2. *Polyphase systems*. The mixing of systems composed of several liquid or solid phases primarily involves the subdivision or deaggregation of one or more of the phases present, with subsequent dispersal throughout the mass of material to be mixed. In a general sense, the processes of homogenization, suspension formation, and emulsification may be considered forms of mixing. Inasmuch as these topics are covered in Chapters 5, 16, and 17, they are considered from only a mechanistic standpoint here.

The mixing of two immiscible liquids requires the subdivision of one of the phases into globules, which are then distributed throughout the bulk of the fluid. The process usually occurs by stages during which the large globules are successively broken down into smaller ones. Two primary forces come into play here: the interfacial tension of the globules in the surrounding liquid, and forces of shear within the fluid mass. The former tends to resist the distortion of globule shape necessary for fragmentation into smaller globules, whereas the forces of shear act to distort and ultimately disrupt the globules. The relationship between these forces largely determines the final size distribution in the mixture.

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. In the case of low-viscosity systems, high shear rates are required and are commonly produced by passing the fluid under high pressure through small orifices or by bringing it into contact with rapidly moving surfaces. Devices for accomplishing these high rates are described in Chapter 17, Emulsions.

Highly viscous fluids, such as are encountered in the production of ointments, are efficiently dispersed 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 material to ensure a uniform dispersion throughout the completed mixture.

The mixing of finely divided solids with a liquid of low viscosity in the production of a suspension depends on the separation of aggregates into primary particles and the distribution of these particles throughout the fluid. These processes are often carried out in a single mixing operation, provided that shear forces of sufficient intensity to disrupt aggregates can be generated. High-speed turbines, frequently fitted not a problem, or when deaggregation is to be carried out following a general mixing step, the equipment used in mixing of suspensions is essentially the same as that previously discussed for liquids of comparable viscosity.

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. In these cases, the forces required to induce shear are considerable, and equipment used is of heavy design. The choice of a mixer is limited to those that either knead or mull the material. Kneaders operate by pushing masses of the material past each other and by squeezing and deforming them at the same time. Such mixers may take several forms, but usually have counter-rotating blades or heavy arms that work the plastic mass. Shear forces are generated by the high viscosity of the mass and are effective in deaggregation as well as distribution of the solids in the fluid vehicle. A diagram of a sigma-blade mixer with overlapping blades is shown in Figure 1-8.

Mulling mixers are efficient in deaggregation of solids, but are typically inefficient in distributing the particles uniformly through the entire mass. Previously mixed material of uniform composition, but containing aggregates of solid particles, is suitable for mixing in these devices. In the event of segregation during mulling, a final remixing may be necessary.

Roller mills consisting of one or more rollers are in common use. Of these, the three-roll type seems to be preferred (Fig. 1-9). 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 of speed. Material coming between the rollers is crushed, depending on the gap, and is also sheared by the difference in rates of movement of the two surfaces. In Figure 1-9 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

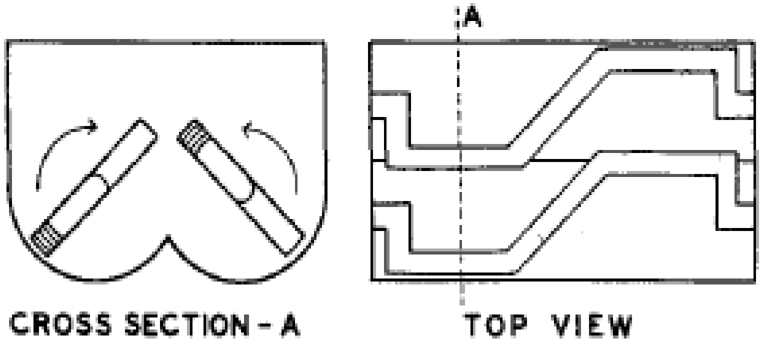

FIG. 1-8. *Schematic drawing of a top-loading sigma-blade mixer with overlapping blades. The top view shows the relationship of the counter rotating blades to the overall geometry of the mixer.*

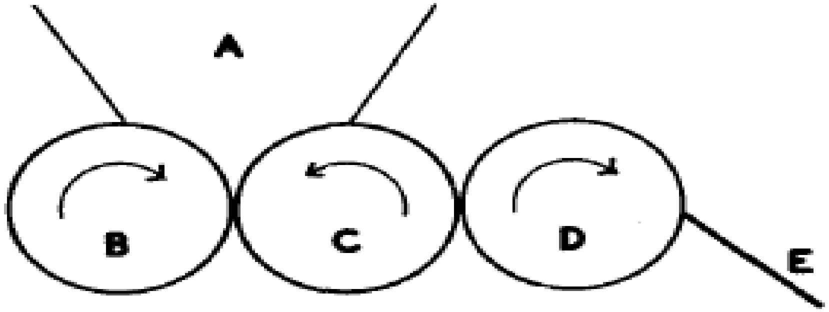

FIG. 1-9. *Cross section of a three-roll mill showing hopper (A), rolls (B,C,D), and scraper (E). Directions of roller rotation are indicated. Speed of rotation of the rollers increases from B to D. Material placed in the hopper passes between rolls B and C and then C and D in succession and is finally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

smooths the mixture, which adheres to roll C. A scraper, E, is arranged to continuously remove the mixed material from roller D. The arrangement is such that no material can reach the scraper that has not passed between both sets of rolls.

The extreme case of solid-liquid mixing is one in which 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 of the 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 lump; however, the process is not one of fluids mixing, but one of 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 under that heading later in this chapter.

Correlation. 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 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-

The Reynolds number is commonly defined by the expression:

$$R_e = \frac{vL\zeta}{\eta} \tag{3}$$

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:

$$F_r = \frac{V^2}{gL} \tag{4}$$

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:

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

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 interparticulate 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 preparation. An excellent discussion of the statistics of small particles is given by Herdan.[7]

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:

$$\alpha_s = \frac{s}{\Sigma n_i d_i^2} \qquad (11)$$

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. In general, much more rapid and efficient interchange of momentum would be expected if loss by inelasticity was minimal.

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.

Mixing Mechanisms. It has been generally accepted that solids mixing proceeds by a combination of one or more mechanisms.

1. *Convective mixing.* This mechanism may be regarded as analogous to bulk transport as discussed in connection with fluids mixing. Depending on the type of mixer employed, convective mixing can occur by an inversion of the powder bed, by means of blades or paddles, by means of a revolving screw, or by any other 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. Depending on the flow characteristics of the powder, these can occur singly or in such a way as to give rise to laminar flow. When shear occurs between regions of different composition and parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers. Shear occurring in a direction normal to the interface of such layers is also effective since it too reduces the scale of segregation.

3. *Diffusive mixing.* Mixing by "diffusion" is said to occur 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 results in a reduction of the intensity of segregation. Diffusive mixing occurs at the interfaces of dissimilar regions that are undergoing shear and therefore results from shear mixing. It may also be produced by any form of agitation that results in interparticulate motion.

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. As mentioned previously, particulate solids tend to segregate by virtue of differences in the size, density, shape, and other properties of the particles of which they are composed. The process of segregation occurs during mixing as well as during subsequent handling of the completed mix, and it is most pronounced with free-flowing powders. Powders that are not free-flowing or that exhibit high forces of cohesion or adhesion between particles of similar or dissimilar composition are often difficult to mix owing to agglomeration. The clumps of particles can be broken down in such cases by the use of mixers that generate high shear forces or that subject the powder to impact. When these powders have

The requirements for segregation, as previously postulated, can arise in a variety of ways. Differences in mixture component mobilities can result from differences in particle sizes, shapes, density, and surface characteristics. While other characteristics may also be important, these are recognized as significant in most cases. The second requirement for segregation can be met by the earth's gravitational field, or by a centrifugal, electrical, magnetic field generated in the course of processing. Even in the absence of such fields, this requirement can be satisfied by a gradient in shear rate within the powder bed.

Equipment

Batch Mixing. A 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 is accentuated by means of baffles or simply by virtue of the shape of the container. The popular twin-shell blender is of this type and takes the form of a cylinder that has been cut in half, at approximately a 45-degree angle with its long axis, and then rejoined to form a "V" shape. This is rotated so that the material is alternately collected in the bottom of the V and then split into two portions when the V is inverted. This is

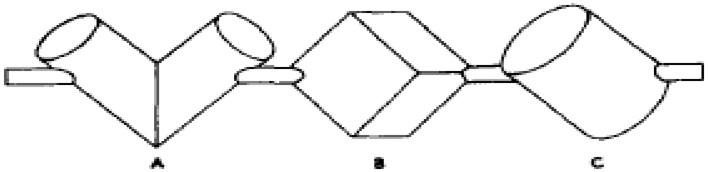

FIG. 1-11. *Three types of tumbling mixers shown mounted on a common shaft:* A, *twin-shell;* B, *cubic;* C, *cylindric. In operation, the asymmetric geometry results in a sideways movement of material in addition to the tumbling action of the mixers. Of the three types, the twin-shell is the most popular.*

Other mixers of this same general type take the form of cylinders, cubes, or hexagonal cylinders (Fig. 1-11), and may be rotated about almost any axis depending on the manufacturer.

The efficiency of tumbling mixers is highly dependent on the speed of rotation. Rotation that is too slow does not produce the desired intense tumbling or cascading motion, nor does it generate rapid shear rates. On the other hand, rotation that is too rapid tends to produce centrifugal force sufficient to hold the powder to the sides of the mixer and thereby reduce efficiency. The optimum rate of rotation depends on the size and shape of the tumbler and also on the type of material being mixed, but is commonly in the range of 30 to 100 rpm.

A second class of mixer employs a stationary container to hold the material and brings about mixing by means of moving screws, paddles, or blades. Since this mixer does not depend entirely on gravity as do the tumblers, it is useful in mixing solids that have been wetted and are therefore in a sticky or plastic state. The high shear forces that are set up are effective in breaking up lumps or aggregates. Well-known mixers of this type include the following. (1) The ribbon blender (Fig. 1-12), consists of a horizontal cylindric tank usually opening at the top and fitted with helical blades. The blades are mounted on a shaft through the long axis of the tank and are often of both right- and left-hand twist. (2) In the helical flight mixer, powders are lifted by a centrally located vertical screw and allowed to cascade to the bottom of the tank. Of these two types, the ribbon blender is the more popular.

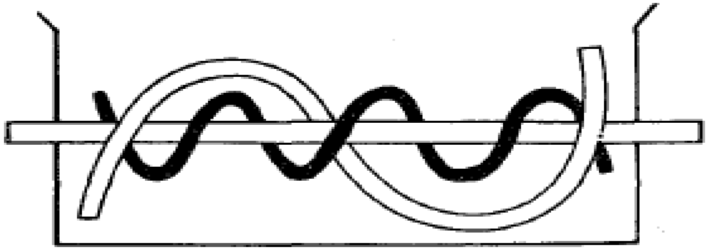

FIG. 1-12. *Side view of a top-loading ribbon blender. The blades are mounted on the horizontal axle by struts (not shown) and are rotated to circulate the material to be mixed. The spiral blades are wound (in most cases) in opposite directions to provide for movement of material in both directions along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

Continuous Mixing.

ous mixing equipment. Continuous mixing processes are somewhat analogous to those discussed under fluids mixing. Metered quantities