Principles of pharmaceutical processing

1-mixing **4-filtration**
2-milling **5-sterilization**
3-drying **6-prefprmulation**
7- sterile products

mixing

- Is defined as a process that tends to result in a randomization of dissimilar particles within a system.
- 2 types of mixing 1- solid 2-fluid mixing
- Fluid mixing
- Fluids may generally depend on shear rate and shear stress
- The flow characteristics and mixing behavior of fluids are governed by 3 primary laws 1- conservation of mass 2- conservation of energy 3-classic laws of motion

Mixing mechanisms of fluids

1-bulk transport   2-turbulent flow

3-laminar flow   4-molecular diffusion

1-Bulk transport

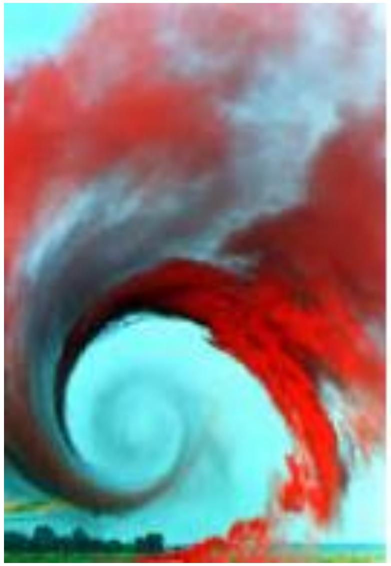
The movement of a relatively large portion of the material being mixed from one location in the system to another constitutes bulk transport. A simple circulation of material does not necessarily result in efficient mixing.

2-Turbulent mixing

- The phenomenon of turbulent mixing is a direct result of turbulent fluid flow which is characterized by a random fluctuation of the fluid velocity at any given point within the system. The fluid velocity at a given instant may be expressed as the vector sum of its components in the x,y and z directions. In the case on turbulent flow in a pipe, the mean velocity in the direction of flow through the pipe is positive, and varies some what depending on the distance from the pipe wall . Turbulent flow can be conveniently visualized as a composite of eddies of various sizes.

eddy

Is defined as a portion of 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 and smaller size until they are no longer distinguishable.



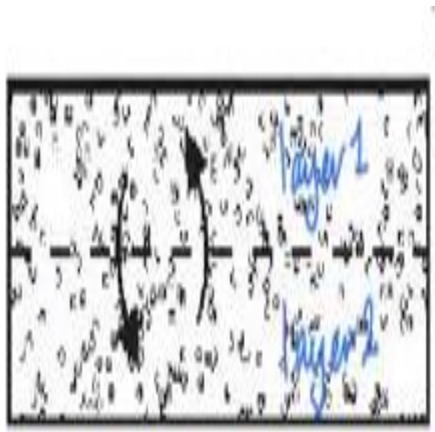
3-laminar mixing

Streamline or laminar flow is frequently encountered when

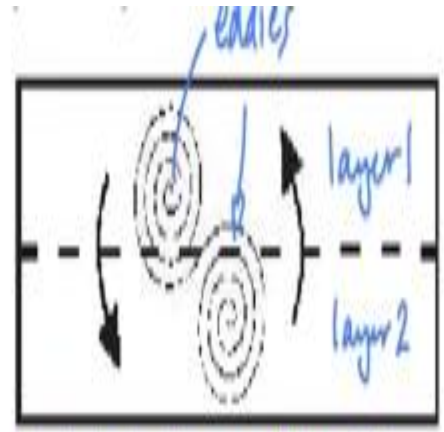
1- highly viscous fluid are being processed. It can also occur if

2-stirring is relatively gentle &

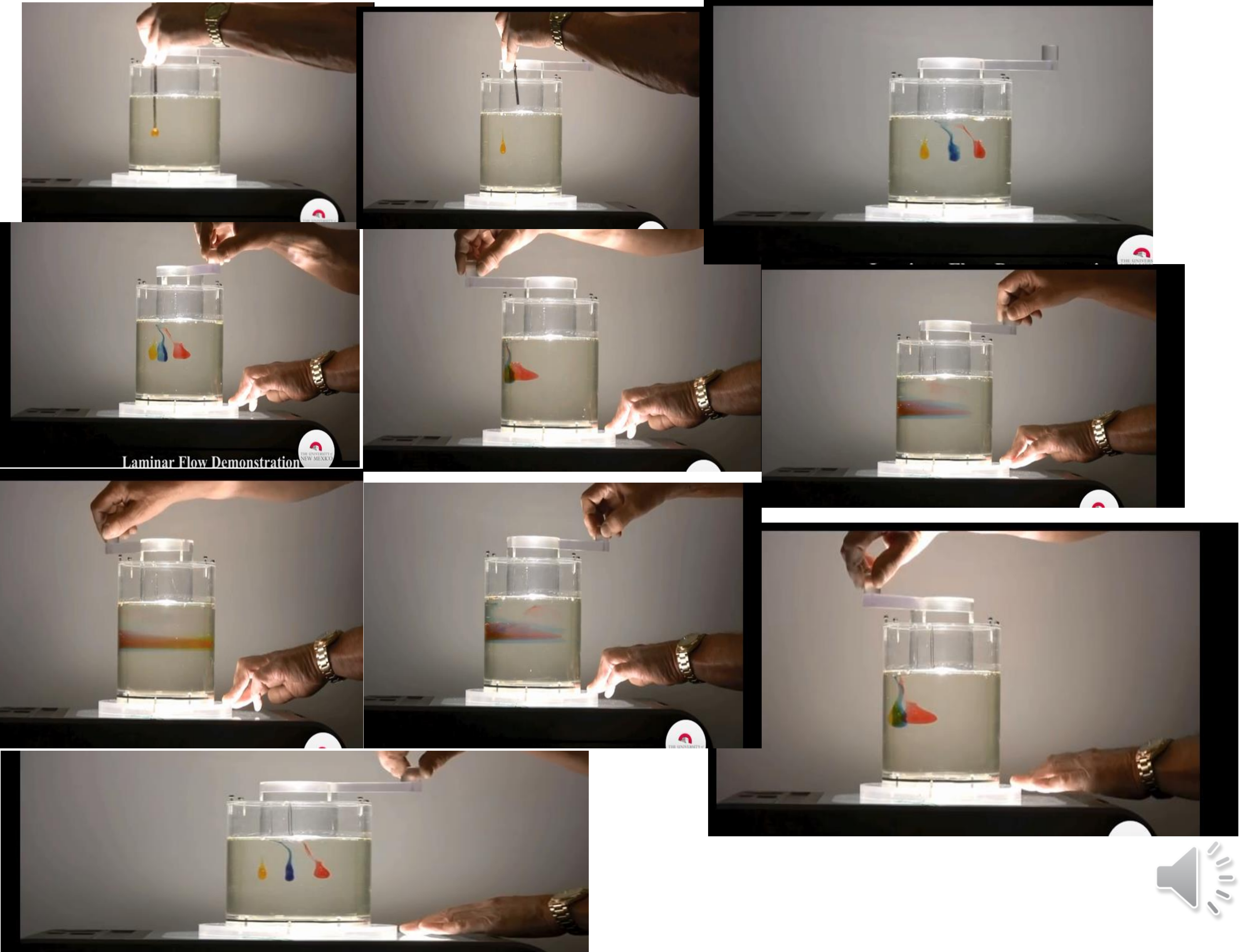
3- may exist adjacent to stationary surface in vessels in which the flow predominantly turbulent.

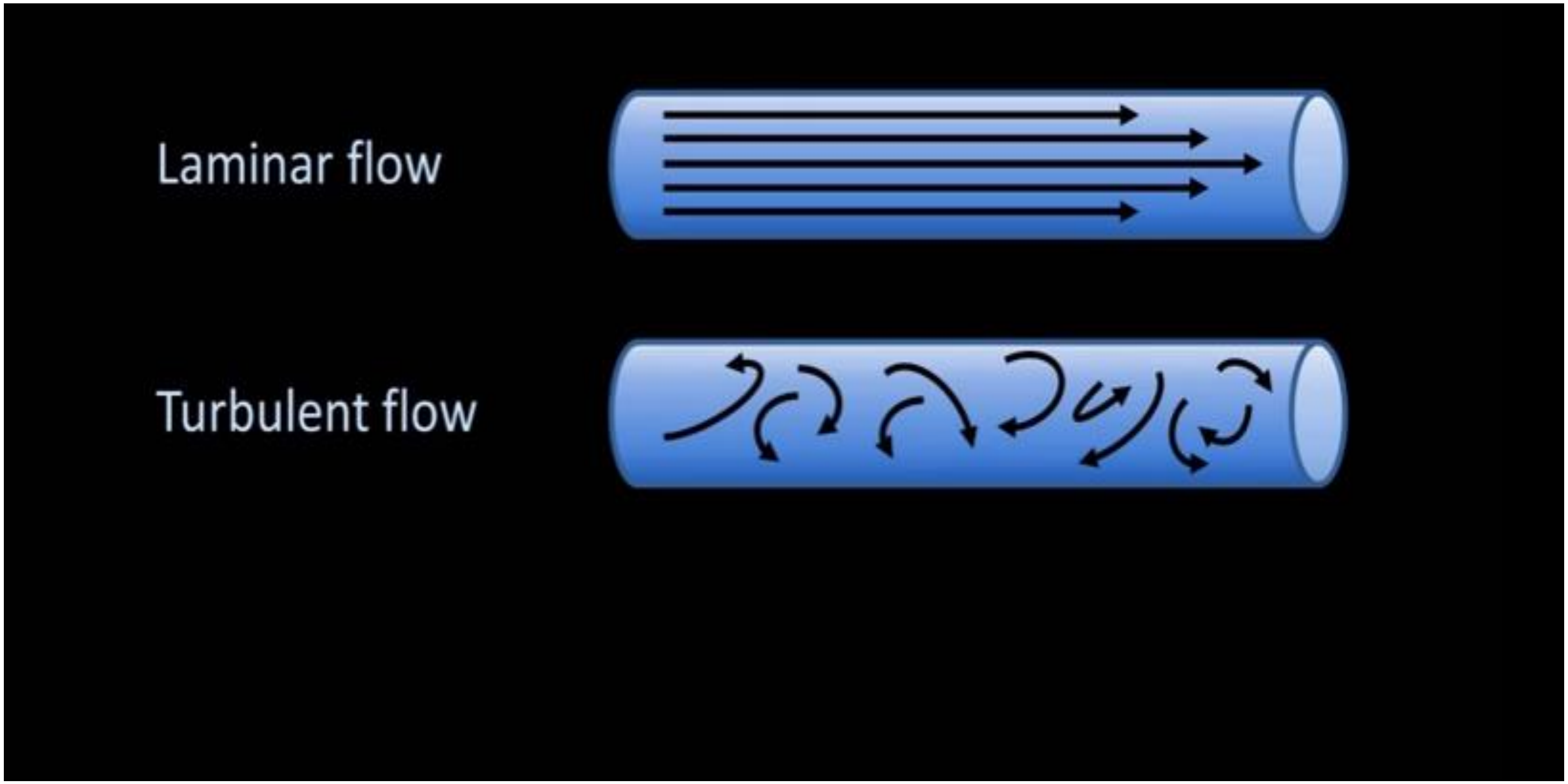


laminar flow : molecular mixing



turbulent flow : eddies mix


Laminar Flow Demonstration


Laminar flow
Turbulent flow

- When 2 dissimilar liquids are mixed through laminar flow, the shear that is generated <u>stretches</u> the interface between them. If the mixer employed <u>folds</u> the layers back upon themselves, the no. of layers & hence the interfacial area between them, increase exponentially with time.

- This relationship is observed because the rate of increase in interfacial area with time is proportional to the instantaneous interfacial area. Example . Consider the case where the mixer produces a folding effect & generates a complete fold every 10 seconds. Given an initial fluid layer thickness of 10 cm **a thickness reduction by a factor of 10^{-8} is necessary to attain layers 1 nm thick**, which **approximate molecular dimensions**. Since a single fold results in a layer thickness reduction of one half, n folds are required where

$(1\backslash 2)^n = 10^{-8}$

$n = 26.6$

10 X26.6=266 sec or 4.43 min

Good mixing at the molecular level requires a significant contribution by molecular diffusion after the layers have been reduced to reasonable thickness by laminar flow.

4- 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 result in complete mixing.

The process described by Fick's 1st law of diffusion

Dm\dt =–DA dc\dx

D depends on the viscosity and the size of the diffusing molecules.

Conc. Gradients at the boundaries is a decreasing function of time, approaching zero as mixing completion.

The concentration gradient at the original boundaries is a decreasing function of time, approaching zero as mixing approaches completion

Scale & intensity of segregation

Danckwerts has suggested 2 criteria to describe degree of mixing (quality of randomness or goodness of mixing)

1-scale of segregation

2-intensity of segregation

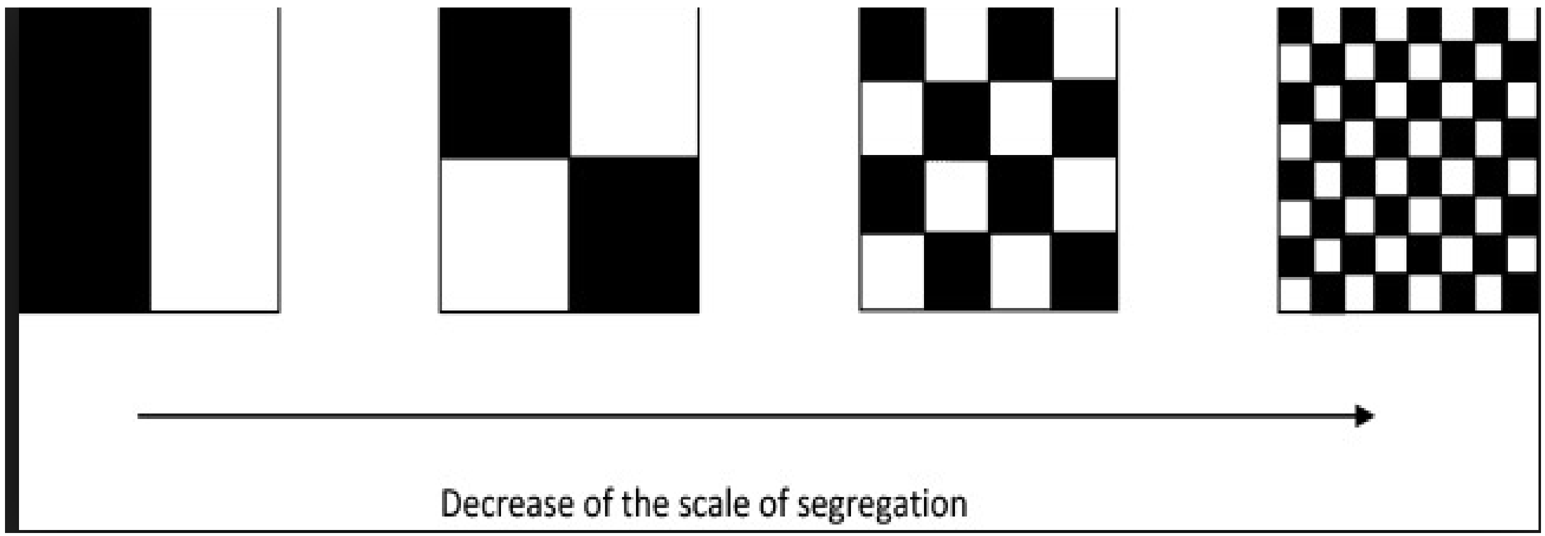
Scale segregation is expressed in 2 ways

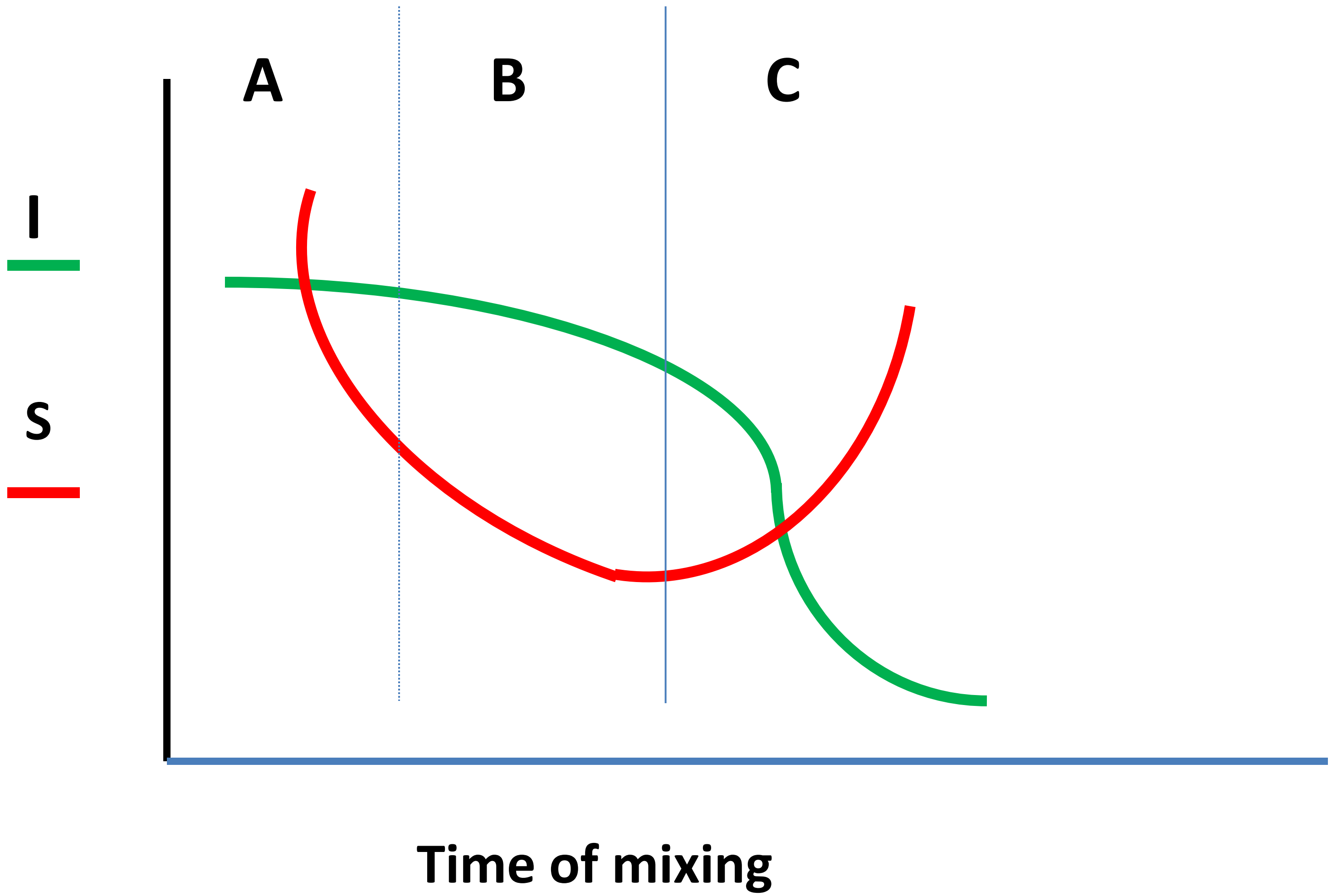
Linear or volume scale

Linear scale represent an average value of diameter of the lumps where the volume scale represent the average lump volume.

Intensity of segregation is a measure of the ***variation*** in composition among the various portions of the mixtures.

When mixing is complete, the intensity of segregation is zero.


Decrease of the scale of segregation


A
B
C
I
S
Time of mixing

Equipment

Batch mixing –when the material to be mixed is limited in volume to that which may be conveniently contained in a suitable mixer.

System for batch mixing consist of 2 primary components:

1-tank which is suitable to hold the material being mixed

2-a means of supplying energy to the system

Power may be supplied to the fluid mass by means of an impellers ,air stream or liquid jet. Besides supplying power also are used to serve & direct flow

1- impellers

The distinction between impeller types is made on the basis of type of flow pattern they produce or on the basis of the shape and pitch of the blades. 3 basic types of flow may produced: radial, axial & tangential. These may occur singly or in various combinations.

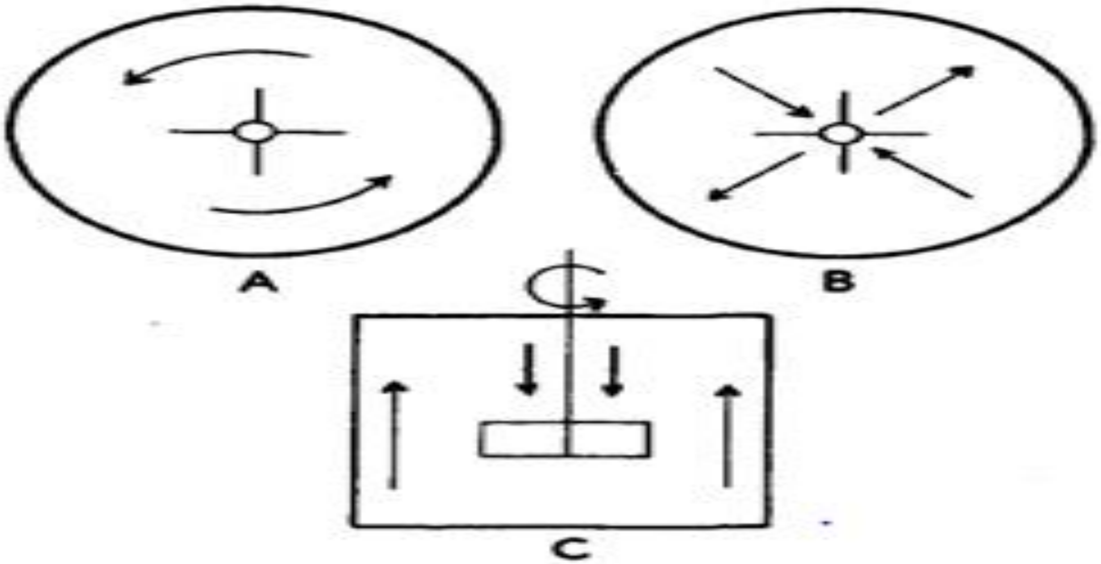


FIG. 1-2. A and B, *Diagrammatic representation of cylindric tanks in which tangential and radial flow occur, respectively.* C, *Side view of a similar tank in which axial flow occurs. These diagrams represent systems in which only one type of flow occurs, in contrast to the usual situation in which two or more of these flow patterns occur simultaneously.*

Propellers: screw with blades (3 blades design)-blades pitch equal to the daimeter

Turbines 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,

Paddles also are employed as impellers and are normally operated at low speeds, 50 rpm or less. Their blades have a large surface area in relation 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 or semisolids,

2-Air jet

- Subsurface jets of air or less commonly of some other gas, are effective mixing devices for certain liquids. The liquids must be of low viscosity, non foaming, unreactive with the gas employed & reasonably non volatile. the jets are arranged so that the buoyancy of the bubbles lifts liquid from the bottom to the top of the mixing vessel brings fluid from all parts of the tank to the region of the jet. This is accomplished with a draft tubes. These serve to confine the expanding bubbles and entrained liquid resulting in a more efficient lifting action by the bubbles.

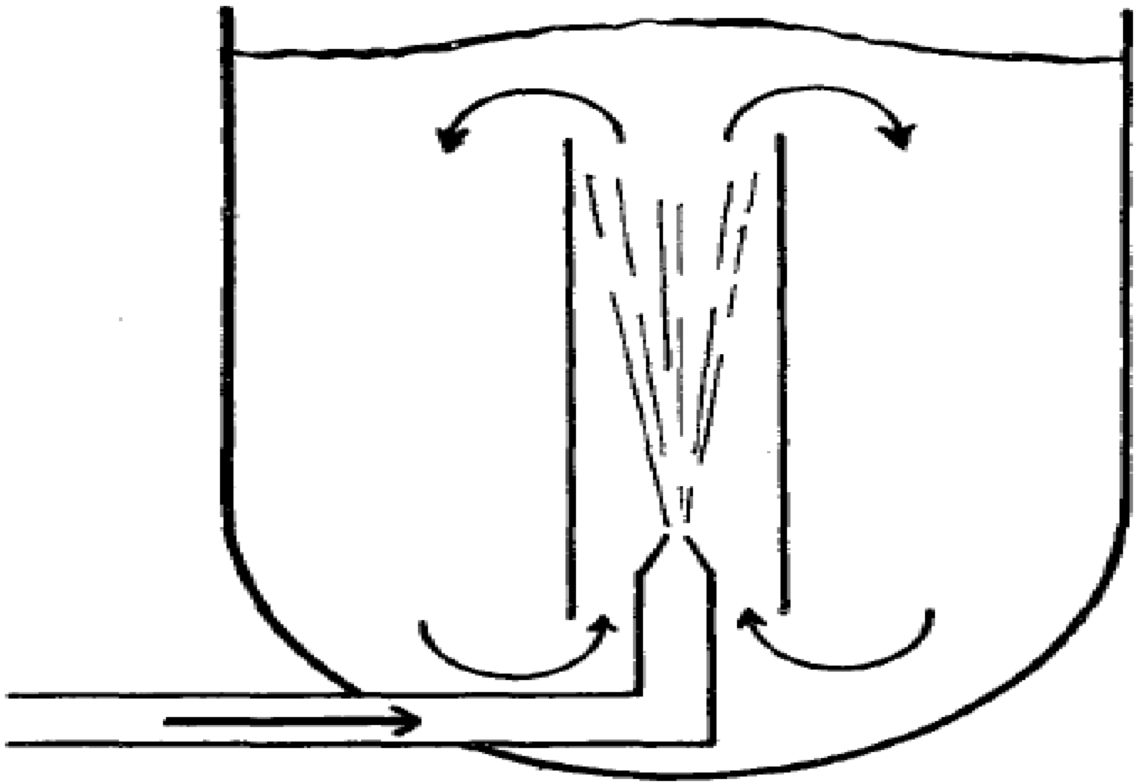


FIG. 1-4. *Vertical tank with centrally located air jet and draft tube. Bubbles confined within the draft tube rise, inducing an upward fluid flow in the tube. This flow tends to circulate fluid in the tank, bringing it into the turbulent region in the vicinity of the jet.*

3-Fluid jets

When liquids are to be pumped into a tank for mixing .

The fluids are pumped through nozzles arranged to permit good circulation of material throughout the tank, like propellers, they generate turbulent flow in the direction of their axes.

4- Baffles

For bulk fluid flow to be most effective ,an intermingling must occur between material from remote regions in the mixer. To accomplish this , it is frequently necessary to install auxiliary devices for directing the flow of the fluid, usually baffles plates.

Continuous mixing

- The process of continuous mixing produces an uninterrupted supply of freshly mixed material & is often desirable when very large volumes of material are to be handled. It can be accomplished in 2 ways
- 1-in a tube or pipe through which the material flows & in which there is a little back flow or recirculation
- 2- in chamber in which a considerable amount of holdup & recirculation.
- to ensure good mixing efficiency, such devices as vanes baffles ,screws, grids or combination of those devices are placed in the mixing tube

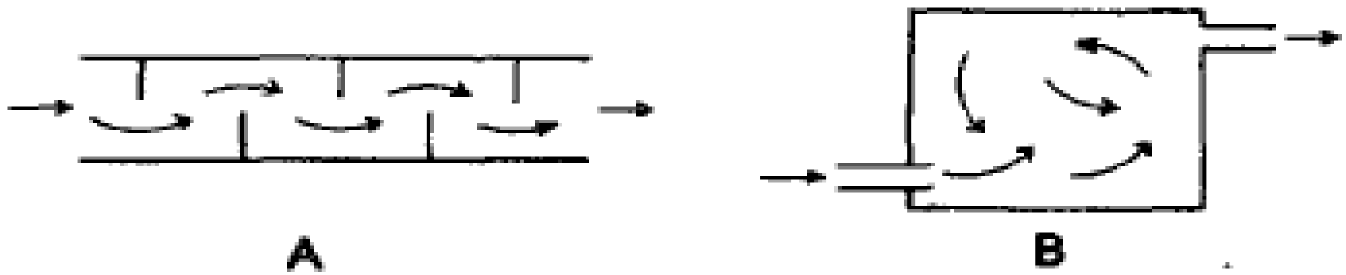


FIG. 1-5. *Continuous fluids mixing devices.* A, *Baffled pipe mixer;* B, *mixing chamber with flow induced recirculation. Both types induce turbulence in the fluid; however, recirculation is desirable when overall fluctuations occur in the material fed to the mixer, since these fluctuations will not be eliminated by simple transverse mixing in a pipe.*

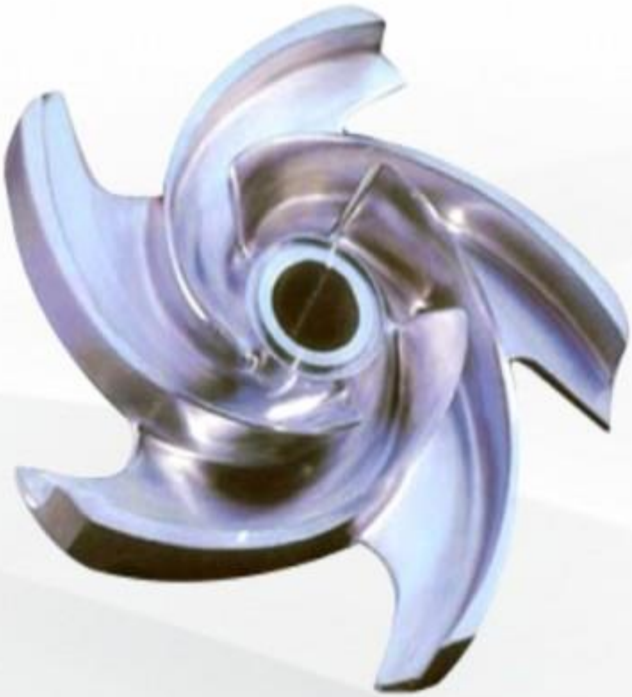
Mixer selection---equipment selection

Factors that must be taken into consideration include
1-the physical properties of the materials to be mixed such as the density, viscosity and miscibility
2-Economic considerations regarding processing ex. time required for mixing and the power expenditure necessary.
3- cost of the equipment and its maintenance.

Mixer selection---equipment selection

- 1- monophase system : fluids of relatively low viscosity are best mixed by method that generate a high degree of turbulence & at the same time circulate the entire mass of material. These requirements are satisfied by air jets , fluid jets & the various high speed impellers. A viscosity of approximately 10 poise may be considered as a practical upper limit for the application of these devices.

  Thick creams & ointments &pastes are of such high viscosity that is difficult if not impossible to generate turbulence within their bulk & laminar. Mixing may be done with a turbine of flat blade design. These devices is insensitive to the power consumption to density and or viscosity. They are good choice when emulsification or added solids may change these quantities during the mixing.



Open Impeller

Closed Impeller

2- poly phase system

- The mixing of 2 immiscible liquids requires the subdivision of one of these phases into globules, then distributed throughout the bulk of the fluid. These globules are successively broken down into smaller one. 2 primary forces play here: 1-the interfacial tension of the globules in the surrounding liquid and 2- forces of shear within the fluid mass. The first force tends to resist the distortion of globule shape fragmentation to small globule where the opposite with the 2^{nd} force.
- The selection of equipment depends upon the viscosity of the liquids and this is made according to the mechanism by which intense shearing forces can best be generated.
- In case of low-viscosity system, high shear rates are required and produced by passing the fluid under high pressure through small orifices or by bringing it into contact with rapidly moving surfaces

Highly viscous fluids such as are encountered in the production of ointments, are efficiently dispersed by the shearing action of 2 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 out the walls. These mixers generate shear to reduce globule size and induce sufficient circulation of materials to ensure efficient mixing.

- the mixing of finely divided solids with a liquid of low viscosity in the production of a suspension depends on the separation of aggregates & distribution of these particles in the fluid. This process occurs in a single mixing operation provided that shear forces of sufficient to disrupt aggregates.
- As the % of solids is increased or if highly viscous fluids are employed, the solid – liquid system takes on the consistency of a paste or dough. The choice of mixer is either knead or mull the materials. Kneaders operate by pushing of the material by squeezing & deforming them at the same time. Such mixers take several forms.

- Usually have counter – rotating blades or heavy arms that work the plastic mass. Shear forces are generated by the high viscosity of the mass & are effective in deaggregation & distribution of the solids in the fluid vehicle.

Sigma blade mixer with overlapping blades

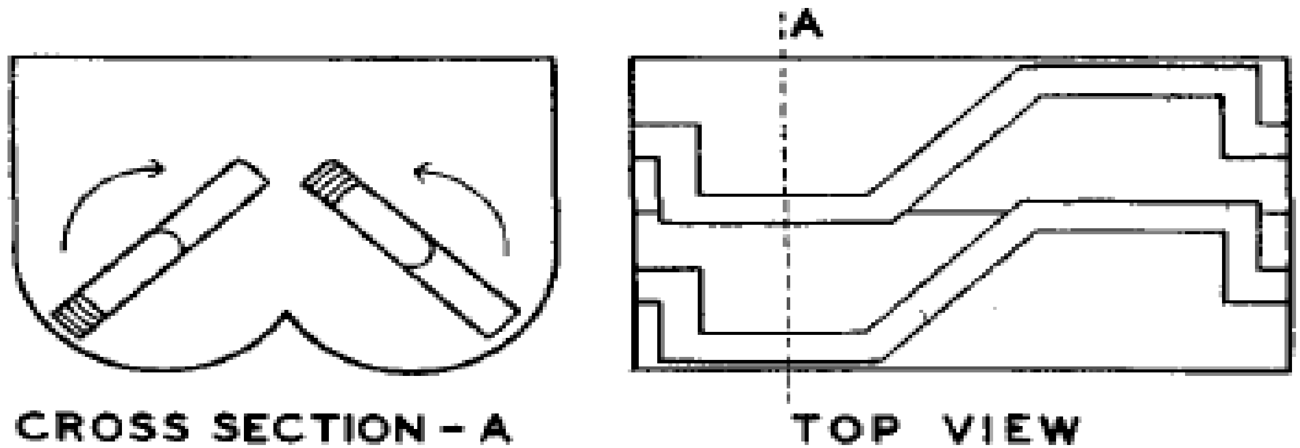
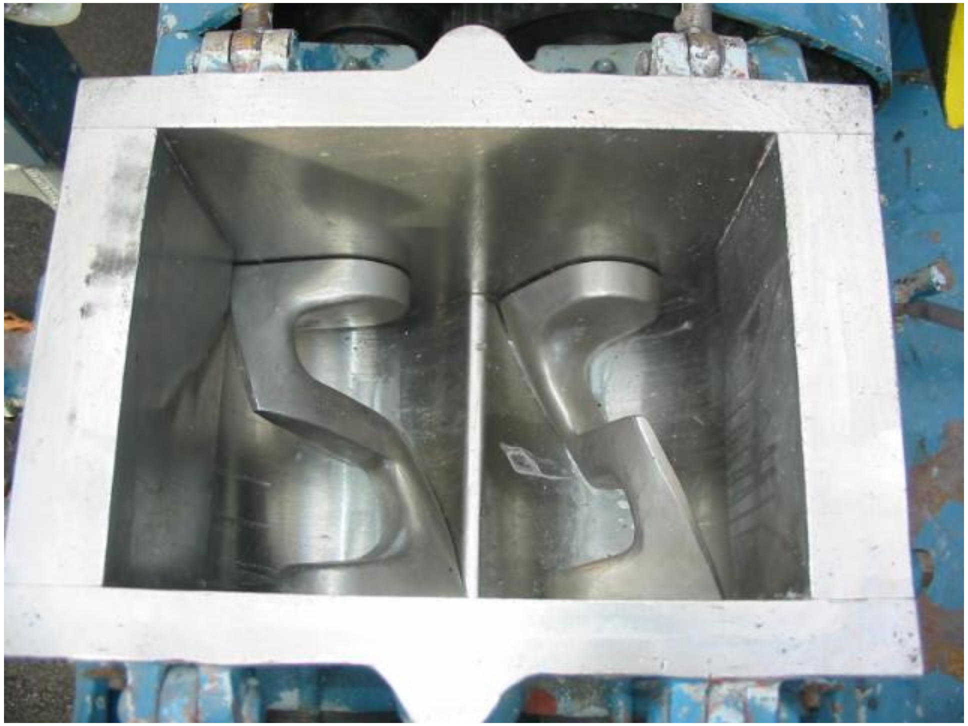


FIG. 1-8. *Schematic drawing of a top-loading sigma-blade mixer with overlapping blades. The top view shows the relationship of the counter rotating blades to the overall geometry of the mixer.*



Diosna High shear

- Mulling mixer are efficient in deaggregation of solids , but are inefficient in distributing the particles uniformly through the entire mass. Previously mixed material of uniform composition, but containing aggregates of solid particles. In the events of segregation during mulling , a final remixing may be necessary.
- The 3 – roll type are preferred.
- In operation rollers composed of a hard abrasion resistant material & arranged to come into close proximity to each other are rotated at different rates of speed. Material coming between the rollers is crushed depending on the gap & is also sheared by the difference in rates of movement of 2 surfaces.

3-roll mill

- The material passes from the hopper A between rolls B & C & is reduced in size in the process. The gap between rolls C & D which is less than that between B & C, further crushes & smooths the mixture which adheres to roll C. A scraper E is arranged to continuously remove the mixed material from roller D.

3 rol

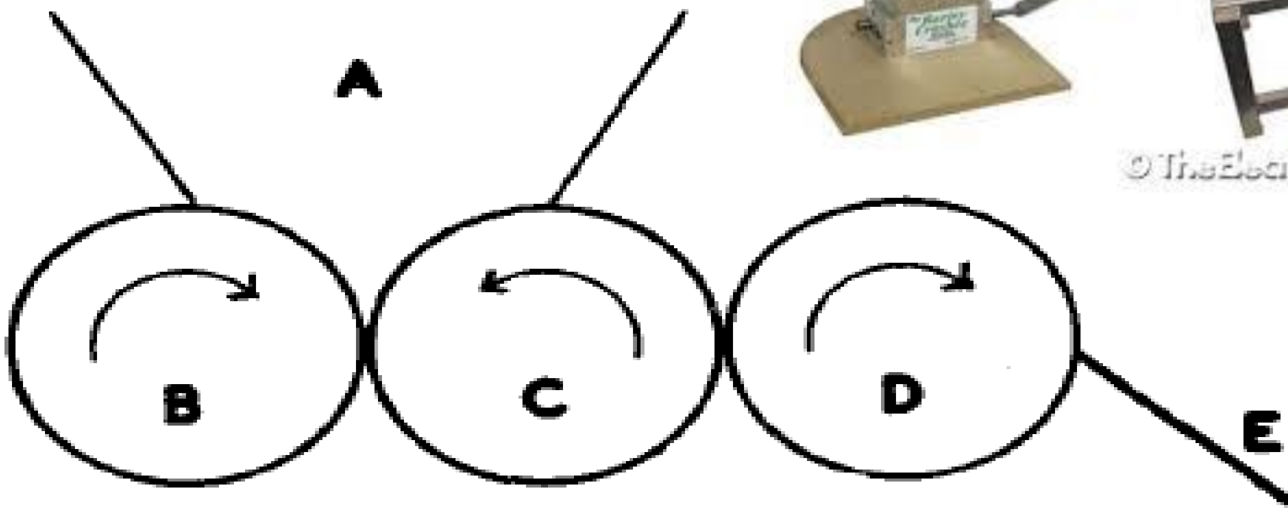
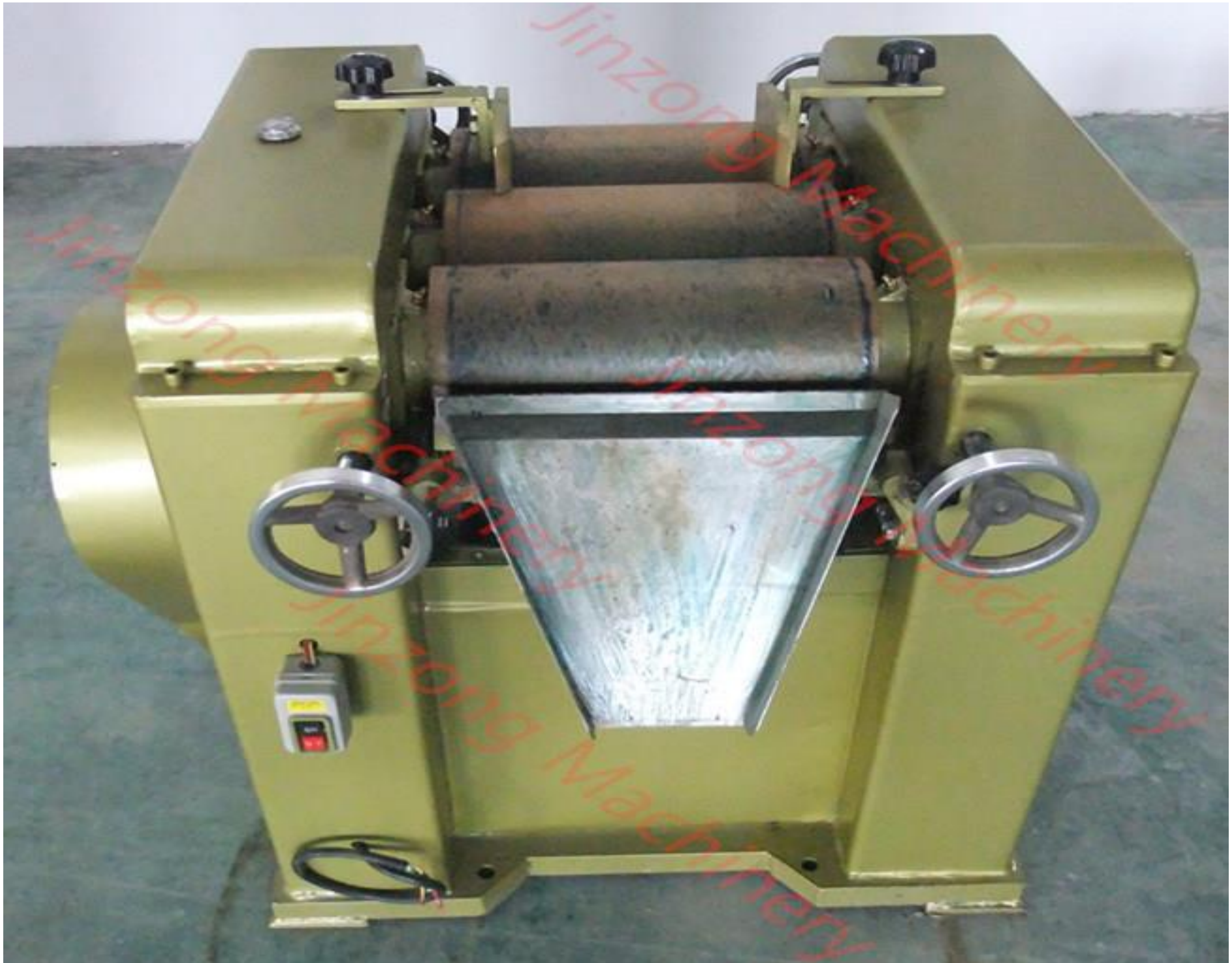


FIG. 1-9. *Cross section of a three-roll mill showing hopper (A), rolls (B,C,D), and scraper (E). Directions of roller rotation are indicated. Speed of rotation of the rollers increases from B to D. Material placed in the hopper passes between rolls B and C and then C and D in succession and is finally collected on the scraper.*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Solid – liquid mixing

- In which a small volume of liquid is to be mixed with a large quantity of solids. This process is one of coating the solid particles with liquid & of the transfer of liquid from one particle to another. The liquid is added slowly to reduce the tendency of the particles to lump. But when the particles tend to stick together because of surface tension of the coating liquids, 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.

Correlation.

istics 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 methods of scale-up are usually considered in relation to the problem of going from laboratory scale to pilot plant to production scale, they are also of fundamental value in understanding the proper operation of a given mixer, regardless of its size.

Exact analytic descriptions of the flow patterns, turbulent or otherwise, that occur in mixers are generally so complex as to defy solution, if indeed they may be mathematically formulated at all. For these reasons, an empiric approach, involving comparison of the system under study with systems of known performance, is employed for the prediction of the desired operational conditions. Significant variables that must be taken into account include the dimensions of the mixer and its mechanical components as well as their location within the mixer. Included also are impeller speed or jet pumping rate, fluid density, fluid viscosity, and height of fill of the mixer. In short, any factor that can possibly influence the behavior of the materials as they are mixed is potentially important.

1. Dimensionless groups. The method is based upon dimensionless groups that characterize the mixing systems. These groups consist of combinations of the physical and geometric quantities that affect the fluid dynamics and hence also affect the mixing performance of a given piece of equipment. The measurable quantities consti-

ie Reynolds number is commonly defined
ie expression:

$$R_e = \frac{vL\zeta}{\eta} \qquad (3)$$

where v is the velocity of the fluid relative to the surfaces of the equipment involved. The density and dynamic viscosity are denoted by ζ and η, respectively. The dimension of length, L, is chosen in various ways depending on the system. For example, in the case of fluid flowing through a pipe, it is taken as pipe diameter. For gas bubbles, it is taken as bubble diameter, and for impellers, as impeller diameter. The subgroup $vL\zeta$ is indicative of inertial forces in the system, and the Reynolds number indicates the ratio between these and the viscous forces. At high Reynolds numbers, the former predominate and the flow is turbulent, whereas at low values of R_e, laminar flow occurs. A transition range is known to exist since the transition from laminar to turbulent flow is not abrupt.

In systems in which gravitational effects occur, the Froude number should be taken into account. This group is defined by the equation:

$$F_r = \frac{V^2}{gL} \qquad (4)$$

where v and L are the terms previously defined and g is the acceleration of gravity. In the case of high Froude numbers, the inertial forces predominate over those due to gravity. Should such conditions prevail in an unbaffled tank agitated by a vertical, centrally located turbine, vortex formation results. This group is important whenever there is an interaction between gravitational and inertial forces.

The power that may be dissipated in a mixer by an impeller or other device is related to the power number:

$$P_n = \frac{p'}{v^2 \zeta} \tag{5}$$

where p′ is the pressure increment responsible for flow. The power number is thus the ratio between the forces producing flow and the inertial forces that resist it. The power number can also be written as:

$$P_n = \frac{Pg}{\zeta \omega^3 d^5} \tag{6}$$

where P is the power input, d is the impeller diameter, and ω is its rotational velocity.

sionless equation for correlating power input contains several dimensionless groups in addition to the Reynolds and Froude numbers, these latter two quantities are usually sufficient for correlations with the power number if geometrically similar systems are investigated. The power number is thus commonly written as a function of R_e and F_r in the exponential form:

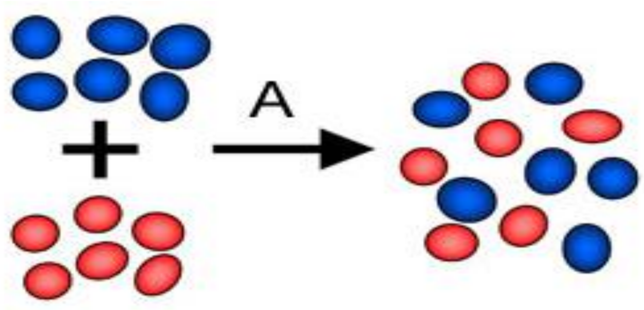
$$P_n = G R_e^a F_r^b \tag{7}$$

dimensionless groups in predicting and calculating the influence of systematic variables on the mixing process. The same general technique is also useful in correlations involving more complex systems, which require additional groups for satisfactory calculations.

$$P = G g^{-1} \eta \omega^2 d^3 \tag{9}$$

Thus, power input is proportional to viscosity, and dependent on the second and third powers of the propeller velocity and diameter, respectively. The density of the fluid is not a factor under these conditions of operation.

Particulate Solids Variables. Particle size and particle size distribution are important since they largely determine the magnitude of forces, gravitational and inertial, that can cause inter-particulate movement relative to surface forces, which resist such motion. As a consequence of high interparticulate forces, as compared with gravitational forces, few powders of less than 100 microns mean particle size are free-flowing. Most powders, including those encountered in pharmaceutical systems, have a wide range in particle size with the actual distribution determined to some extent by the method of prepara-



free-flowing if the particles do not stick together

Particle density, elasticity, surface roughness, and shape also exert their influence on the bulk properties of powders. Of these, particle shape is perhaps the most difficult variable to describe and is commonly expressed by scalar quantities known as shape factors. When applied to solids mixing, shape factors provide a number index to which mixing rate, flow rate, segregation rate, angle of repose, and other static or dynamic characteristics can be related. However, the limitations as well as the attributes of shape factors should be understood.

As scalar quantities, shape factors serve as proportionality constants between mean particle diameters and particle surface area and volume. They also serve to relate results of experimental particle size measurements by different methods. In spite of their utility in these ways, shape factors do not describe the shape of the particles they characterize. Thus, a single factor can in no way be considered a unique indication of shape. For example, one cannot differentiate between rods and flat discs by the use of a single shape factor. This limitation somewhat complicates correlations and interpretations of particulate shape effects on mixing.

A large number of shape factors have been defined and used in studies of multiparticulate solids systems. A typical example is that of a surface shape factor, α_s, defined by the expression:

$$\alpha_s = \frac{s}{\Sigma n_i d_i^2} \tag{11}$$

The total surface area of the powder is s, having n_i particles of projected diameter d_i. Powders whose particles are highly irregular in shape generally exhibit large values of α_s.

Example. To calculate a value of α_s that is useful for purposes of comparison with other materials, consider a system of monodisperse spheres of diameter 2r. The surface shape factor α_s will be independent of sample size, so that for simplicity, a single particle will be taken as the sample. In this case, equation (11) takes the form.

$$\alpha_s = \frac{4\pi r^2}{(2r)^2} = \pi$$

Had the idealized particles been perfect cubes, having edges of length d, then equation (11) would become:

$$\alpha_s = \frac{6d^2}{d^2} = 6$$

The value for α_s can be seen to increase substantially as the particles become more angular and deviate from a spherical shape.

Forces Acting in Multiparticulate Solids Systems. As pointed out previously, forces that operate at a particulate level during the mixing process are essentially of two types: (1) those that tend to result in movement of two adjacent particles or groups of particles relative to each other and (2) those that tend to hold neighboring particles in a fixed relative position. This division is arbitrary, and often a clear distinction cannot be made, for reasons that will become evident.

In the first category are forces of acceleration produced by the translational and rotational movements of single particles or groups of particles. Such motion can result either from contact with the mixer surfaces or from contact with other particles. In either case, the efficiency of momentum transfer is highly dependent on the elasticity of the collisions.

Gravitational forces also operate and, of course, act on all particles at all times in proportion to their mass.

Included in the second category of forces, namely those that resist particulate movement, are interparticulate interactions associated with the size, shape, and surface characteristics of the particles themselves. Powders that have high "cohesive" forces due to interaction of their surfaces can be expected to be more resistant to intimate mixing than those whose surfaces do not interact strongly. Factors that influence this type of interaction are surface polarity, surface charge, and adsorbed substances such as moisture.

In moving from one location to another, relative to its neighbors, a particle must surmount certain potential energy barriers. These arise from forces resisting movement insofar as neighboring particles must be displaced. This effect is a function of both particle size and shape and is most pronounced when high packing densities occur. Particle shape is important because as the shape of a particle deviates more significantly from a spherical form, the free movement it experiences along its major axes also diverges.

solid -solid mixing mechanisms

- 1-convective mixing is an analogous to bulk transport. This mixing can occur by an inversion of the powder bed by means of 1-blades or paddles, 2- revolving screw or by any method of moving a relatively large mass of material from one part of the powder bed to another.

2-shear mixing

- As a result of forces within the particulate mass , slip planes are set up and this give rise to laminar flow. When shear occurs between regions of different composition & parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers.

3-Diffusive mixing by diffusion

- When random motion of particles within a powder bed causes them to change position relative to one another. Such an exchange of positions by single particles result in a reduction of the intensity of segregation. Diffusive mixing occurs at the interfaces of dissimilar regions that are undergoing shear & therefore results from shear mixing.

The mixing of particles whose surfaces are nonconducting (electrically) often results in the generation of surface charges, as evidenced by a tendency of the powder to clump following a period of agitation. Surface charging of particles during mixing is undesirable, for it tends to decrease the process of interparticulate "diffusion."

Charging of powder beds and the undesirable effects it produces can be prevented or reduced in many cases by surface treatment, which is usually accomplished by adding small amounts of surfactants to the powder, thereby increasing the conductivity of the surface. The problem can also be solved in some cases by mixing under conditions of increased humidity (above 40%).

Segregation mechanisms

- The requirements for segregation
- 1-differences in mixture components mobilities can result from differences in particle sizes, shape, density, & surface characteristics.
- 2-segregation can be met by the earth's gravitational field or by centrifugal .electrical, magnetic field generated in the course of processing.

- Particulate solids tend to segregate by virtue of differences in the size, density, shape & other properties of particles. The process of segregation occurs during mixing & during subsequent handling of the completed mix, & it is pronounced with free flowing powders. Powders that are not free flowing or exhibit high forces of cohesion or adhesion between particles of similar or dissimilar composition are difficult to mix owing to agglomeration.

- The clumps of particles can be broken down by the use of 1- mixers that generate high shear forces or 2- subject the powder to impact.

Equipment ---batch mixing

- Common type of mixer consists of a container of one of several geometric forms which is mounted so that it can be rotated about an axis. The resulting tumbling motion accentuated by means of baffles or simply by virtue of the shape of the container.
- The popular twin shell blender is of this type & takes the form of a cylinder that has been cut in half . At approximately a 45- degree angle with its long axis & then joined to form a V shape. This is rotated so that the material is alternately collect

In the bottom of the V is inverted. This is effective because the bulk transport & shear which occur in tumbling mixers .

Other mixers take the form of cylinders , cubes or hexagonal cylinders & may be rotated about almost any axis .

1- tumbler

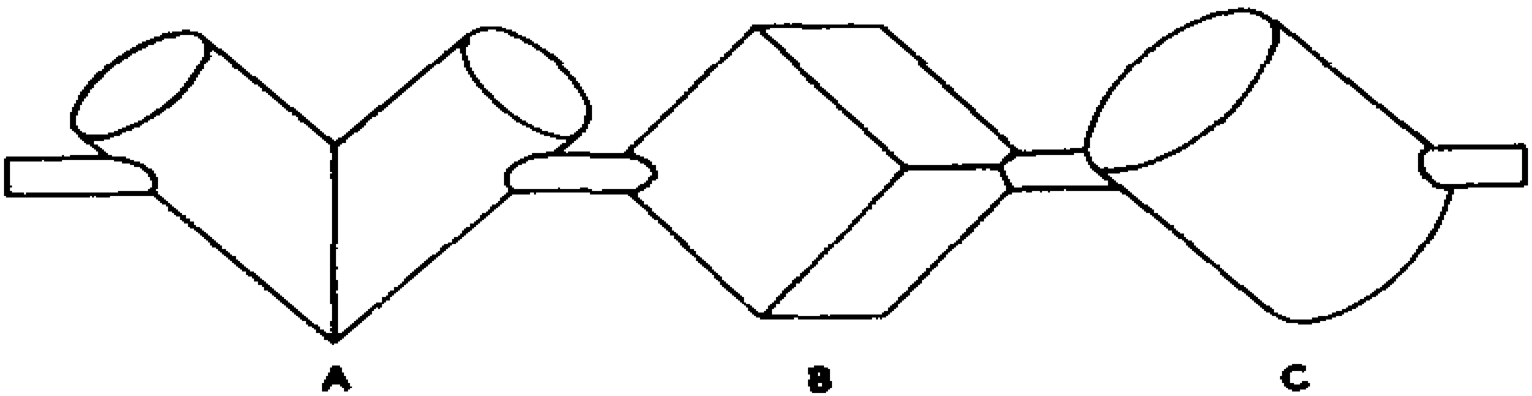


FIG. 1-11. *Three types of tumbling mixers shown mounted on a common shaft:* A, *twin-shell;* B, *cubic;* C, *cylindric. In operation, the asymmetric geometry results in a sideways movement of material in addition to the tumbling action of the mixers. Of the three types, the twin-shell is the most popular.*

The efficiency of tumbling mixers is highly dependent on the speed of rotation .

Rotation is too slow

- Does not produce the desired intense tumbling or cascading motion.

Rotation is too rapid

- Tends to produce centrifugal force sufficient to hold the powder to the sides of mixers & thereby reduce the efficiency.

- The optimum rate of rotation depends on the size & shape of the tumbler & also on the type of material being mixed but is commonly in the range of 30 to 100 rpm.

- 2nd class of mixers employs a stationary container to hold the material & brings about mixing by means of moving screws , paddles or blades.

Stationary mixers

- Does not depend on gravity
- It is useful in mixing solids that have been wetted
- The high shear forces are effective in breaking up lumps or aggregates.

Well known mixers are

- 1-the ribbon blender consists of horizontal cylindric tank usually opening at the top & fitted with helical blades which mounted on a shaft through the long axis of the tank & are often of both sided right & left hand twist.
- 2- in the helical flight mixer powders are lifted by a centrally located vertical screw & allowed to cascade to the bottom of the tank.

Ribbon blender

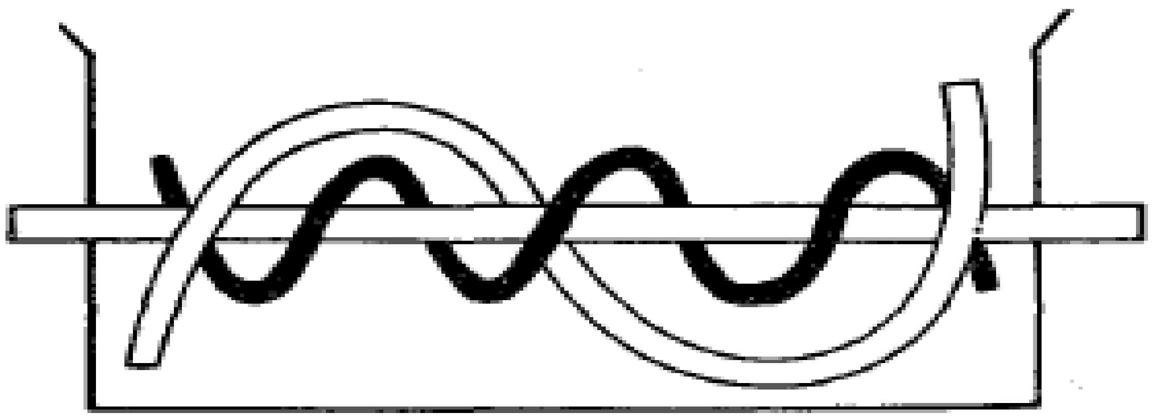


FIG. 1-12. *Side view of a top-loading ribbon blender. The blades are mounted on the horizontal axle by struts (not shown) and are rotated to circulate the material to be mixed. The spiral blades are wound (in most cases) in opposite directions to provide for movement of material in both directions along the axis of the tank. These mixers may be emptied either through ports in the bottom or by inverting them.*