed with a turbine-agitated tank having vertical side-wall baffles. If the turbine impeller is located near the middle of the tank, two regions of mixing occur above and below the impeller as shown in Fig. 1.9. Mass transport between these zones is relatively slow. This has the effect of two areas of rapid mixing, and the net effect of such a mixer is analogous to that obtained by the operation of two tanks, of the type shown in Fig. 1.8, in series. Complex arrays of interconnected tanks, both in series and parallel, can be used for special mixing situations. The

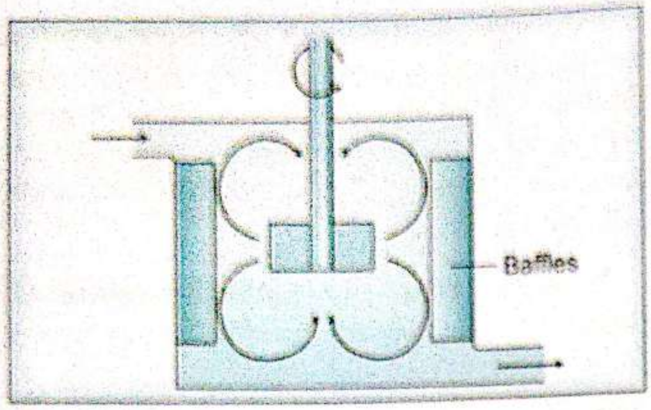


Fig. 1.9: Diagrammatic representation of a turbine-agitated, continuous mixing tank with vertical side-wall baffles

differential equations that arise from such systems may be solved by a variety of methods depending on their form. The reader is referred to mathematical texts for the appropriate techniques. The great variety of agitation systems that may be used for continuous mixing in tanks has been discussed in connection with batch mixing.

Practical Considerations

Vortexing

A vortex develops at the center of the vessel when liquids are mixed by a centrally-mounted vertical-shaft impeller. This particularly is characteristic of turbine with blades arranged perpendicular to the impeller shaft. These impellers tend to induce tangen-tial flow, which does not itself produce any mixing, except possibly near the tank walls where shear forces exist, instead, swirl and the vortex formation. This is true except at very low impeller speeds or at very high liquid viscosities (>20,000 cps), neither of which is normally encountered in practice in the pharmaceutical industry. When a vortex is formed, air is drawn into the impeller and is dispersed into the liquid, which is undesirable, as it may lead to foaming, especially if surfactants are present, and also because the full power of the impeller is not imparted to the liquid. The entrapped air also causes oxidation of the substances in certain cases and reduces the mixing intensity by reducing the velocity of the impeller relative to the surrounding fluid.

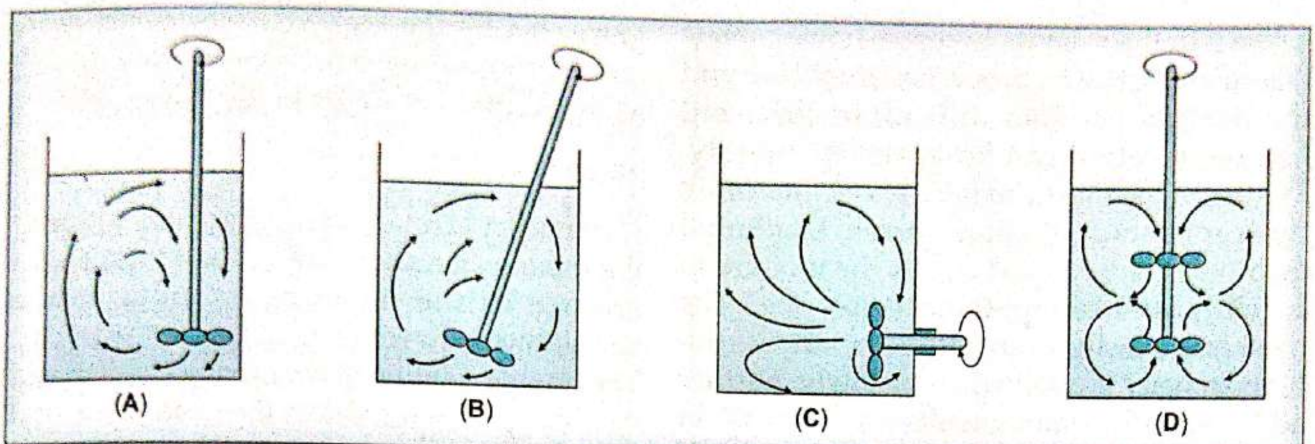
Apart from the above two problems, vortexing makes it difficult to scale-up the process, as it is impossible to achieve kinematic and geometric similitudes (kinematic similarity is achieved when flow patterns in small- and large-scale vessels are similar, whereas geometric similarity is achieved when the corresponding dimensions of the small- and large-scale vessels are in the same ratio). Vortices may be avoided by (i) changing arrangement of the impeller, (ii) changing the tank geometry, (iii) using a push-pull propeller, (iv) using baffles and (v) using diffuser ring.

Mounting an impeller either to an off-center position (Fig. 1.10A), inclined position (Fig. 1.10B) or side-entering position (Fig. 1.10C), thus destroying mixer symmetry, is the preferred method in the industry.

Side-entering propellers are often effectively employed. Swirl is seldom a problem with such an arrangement, as the tank geometry relative to the impeller provides a baffling effect and results in circulation of material from top to bottom in the vessel. A major drawback of such a system is the difficulty in sealing the propeller entry port. The packing around the shaft must assure a positive seal but must allow reasonably free rotation. Such a seal is also a source of contamination and may be difficult to clean. An asymmetric or angular tank geometry relative to the impeller may be used to produce an effect similar to that of baffles. Such a technique is useful in swirl prevention, but in many cases necessitates a longer mixing time than that required with a properly baffled tank of equivalent size.

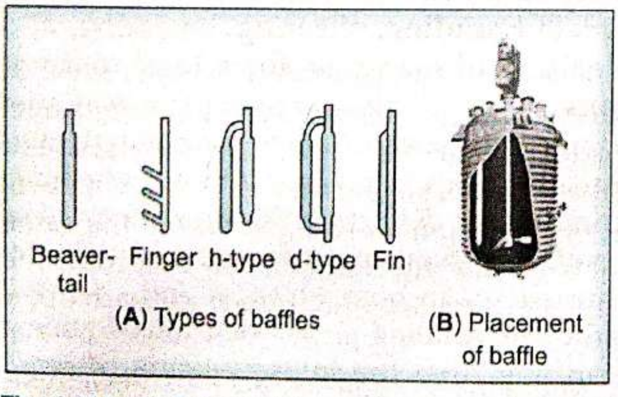
This is due to the presence of regions within such tanks in which circulation is poor. Vortexing may also be avoided by the use of a push-pull propeller in which two propellers of opposite pitch are mounted on the same shaft so that the rotatory effects are in the opposite direction and thus cancel each other (Fig. 1.10D).

Alternatively, baffle plates (baffles), auxiliary devices that convert tangential flow into axial flow, may be used. Various types of



Figs 1.10A to D: Different arrangements of impellers in a vessel with flow pattern to prevent vortex: (A) Off-centre; (B) Inclined; (C) Side-entering; (D) Push-pull propeller

baffles are commercially available with their placement depending largely upon the type of agitator used (Figs 1.11A and B). Side-wall baffles, when vertically mounted in cylindrical tanks, are effective in eliminating excessive swirl and further aid the overall mixing process by inducing turbulence in their proximity. For these reasons, the power that can be efficiently applied by the impeller is significantly increased by the use of such baffles. Vertical movement of the fluid along the walls of the tank can be produced by arranging baffles in a steep spiral down the tank sides. It should be pointed out that if an elaborate baffle system seems necessary, the situation is best corrected by a change in the impeller design, so as to provide the desired general flow pattern. Baffles are always used in turbulent flow systems with a gap between the baffle and container wall to prevent stagnation behind the baffles. Difficulty of cleaning baffled vessels is an impediment in their use for preparing sterile products. A diffuser/stator ring that fits around the impeller can be used. This arrangement gives a high degree of turbulence which may be desirable, especially if emulsification is required. Vortexing can be avoided by operating a closed, airtight vessel to its full capacity. This method is ideal for achieving geometric and kinematic similarities. High-velocity mixing results in splashing of the liquids onto the sides of the tank above the liquid level and on the cover. Vortexing problem may result in poor reproducibility of the batches. This annoyance can be ameliorated by intermittent spraying of the continuous phase through nozzles located inside the tank.



Figs 1.11A and B: Various types of commercially available baffles: (A) Types of baffles; (B) Placement of baffle

SEMISOLID MIXING

Mixing Mechanism

The mechanism involved in mixing semisolids depends on the characteristic of the material which may show a considerable variation. When a powder and a liquid are mixed, at first they are likely to resemble closely the mixing of powders, however, at later stages the mixing mechanisms of liquids become predominant.

To the initial powder (*powder state*) when a small amount of liquid is added, the powder balls up and forms a pellet (*pellet state*), until eventually all the material is in this state. At this stage the mass has a coarse granular appearance, and the rate of attainment of homogenization is low. As the liquid content is increased further, the granular appearance is lost and the mixture becomes homogenous (*plastic state*). Plastic properties are shown and the mixture becomes difficult to shear but homogenization can be achieved rapidly. Mixing of the plastic material is facilitated by the application of shear forces. Continual incorporation of liquid causes the mixture to a attain paste like appearance (*sticky state*). The mass flows easily, even under low stresses but homogeneity is attained only slowly. Further addition of the liquid results in a decrease in consistency until a fluid state is reached (*liquid state*). In this state, the rate of homogenization is rapid and the behaviour of the mixture is described by the theory of liquid mixing as discussed previously.

Equipments

Kneaders

Sigma-Blade Mixer

Sigma-blade mixer has counter-rotating blades or heavy arms that work the plastic mass. The blades rotate tangentially with a speed ratio of about 2:1. The shape and difference in rotational speed of the blades facilitate lateral pulling of the material and impart kneading and rolling action on the material (Fig. 1.12). Shear forces are also generated by the high viscosity of the mass and are thus effective in deaggregation as well as distribution of solids in the fluid vehicle.

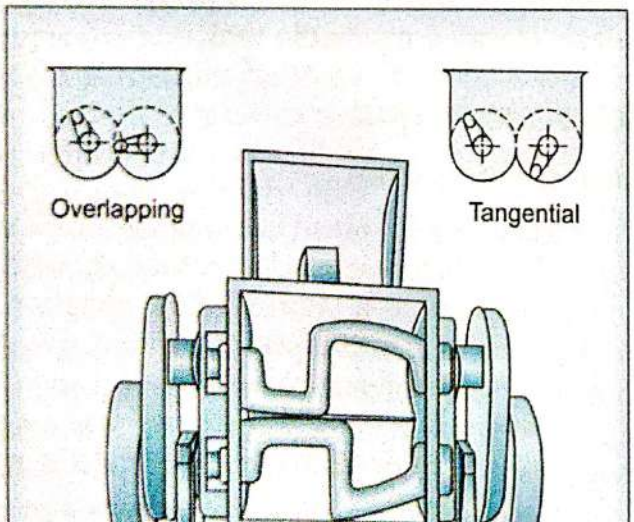


Fig. 1.12: Schematic representation of a top-loading sigma-blade mixer with overlapping blades

Planetary Mixer

It imparts planetary mixing action, whereby the mixing element rotates round the circumference of the mixer's container, while simultaneously rotating about its own axis. The double rotation of the mixing element and its offset position reduces the dead zones and avoids vortex formation. The schematic diagram of the planetary mixer is shown in Fig. 1.13.

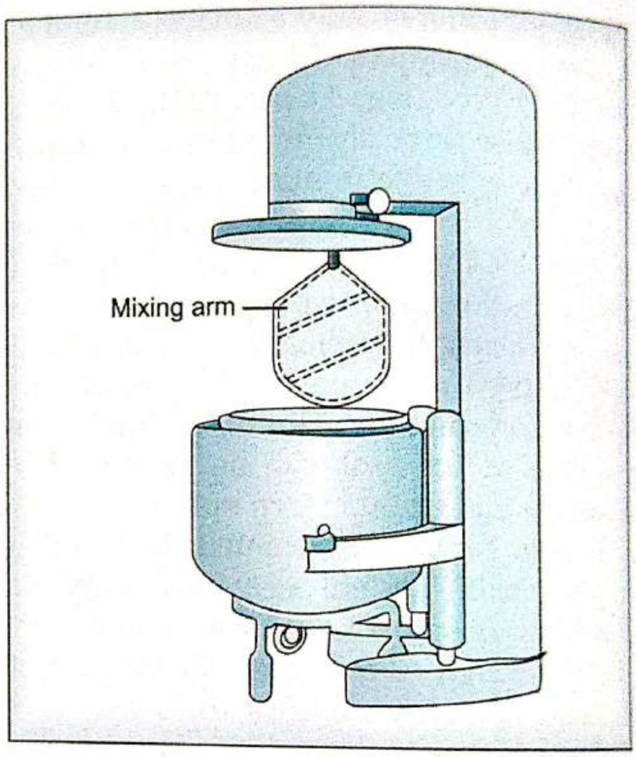


Fig. 1.13: Schematic representation of a planetary mixer

Mulling Mixers

Mulling mixers provide forces that incorporate kneading, shearing, smearing, and blending of materials for a total uniform consistency. This process produces just enough pressure to move, intermingle and push particles into place without crushing, grinding, or distorting the ingredients. The result is a final mixture of truly uniform consistency in both physical and chemical structure. Mulling is an extension of mixing resulting from the intensification of work forces (Fig. 1.14). The work forces are applied via the tread of weighted mulling wheels. The

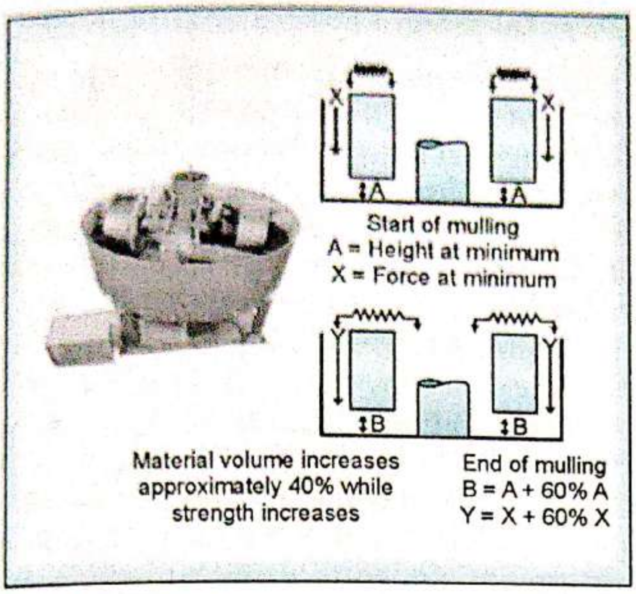


Fig. 1.14: Schematic representation of the mulling mixer and mulling pressure

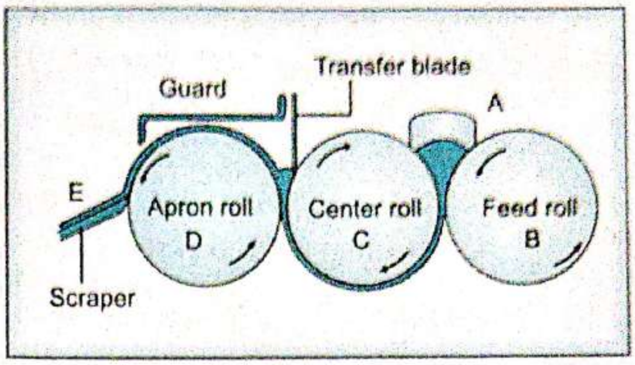


Fig. 1.15: Cross section of a three-roller mill

weight, and thereby the mixing efficiency, is controlled through a spring suspension arrangement on the wheel that is fully adjustable, and allows the user to increase or decrease the amount of work that is applied to the mixture via the mulling wheel. This extension of mixing has proven to be a successful method in a wide range of applications. Mulling mixers are efficient in deaggregation of solids, but are typically inefficient in distributing the particles uniformly throughout the entire mass. These devices are suitable for mixing previously mixed material of uniform composition, but containing aggregates of solid particles. In the event of segregation during mulling, a final remixing may be necessary.

Mills

Roller Mills

Roller mills consist of one or more rollers and are commonly used. Of these, the three-roller types are preferred (Fig. 1.15). In operation, rollers composed of a hard, abrasion-resistant material, and arranged to come into close proximity to each other are rotated at different rates. Depending on the gap, the material that comes between the rollers is crushed, and also sheared by the difference in rates of movement of the two surfaces. In Fig. 1.15 the material passes from the hopper, A, between rolls B and C, and is reduced in size in the process. The gap between rolls C and D, which is usually less than that between B and C, further crushes and smoothens the mixture, which adheres to the roll C. A scraper, E, is arranged so as to continuously remove the mixed material from the roller D. The arrangement is such that no material that has not passed between both the sets of rolls can reach the scraper.

In extreme cases of solid-liquid mixing, a small volume of liquid is to be mixed with a large quantity of solids. This process is essentially one of coating the solid particles with liquid and subsequent transfer of liquid from one particle to another. In this type of mixing, the liquid is added slowly to reduce the tendency of the particles to form a lump. However, the process is not for fluids mixing, but for solids mixing. When the particles tend to stick together because of the surface tension of the coating liquid, the equipment used is the same as that for pastes. If the solids remain essentially free flowing, the equipment is the same as that used for solids mixing, which is discussed later in this chapter.

Colloid Mill

A colloid mill consists of a high-speed rotor (3,000 to 20,000 rpm) and a stator with conical milling surfaces between which an adjustable clearance ranging from 0.002 to 0.03 inches is present, as indicated by the schematic diagram in Fig. 1.16. The material to be grounded should be pre-milled as finely as possible to prevent damage to the colloid mill.

In pharmacy, the colloid mill is used to process semisolids and not dry materials. The pre-milled solids are mixed with the liquid vehicle before being introduced into the colloid mill. Interfacial tension causes a part of the material to adhere to, and rotate with, the rotor. Centrifugal force throws a part of the material across the rotor, and onto the stator. At a point between the rotor and stator, motion imparted by the rotor ceases, and hydraulic shearing forces exceed the particle-particle attractive forces which hold the individual particles in an aggregate. The particle size of milled particles may be smaller than the clearance, because the high shear is the dispersing force. For example, in emulsification, a clearance of 75 µm may produce dispersion with an average particle size of 3 µm. The milled liquid is discharged through an outlet in the periphery of the housing and may be recycled.

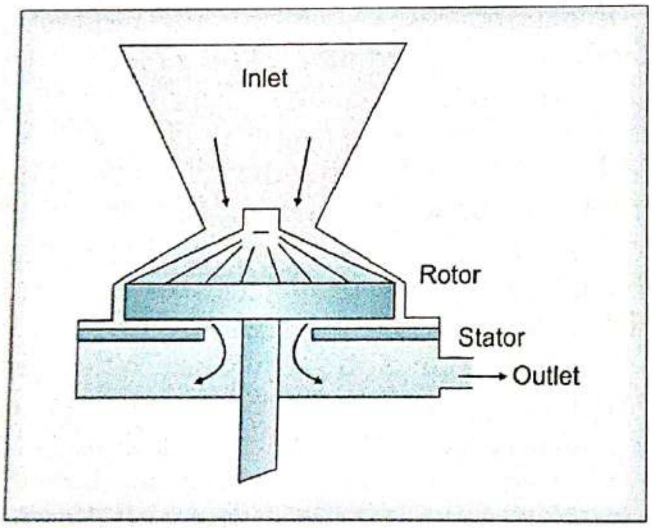


Fig. 1.16: Schematic representation of a colloid mill

Rotors and stators may be either smooth-surfaced, or rough-surfaced. With smooth-surfaced rotors and stators, there is a thin, uniform film of material between them which is subjected to maximum amount of shear. Rough-surfaced mills add intense eddy currents, turbulence, and impaction to the shearing action. Rough-surfaced mills are useful with fibrous materials because fibers tend to interlock and clog smooth-surfaced mills.

Mixer Selection

One of the first and often most important considerations in any mixing problem is equipment selection. Factors that must be taken into consideration for appropriate mixer selection include (1) the physical properties of the materials to be mixed, such as density, viscosity, and miscibility, (2) economic considerations regarding processing, for example, the time required for mixing and power expenditure necessary and (3) cost and maintenance of the equipment. In any given case, one or more of these factors may be taken into consideration, however, the selection of equipment depends primarily upon the viscosity of the liquids, and is made according to the mechanism by which intense shearing forces can best be generated.

Low Viscosity Systems

Monophasic systems of low viscosity are classified as positive mixtures, and if given time, mix completely without external agitation. Agitation reduces the time required for mixing, allowing a fast decay in the intensity of segregation. In general, for low viscosity liquids no great problems are encountered unless the operational scale is very large. The viscous character and density of the fluid(s) to be mixed determine, to a large extent, the type of flow that can be produced, and therefore, also the nature of the mixing mechanisms involved. Fluids of relatively low viscosity are best mixed by methods that generate a high degree of turbulence, and at the same time circulate the entire mass of material. These requirements are satisfied by air jets, fluid jets, and the high-speed propellers discussed earlier. A viscosity of approximately 10 poises may be considered as a practical upper limit for the application of these devices.

Intermediate Viscosity Systems

The mixing of systems composed of immiscible liquids (emulsions) or finely divided solids with a liquid of low viscosity (suspensions) depends on the subdivision or deaggregation of one or more of these phases, with subsequent dispersal throughout the mass of the material to be mixed. These processes are often carried out in a single mixing operation, provided that shear forces of sufficient intensity to disrupt aggregates can be generated. At low solid–disperse phase concentrations the flow properties are Newtonian and mixing by propellers is satisfactory as long as the dispersed components oppose settling. Under such conditions it may be desirable to increase the impeller size and decrease its speed. Emulsions and suspensions are of such viscosity that it is difficult, if not impossible to generate turbulence within their bulk, and laminar mixing, and molecular diffusion must be relied upon. Mixing of such fluids may be accomplished with a turbine of flat blade design. A characteristic feature of such impellers is the relative insensitivity of their power consumption to the density and/or viscosity of the material. For this reason, they offer a particularly good choice when emulsification or dispersion of added solids may affect these properties of the material significantly during the mixing operation. This property of turbines is due to the mechanisms by which they produce their characteristic radial flow, viz. (1) density- and viscosity-dependent fluid entrainment into the area of the blades and (2) centrifugal displacement in the axial direction. The effects of density and viscosity tend to cancel out, since they contribute in both a positive and negative way to the circulation.

When compared with a propeller of similar size, flat blade turbines of the radial flow type have a significantly lower pumping capacity, which makes them less suitable for mixing in large tanks. In case of suspensions, when deaggregation is to be carried out following a general mixing step, the high-speed turbines, frequently fitted with stators to produce increased shearing action, are often employed. Preparation of fine emulsions, whereby large globules are successively broken down into smaller ones, is accomplished by the process termed as 'Homogenization', as described in Chapter 2.

High Viscosity Systems

Viscous ointments are efficiently mixed by the shearing action of two surfaces in close proximity, and moving at different velocities with respect to each other. This is achieved in paddle mixers, in which the blades clear the container walls by a small tolerance. Such mixers are relatively efficient, since they not only generate sufficient shear to reduce globule size, but if properly constructed, also induce sufficient circulation of the material to ensure a uniform dispersion throughout the complete mixture. The comparative mixing characteristics of the various types of impellers are shown in Table 1.1.

As the percentage of solids is increased, or if highly viscous fluids are employed, the solid-liquid system takes on the consistency of a paste or dough. For thicker pastes and plastic masses, a kneading, stretching and folding action is employed. The forces required to induce shear are considerable, and the equipment used is of heavy design. In such cases, sigma-blade mixer and muller mixer are the commonly used mixers. Considerable variation in rheological properties may occur during mixing, and thus a robust mixer construction is essential. The differential speed of the rolls of a roller mill induces high shear rates in the material suitable for paste mixing. With more fluid dispersions, the colloid mill may be used. Many of the mixing characteristics attributed to the various impellers, jets and other mixing equipment can be considerably altered, often unfavorably, by changes in the relative size, shape, or speed of their component parts. Although the methods of scale-up are usually considered in relation to the problem of going from laboratory scale to pilot plant to production scale.

SOLID MIXING

The theory of solid mixing has not advanced much beyond the most elementary concepts and, consequently, is far behind the one which has been developed for fluids. This lag can be attributed primarily to an incomplete understanding of the ways in which particulate