REVIEW ARTICLE

Milling of Pharmaceutical Solids

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Perhaps due to its complex nature and to the inadequacy of quantitative theories of size reduction, there is little pharmaceutical literature on the mechanical operation of size reduction, which is a factor at some stage in the production of most dosage forms. Comminution is a generic term for size reduction. Many other terms—grinding, disintegration, pulverization, and dispersion—have been used synonymously for comminution. In this review, mechanical size reduction of solids will be referred to as milling.

A real particulate system always consists of a mixture of particles in a range from the minimum to the maximum particle size. The size characteristics of a real particulate system are completely expressed by a size–frequency curve, which is a plot of the quantity or percentage, by number or weight, that is within a certain size range against particle size. The distribution of many milled or chemically precipitated particles is asymmetrical or skewed (1, 2). Many asymmetrical frequency curves have a log-probability distribution and can be made symmetrical if the logarithms of size are used rather than size (3, 4). Size distribution may also be represented by a plot of the cumulative percent larger (or smaller) than a stated size against particle size. The immediate objective of milling is to satisfy the size limiting specifications, which may be expressed as a minimum and maximum size, a size–frequency distribution curve, or a specific surface.

As an arbitrary classification for pharmaceutical milling, coarse milling produces particles larger than 20 mesh, intermediate milling produces particles from 200 to 20 mesh, and fine milling produces particles smaller than 200 mesh. Ultrafine refers to sizes approaching 1 μm. A mill may operate satisfactorily in more than one case; e.g., a comminuting machine[1] may be used to prepare a 20-mesh tablet granulation and to mill a crystalline material to a 200-mesh powder.

The importance of size reduction and its control has been recognized for many years, but there seems to be no way to relate the coefficients describing the physical properties of a solid to the physical process that occurs during milling. The ability to resist size reduction depends on hardness, which is the resistance to crushing, and is an indication of abrasiveness or mill wear. Since values of the Moh hardness index (5) are available for minerals but not for drugs, by analogy a medicinal compound is qualitatively

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[1] Fitzpatrick.

said to be soft, intermediate, or hard. A grindability index has not been generally accepted for materials other than coal, because of the wide variety of grinding equipment that may be used and the dissimilar physicochemical properties of materials. There does not seem to be a quantitative relationship of grindability to hardness (6). Grindability depends not only on the properties of the material but also on the manner in which size reduction is achieved.

In pharmacy the extent of size reduction is determined by the improvement of clinical efficacy and product characteristics and by the facilitation of production rather than cost of the milling operation.

A 0.5-g dose of micronized griseofulvin administered orally produced serum levels indistinguishable from those produced by a 1.0-g dose of nonmicronized griseofulvin (7). Other examples of the effect of particle size of drugs and its relationship to absorption and clinical activity have been cited (8).

Particle-size distribution may affect texture, taste, and rheology of oral suspensions in addition to absorption (9). The effects of specific surface and particle-size distribution on rheology and product injectability and on the effectiveness of intramuscular suspensions of procaine penicillin G were reported (10). Solvolytic decomposition of solids initially occurs at surface irregularities and is increased by the presence of solvates or moisture. Micronization and subsequent drying increase the stability since the occluded solvent is removed (11).

The flowability of powders and granulations in high-speed filling equipment and in tablet machines affects product uniformity. Relationships between flow rate and particle size have been reported (12–14). In solid–solid blending, large and small particles tend to segregate; this may be countered by milling the components to a small size with a narrow size range (15). When small quantities of a liquid are to be blended into a powder, particle size should be uniform to obtain batch-to-batch uniformity (16). Extraction of animal glands and crude vegetable drugs is facilitated by milling to an optimum size. The drying of wet masses, e.g., tablet granulations, is facilitated by milling, which increases the surface and reduces the distance the solvent must diffuse to the outer surface. The role of particle-size reduction in tablet manufacturing operations has been discussed (17).

THEORY OF COMMINUTION

Solids under stress are strained and deformed. Mechanical behavior can be illustrated in the stress–strain curve shown in Fig. 1. The initial linear portion of the curve is defined by Hooke's law, i.e., stress is proportional to strain, and Young's modulus, i.e., the ratio of stress to strain expresses the softness or stiffness in dynes per square centimeter. The curve becomes nonlinear at the yield point, which measures the resistance to permanent deformation. With further stress the region of irreversible plastic deformation is reached. The total area under the curve represents the energy of fracture and is an
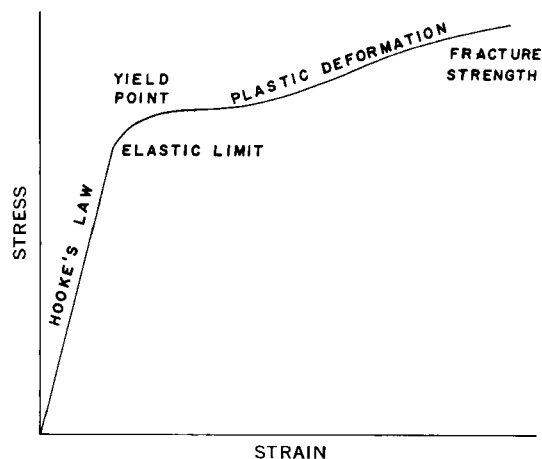

Figure 1—*Stress–strain behavior, with the area under the curve representing the energy required to fracture the solid.*

approximate measure of the impact strength of the material.

For most metals the stress–strain curve in the elastic region of Hooke's law is reversible, but for polymeric materials hysteresis is frequent. If a force is released and applied to a polymeric material, an elastic loop or hysteresis occurs in the stress–strain cycle; the area of the loop represents the dissipation of stress energy (usually as heat).

When the application and release of a force cause permanent deformation, energy is expended and cracks may be initiated. The furthest extension of a crack is the point of greatest stress. Since the surface of a particle is irregular, the force is initially applied to the higher portion of the surface with the result that high stresses and temperatures exist locally in the material. A force that exceeds the elastic limit fractures the particle. As fracture occurs, the points of application of force are shifted. Stress waves released by the initial fracture release energy, producing other regions of high stress from which new cracks or fractures may occur. If force is rapidly applied by impact, cracks may form before the strain energy has reached equilibrium in the particle and thereby decrease the total work input required for fracture.

Crystalline materials fracture along crystal cleavage planes; noncrystalline materials fracture at random. If an ideal crystal were pressed with an increasing force, the force would be distributed uniformly through its structure until the crystal disintegrated into its individual units. A real crystal fractures under much less force into a few relatively large particles and a number of fine particles with relatively few particles of intermediate size. It seems that the size of the larger particles is related to the size reduction process and that the size of the finer particles is related to the structure of the material. Crystals of pure substances have internal weaknesses due to missing atoms or ions in their lattice structures and flaws arising from mechanical or thermal stress (6).

The Griffith theory (18, 19) of cracks and flaws assumes that all solids contain flaws and microscopic

cracks, which increase the applied force according to the crack length and focus the stress at the atomic bond of the crack apex. The Griffith theory may be expressed (20, 21) as:

$$T = \sqrt{\frac{Y\epsilon}{c}} \qquad \text{(Eq. 1)}$$

where T is tensile stress, Y is Young's modulus, ϵ is the surface energy of the wall of the crack, and c is the critical crack depth required for fracture. A linear relationship between the square of tensile strength of minerals and the critical height for drop weight impact suggests that the square of tensile strength is a useful criterion of impact fracture (22).

Thermodynamic treatment of the milling process has been attempted, but there is confusion about the meaning of surface tension, surface stress, and surface energy of solids, and there is some question as to whether or not a reversible path may be devised for a milling process. Thermodynamics have shown that the work to fracture a particle is dependent on surface energy (23) and that the yield stress is dependent on the rate of strain and temperature of the fluid filling the particle pores (24). Fracture is predicted to be more efficient at elevated temperature (25).

The weakest flaw in a particle determines its fracture strength and controls the number of particles produced by fracture. Although particles with the weakest flaws fracture most easily and produce the largest particles, they are not necessarily the easiest to mill to a desired size because they may require several more stages of fracture than particles of the same size whose weakest flaw is stronger.

The goal of milling is to form cracks that propagate through the deformed particles at the expense of strain energy and produce fracture. The useful work is directly proportional to the new surface area; since the crack length is proportional to the square root of the new surface formed, the useful work is proportional to the square root of the diameter of the milled particles minus the initial diameter (26). The useful energy, E^*, expended is:

$$E^* = E\left(\frac{\sqrt{D_1}}{\sqrt{D_1} - \sqrt{D_2}}\right) \qquad \text{(Eq. 2)}$$

where D_1 is the diameter of the material to be milled, D_2 is the diameter of the milled material, and E is the energy input.

Size reduction begins with crack fracture, which requires a certain minimal energy; however, milling conditions are so random that many particles receive impacts that are insufficient to fracture them and some particles are fractured by excessively forceful impact. Hence, milling is an inefficient operation. The energy not used in fracture is dissipated in the milling equipment as heat, vibration, sound, and inefficiency of transmission; it is dissipated in the material as interparticulate friction, friction between the material and the mill, and elastic deformation of unfractured particles.

The fracture mechanism is impact when a force of sufficient magnitude is rapidly applied normal to the surface, is directed toward its center, and results in the formation of two or more fragments. If the force is slowly applied, the fracture mechanism is compression. Attrition is the fracture mechanism by which force is applied parallel to the surface of the solid and results in extremely fine particles.

ENERGY FOR COMMINUTION

The energy required to reduce the size of particles is inversely proportional to the size raised to some power. This may be expressed mathematically as (27):

$$\frac{dE}{dD} = -\frac{C}{D^n} \qquad \text{(Eq. 3)}$$

where dE is the amount of energy required to produce a change in size, dD, of unit mass of material, and C and n are constants.

In 1885, Kick (28) proposed that the energy expenditure, E, for size reduction is directly related to the reduction ratio, D_1/D_2, where D_1 and D_2 are the diameters of the material to be milled and the milled material, respectively. Thus, if a given quantity of energy is required to mill a given weight of material from 500 to 250 μm, the same energy would be required to reduce the size from 50 to 25 μm. Kick's proposal may be expressed as:

$$E = C \ln \frac{D_1}{D_2} \qquad \text{(Eq. 4)}$$

where C is a reciprocal efficiency coefficient. In the engineering literature, $C = K_k f_c$, where f_c is the crushing strength of the material, and K_k is known as Kick's constant. If $n = 1$, the general differential equation reduces to Kick's equation. Kick's proposal was developed on a stress–strain diagram for cubes under compression and represents the energy required to effect elastic deformation before fracture occurs. It is most applicable to coarse grinding (29).

In 1867, von Rittinger (30) proposed that the energy required for size reduction is directly proportional to the increase in surface as expressed by the relationship:

$$E = k_1(S_2 - S_1) \qquad \text{(Eq. 5)}$$

where k_1 includes the relationship between the particle surface and diameter, and S_1 and S_2 are the specific surfaces before and after milling, respectively. In terms of particle diameters:

$$E = C'\left(\frac{1}{D_2} - \frac{1}{D_1}\right) \qquad \text{(Eq. 6)}$$

where D_1 and D_2 are the diameters before and after milling, respectively. In the engineering literature, $C' = K_r f_c$, where K_r is known as Rittinger's constant. If $n = 2$ (because the surface is proportional to the square of the diameter), the solution of the general differential equation yields Rittinger's equation. Rittinger's relationship is most applicable to fine grinding (29).

In 1952, Bond (26, 31) suggested that the energy required for size reduction is inversely proportional to the square root of the diameter of the milled ma-
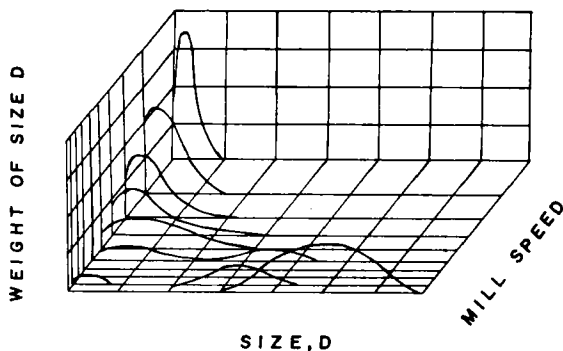
Figure 2—*Diagrammatic representation of changes in particle-size-frequency distribution as milling progresses (34).*

terial. Mathematically, this may be expressed:

$$E = 2C' \left(\frac{1}{\sqrt{D_2}} - \frac{1}{\sqrt{D_1}} \right) \qquad \text{(Eq. 7)}$$

If $n = 1.5$, the solution of the general differential equation yields Bond's equation.

Bond expressed the energy expended in milling in terms of a work index, W_i. The work index is the amount of energy required to reduce a unit mass of material from a theoretically infinite particle size to such a size that 80% passes through a 100-μm screen. It is calculated by Eq. 8:

$$W_i = \left(W \sqrt{\frac{D_2}{100}} \right) \left(\frac{\sqrt{D_1/D_2}}{\sqrt{D_1/D_2} - 1} \right) \qquad \text{(Eq. 8)}$$

where W is the work input. The work index is not a true constant because the value changes with a shift in particle-size distribution and with structural characteristics of the material. It is probably the best available method for comparing the efficiency of milling operations, and its most useful value is determined under conditions of the final operation. The dry grind work index is usually 1.3 times the wet grind value.

If n is replaced by $(1 + n)$ in the general differential equation and the equation is integrated (32, 33):

$$W = W_i \left[1 - \left(\frac{1}{D_1/D_2} \right)^n \right] \left(\frac{100}{D_2} \right)^n \qquad \text{(Eq. 9)}$$

The n may be considered as an exponent expressing variation in resistance to fracture with size change and with change in efficiency which may be influenced by particle size.

SIZE DISTRIBUTION

When a material is milled, the particles have a variety of sizes as determined by the flaw structure. The variation in size is usually expressed as a size-frequency distribution curve, which is a plot of the percentage frequencies of the various particles against size. With progressive milling, the particle size-frequency distribution has a narrower range and a finer mean size. Changes in size distribution as milling proceeds are illustrated in Fig. 2. If the initial material has a monomodal size distribution, as milling proceeds it develops a bimodal size distribu-

tion. The primary component gradually decreases in weight as milling progresses, and the secondary component increases in weight. This reduction in weight is accompanied by a decrease in modal size of the primary component and is caused by preferential fracture of the larger particles. The modal size of the secondary component remains constant. Further milling tends to eliminate the primary component. If the material is transferred to a second mill for finer size reduction, the process is repeated (34). As the particle-size distribution changes, milling characteristics, e.g., work index, change because the abundance or shortage of flaws varies at different sizes.

At least two specifications are required to characterize a specific size distribution, e.g., 85% through a 60-mesh screen and 5% through a 325-mesh screen. In the simplest case, one number establishes the limits of particle sizes involved and another determines the weight relationships in the various size ranges. Schuhmann (35) experimentally verified the empirical equation:

$$y = 100(D/k)^a \qquad \text{(Eq. 10)}$$

where y is cumulative weight percent smaller than size D, k is a size modulus for a given distribution, and a is a distribution modulus. The Schuhmann equation describes the size relationships of many fractured homogeneous materials. As shown in Fig. 3, when the cumulative weight percent less than stated size is plotted on log–log paper against size, a straight line is obtained with a slope of a, and it intersects the 100% ordinate line at the theoretical maximum-sized particle equal to k (36). For pure impact grinding, $a \rightarrow 1$; for abrasion grinding, $a \rightarrow 0$.

As a general rule, milled powders have a log-probability distribution (37). The method of size distribution analysis favored by the author involves the log-normal distribution equation:

$$\Delta y = \frac{1}{\sqrt{2\pi} \ln \sigma} \int_{\ln D_1}^{\ln D_2} \exp \left\{ -\left[\ln \frac{D}{D_g} \middle/ (\sqrt{2} \ln \sigma) \right]^2 \right\} d(\ln D)$$

$$\text{(Eq. 11)}$$

where Δy is the weight fraction of particles between diameters D_1 and D_2, D_g is the geometric mean diameter, and σ is the geometric standard deviation (38).

The manipulations of these equations are tedious, and calculations are simplified by the use of log-probability paper. Particle size is plotted on the log grid, and cumulative percent smaller than the stated size is plotted on the probability grid. The best straight line is drawn through the experimental points, and the geometric mean diameter is the 50% value on this line. The range of particle sizes is indicated by the standard deviation, which is equal to the 84.13% size read from the straight line divided by the 50% size (or 50% size divided by the 15.87% size). Once the geometric mean diameter and the standard deviation are evaluated, other diameters may be easily calculated (39–42). Depending on the particulate system used, the most relevant diameter is calculated. For example, by calculating the mean
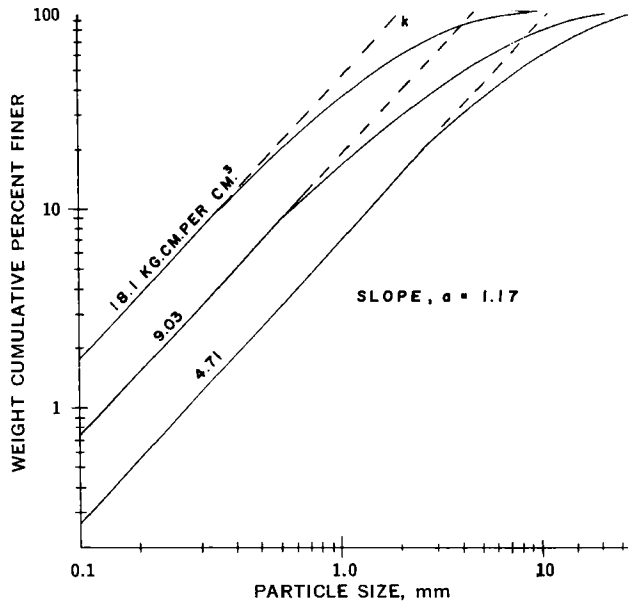
Figure 3—*Size distributions resulting from impact of lumps of salt at various levels of impact energy (36).*

volume-surface diameter, D_{vs}, and using Eq. 12:

$$S = \frac{6}{D_{vs}\rho} \qquad (Eq.12)$$

one may find the specific surface, S, for a powder with a density ρ.

Experimental proof of the relationship between energy and size reduction is difficult because it is experimentally impossible to fracture particles of one uniform size to particles of a smaller and still uniform size as required by Eqs. 4, 6, and 7. It is also impossible to describe accurately the weight relationships of sizes in a given material by a single number since, for a given size modulus, there is theoretically an infinite number of size distributions to which the modulus may refer. In addition, the energies required to produce each size distribution from a given size will be different.

A second difficulty in verifying energy–size reduction relationships is the definition of energy actually causing fracture and other forms of energy in the milling process. Since fracture is dependent on strain energy of elastic deformation, it seems likely that the energy is related to size reduction. Strain energy absorbed by slow compression is easy to measure; strain energy absorbed by impact is very difficult to measure due to the complex milling process involving translatory motion, vibratory motion, plastic deformation, and sound.

A third difficulty in establishing energy–size reduction relationships arises from the fact that each equation implies that n is a constant independent of the mechanism of size reduction and independent of the amount of size reduction. Probably n is not a constant but is a variable depending on the material and the manner in which it is fractured. The following derivation illustrates a general method by which n and C may be calculated using a single distribution plot for any milling test.

When Eqs. 3 and 10 are combined, the energy, E, required to reduce an element of weight of material, dy, from size D_m to size D is:

$$E = \int_{D_0}^{k} \int_{D_m}^{D} (-C \, dD_1/D_1^{\,n}) \, dy \qquad (Eq.13)$$

As size distribution is described by the Schuhmann equation:

$$dy = \left[\frac{100a}{k^a} D^{a-1} \right] dD \qquad (Eq.14)$$

Thus:

$$E = \int_{D_0}^{k} \int_{D_m}^{D} (-C \, dD_1/D_1^{\,n}) \left(\frac{100a}{k^a} D^{a-1} \, dD \right) \qquad (Eq.15)$$

$$E = \frac{Ca}{(n-1)k^a} \left[\frac{k^{a-n+1}}{a-n+1} - \frac{k^a}{aD_m^{\,n-1}} - \frac{D_0^{\,a-n+1}}{a-n+1} + \frac{D_0^{\,a}}{aD_m^{\,n-1}} \right]$$

$$(Eq.16)$$

For materials following the Schuhmann distribution, $D_0 \rightarrow 0$. Thus:

$$E = \frac{Ca}{n-1} \left[\frac{k^{1-n}}{a-n+1} - \frac{1}{aD_m^{\,n-1}} \right] \qquad (Eq.17)$$

If D_m is large compared to k, then:

$$E = \frac{Ca}{(n-1)(a-n+1)} k^{1-n} \qquad (Eq.18)$$

When plotted on log–log paper, as shown in Fig. 4 for impact fracture of sodium chloride, Eq. 18 yields a straight line, where a and C are constant and the slope is $(1 - n)$. Thus, if several milling experiments are conducted in which the energy inputs and the size distributions are measured, n, the exponent in fundamental energy–size reduction equations, may be determined. The sole restriction is that for both size distributions the shapes of the size distribution curves remain the same and are displaced only laterally with a change in energy input.

Equation 18 is real only if n is greater than 1 and less than $(a + 1)$. From measured size distributions, a can be as great as 1.5 and is usually approximately 0.8. Thus, the values of n range from 1 to 2.5. This range was empirically chosen for Eqs. 4, 6, and 7. For hard, brittle material, $(a - n + 1)$ approaches zero, and its real value cannot be accurately determined. Consequently, the constant C cannot be determined accurately; however, for any specific mill-
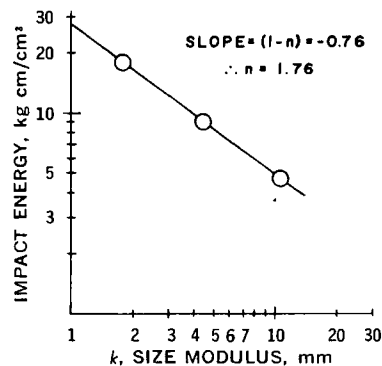
Figure 4—*Energy–size reduction relationship for salt (36).*

ing conditions, the term:

$$A = \frac{Ca}{(n-1)(a-n+1)} \qquad \text{(Eq. 19)}$$

is constant. The general energy–size reduction equation may then be expressed as:

$$E = Ak^{(1-n)} \qquad \text{(Eq. 20)}$$

where A is a mill constant, which can be determined easily for any size reduction test when the exponent n has been determined as discussed.

In many industries, the relationship of energy input to accomplished size reduction is an important economical consideration. In pharmacy, where relatively small quantities of materials are milled and the influence of size is paramount to the efficacy or physical stability of a pharmaceutical, energy consumption is not a major factor. The proposed theories of size reduction are suitable for specific applications and are best used in a qualitative manner, but the only reliable means for determining the size reduction provided by a given mill is to make experimental tests with the actual material.

LIMIT OF COMMINUTION

The general differential equation of size reduction and its special cases predict that given sufficient time a material may be reduced to unlimited fineness. Unfortunately in these equations the size and energy input are inadequately defined. If the ultimate size reduction by mechanical means were attributed to the unit of the crystal lattice, the limit of size reduction would be approximately 10^{-3} μm (or a specific surface of approximately 6×10^7 cm^2/cm^3). Milling limit refers to the size distribution to which a milling operation tends as a result of material characteristics, mill characteristics, and operating conditions when given sufficient time.

Time affects the milling process. When the resident time in a mill is a few minutes, the material is subjected to a relatively constant fracture-producing environment. Changes in milling conditions that are insignificant for short milling periods may be controlling factors in prolonged milling. In prolonged milling, the milling environment is not necessarily constant.

At 10 μm, aggregation due to van der Waals' force begins; at 1 μm, it is intense as crystals fracture across cleavage planes involving a valence type of force (43, 44).

With prolonged milling, the probability that an individual particle would be involved in a fracture diminishes as the particle becomes smaller. In general, as size reduction proceeds, the mean stress required to cause fracture increases through the depletion of cracks while the magnitude of local stress available decreases. As size reduction proceeds because of the diminishing local stress and increasing aggregation, increases in energy expenditures are fruitless, and size reduction ceases at some practical milling limit (45).

Harris (46) proposed an empirical equation ex-

pressing a limiting specific surface, S_m:

$$S = S_m[1 - \exp(-KE^n)] \qquad \text{(Eq. 21)}$$

where E is energy input, and K is a constant depending on conditions of milling. As shown in Fig. 5, Kaneniwa et al. (47) demonstrated that after 5 hr of ball milling the size reduction of sulfadimethoxine reached a limiting value. The rate of increase in surface area decreased gradually with the lapse of milling time and approached zero where the minimum diameter or maximum surface area was obtained. The data fitted the equation:

$$\frac{dS}{dt} = k_1 \exp(-k_2 S) \qquad \text{(Eq. 22)}$$

where k_1 and k_2 are parameters depending on physical properties of the material and coherency, respectively.

The mill and its operation influence the mill limit. Excessive clearance between the impacting surfaces limits size reduction. In wet milling, the fineness decreases with increased viscosity, which depends on the dispersion medium, the size and concentration of particles, and shear rate. In tumbling mills, as the particles become smaller and more numerous, friction diminishes and the material behaves as a semisolid. Large particles may arch and protect smaller particles from impact. As a result of surface energy, fine particles may coat the grinding medium and cushion larger particles from impact.

RATE OF MILLING

Rate of milling involves the mass and size of particles and the time in the mill. There is experimental evidence that batch milling of brittle materials in small mills follows a first-order law (48, 49). The initial particles are fractured, producing first-generation particles which are fractured to produce second-generation particles, which are also fractured and so on. Since this process is analogous to radioactive decay processes, some radiochemical terminology has been introduced into milling technology. The decay constant, λ, is a function of particle size, so with the numerous equations involved it becomes necessary to utilize computers. The decay constant varies with the size of the material introduced into the mill (50) and the size of the grinding medium in a ball mill (51).

With impact milling following a first-order rate, the number, N, of particles that survive fracture is the product of the initial number, N_0, and the probable fraction surviving fracture at time t:

$$N = N_0 \exp(-\lambda t) \qquad \text{(Eq. 23)}$$

If the average mass of a particle in a given size range is constant, then N/N_0 is equivalent to M/M_0, where M is the mass of particles yet unfractured and M_0 is the initial mass. The milling rate is:

$$\frac{dM}{dt} = -\lambda M \qquad \text{(Eq. 24)}$$

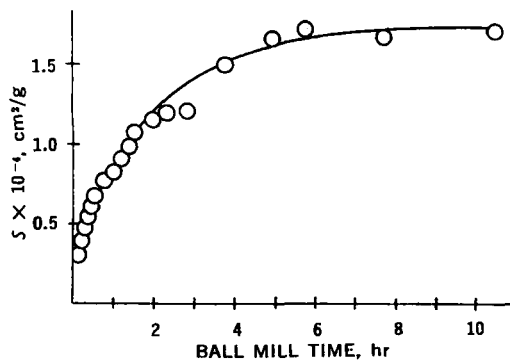When milling time is brief, the survival probability

Figure 5—*Increase of surface area of sulfadimethoxine with lapse of ball-milling time (47).*

is approximately $(1 - \lambda t)$ and the most probable fraction of initial material fractured is $1 - (1 - \lambda t)$ or λt. The weight of material that has been reduced in size is:

$$M_0 - M = M_0 \lambda t \qquad (Eq. 25)$$

The total mass of material in a size range smaller than the largest size may increase, although the amount of original material in that size range must always decrease. Because particles resulting from fracture of larger particles may enter the size range of interest faster than the original material is fractured to a smaller size, the total mass of the size range of interest is increased. Sedlatschek and Bass (52) proposed a set of first-order differential equations to describe the milling process and verified them over a 30-min milling period. The weight percent of particles, M_i, having a size range between D_{i-1} and D_i, has a rate change, dM_i/dt, given by:

$$-\frac{dM_i}{dt} = \lambda_{ii} M_i - \sum_{k=i+1}^{n} \lambda_{ki} M_k \qquad (Eq. 26)$$

where the rate of change, dM_1/dt, is:

$$-\frac{dM_1}{dt} = -\sum_{k=2}^{n} \lambda_{k1} M_k \qquad (Eq. 27)$$

In general, $\lambda_{ii} = \Sigma^i_{k=i-1} \lambda_{ik}$ while $\Sigma^n_{k=1} M_k = 100\%$.

Consider particles of a material that has been milled into four arbitrary groups, $i = 1, 2, 3,$ and 4, with size limits 0.0–0.1, 0.1–0.2, 0.2–0.3, and 0.3–0.4 mm, respectively. For these limits, Eqs. 26 and 27 have the following forms. For Group 4, the largest size:

$$-\frac{dM_4}{dt} = \lambda_{44} M_4 \qquad (Eq. 28)$$

For Group 3:

$$-\frac{dM_3}{dt} = \lambda_{33} M_3 - \lambda_{43} M_4 \qquad (Eq. 29)$$

For Group 2:

$$-\frac{dM_2}{dt} = \lambda_{22} M_2 - \lambda_{32} M_3 - \lambda_{42} M_4 \qquad (Eq. 30)$$

For Group 1:

$$-\frac{dM_1}{dt} = \lambda_{41} M_4 - \lambda_{31} M_3 - \lambda_{21} M_2 \qquad (Eq. 31)$$

For a mass balance:

$$\lambda_{44} = \lambda_{43} + \lambda_{42} + \lambda_{41} \qquad (Eq. 32)$$

$$\lambda_{33} = \lambda_{32} + \lambda_{31} \qquad (Eq. 33)$$

$$\lambda_{22} = \lambda_{21} \qquad (Eq. 34)$$

These equations express the rate at which the largest size Group 4 decays; the rate at which Group 3, the next size smaller, decays as modified by the contributions from Group 4; the rate at which Group 2 decays as modified by the contributions from Groups 4 and 3; and the rate at which the smallest size of material decays as modified by the contributions of all groups.

The process has also been described by use of an integro-differential equation (53). Matrix algebra methods requiring computer solution have been suggested (54).

At present, there is no theory by which one may take a given weight–size distribution and calculate the mill size and milling rate required to produce a desired weight–size distribution of milled material.

EQUIPMENT

Ball Mill—Tumbling mill is a generic term used to refer to ball, compartment, pebble, rod, and tube mills (48, 55). These mills have a cylindrical or conical shell, rotating on a horizontal axis, while partly filled with a grinding medium such as balls of steel, flint, or porcelain or in a shell lined with a nonmetallic liner. The rod mill uses a rod-shaped grinding medium. The impact of rods is probably received by the largest particle between two rods; therefore, the rod mill tends to produce a narrower particle-size distribution than the ball or tube mill. A tube mill is a tumbling mill in which the length is several times greater than its diameter. The compartment mill consists of a cylinder or cone divided into several sections by perforated partitions in which the particle size of the material being milled becomes progressively smaller as the material approaches the discharge end. Tumbling mills are available as batch-operated or continuous types.

Only the ball mill is discussed in this review because in pharmacy it is the most commonly used type of tumbling mill. A ball mill consists of a horizontally rotating ceramic jar or metallic cylindrical-shaped vessel with its length slightly greater than its diameter and a charge of porcelain or steel balls. Metallic jar mills with a one piece cover are commercially available in sizes ranging from 8.25 × 9.52 cm (3.25 × 3.75 in.) with a batch capacity of approximately 150 g to jars with a capacity of 15 kg (56). For large-scale operations, huge mills, such as are used in the ore and fuel industry, are readily available.

A ball mill grinds by impact and attrition. As a ball mill rotates, a cascading and cataracting motion is imparted to the balls. When the mill is operating properly, the load nearest the wall of the cylinder breaks free and is quickly followed by other sections so that the top layers of balls travel at a faster speed than the lower layers, causing attrition of the mate-

rial between them (cascading). Simultaneously, balls are cataracted or fall into the air from the part of the load that is highest on the wall onto the lower part of the load with sufficient impact to fragment the larger particles there.

To attain the proper motion, the mill must be operated at the proper speed. Critical speed is that speed at which the centrifugal force on the balls in contact with the mill wall at the height of their path is equal to the gravitational force. At critical speed, no size reduction occurs because the balls are held against the wall and revolve with the mill. Critical speed, n_c, may be related to mill size by (48):

$$n_c = \frac{76.65}{D} \qquad \text{(Eq. 35)}$$

where D is the diameter of the mill in feet. A larger mill attains its critical speed at a slower revolution rate than a small mill; e.g., a 228.6-cm (90-in.) ball mill and a 11.4-cm (4.5-in.) jar mill may have critical speeds of 28 and 125 rpm, respectively (57). In practice, mills are operated at speeds varying from 60 to 85% of the critical speed.

Commercial grinding media are made of flint (Belgian and domestic currstone), porcelain, and various alloys and steels. Mills may be lined with flint, porcelain, rubber, and metal. In pharmacy, porcelain and stainless steel balls and jars are most commonly used.

The charge or quantity of grinding medium is expressed in terms of the percent of volume of the mill. For optimum results the mill should be 50% filled with grinding medium. If restricted by the size of a mill and the batch, with steel balls the charge of balls may be reduced to as low as 30% of the volume of the mill; however, the milling time will be increased.

The amount of material to be milled should fill the void within and just cover the grinding medium. More material than 25% of the total volume of the mill causes the balls to spread through the material so they cannot make effective contact with each other. If small batches must be milled in a given mill, the grinding medium should be removed so that the material to be milled is just covered.

Small balls facilitate fine grinding. The smaller sized balls provide smaller voids than larger balls; consequently, the void through which material can flow without being struck by a ball is less and the number of impacts per unit weight of material is greater. Void volume could be reduced by mixing ball sizes; however, the packing may then be too close and interfere with ball movements. Thus, the smallest size of grinding medium that fragments the particles is suggested. The optimum size should not change appreciably with mill size. Stainless steel balls from 1.27 to 5.08 cm (0.5 to 2 in.), increasing in size by 0.31-cm (0.125-in.) increments, are commercially available. Balls of 1.27 cm (0.5 in.) are usually the smallest size available in other grinding media.

Excessively large balls produce excess grinding energy which is expressed as heat. The relationship of size in inches of the balls, D_b, to the size, D, of the material to be milled is (27):

$$D_b^2 = KD \qquad \text{(Eq. 36)}$$

where K is a constant, which is 55 for hard materials and 35 for soft materials.

Increasing the total weight of balls of a specific size increases the efficiency of milling. Since optimum milling conditions are generally obtained when the bulk volume of the balls is 50% of the volume of the mill, the weight of the balls is increased by using a grinding medium of a greater density. Thus, steel balls grind faster than porcelain balls because they are three times more dense.

In selecting a grinding medium, consideration must be given to any interaction it may have with the drug to be milled. In production the grinding medium should be examined for wear, and the drug should be tested for contamination by components of the mill. When using glass or porcelain balls in the production of ophthalmic and parenteral products, problems with particulate matter may arise if attrition of the glass or porcelain occurs.
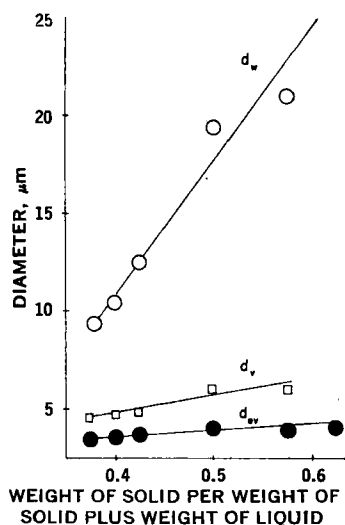
To discharge dry-milled material from the larger mills, the grinding cover is removed and replaced by a slotted discharge grate. Dry mills may be enclosed in discharge housings to control dust and cross-contamination. Other special features may be added to the ball mill (57). An air vent plug is useful to relieve pressure that may develop during milling, to eliminate a partial vacuum that may form during discharge, and to allow sampling during the milling cycle. The mill may be jacketed so that it may be cooled when milling waxy or low melting materials or warmed to maintain a fluid consistency if the entire formula for an ointment is to be milled.

Slip refers to the relative motion between the layer of balls and the surface of the wall. Slip is caused by the smooth surface of the cylinder wall, low viscosity of the material, material with a low coefficient of friction or a light charge of balls and material. In addition to decreasing the efficiency of milling, slip allows most of the weight of the balls to fall on the cylinder wall, resulting in wear and contamination. Slip is most prevalent in steel ball mills. Slip may be reduced by increasing the viscosity or by adding horizontal baffle bars.

Ball milling may be facilitated by the addition of liquid. As shown in Fig. 6, with all other factors being constant, as more water is present, ball milling becomes more efficient (58). The difference in the means is a measure of the degree of skew of the size-frequency curve. As the concentration of the liquid is increased, the difference among the means is decreased, indicating that the size-frequency distribution has become more symmetrical.

In milling wet and adhesive materials, a somewhat slower speed is used than in dry milling to prevent the mass from being carried around with the mill. A low viscosity allows the grinding medium to move with excess speed; this, combined with the thin protective film around the medium, may cause excess wear, contamination, and heat. A high viscosity re-

25
20
15
10
5

DIAMETER, μm

d_w
d_v
d_{wv}

0.4 0.5 0.6
WEIGHT OF SOLID PER WEIGHT OF
SOLID PLUS WEIGHT OF LIQUID

Figure 6—*Effect of moisture on wet ball milling (58). Key:* O, *mean weight diameter;* □, *mean volume diameter; and* ●, *arithmetic diameter.*

stricts the motion of the grinding medium, and the impact component of milling is reduced. With 1.27-cm (0.5-in.) steel balls, a viscosity from 1000 to 2400 cps is optimum for wet milling.

Wetting agents and some electrolytes may increase the efficiency of milling and the physical stability of the product by nullifying electrostatic forces produced, when bonds are broken, and by preventing rewelding of cracks and particles. Physiological and toxicological considerations prohibit the indiscriminate use of wetting agents in pharmaceuticals; however, some formulations contain wetting agents that could be incorporated at the milling stage to facilitate size reduction and to reduce aggregation.

The vibrating ball mill uses a horizontal or vertical eccentric-activated drive mechanism which vibrates the mill 1500–2500 cpm with an amplitude of several millimeters (59). This energy for size reduction is transmitted through vibration of the mill. The acceleration of the balls is often greater than the acceleration due to gravity in a conventional ball mill, and the short, sharp impacts result in faster milling. The rate of milling is proportional to the cube of the frequency and to the amplitude of the vibration; however, most commercial vibrating mills operate at one frequency and one amplitude. The charge of balls is approximately 80% of the volume of the mill. In general, the size of the material to be milled should not exceed 60 mesh.

Experimental determination of grindability in an open-circuit ball mill is performed on a standard weight of material in a standard mill, with sieve analyses being performed on the material sampled at regular intervals (60). The samples are returned to the mill. Grindabilities are obtained from size distribution plots. Grindability, G_i, is related to the mesh of the grind, D_i, by the expression (61):

$$G_i = \frac{M_i - M_f}{\theta} = \frac{K''}{\omega} D_i^a \qquad \text{(Eq. 37)}$$

where M_f is the cumulative weight smaller than the reference mesh, D_i, in the material at the start of milling, M_i is the corresponding value in the milled material after θ revolutions of the ball mill, K'' is a

constant, ω is mill speed, and a is the same constant as in Eq. 10. Therefore, if grindability is known at size D_i, it may be determined graphically at size D_1 if the Schuhmann distribution of the material is known.

The ball mill may mill materials to a 1-μm diameter, and it is unsurpassed for milling hard, abrasive materials. For general use the ball mill has the advantages that it may be used for dry or wet milling, for batch or continuous operation, and for grinding and blending simultaneously at low labor costs. Batch operation of ball mills is especially useful in pharmaceutical operations. The ball mill can be closed tightly so that dust and associated toxic hazards to employees are controlled. Unstable drugs may be sealed with an inert atmosphere and milled. Not only is the ball mill easily sanitized, but it can be sterilized and sealed for sterile milling in the preparation of ophthalmic and parenteral products.

Hammer Mill—Size reduction in an impact mill is based on a high velocity impact by which most solids act as brittle materials to form particles that are more nearly cubical than those formed by other mills (62). The most familiar impact mill is the rotary hammer mill. A hammer mill has a high speed, usually horizontal, rotor to which are mounted stationary or swinging hammers rotating in a cylindrical casing which may be lined with breaker plates. Hammer mills operate up to 10,000 rpm, and the tip of the hammer may reach a velocity of 7620 m (25,000 ft)/min. The clearance between the housing and the hammers contributes to size reduction. The material to be milled is gravity fed at the top or center, thrown out centrifugally, and fractured by impact of the hammers or breaker plates around the periphery of the casing. The bottom of the casing is formed by a cylindrical grating or retaining screen, which retains the material within the milling chamber until it has been reduced to a size; then the material is discharged through the openings in the screen. Because inertial forces vary with mass as the inverse cube of the diameter, with a constant velocity small particles impact with much less kinetic energy than larger ones, and the probability of particles less than a certain size fracturing decreases rapidly. Thus, the impact mill tends to produce a narrow size distribution. This effect is reinforced by the small particles passing through the screen almost as fast as they are formed. For these reasons the hammer mill tends to produce a minimum of fines in a granulation process.

The wide variety of hammer mills in sizes from 5 to 500 hp provides a selection for almost any type of size reduction (63–69). Hammer mills are used in the pharmaceutical industry to process dry materials, wet filter-press cakes, ointments, and suspensions. Hammer mills are not satisfactory for milling abrasive, elastic, or oily materials. Solids with a high moisture content, e.g., 8%, often clog a mill. Crystalline and brittle materials are best fractured by impact from a blunt hammer; fibrous materials are best reduced in size by the cutting edge of a hammer.
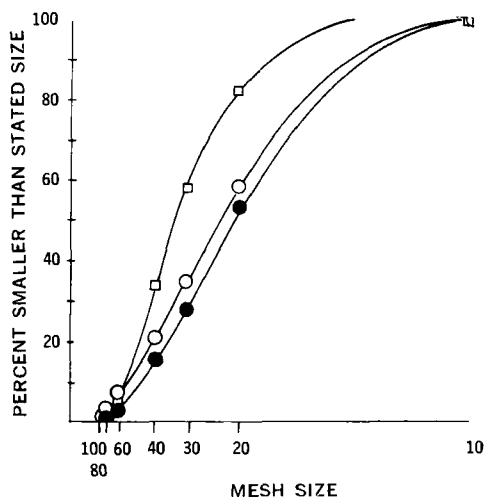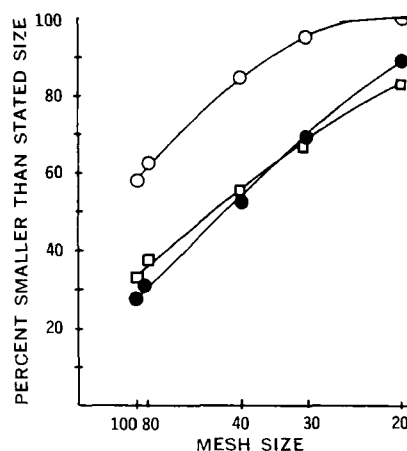
Figure 7—*Effect of speed on the size–frequency distribution of boric acid flakes milled with Mill I operating with impact forward and fitted with a round hole No. 4 screen (hole size 6.35 mm). Key: ●, 1000 rpm; ○, 2450 rpm; and □, 4600 rpm.*

Mill I[2] (70) has a rotor which may be turned 180° so that the blunt edge can be used for pulverizing or emulsifying and the knife edge can be used for cutting or granulating. In the preparation of compressed tablets by the wet granulation method, it is operated at 2450 rpm with knife edges, using circular or square holes with a size determined by what will pass without clogging [usually 1.9- or 2.54-cm (0.75- or 1-in.) holes]. In processing a dry granulation, the material may be milled at 1000 or 2450 rpm with knife edges and circular holes in the screen [usually 0.23- or 0.27-cm (0.093- or 0.109-in.) holes]. In granulating, the rate of introduction of material should not be excessive as this produces an excess of fines and sticking.

For a given hammer mill, the size of the milled product may be regulated by rotor speed, screen size, and the rate of introduction of material. The speed of the rotor is the major factor in regulating size reduction. The effect of rotor speed on particle-size distribution is illustrated in Fig. 7, which shows the size–frequency curves for boric acid granules milled at 1000, 2450, and 4600 rpm in Mill I fitted with a No. 4 screen having 6.35-mm circular holes. At very slow speeds, the rotor turns so slowly that instead of size reduction a blending action is obtained with an overload and a rise of temperature. The presence of spheroidal particles indicates that the mill is operating with an attrition action and that a faster speed should be used to obtain an impact action. At very high speeds, it is possible that there is insufficient time between hammers for the material to fall for impact. In the wet milling of emulsions and suspensions with higher speeds, the swing hammers may lay back with an increase in clearance; in such cases, it may be more effective to use fixed hammers.

Screw feeders may be added to hoppers to provide a uniform rate of introduction. Lack of uniform introduction produces a wide size–frequency distribu-

Figure 8—*Effect of screen size on the size–frequency distribution of a terra alba granulation milled with Mill I operating at 2450 rpm, and a comparison of the granulation after milling with Mill I and Mill II. Key: ○, Mill I, 0.84 mm; ●, Mill I, 1.65 mm; and □, Mill II, No. 10 screen.*

tion, because the packed material passes radially and the loose, open material passes tangentially. With a heavy introduction, there are more fines due to attrition between particles. The location of the hopper inlet may affect the amount of fines. A horizontal inlet produces the finest grinding because it provides the maximum metal surface for impact. The forward, vertical inlet is best when fines are not wanted, because the product is immediately exposed to the screen and the amount of solid surface for impact is minimized. This tends to give a narrow size–frequency distribution. The material may be introduced into a hammer mill by air injection which provides more impact, increases the capacity, and permits cooler operation.
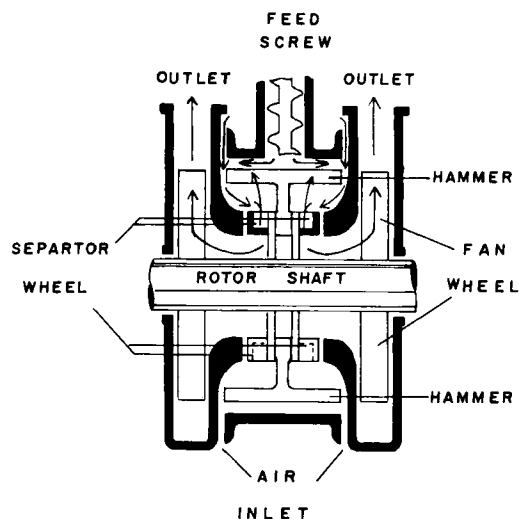
Many types and sizes of openings exist in screens, but the influence of the screen on particle size is secondary to the speed of the rotor. The effect of the screen size on the size–frequency distribution of a tablet granulation passed through a 4-mesh screen, after wet granulating with acacia a blend of terra alba and two active ingredients comprising 4.2% of the formulation, is shown in Fig. 8. The dried granulation was milled at 2450 rpm through a Type A plate, having 1.65-mm openings, and a Type B screen, having 0.84-mm openings[3]. The granulation was also milled at medium speed with Mill II[4] fitted with a No. 10 screen. The size–frequency distributions produced by milling with Mills I and II are compared in Fig. 8. Perforated retaining screens are preferred to woven screens because of the greater mechanical strength. The size of the milled material is smaller than the openings of the screen because the particle passes through the opening on a path approximately tangential to the rotor (71).

The circular perforated screen is the strongest and least likely to clog; it is suggested for milling fibrous materials. The herringbone screen consists of slotted holes repeated across the surface of the screen at 45°

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[2] Fitzpatrick model D comminuting machine.

[3] R. J. Braun, Smith Kline & French Canada, Ltd., personal communication.
[4] Tornado.

Figure 9—*Mill III, an example of a high-speed hammer mill with an internal classifier (72).*

Figure 10—*Mill IV. (73) and Mill II (65), examples of a vertical rotor with hammers operating inside of a 360° circular screen.*

to the length of the screen. The herringbone screen is recommended for the milling of crystalline materials and for continuous operation. A herringbone screen with the width of the slot equal to the diameter of a circular hole mills coarser than the circular hole. A cross slot at right angles to the path of the hammer is not used in fine milling because it clogs easily; it is recommended for milling suspensions. The jump-gap screen consists of bars arranged so that the particle approaches a ramp that deflects it into the chamber away from the opening of the screen; it is used with abrasive and clogging materials.

Hammer mills are easy to install and operate. Simplicity of design permits rapid and easy cleaning, so a mill may be used for several products. The speed of the rotor and the retaining screen can be rapidly changed. Size reduction of 20–40 μm may be anticipated. The simple hammer mill is generally not capable of producing the particle size that is required for injectables. For producing ultrafine material, a hammer mill should be operated with internal or external classification.

Several high-speed classifier mills of individual design are marketed. They do not have screens and use some type of pickup fan to remove the acceptable material from the milling chamber, and they require dust collectors to collect the particles in the micron range. Air or an inert gas may be used to convey the material through the system. The temperature of the milled product is lower than in screen hammer mills because the increased volume of air removes some of the heat of milling.

Mill III[5] (72) (Fig. 9) is an example of a high-speed hammer mill with an internal classifier, and it is capable of milling from 1 to 20 μm. Its horizontal rotor disk is fitted with swing hammers and fan wheels which draw air into and through the mill and into the ducts leading to the collectors. The material to be milled is introduced by a screw feed, comes in contact with the hammers, and is diverted into two
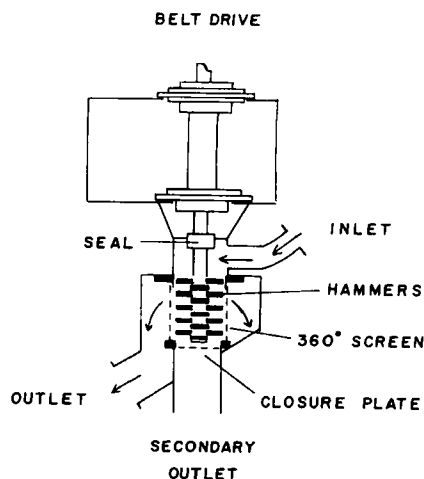
high velocity air streams with a spiral motion to either side of the hammers as size reduction occurs between the hammers and the ridged liner. The air stream carries the particles toward the classifier wheels, which consist of short, radial vanes at the periphery of the rotor disk. The particles are subjected to the opposing forces of centrifugal force and aerodynamic drag, which separate the oversized particles from the fine particles. For the oversized particles, the centrifugal force exceeds the drag, and they are thrown toward the wall of the milling chamber where they enter the impact zone for further reduction. The air stream carries the fine particles inward from the grinding zone toward the shaft, through the vanes of the classifier wheels into the fans, and out the discharge outlet to a dust collector. Size reduction is controlled by the speed of the rotor and by the size and number of vanes on the classifier.

Mill IV[6] (73) and Mill II (65) (Fig. 10) consist of a vertical or angular rotor fitted with fixed or swing hammers, and it is run at close clearance inside of a 360° screen. The material to be milled enters parallel to the axis rather than tangentially as in most hammer mills, and it is discharged radially through the cylindrical screen. The disintegrator combines attrition, cutting, impact, and screen effect. Tough and elastic materials may be milled by a disintegrator. Its major advantage is the capability of milling suspensions with 40–80% solids and possessing a stickiness and resistance to flow which clogs screens.

Thermolabile, volatile, and low melting materials may be milled by passing refrigerated air or dry ice through the hammer mill with the material (74). Cryogenic techniques chill the material to a low temperature at which it generally is more brittle. Hammer mills may be equipped with a jacket for somewhat limited temperature control and to reduce sticking to the mill parts. To avoid oxidation, a mill may be equipped with a cover manifold so that milling occurs in an inert atmosphere of carbon dioxide or nitrogen. Since air-borne particles provide a po-

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[5] Mikro-Atomizer.

[6] Rietz disintegrator.

tential for an explosion, it is advisable for all electrics to be explosion proof.

Fluid-Energy Mill—Most mechanical mills are limited to a size reduction of approximately 325 mesh; fluid-energy mills are used for ultrafine milling to a size less than 5 μm. In the fluid-energy mill, the material is suspended and conveyed at high velocity by a compressed gaseous fluid through an extreme turbulence, which causes size reduction because of interparticular impact and attrition. Although any gaseous fluid may be used, air compressed at 100 psi is generally used because most pharmaceuticals have a relatively low melting point or are thermolabile. The air is introduced so as much as possible of the pressure is converted to kinetic energy. All of the particles are not reduced to the desired size, and internal classification returns the oversize particles for further milling. Most fluid-energy mills use the energy of the fluid stream to effect a centrifugal classification, although a mechanical device may be used.

Mill V[7] (75) (Fig. 11) consists of a shallow circular grinding chamber, from 5.08 to 121.9 cm (2 to 48 in.) in diameter, in which the material to be milled is acted upon by gaseous fluid jets issuing from several orifices spaced around the periphery of the chamber so that fluid enters tangentially to produce a vortex. When the compressed gaseous fluid enters the small grinding chamber, it expands and imparts a high-velocity rotation to the material. Since most fluid energy is expended near the point of entry, the movement and impact of the particles are violent. The coarse particles are centrifuged to the periphery and subjected to further size reduction. The fine particles spiral inward by centripetal force and pass through a central outlet to a collector.

Mill VI[8] (76) consists of a vertical, elongated cylinder constructed in an elliptical shape. The material to be milled enters at the bottom of the mill and is subjected to high-velocity jet streams, which create rapidly circulating flow and impact of the particles. As the gaseous fluid flows around the upper bend of the casing, the large particles are thrown toward the periphery of the cylinder by centrifugal force and are returned with some gaseous fluid down the stack for further size reduction. The fluid being displaced carries the fine particles inward through an outlet to a collector.

In Mill VII[9] (77) (Fig. 12), two opposing jet streams provide head-on impact of particles. The 2.54-cm (1-in.) research model is the smallest fluid-energy mill marketed; it uses approximately 6.5 ft[3]/ min of air at 100 psi and can mill up to 1000 g/hr.

A finer particle size is obtained by slower rates of introduction of the material into the mill and by using higher pressures. Expansion of the compressed air results in cooling, which avoids temperature rise of the material. An inert gas may be used as the fluid if the medicinal compound is susceptible to atmospheric oxidation. To facilitate ultrafine milling,
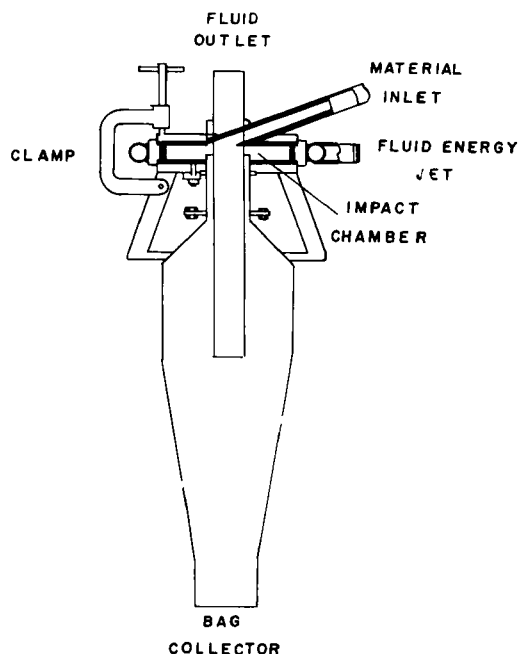

Figure 11—*Mill V, 5.08-cm (2-in.) laboratory model, a fluid-energy mill using a fine high-velocity stream at an angle around a portion of the impact-classifying chamber (75).*

the material should be reduced to approximately 100-mesh size before processing in a fluid-energy mill.

Fluid-energy mills have the advantage that they may be used to mill abrasive materials. Moreover, since there are no moving parts, there is no contamination of the product due to wear. In addition to pulverization, fluid-energy mills may be used to blend, dry, or remove water of hydration. In pharmaceutical milling the fluid-energy mill has the advantage of being easily sterilized and operated by use of sterile air; it also provides low product contamination (78). Agglomeration and packing of material may present problems.

Disk Attrition Mill and Pin Mill—A single-runner, disk attrition mill consists of a vertical or horizontal steel plate, which rotates at relatively high velocity in close proximity to a similar stationary plate to produce a shearing force which reduces particle size. The clearance between the plates is adjustable to allow control of size. In a double-runner, disk attrition mill, both disks rotate at high speeds in opposite directions.

Mills with different patterns of grooves, corrugations, or teeth on the disks perform various operations such as grinding, tearing, shredding, and blending (79–82). A single-runner attrition mill with plates with concentric circular rows of projecting spikes on the rotating plate meshing with those on the stationary plate acts much as a hammer mill. A pin mill, such as Mill VIII[10] (Fig. 13), is a high-speed mill having pin breakers instead of hammers. These may be on a rotor with stator pins between circular rows of pins on the rotor disks or they may be on rotors operating in opposite directions to secure an in-

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[7] Micronizer.
[8] Jet-O-Mizer.
[9] Air Impact Pulverizer.

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[10] Contraplex.
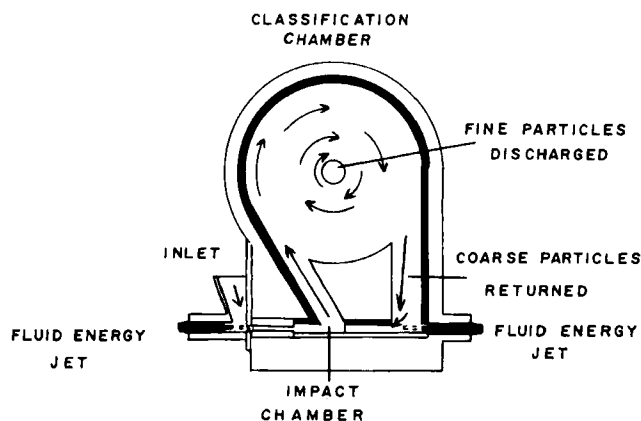
Figure 12—*Mill VII, another type of fluid-energy mill using fluid streams to convey particles at high velocity into a chamber where the two streams impact upon each other (77).*

creased differential of speed. Soft material may be milled so it passes through a 200-mesh screen. For heat-sensitive materials, the disks should be cooled.

Rotary Cutter—A rotary cutter consists of a horizontal rotor, with two to 12 knives spaced uniformly on its periphery, turning from 200 to 900 rpm, with a clearance of several thousandths of an inch, in a cylindrical casing with several stationary knives. The bottom of the casing has a screen which controls the size of the material discharged from the mill. In some models the stationary knives are alternated with screens around the casing to provide maximum discharge area and to keep the fines to a minimum.

Rotary cutters are used with fibrous and resilient materials, such as crude drugs, where successive shearing action is more effective than compression, impact, or attrition. The material to be milled should not exceed the length of the knife and be less than 2.54 cm (1 in.) thick. The size limit is approximately 80 mesh. If a size less than 20 mesh is desired, a pneumatic collection system is required. Rotary cutters and granulators are similarly designed. A granulator yields more or less irregular shaped particles; a cutter may yield cubic or square-shaped particles.

Roller Mill—Roller mills consist of two to five smooth rollers operating at different speeds. The plastic material, *e.g.*, ointment or paste, is introduced between the first two or low-speed rollers and is discharged from the final or high-speed roller by a scraper blade. The material passes from the surface of one roller to that of the next because of the differential speed, which also applies shear to the film of material passing between the rollers.

Roller mills differ from ring-roller mills. Ring-roller mills have rollers that operate in conjunction with grinding rings, and pressure or centrifugal force on the rollers comminutes the material between the ring and roller. Ring-roller mills are rarely used in pharmaceutical milling.

Roller mills may be used in the final step in the production of ointments and pastes. The clearance between adjacent rollers may be adjusted to as little as 0.002 cm (0.001 in.) to ensure smoothness and uniformity of a topical preparation. When milling
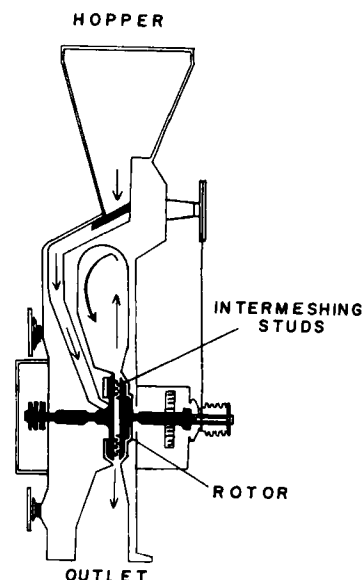
Figure 13—*Mill VIII, an example of a pin mill with concentric, intermeshing rows of pins or studs on the rotor and stator (66).*

with a three-roller mill, the rollers are adjusted so that the layer of material on the middle roller is two to three times the thickness of the layer on the final roller. Thus, the finer milling is accomplished between the middle and final rollers. When using good manufacturing procedures, the insoluble drugs are reduced in size before incorporation into the ointment vehicle and then the entire formulation is blended. Thus, passage through a roller mill is not the major procedure of size reduction, but the shearing and crushing action between the rollers breaks up any aggregated particles within the vehicle. The production rate is determined by the clearance between the rollers, the roller speed, and the size of the roller mill. Production rates vary from 22.7 kg (50 lb)/hr for a 10.2 × 20.3-cm (4 × 8-in.) laboratory mill to 317.8 kg (700 lb)/hr for a 35.5 × 76.2-cm (14 × 30-in.) production roller mill. After the mill has been operating and the rollers have become warm and expanded, an adjustment of the initial roller settings may be required. The temperature may be controlled by circulating water through the rollers.

Colloid Mill—Precisely defined, a colloid mill is not a mill, *i.e.*, a mechanical device for size reduction of solids by impact, cutting, or attrition. A colloid mill does not reduce the size of hard, crystalline particles by fracturing them across crystal planes; however, it does disperse aggregated solids into their individual particles. Homogenizers, viscolizers, dispersators, and specifically designed mixers are used to disperse and blend (83, 84), but they are not discussed because their prime function is emulsification. Although colloid mills are widely used in the emulsification operation, they are discussed from the viewpoint of the dispersion of solids in a liquid vehicle.

As shown in Fig. 14, a colloid mill consists of a high-speed rotor and stator with conical milling surfaces between which there is an adjustable clearance of 0.002–0.25 cm (0.001–0.1 in.). A clearance greater
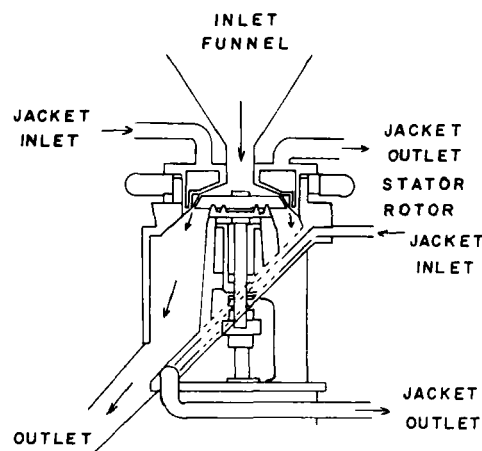
Table I—Factors in Selection of a Mill

Material

Physical property: hard, soft, fibrous, elastic, hygroscopic, solvated
Size
Moisture content
Melting point
Flammability
Thermolability
Subsequent processing

Operation

Size specification of milled material
Ease of sanitization
Ease of sterilization
Ease of adjustments during operation
Contamination of milled material
Versatility
Capacity
Batch or continuous
Wet or dry
Rate of introduction of material
Space occupied
Labor cost

Auxiliary Equipment

Dust collector
Mechanical introduction of material
Temperature control: jacket, refrigerated air, liquid nitrogen, dry ice
Inert atmosphere: carbon dioxide, nitrogen
Air sweep

Safety

Explosivity
Irritativity
Toxicity
Safety features incorporated into mill

Figure 14—*Mill IX, an example of a jacketed colloid mill with a smooth-surfaced rotor shaped like the frustum of a cone (85).*

than 0.05 cm (0.02 in.) is seldom used in pharmaceutical operations. Rotor speeds range from 3000 to 20,000 rpm and are often greater for small mills than for production models. Mill speed refers to the peripheral speed of the rotor, i.e., product of the operating speed and the circumference of the rotor. The characteristics of a colloid mill depend on the design of the rotor and stator, the horsepower of the drive motor, operating speed, diameter of the rotor, clearance, and time in the milling zone.

A colloid mill is not used to process dry materials. The individual components of a product are premixed with a liquid vehicle before being introduced into the colloid mill. Solids to be dispersed should be fine enough, i.e., 100 mesh, to prevent damage to the mill. The material is generally introduced by gravity to the center of the rotor. Interfacial tension causes part of the material to adhere to, and to rotate with, the rotor. Centrifugal force throws part of the material across the rotor onto the stator. At a point between the rotor and stator, the motion imparted by the rotor ceases, and hydraulic shearing force exceeds the particle–particle attractive forces holding the individual particles in an aggregate. The particle size of milled particles is usually smaller than the clearance, because the high shear is the dispersing force. In emulsification a clearance of 75 μm may produce a 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.

Production rate varies inversely with the viscosity of the dispersion. Widening the clearance increases

the production rate, but it provides a poorer dispersion. Colloid mills, in which the liquid flow is concurrent with the centrifugal force of the rotor or countercurrent, are marketed. Materials with a viscosity as great as 10,000 cps can be processed in a colloid mill having concurrent flow if the mill operates at 1524–2286 m (5000–7500 ft)/min. A countercurrent flow at a maximum speed of 3048 m (10,000 ft)/min is common for systems with a viscosity less than 2000 cps. Dilatant systems, which exhibit an increase in viscosity as the shearing stress is increased, may overload and damage colloid mills.

Colloid mills may have smooth-surfaced or rough-surfaced rotors and stators. In Mill IX[11] (85), the rotor and stator are smooth faced so that the thin film of material between them will have a uniform cross section and will be subjected to the maximum amount of shear. A laboratory model of Mill IX with a 5.08-cm (2-in.) rotor is marketed; it operates at 13,500 rpm and has a production rate from 2 to 25 gallons/hr. If the peripheral speed of the rotor is not high enough, insufficient hydraulic shear is developed. Larger mills have rotors that are large enough to provide high linear speeds at the rotor edge; however, with small mills it is advisable to have a belting system or a variable speed drive that ensures adequate peripheral speed.

Mill X[12] (86) has a grooved conical rotor and stator operating at 3600 rpm. The rough-surfaced mill adds intense eddy currents, turbulence, and impaction of the particles to the shearing action. Rough-surfaced mills are useful with fibrous materials because fibers tend to interlock and clog smooth-faced mills. Mill XI[13] (87) operates at a peripheral speed of 3048 m (10,000 ft)/min and may be fitted with a three-way valve and by-pass tube. The production rate of milk of magnesia is 80, 250, and 660 gallons/ hr in colloid Mill XI with a rotor diameter of 5.08, 10.16, and 20.32 cm (2, 4, and 8 in.), respectively.

A colloid mill tends to incorporate air into a suspension. Aeration may be reduced by the use of a

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[11] Premier.
[12] Charlotte.
[13] Gaulin.

vertical rotor, which seals the point where the rotor shaft enters the housing and maintains the rotor and stator always in contact with the liquid. Because milling operations waste energy as heat, the temperature of a product may rise as much as 40° during milling. By passing cooling water through the mill jacket, the temperature of the dispersion may be reduced as much as 20°. Sanitary design mills, which may be sterilized, are available, from a laboratory model with a capacity of 1–50 gallons/hr to a production model with a production rate exceeding 1000 gallons/hr. Colloid mills may be used in-line to prevent clogging of highly instrumented handling systems transporting suspensions. Colloid mills may be used in spray-drying operations in-line immediately preceding the spray nozzle to prevent clogging and to produce a more uniform product.

OPERATION

Fine materials, *e.g.,* dextrin, starch, and sulfur, suspended in air are potential explosion hazards. If the material is known to be combustible, it should be milled in an inert atmosphere. All electric switches should be explosionproof. To avoid static electricity, which may ignite dusts, mills should be grounded.

The mill room should have an adequate ventilation system, which removes dust so that air-borne contamination of other areas of the laboratory does not occur. Batch tickets for irritating and toxic drugs should bear warning statements. Personnel must be impressed with safety precautions of respirators and goggles, and they should have periodical medical examinations.

The rate at which the material to be milled is introduced should be constant to avoid fluctuations of particle size–frequency distribution. Frequently, overhead delivery is controlled by rotary or slide-gate valves to provide continuous and uniform flow to the milling chamber. If the rate is relatively slow, the milled material is readily discharged and the quantity of fines is minimized. If the rate is fast, *i.e.,* choke feed, the material is in the milling chamber for a longer time because its discharge is impeded by the mass of material and a greater size reduction is obtained although the capacity of the mill is reduced. Choke feed may be used when a small amount of material is to be milled in one operation, but it may cause an increase in temperature of the material.

The rate of discharge should be equal to the rate at which the material is introduced. Many mills are designed so that the force of gravity provides free discharge through the bottom of the mill. For ultrafine milling, a fluid carrier is used to convey the material from the milling chamber to the collector. A milling system in which the material from the grinding chamber is passed through a size separation device and the large particles are returned to the grinding chamber for further size reduction is known as a closed-circuit mill.

Since milling is not an efficient process, heat is produced and is mainly removed by the air and the milled material leaving the mill because the heavy construction of the mill restricts radiation loss. Most properly used mills operate below 100° (88). If thermolabile material or low melting material is to be milled, the milling chamber should be cooled. Jacketed hammer mills are of little value because of the small area, short retention time, and poor heat transfer coefficient. Air inlets may help somewhat. An airswept hammer mill or pin mill has large air inlets, and the milled material is conveyed by air from the mill to the collector. Approximately a 20° drop in temperature may be achieved by the use of dehumidified and refrigerated air. Its use is limited to the temperature at which condensation occurs.

Stainless steel equipment is routinely used to minimize contamination and reaction with drugs. To comply with regulations of the Food and Drug Administration and the U.S. Department of Agriculture, the stainless steel should be Type 304 with No. 4 finish; where specific corrosion or sterile considerations are involved, the stainless steel should be Type 316. If coolants such as dry ice or liquid nitrogen are used, the mill must be constructed of stainless steel because cast iron becomes brittle and may shatter at low temperature. Waxy materials, *e.g.,* stearic acid and beeswax, may be chilled and milled with dry ice in a hammer mill to a 100-mesh size. The fluid-energy mill may be used to mill waxy materials to an ultrafine size. The air enters the fluid-energy mill at approximately 20° and 100 psi so the mill is cooled by the expansion of the air.

Table I lists factors to be considered in the selection of a mill (89). When a tentative selection has been made, a test milling should be conducted on the material to be milled. Most mill manufacturers have pilot laboratories for milling tests. The industrial pharmacist should evaluate the pilot study personally to observe the temperature of the inlet and outlet air, the temperature of the milled material, and the size reduction performance at different rates of introduction of the material, at different mill speeds, and with various classifier settings. Samples should be collected from each, and a size–frequency analysis should be made for comparison. The final milling should be under the most severe conditions, with recycling for several minutes to determine if there is a gradual buildup in the milling chamber. The development of milling specifications is primarily a pilot responsibility because laboratory procedures of size reduction do not duplicate milling conditions in production mills.

In addition to size reduction, milling may alter the crystalline structure and cause chemical changes in some materials (37). Wet milling may be useful in the production of a suspension containing a *metastable* form that causes crystal growth and caking. If cortisone acetate crystals are allowed to equilibrate with the aqueous vehicle, subsequent wet milling will yield a satisfactory suspension (90). By means of a vibratory mill, starch, amylose, and amylopectin can be broken down mechanically to a wide molecular weight range but not to monomeric units (91). Powdered polyvinylpyrrolidone breaks down into lower molecular weight polymers during ball milling.

The rate of decrease of the molecular weight of the polyvinylpyrrolidone is influenced by the atmosphere (92). Pure C_{12}- and C_{16}-fatty acids may be decarboxylated and converted to the hydrocarbon containing one less carbon atom by ball milling with wet sand (93). When well-dried microcrystalline cellulose[14] was milled from 1 to 25 hr, the crystallinity decreased with milling but remained relatively high due to aggregation of microcrystals (94). In using a colloid mill to disperse solids in a suspension containing polymeric suspending agents, it should be realized that excessive shearing may damage polymeric materials so that there is a loss of viscosity (95).

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RESEARCH ARTICLES

Effect of Ethanol on Intestinal Absorption of Theophylline

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Abstract □ The purpose of this investigation was to determine directly the effect of ethanol on the absorption of theophylline from the small intestine of the rat. In the first part of the investigation, a 50-mg % solution of theophylline containing 0, 5, 10, or 20% ethanol was placed in a ligated segment of small intestine of anesthetized rats and sampled at intervals. Theophylline absorption was significantly increased by 5% ethanol and decreased by 20% ethanol. There was a positive rank-order correlation between theophylline absorption rate from the four solutions and water net flux. In the second part of the investigation, a segment of small intestine of anesthetized rats was perfused with theophylline solutions containing 0 or 2% ethanol. The concentration of ethanol was kept constant by continuous infusion of ethanol into the circulating perfusion solution. Theophylline absorption and water net flux were significantly increased by 2% ethanol. Intra-venous infusion of ethanol at a rate sufficient to produce the same plasma concentration of ethanol as was observed upon intestinal perfusion with a solution containing 2% ethanol had no effect on theophylline absorption from the small intestine. The intestinal clearance of theophylline was independent of concentration in the 10–200-mg % range. Ethanol solutions without theophylline produced the same changes in water net flux as did the theophylline-ethanol solutions. It is concluded that the effect of ethanol on the intestinal absorption of theophylline is probably due to solvent drag, secondary to a change in water flux induced by alcohol.

Keyphrases □ Ethanol—effect on intestinal absorption of theophylline, rat small intestine □ Theophylline—effect of ethanol on intestinal absorption, rat small intestine □ Absorption—effect of ethanol on theophylline intestinal absorption, rat small intestine

The relatively slow and erratic absorption of theophylline from solid oral dosage forms has led to the development of various liquid dosage forms of this drug, including hydroalcoholic solutions (1). It has been claimed that the ethanol in hydroalcoholic solutions of theophylline enhances the absorption of the drug, but there have been conflicting reports.

A solution of theophylline containing 20% ethanol produced a significantly larger increase in the vital capacity of asthmatic patients than did the same dose of theophylline in aqueous solution (2). On the other hand, in a study of theophylline concentrations in the blood of two subjects, after oral administration of theophylline in solution, a more rapid absorption was found from aqueous solution by one subject and a more rapid absorption from the hydroalcoholic solution by the other (3). Flora (4) observed no significant differences in plasma theophylline concentrations of human volunteers receiving theophylline in aqueous solutions containing either 1.43 or 8.44 ml ethanol [15 ml of a 9.5% (v/v) and 42.2 ml of 20% (v/v) solution, respectively]. Studies on rabbits (5) showed more rapid absorption of theophylline from a solution containing 20% ethanol than from an aqueous solution without ethanol.

The purposes of this investigation were to deter-