Drug Development and Industrial Pharmacy, 27(7), 599–612 (2001)

REVIEW

Powder Mixing

Helena J. Venables and J. I. Wells

School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK

ABSTRACT

The factors affecting powder mixing are reviewed. Methods of analyzing a random mix are discussed (indices, the Poisson distribution, and analyses of variance [ANOVA]). The influence of particle size, shape, and density are described, along with scale of scrutiny and sampling. Segregation and agglomeration are major problems in powder mixing, and their prevention and minimization are therefore paramount. Ordered mixing reduces segregation, but also introduces other problems. Regulating the particle size of the drug and altering particle shape minimizes segregation and agglomeration.

Key Words: *Agglomeration; Ordered mixing; Particle size; Powder mixing; Random mixing; Sampling; Scale of scrutiny; Segregation*

INTRODUCTION

Mixing is the fundamental process in solid and semisolid particulate dosage forms to ensure content uniformity and, in many cases, dissolution rate. A high particle population is required for low-dose drugs; therefore, particle size control and milling (particle size reduction) are extremely important (1). However, milling increases cohesion between drug particles, and the agglomerates produced must be deaggregated. In ordered mixing, these cohesive forces are converted into adhesion; the small drug particles adhere to larger excipient particles, which act as carriers (2).

Particle size affects many pharmaceutical processes; a small size improves bioavailability, but leads to flow problems and segregation. Particle shape and density may also lead to segregation (3). Segregation is a big problem in mixing, but can be minimized through granulation or changes in particulate characteristics of the drug or excipients (the components of a powder mix other than drug). Choice of an appropriate mixer is also important along with mixing time (4).

Agglomeration is a problem with small particle sizes as cohesiveness is increased. This affects granulation, fluidization, and the dispersion of drugs into liquids (5). Drug content variation increases with

decreasing drug content, and this is therefore important when attempting to achieve blend uniformity with a low-dose drug (6).

Sampling is a process involving many errors, and great care must be taken to produce an accurate and representative sample from the blend as a whole. The scale of scrutiny is important here (7). Scale-up from pilot-scale to large-scale mixers may also affect a mix, and testing and validation are necessary (8).

Many factors affect powder mixing efficiency. To ensure maximum efficiency, these must be optimized throughout all stages of manufacture, with clearly defined standards during production and quality control (9). This article is part of a much larger subject for which far more work is needed. Not enough time is taken by most pharmaceutical companies to raise awareness of bias and other errors when mixing and sampling. Its importance should not be underestimated.

This treatise discusses

1. The different aspects of powder mixing
2. The properties of a powder that affect a mix
3. How to avoid poor homogeneity

RANDOM MIXING

Random mixing is a statistical process in which a bed of particles is repeatedly split and recombined until there is an equal chance of any individual particle being at any given point in the mix at any one time (10).

After a certain time, the disorderliness is at a rough, stable maximum and is referred to as a random mix. The probability of finding a certain particle at any point is constant and equal to the proportion of that type of particle in the mixture as a whole (11). In an ideal "perfect" mix, a black particle will always be adjacent to a white particle in a chessboardlike pattern. A random mix results in groups of the same particles next to each other (8).

The following equation can be applied to calculate the standard deviation of a random mix:

$$\sigma^2 = \frac{(\alpha\beta)}{n} \tag{1}$$

where σ is the standard deviation (σ^2 is variance), α and β are the mean proportions of each component, and n is the number of particles overall in the mix (11). On a theoretical basis, Eq. 1 is accurate, but particles are of unequal size and not identical. Stange (12) derived a more complex equation to calculate the variance of a mix, including differences between particles of like size, shape, and density. This equation has since been simplified, and there are now many equations that are dependent on different variables (10).

When more than two components are mixed, the χ^2 (chi-square) rule is applied:

$$\chi^2 = \frac{\sum (O - E)}{E} \tag{2}$$

where O is the observed characteristic (e.g., number of drug particles), and E is the expected characteristic. The χ^2 limits are independent of the proportions of components, unlike the binary mixture (Eq. 1), and the mixer characteristics are taken into account. By comparing results in a χ^2 table, it is possible to assign a value for the "goodness" of a mixture. This rule may be applied to binary mixtures (13).

The Poisson distribution provides another approach to random content and has broad validity for up to 20% w/w of the coarse component in the mix. Equation 3 shows the Poisson distribution applied to ingredient A:

$$C_A = \frac{100\sqrt{m_A}}{M_A} \tag{3}$$

where C_A is the coefficient of variation ([Standard deviation/Mean] $\times$ 100%) of A and is a percentage of the mean content by mass M_A of A; m_A is the representative mean particle mass of A (14). These indices may give high variances for factors other than segregation, and it is difficult to determine their significance. Sampling variability is not adequately handled, and deviations from a perfect mix occur for different reasons (e.g., drug content variability, agglomeration, mixer choice, etc.) (15).

The analysis of variance (ANOVA) technique is an alternative that isolates the effect of segregation. In a computer simulation study, ANOVA was the only effective way to identify segregation correctly and reliably (15). Under specified circumstances, most indices reflect the variance of distribution in a random mix (10). However, the ANOVA technique should be used for more accurate and reliable segregation analysis (15).

PARTICLE SIZE

As particle size is reduced, surface area is increased; this affects many pharmaceutical processes. Absorption, drug dissolution rate, and content uniformity are all affected by particle size. In general, a small particle size and narrow size distribution are required to improve bioavailability, but this can lead to flow problems and segregation (3). Smaller particles are able to fit through the voids created by larger particles in a powder mix (percolation) and can cause significant segregation (16). Segregation can be caused by vibration, so pharmaceutical processing usually specifies particle size (17). Particle size also has an effect on ordered mixing. As the particle size decreases below 100 μm, the extent of ordering increases. Below 40 μm, the ordering is virtually complete. Due to the increased surface area of the smaller particles, interparticulate forces (van der Waals) are increased when short-range electrical forces are greater than gravitational mass (2).

When determining the size of a particle, it is often conveniently approximated to a sphere with a diameter that is the equivalent diameter of the particle. Other sizes are also used (e.g., Feret's and Martin's diameters), depending on the orientation and shape of the particles (see Fig. 1) (17). With a microscope, the shape of fine particles and presence of aggregates can be determined, whereas with some other methods, this may not be possible (18). Sieving is probably the oldest method for classifying particles and still is popular today. By adaptation, particle sizes of less than 75 μm can be detected (e.g., Alpine air jet) (19). Another method is sedimentation analysis, which allows a homogeneous suspension of particles to settle in a liquid under gravity. The average particle size can be calculated using Stoke's law (Eq. 4):

$$V = \frac{2a^2 g(\sigma - \rho)}{9\eta} \tag{4}$$

where a is the radius of the particle, σ is its density, ρ is the density, η is the viscosity of the liquid, v is the velocity of sedimentation, and g is the acceleration due to gravity.

Elutriation uses a similar method, but with an upward current of water or air (18). Other methods, including adsorption, light scattering, and X-ray scattering, are also available (20).

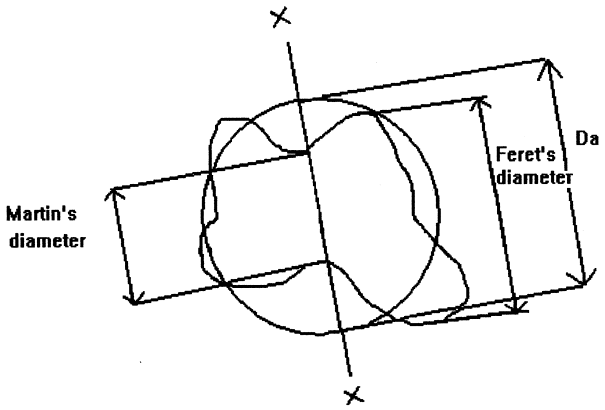

Figure 1. Particle size measurements. (After Ref. 24.) Martin's diameter is the length of the line bisecting the particle. Feret's diameter is the distance between two tangents on opposite sides of the particle. Perimeter diameter is the diameter of a circle with the same circumference as the particle. Projected area diameter Da is the diameter of a circle with the same area as the particle.

The Coulter Counter™ remains the most important advance made in particle size analysis. Individual particles pass through an orifice, and the change in electrical conductivity is measured and converted to an equivalent volume sphere. The speed with which this is achieved and its precision are unrivaled by other techniques (19). Agglomeration is avoided by ultrasonic agitation and a dispersant. Particle size and distribution can be measured automatically (17).

PARTICLE SHAPE

With nearly spherical particles, powder is easier to mix than with irregularly shaped particles. Acicular or flat particles prolong the mixing time due to aggregation. Fine material falls through voids (percolation), allowing segregation to occur (21).

Powders with similar particle size tend to have good flow properties, but with irregularly shaped particles, it varies due to differences in interparticulate contact areas. Spherical particles have optimal flow properties due to minimum interparticle contact, while acicular particles have poorer flow properties (22). The high internal and surface friction angles on flat, angular, or rough particles with low friction angles tend to cause segregation. These different flow properties cause differing repose angles and lead to segregation (16).

As Riley (23) observed: "The size of a particle indicates the quantity of matter in it; its shape indicates the pattern in which this quantity is fitted together." General qualitative terms can be applied to particles (Table 1), but these are inadequate as a quantitative term is needed (24).

Two views regarding particle shape exist: (1) As long as there is a number for comparison, the actual shape is unimportant. (2) From measurement data, it should be possible to reconstruct the original shape of the particle.

Combinations of particle sizes are referred to as *shape factors*. Shape coefficients are determined by the relations between particle length l, surface l^2, or volume l^3 and measured sizes (24). To reconstruct a particle, an infinitely large number of measurements is needed. There are three approaches:

1. Measure diameters of a selection of particles and assign a representative mean value. To measure individual shape, three parameters are required: length, breadth, and thickness. These measurements can prove difficult to take for certain shapes (e.g., parallelopiped). Ratios of areas or volumes have been used as alternatives (23).
2. Compare particles with a standard geometric shape using a standard parameter (23). Using two coefficients f (surface coefficient) and k (volume coefficient), the surface area and volume can be calculated, and the ratio f/k can be used as a quantitative measurement for shape (18).
3. Measure the bulk properties of a powder and classify the particle shape accordingly. This takes into account the bulk behavior and interrelationships between particles as well as shape. The measurements are simple and rapid, but determination of the correlation between all particle sizes and all particle shapes is very difficult to achieve. No universally acceptable shape index has been found (23).

Table 1

Particle Shape Measurement

Acicular	Needle shaped
Angular	Sharp edged or having a roughly polyhedral shape
Crystalline	Freely developed in a fluid medium, of geometric shape
Dendritic	Having a branched crystalline shape
Fibrous	Regularly or irregularly threadlike
Flaky	Platelike
Granular	Having approximately an equidimensional irregular shape
Irregular	Lacking any symmetry
Modular	Having a rounded, irregular shape
Spherical	Global shape

Source: From Ref. 24.

Shape differences can cause segregation, although it occurs most easily with differences in particle size (25). Campbell and Bauer (26) found that, with a mix of acicular and angular particles, the least segregation occurred with equivalent diameters of particles. Rippie et al. (27) paired spheres of a fine component in a mix and decreased the intensity of segregation. This was explained by less competition for void spaces. Highly angular particles also required less input energy to cause segregation than spherical particles (10). Near spherical excipients, such as spray-dried lactose, can be used to improve flow and minimize segregation. Eliminating acicular particles can be achieved by recrystallization and/or milling (22).

PARTICLE DENSITY

With density differences in the components of a mix, various problems can arise. Mixing time is increased, and segregation may occur. Gravitational forces pull the more dense particles to the bottom, leaving the less dense particles on top, and vibration may cause segregation (21).

There are three different particle densities for individual particles:

1. *True density* is the mass divided by the volume of the particle, excluding open pores (those connected to the particle surface) and closed pores (those not connected to the surface and irrespective of structure).
2. *Apparent density* is the mass divided by volume, excluding open pores, but including closed pores; it is useful when the particle is immersed in a fluid, and the open pores are penetrated (e.g., during sedimentation calculations).
3. *Effective density* is defined as the mass divided by the volume of a particle; it includes both

open and closed pores and applies when the external surface is seen as a boundary of a particle or when fluid is unable to penetrate open pores (18).

None of the densities defined above should be confused with *bulk density* of materials, for which the measured volume includes the voids between the particles (3). This void space between particles in a mix varies with the size and shape of the particles and affects the packing of the powder. Fine particles may bridge together, and not all particles are spherical (18). One method for measuring the bulk density of a powder is Carr's consolidation index (Eq. 5):

$$\text{Carr's index (\%)} = \left[\frac{(\text{Tapped density} - \text{Poured density})}{\text{Tapped density}}\right] \times 100 \quad (5)$$

Rippie et al. (27) found that density effects alone do not greatly affect segregation, but combined with different particle sizes, segregation increases (10). Segregation may occur with large particle differences in density, but most easily occurs with different particle sizes (25).

DRUG CONCENTRATION

Although the small concentration of active ingredient in a low-dose formulation (< 1% w/w) has always been assumed to be the reason for poor content uniformity, not much experimental evidence is available. The use of trituration can increase homogeneity in a mix. Dose uniformity is dependent on drug particle mass and size and the drug mean content (6).

Drug content variation increases with decreasing drug content, but drug : excipient ratio has no affect. The critical particle size of drug is limited by the drug content. The critical agglomerate size is also dependent on drug content, but not on proportion. The geometric dilution approach to avoid poor homogeneity was less effective than one-step mixing, even with the smallest drug proportion with the addition of a nonsegregating diluent (6).

ORDERED MIXING AND PARTICLE CHARGE

Cohesion in powder mixes affects powder flow and the efficiency of mixers (10) and is caused by particle-particle interactions (28). As the surface area increases with decreasing particle size, these interactions also increase. Fine particles, therefore, are more prone to segregation due to aggregate formation (8). Travers and White (29) first found that segregation could be prevented when the fine particles in a mix were adsorbed onto "host" crystals. The realization was then made that these so-called ordered mixes were better than the best random mixes (30). Both gravitational and surface electrical forces are present in random and ordered mixes. In an ordered mix, the gravitational force is weak compared to the electrostatic forces, while the opposite is true for a random mix (2). When an ordered mix is completed, there is an even coating of fine particles (usually drug) surrounding the coarse (usually excipient) particles. In a perfect situation, the standard deviation of the fine components is zero, but in reality, errors associated with analytical and sampling procedures create a variance (10).

Larger particles are influenced by gravitational forces to a greater extent; therefore, the forces affecting ordering and randomization are present in all mixes (2). In a mix containing wide particle size distributions, it can be said that randomization and ordering are both present in equilibrium. This is a "total" mix (10). When fine particles in an ordered mix randomly mix, this is called a *partially ordered random* (POR) mix (2). Ordered mixtures can be produced by adhesional forces or coating processes, and there is very little difference between the two. The size of the carrier particle controls the size of the single ordered unit and, therefore, the level of segregation and the homogeneity of the system. A homogeneous carrier particle size avoids segregation (31).

Many experiments have been carried out to investigate the various properties of interactive mixtures. To improve the mix, macroporous or rough-surfaced carrier particles can be used (30). One or more excipients in a mix may adversely affect it by removing drug particles from the carrier particles, but as each new excipient is added to the system, the mix behaves differently (10). By giving particles opposite charges through triboelectrification, the ordered mix may be stabilized. Triboelectrification alters the surface properties of particles in a powder

Table 2

Pharmacopoeial Requirements for Aspirin Content in Tablets

British Pharmacopoeia	The content of aspirin must lie within 95.0% and 105.0% of the prescribed amount (Ref. 36).
European Pharmacopoeia	The content must lie within 10% of the stated amount (Ref. 37).
U.S. Pharmacopeia	The content must lie between 90.0% and 110.0% of the stated amount (38).

mix to encourage interparticulate adhesion, which leads to a stable ordered mix. The drug is usually charged negatively and the excipient positively, and this has been used to maintain the homogeneity of a mix through processing conditions (32).

In a mix of fine pyridoxine hydrochloride particles with coarse fructose agglomerates, the stability of the mix was very sensitive to the moisture content of the carrier particles. With a low moisture content, the ordered mixes were quite unstable, but with a slight increase in moisture content, a very stable mix was produced. This led to the suggestion that ordered mixing could be a spontaneous form of granulation (33). In a computer simulation of ordered mixing, it was determined that, to obtain the greatest homogeneity, the carrier particles should be of the largest size possible and of the narrowest size range possible (34). Fluid bed granulation was used on an interactive mixture, and tablets were made. The mixture was very resistant to segregation, and the tablets produced met USP requirements (Table 2; 35).

Powder mixing is rarely purely a random event. Some interaction will occur, leading to a partially random and partially ordered mix. Ordered mixing is an important factor that prevents segregation of powder mixes (8).

AGGLOMERATION AND DEAGGLOMERATION

When the particle size of a powder decreases, there is an increase in cohesiveness between the particles. This encourages agglomerate formation, which affects a mix and, therefore, many aspects of processing. These cohesive properties lead to problems with granulation, fluidization, and the dispersion of drugs into liquids. Agglomeration can occur during pharmaceutical processes such as mixing, fine grinding, transport, blending, and flow (5).

There are many different methods available for dispersing agglomerates. Vigorous convective and shear mixing can break up the agglomerates, and the particles are dispersed into the powder. Size reduction techniques may also be effective (e.g., sieving and ball milling), which uses impact and attrition (internal milling by the particles themselves) methods, breaking down aggregates efficiently. Sieving may also aid homogeneity through the use of blend, sieve, blend techniques. Mixing coarse, equal size particles of an excipient with a cohesive powder can break the cohesive forces between the particles (39). Ultrasonic forces can be used to disperse agglomerates in a liquid. An ordered mix is created, using the excipient as a carrier particle. The agglomerates are broken down, and the drug is dispersed throughout the powder. This also improves the dissolution rate of the resultant dosage form (5).

The degree of dispersion achieved through deagglomeration can be measured in different ways:

1. The particle size can be followed as it decreases.
2. Mixture homogeneity in the form of coefficient of variation (CV) can be measured.
3. Dissolution rate can be measured as an indication of the particle sizes in the powder.

The most accurate of these methods is particle size decrease after dispersion. However, the particle size cannot always be measured. The area under the dissolution curve can be used to predict agglomerate breakdown in this situation (5).

During mixing, small agglomerates are quickly produced during the initial stages and are dispersed throughout the mixture. The single, primary particles on carrier particles in an ordered mix are slowly eroded from the surface by these stable aggregates (40). Use of a pestle and mortar, followed by ultrasonification has been found effective for deagglomeration (41).

SEGREGATION

> Segregation refers to the separation of the coarse from fine material during the flow of a powder or the vibration of a bed of powder (42).

Segregation is also known as *demixing*, and the main factors at a particulate level are differences in particle size, shape, and density. As powder mixes

are not usually composed of unisize spherical particles, segregation is a big problem (8).

There are three main mechanisms of segregation: (1) size segregation, (2) density segregation, and (3) trajectory segregation. Size segregation, also known as *percolation segregation*, in a flowing powder can be understood by picturing a powder falling onto a base plate and forming a cone. The coarse particles roll down the surface, leaving a high concentration of fines behind. Size segregation is a surface phenomenon that occurs at every inclined surface formed in a powder (42). In the mixing of powder using an upright mixer, placing the coarse particles on top of the fines will not result in mixing. If the fine material is placed on top, mixing occurs until segregation develops, and the fines fall to the bottom. The small particles fall through the voids between the larger ones (21).

Other factors than particle size are responsible for this type of segregation. Particle shape affects a powder mix as spherical particles are easier to mix than any other shape. Flat or acicular particles prolong the mixing time due to their tendency to agglomerate. Fine particles fall through the voids created between the irregular-shaped particles, allowing segregation. Agglomerates rise to the surface of a mix, resulting in segregation (21). Size segregation, therefore, depends on the influence of powder properties (e.g., particle size, shape, friction flow patterns when filling and emptying the container and when mixing and vibration are applied to the bed) (42).

Density segregation can occur in two ways:

1. When a falling group of particles is observed, the heavier particles remain where they have fallen, and the lighter particles fall to the side (42).
2. In a vibrated bed (e.g., tablet machine hopper), large, dense particles move upward as smaller particles are compacted beneath them, supporting the weight of the larger particles (8). With monosize particles, the heavier particles sink to the bottom of the mix, while the lighter ones rise to the top (42).

With trajectory segregation, for the same density and velocity in free flight, a particle will travel a distance that is proportional to the square of its diameter. In a mixer, therefore, larger particles will travel to the walls of the mixer, leaving the smaller particles in the center. This occurs in mixers in which particles flow over a surface or in transport when particles may be poured into a heap (43).

Segregation may also occur in an ordered mix, and three different methods have been observed:

1. Ordered unit segregation occurs when there is a size difference between the carrier particles; this leads to drug-rich areas in the mix.
2. Displacement segregation involves another constituent in a mix competing for the available sites on the carrier particles, thereby displacing some adsorbed drug particles. The lubricant magnesium stearate acts this way in certain circumstances.
3. Saturation segregation involves any excess material, for which there are no available sites on the carrier particles, undertaking percolation if too much is added (8).

When attempting to quantify the extent of segregation in a mixture, two statistical quantities can be applied. The scale of segregation and the intensity of segregation both represent aspects of the "goodness" of a mix and provide quantitative information, allowing comparison for different degrees of mixing (44). Different methods of mixing affect these statistical measurements in different ways. Convective mixing reduces the *scale* of segregation value, while diffusional mixing reduces the *intensity* of segregation value (43). A set of indices, the Johanson indices, also provides a quantitative means for predicting segregation and flow properties in a mix. The indices were derived from the flow properties of basic bulk solids (16).

For a binary mixture, segregation increases with particle size, but particle shape has no effect. However, rate may be affected by shape (43). Segregation occurs most easily with a particle size difference, although it does occur with differences in shape and density (25). The convection mechanism minimizes segregation (4). In a rotating drum in continuous flow, size segregation will occur with even very slight variations in particle size (45). Segregation is equally problematic with ordered mixtures, and segregation patterns are more unpredictable than with random mixtures (46). In a total mix, content uniformity can be very low with conditions common in pharmaceutical processing. Fines dislodged from their carrier particles undergo size segregation, but this can be reduced by choice of excipient and by minimizing vibration (47).

Granulation is commonly used to prevent segregation (48). When handling a mix, the most serious cause of segregation occurs during and after storage in a hopper, in which heaps of the material are formed. By reducing the formation of sloping surfaces in the hopper, the effect can be reduced (49). When pouring powder from one container to another, the air leaving the new container flushes out the fines, causing a large amount of segregation (50).

Avoiding segregation may not be possible, but it can be minimized easily. Changes in particulate characteristics of drug and excipients may eliminate particle size differences or improve adhesion between a coarse diluent and fine particle drug. Granulation may fix relative positions of drug and excipient, and equipment design may also help minimize problems (9). The type of mixer used may improve the quality of a mix (e.g., the use of a Nautamix or Ribbon blender rather than tumbler mixer) (4). Avoiding sloping surfaces in machinery will also help reduce segregation (49).

SELECTION OF MIXER

Ideally, the particle movement in a mixer should be three-dimensional and random; there should be individual particle movement even in groups of particles, and "dead" regions in a mixer should be avoided. All mixers are based on one of three mechanisms (9):

1. Convective mixing occurs when circulation patterns are set up in a powder mix (49). A spatula inserted into a heap of powder removes a small pile.
2. Shear mixing occurs with convective mixing when slip planes are formed behind the spatula; these planes collapse, with further mixing occurring in the heap (8). The effect is seen in mixers that involve a moving blade and general rotation (48).
3. Diffusive mixing occurs when particles roll over each other on a sloping surface of powder (49). The powder is raised in a drum mixer past its angle of repose (the angle of inclination at which a particle will begin to slide, overcoming frictional forces). Particles fall with greater velocity at the surface, and individual particles migrate from layer to layer (8).

Convective and shear mixing produce a rough mix as groups of particles are left unseparated (8). Diffusional mixing is used to produce a true random mix (48). Diffusional and shear mixing demand unisize particles, or segregation can occur. In industrial practice, in which particles often have very different properties, these methods result in segregation. Convective mixing is the only method that gives minimal segregation (51).

The capacity of a mixer should also be considered. Some mixers may hold a large amount of powder, but will only efficiently mix a proportion of this amount due to dilation of the powder bed (1).

Mixer Type

Mixers can be classified into two groups: (1) segregating mixers, which rely mainly on shear or diffusive mixing; and (2) nonsegregating mixers, which rely mainly on convection (51). A segregating mixer is an empty drum that rotates about a horizontal axis. Baffles fitted across the axis of the mixture may improve the mix by setting up convective currents within the powder bed, which minimizes segregation (51). Tumbler mixers (e.g., Turbula) are the most common type of mixers for dry solids, but some materials can agglomerate during mixing (52). Mixers such as V- and Y-cone blenders introduce a shear effect and have been widely used in the pharmaceutical industry. These may be unsatisfactory if the particles in the mix become airborne as trajectory segregation may then occur (51).

A nonsegregating mixer relies on movement of particles within the powder bed. Ribbon blenders involve a small amount of segregation as the particles roll down an inclined surface and shearing effects. The Nauta mixer involves strong circulation patterns set up in the powder bed. The Lödige mixer and other mixers with mechanical stirrers produce convection currents rather than shear, while in fluidized mixers the powder is mixed by air setting up circulation patterns in the bed. All of the above mixers and others like them have some segregation occurring within them, but generally considerably less segregation than those within the segregating mixer category (51). Their advantages and disadvantages are shown in Table 3.

A fluidized bed mixer was shown to be more practical, less time consuming, more economical, and less segregation prone than conventional mixers (55). In a series of tests, three different mixes were

Table 3

Description of Mixers

Mixer Type	Mechanism	Advantages	Disadvantages	Examples
Drum	Diffusive	• Ordered mixtures are mixed efficiently • Only mild forces exerted, so is useful for friable materials	• Segregation is a big problem, but can be reduced by the addition of baffles • No fine powders can be mixed as agglomerates cannot be broken down	• V • Y-cone • Cube
Screw-paddle	Convective and shear	• Better than tumbler mixers for segregating mixtures (Ref. 4) • Regarded as general purpose mixers (Ref. 52) • Can rapidly produce a good random mix (Ref. 53)	• Cleaning can be difficult • Not suitable for cohesive materials (Ref. 52)	• Ribbon blender • Nauta mixer
Continuous	Various mixers are adapted for continuous operation	• A better quality mix is obtained with segregating materials	• See individual mixers	• Modified ribbon and V mixers • Motionless mixers
Fluidized bed	Air bubbles are passed through fluidized powder	• Can be used for mixing, wet granulation, and drying	• Can only be used for free-flowing powders with particle size > 75 μm • Cohesive/moist powders do not mix well • Extra segregation can occur due to suspended fines falling on the surface	• Fluidized bed mixers
High-speed mixer granulators	Convective and shear	• Internal agitators break up agglomerates • Useful for ordered mixers in which fines agglomerate	• Very specific in use	• Lödige mixer • Diosna mixer

Source: After Ref. 54.

used in various mixers (Table 4). With material A, the most rapid mixing occurred with a V-type or twin mixer, but the more uniform mix was achieved using a ribbon or pan mixer. The double-cone and rotating cylinder mixers produced the worst mixes. With material B, the variations between mixer performances were less noticeable, but the double-cone and rotating cylinder mixers again gave the least uniform mix overall. With material C, the agglomerates remained present using the V mixer and ribbon mixer, although they were reduced in size. Nearly complete mixing was obtained by rough premixing, followed by use of a hammer mill. Among the tumbling mixers, the tetrahedral chamber gave the least segregation (13). The Nauta mixer and ribbon blenders have been found to give much better performance than V mixers, while a large V mixer is best (43). Comparative studies using tumbler mixers showed the twin-shell blender to give better results than the double-cone blender. The larger twin-shell blenders were best (68).

If a mixture contains nonsegregating materials, any type of mixer may be used. If the powder is prone to segregation, a nonsegregation mixer must

Table 4

Materials Used in Experiment

Material A	Free-flowing combination of sand and ilmenite with a different particle size and density
Material B	Free-flowing combination of aluminum oxide and ilmenite with nearly the same particle size and density
Material C	Non-free-flowing combination of barium sulfate and an ilmenite fraction that agglomerated readily

Source: From Ref. 13.

be used to obtain a good mix. The selection of a mixer should be made using these guidelines, although other factors, such as tendency to aggregate, high friability, or the need for frequent cleaning, may limit mixer choice. Sometimes, a sacrifice in mixing quality has to be made (51).

Mixing Time

Mixing creates disorder in a powder bed. When this reaches a stable maximum, an equilibrium is reached. If mixing is continued, segregation occurs due to differences in particle size, shape, or density (11). With large differences, the mixing time must be increased to achieve a satisfactory mix (21). A non-segregating mix may improve with increased mixing time, but this will not improve a segregating mix. Segregation in a mix requires a longer time to become established than is needed to form a good quality mix, and this may be one of the main causes of segregation during mixing as time is not optimized (8). In a multicomponent mixture, an increase in mixing time may be required to obtain homogeneity (56), and preblending may reduce the mixing time. The drug is blended with a small amount of excipient, and this blend is then mixed with the remainder of the excipient (57).

SAMPLING

Taking a large amount of powder for sampling is very expensive and wasteful to analyze, so it must be reduced (58). "Sampling in its strict sense is therefore a simple mass reduction" (58).

The purpose is to collect a manageable amount of the powder that is representative of the batch as a whole. Many small samples are taken from all parts of the whole; together, these samples are representative (7). Theoretically, every particle should have an equal chance to be selected for examination (59), and this should be attained with minimum disturbance to the system (60). The composition of the original powder must therefore be retained during sampling (58). Powder characteristics change under an applied load, and attrition and segregation may occur in transfer. Representative sampling is essential for the relevance of any subsequent testing (7) and is defined by the selection method, which is accurate and reproducible. To produce reliable samples, a correctly designed sampler is required (58).

Certain important rules of sampling should be followed when sampling: (1) Sample from a moving stream of powder, and (2) sample the whole stream for equal periods of time, rather than from part of the stream for all of the time (7). The number, the size of each sample, and the method should all be considered. The acceptable error dictates the number of samples to be taken. The more samples taken, the smaller the error will be (61). Despite extremely careful sampling, error causes a difference in the composition of a sample from that of the batch (62). All analysts have a personal preference for sampling patterns, and random number tables can eliminate this problem (63).

> It is extraordinarily difficult to carry out any selection process without introducing individual preference or bias into the final selection (63).

Sampling can be undertaken in two ways: (1) by taking increments on flowing streams of powder, and (2) by splitting, by which the whole is handled (58). Numerous techniques are used to sample powder, but many are inaccurate. The sample thief can be useful for free-flowing powders; however, it has disadvantages:

1. It can be hard to push into the powder (64).
2. Additional weight at the bottom of the bag may vary sample size (24).
3. Fines may lodge between the tubes (64).
4. Particles may fracture (24).
5. A plug of powder may be pushed ahead of the thief, and surface material contaminates the sample (63).
6. Personal preference introduces bias for the area sampled.

7. Segregation may occur as fines percolate into the sample more easily than coarse particles (24).

The unit-dose compacting sample thief reduces the occurrence of segregation; however, bias is still likely with this method. The spinning riffler has been proven to be a superior method of sampling in experiments and should be used whenever possible. However, there should only be a small percentage of fines present because air currents displace them, and the sample is not representative. It is also quite expensive and time consuming (64). Problems that can affect sampling include segregation, moisture content, not enough information about the powder before sampling, and not enough operator experience (65).

SCALE OF SCRUTINY

When a mixture is examined closely, regions of segregation are often found. The smallest region that can measure imperfections in a mix is the "scale of scrutiny" and can be a length, area, or volume (13). The scale of scrutiny is directly related to the finished product. If the product is a tablet, then it is the weight of a tablet. The lower limit is set by particle size (48). When the scale of scrutiny is large or the particle size small, a large number of particles are present in a sample, and the mix appears uniform (13). Segregation can never be avoided fully, and sampling the final product is therefore preferred (61).

SCALE-UP

In research and development, it is necessary to work on a pilot scale. Unfortunately, the results with an identical mixer on a large scale will not necessarily be the same, and risks are involved (8).

When using small-scale experimental work, the apparatus should be as similar as possible to the large-scale apparatus. Flow patterns will be similar, and results should be comparable. Velocity of flow and quantity of powder must be known; therefore, the power per unit volume of the mixer is a useful concept for scale-up (66). During scale-up, it is essential to evaluate every possible effect that modifications to the mixer size may have (9).

Delonca et al. (67) found that their large-scale model improved the quality of the mix from the small-scale model. Drug deficiency has also been found to be a problem with scale-up due to the adsorption of drug to the wall of the mixer, which did not happen on the pilot scale. Validation and testing, therefore, are necessary at all stages of manufacture of a new product (8).

CONCLUSION

When analyzing the variance of a mix, many methods are available. Indices still remain popular today, as does the Poisson distribution, but both methods have their limits, and the ANOVA technique investigated by Rollins et al. (15) may provide a useful alternative, especially for segregation determination.

The size of the particles in the powder affects mixing in two principal ways: (1) It may cause segregation and flow problems; and (2) it may cause ordering.

The particle size must be set as a standard prior to mixing, and analytical methods such as microscopy, sieving, and the Coulter Counter are useful in determining and controlling these standards. The shape of the particles affects the mix because irregularly shaped particles increase the mixing time due to agglomeration. Segregation also occurs more easily with varying particle shapes, and flow properties can be affected. Spray-dried excipients and recrystallized drug particles can be produced to increase the quality of a mix. Density differences can also lead to segregation and an increase in mixing time. With lower drug concentrations, the uniformity is less, but geometric dilutions (i.e., trituration) are not as effective as the use of a nonsegregating diluent (e.g., Avicel PH-102) in a one-step mix (6). Increased particle charge due to smaller particle sizes leads to cohesion, agglomeration, and segregation. An ordered mix prevents this. Deaggregation methods such as sieving or ultrasonification can also be used. Particle size, shape, and density differences cause segregation. Segregation can be minimized easily by alterations in the particulate characteristics of the drug or excipient being used, use of granulation, or changing the type of mixer used.

Mixers can be grouped into segregating and nonsegregating types, and the choice of mixer should depend on the tendency of the powder to segregate. If mixing is continued after equilibrium is attained, a segregating mix will lose quality; therefore, mixing time should be kept to the minimum possible to obtain homogeneity. The scale of scrutiny must be

Table 5

Guidelines for Mixing

Factor	Optimizing Mixture Homogeneity
Particle size	• An optimum size must be specified for processing (Ref. 3).
Particle shape	• Spherical particles improve flow properties and therefore reduce mixing time (Ref. 21).
Particle density	• Density differences should be avoided as they can lead to segregation (Ref. 21).
Drug concentration	• Low drug concentration can lead to poor content uniformity (Ref. 6).
Particle charge	• A large surface area of particles leads to particle interactions, which results in aggregate formation. Fine particles are therefore more prone to segregation. Ordered mixing can prevent this (Ref. 8).
Mixer choice	• Use segregating mixers for friable or unisize particles. • Use nonsegregating mixers for materials prone to segregation (Ref. 5).
Mixing time	• Must be optimized for each mix to minimize segregation (Ref. 21).
Sampling	• Sample while the powder is in motion. • Sample the whole stream for many short periods of time. • Use common sense to determine a suitable sample size (Ref. 24).
Scale-up	• Ensure testing and validation are carried out at all stages of manufacture (Ref. 8).

carefully considered when sampling. Both small and large samples will give very misleading results. Sampling is integral to analytical techniques at all stages of manufacture, especially in scale-up. Testing must be carried out frequently to ensure the mix reaches the standards that were set.

Powder mixing is a complex process. Even today, there is no simple list of rules that can be followed to create a perfect mix; however, there are guidelines that can be followed to minimize segregation and agglomeration (Table 5). By continually updating mixing methods used in the pharmaceutical industry, these problems can be removed, and powder mixing can be made a much more efficient process. However, this is also dependent on reliable, accurate, analytical data for which sampling is an integral and pivotal issue.

ACKNOWLEDGMENT

We would like to thank Dr. Rob Burrows and Dr. John Hogan from Pfizer Central Research Limited for their continued involvement. We would also like to thank fellow staff and research students at Liverpool John Moores University for their support.

REFERENCES

1. Wells, J.I. *Pharmaceutical Preformulation*; Ellis Horwood: Chichester, UK, 1988; 192–208.
2. Staniforth, J.N. Total mixing. Int. J. Pharm. Tech. Prod. Manuf. **1981**, *2* (1), 7–12.
3. York, P. The design of dosage forms. In *Pharmaceutics. The Science of Dosage Form Design*; Aulton, M.E., Ed.; Churchill Livingstone: London, 1988; 1–13.
4. Harnby, N. A comparison of the performance of industrial solids mixers using segregating materials. Powder Technol. **1967**, *1*, 94–102.
5. DeVilliers, M.M.; Van Der Watt, J.G. The measurement of mixture homogeneity and dissolution to predict the degree of drug agglomerate breakdown achieved through powder mixing. Pharm. Res. **1994**, *11* (11), 1557–1561.
6. Egermann, H.; Pichler, E. Significance of drug content and of drug proportion to the content uniformity of solid dosage forms. Acta Pharm. Jugoslavica. **1988**, *38* (4), 279–286.
7. Svarovsky, L. Characterization of powders. In *Principles of Powder Technology*; Rhodes, M.J., Ed.; John Wiley and Sons: Chichester, UK, 1990; 35–69.
8. Travers, D.N. Mixing. In *Pharmaceutics. The Science of Dosage Form Design*; Aulton, M.E., Ed.; Churchill Livingstone: London, 1988; 550–563.
9. Rees, J.E. Mixing of particulate solids to ensure homogeneity of dosage forms: the need for a critical approach to pharmaceutical process development. Boll. Chim. Farm. **1977**, *116*, 445–462.
10. Staniforth, J.N. Advances in powder mixing and segregation in relation to pharmaceutical processing. Int. J. Pharm. Tech. Prod. Manuf. **1982**, *3* (Suppl.), 1–12.
11. Lacey, P.M.C. The mixing of solid particles. Trans. Inst. Chem. Eup. **1943**, *21*, 53–59.
12. Stange, K. *Chem. Engr. Tech.* **1954**, *24*, 331–333.

13. Orr, C. *Particulate Technology*, 1st Ed.; Collier-Macmillan Ltd.: London, 1966; 87–123.
14. Egermann, H.; Frank, P.; Krumphuber, A. Evaluation of the Poisson-distribution for estimating the quality of drug diluent random powder mixtures. 1. High particle-size of the drug constituent. Pharm. Res. **1992**, *9* (3), 385–389.
15. Rollins, D.K.; Faust, D.L.; Jabas, D.L. A superior approach to indices in determining mixture segregation. Powder Technol. **1995**, *84*, 277–282.
16. Johanson, J.R. Predicting segregation of bimodal particle mixtures using the flow properties of bulk solids. Pharm. Tech. Europe. **1996**, *8* (1), 38–44.
17. Staniforth, J.N. Particle size analysis. In *Pharmaceutics. The Science of Dosage Form Design*; Aulton, M.E.; Churchill Livingstone: London, 1988; 564–599.
18. Heywood, H. The evaluation of powders. J. Pharm. Pharm. **1963**, *15*, 56T–74T.
19. Edmundson, I.C. Particle size analysis. In *Advances in Pharmaceutical Sciences*; Bean, H.S., Beckett, A.H., Carless, J.E., Eds.; Academic Press: London, 1967; Vol. 2, 95–179.
20. Whitby, K.T. Size measurement of particles. in *Kirk-Othmer Encyclopedia of Chemical Technology*, 2nd Ed.; Wiley InterScience: New York, 1964; Vol. 18, 310–323.
21. Train, D. Pharmaceutical aspects of mixing solids. Pharm. J. **1960**, *185*, 129–134.
22. Staniforth, J.N. Powder flow. In *Pharmaceutics. The Science of Dosage Form Design*; Aulton, M.E., Ed.; Churchill Livingstone: London, 1988; 600–628.
23. Riley, G.S. On the assessment of particle shape. In *Powtech '75; Proceedings of the Third International Powder Technology and Bulk Solids Conference*; Goldberg, A.S., Ed.; Heydon and Son, Ltd.: London, 1976.
24. Allen, T. *Powder Technology Theory*, 3rd Ed.; Chapman and Hall: London, 1981.
25. Lloyd, P.J.; Yeung, P.C.M.; Freshwater, D.C. The mixing and blending of powders. J. Soc. Cosmetic Chem. **1970**, *21*, 205–220.
26. Campbell, H.; Bauer, W.C. *Chem. Eng.* **1966**, *73*, 179–185.
27. Rippie, E.G.; Faiman, M.D.; Pramoda, M.K. *J. Pharm. Sci.* **1967**, *56*, 1523–1525.
28. Heistand, E.N. Powders: particle-particle interactions. J. Pharm. Sci. **1966**, *55* (12), 1325–1344.
29. Travers, D.N.; White, R.C.J. *J. Pharm. Pharmacol.* **1971**, *23*, 2605–2615.
30. Staniforth, J.N. Order out of chaos. J. Pharm. Pharm. **1987**, *39*, 329–334.
31. Hersey, J.A. Preparation and properties of ordered mixtures. Aust. J. Pharm. Sci. **1977**, *6*, 29–31.
32. Staniforth, J.N.; Rees, J.E. Short communication. Powder mixing by triboelectrification. Powder Technol. **1981**, *30* (2), 255–256.
33. Staniforth, J.N. Ordered mixing or spontaneous granulation? Powder Technol. **1985**, *45* (1), 73–77.
34. Lai, F.; Hersey, J.A. Simulated ordered powder mixture. Int. J. Pharm. **1987**, *36*, 157–164.
35. Thiel, W.J.; Nguyen, L.T.; Sberna, F.J. Content uniformity of microdose tables (dosage 1 μg–10 μg) produced by fluid bed granulation of interactive mixtures. J. Pharm. Pharm. **1986**, *38*, 335–343.
36. Her Majesty's Stationery Office. *British Pharmacopoiea*; HMSO: London, UK, 1993; Vol. 2.
37. Council of Europe. *European Pharmacopoeia*, 3rd Ed.; European Department for the Quality of Medicines Within the Council of Europe: Strasbourg, 1988.
38. U.S. Pharmacopeial Convention, Inc. *U.S. Pharmacopeia and National Formulary*; National Publishing: Philadelphia, 1999.
39. Staniforth, J.N. Particle size reduction. In *Pharmaceutics. The Science of Dosage Form Design*; Aulton, M.E., Ed.; Churchill Livingstone: London, 1988; 581–599.
40. DeVilliers, M.M. Description of the kinetics of the deagglomeration of drug particle agglomerates during powder mixing. Int. J. Pharm. **1977**, *151*, 1–6.
41. Hayakawa, O.; et al. Experimental analysis of sample preparation conditions for particle size measurement. Powder Technol. **1998**, *100* (1), 61–68.
42. Brown, R.L.; Richards, J.C. *Principles of Powder Mechanics—Essays on the Packing and Flow of Powders and Bulk Solids*; Pergamon Press: New York, 1970; Vol. 10, 129–134.
43. Ridgway, K. Mixing mechanisms in particulate systems (quarterly reviews: aspects of pharmaceutical engineering). Pharm. J. **1972**, *208*, 271–274.
44. Dankwerts, P.V. *The Definition and Measurement of Some Characteristics of Mixtures*; Applied Scientific Research: 1953; Vol. 3, Section A, 279–296.
45. Dury, C.M.; Ristow, G.H. Competition of mixing and segregation in rotating cylinders. Phys. Fluids **1999**, *11* (6), 1387–1394.
46. Lai, F.; Hersey, J.A.; Staniforth, J.N. Segregation and mixing of fine particles in an ordered mixture. Powder Technol. **1981**, *28* (1), 17–23.
47. Staniforth, J.N. Determination and handling of total mixes in pharmaceutical systems. Powder Technol. **1982**, *33* (2), 147–159.
48. Shotton, E.; Ridgway, K.C. *Physical Pharmaceutics*; Clarendon Press: Oxford, UK, 1974; 236–240.
49. Williams, J.C. The mixing of solid particles. Pharm. Ind. **1972**, *34* (11), 816–820.
50. Kaye, B.H. Powder mixing review. Pharm. Technol. **1991**, *15*, 62–70.

51. Williams, J.C. The mixing of dry powders. Powder Technol. **1968**, *2*, 13–20.
52. McDonald, D.P. Mixing and blending. Manuf. Chem. Aerosol News **1961**, *42*, 35–38.
53. Cook, P.; Hersey, J.A. Evaluation of a Nauta mixer for preparing a multicomponent mixture. Powder Technol. **1974**, *9*, 257–261.
54. Hersey, J.A. Powder mixing: theory and practice in pharmacy. Powder Technol. **1976**, *15*, 149.
55. ElGindy, N.A.; Samaha, M.W.; Maradny, H.A. The mixing performance of the fluidized-bed for a multi-component system. Pharm. Ind. **1986**, *48* (4), 403–407.
56. Chowhan, Z.T.; Chi, L.; Yang, I. Mixing of Pharmaceutical solids IV: Effects of concentration and material properties on multicomponent mixing of cohesive powders. Powder Technol. **1981**, *29* (2), 251–256.
57. Carstensen, J.T.; Rhodes, C.T. Optimization of preblending in random mixing. Drug Dev. Ind. Pharm. **1984**, *10* (7), 1017–1023.
58. Gy, P. *Sampling for Analytical Purposes*; Wiley: Chichester, UK, 1988.
59. Hawkins, A.E. Characterizing the single particle. In *Principles of Powder Technology*; Rhodes, M.J., Ed.; John Wiley and Sons: Chichester, UK, 1990; 9–34.
60. Ashton, M.D.; Schofield, C.; Valentin, F.H.H. The use of a light probe for assessing the homogeneity of powder mixtures. Chem. Eng. Sci. **1966**, *21*, 843–849.
61. Hersey, J.A. Sampling and assessment of powder mixtures for cosmetics and pharmaceuticals. J. Soc. Cosmetic Chem. **1970**, *21*, 259–269.
62. Gy, P. Sampling—diving into the unknown. LC-GC **1994**, *12* (11), 808–817.
63. Harnby, N. The sampling of particulate mixtures. In *Powtech '75; Proceedings of the Third International Powder Technology and Bulk Solids Conference*; Goldberg, A.S., Ed.; Heydon and Son, Ltd.: London, 1976.
64. Kaye, B.H. Powder mixing. In *Powder and Powder Mixture Characterization Technology*. Chapman and Hall: London, 1997; 77–95.
65. Bicking, C.A. Sampling. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 2nd Ed.; Wiley InterScience: New York, 1964; Vol. 17, 744–762.
66. Rushton, J.H.; Boutros, R.D. Mixing and blending. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 2nd Ed.; Wiley InterScience: New York, 1964; Vol. 13. 577–613.
67. Delonca, H.; Jeannin, C.; Joachim, J.; Romier, G.; Verain, A. Scaling tests on plough mixers. *Int. J. Pharm.* **1982**, *3* (3), 87–92.
68. Kaufman, N. Mixing of solids. I. E.C. Fundam. **1962**, *1* (2), 104–106.
69. Williams, J.C. Mixing of particulate solids. In *Mixing; Theory and Practice*; Uhl, V.W., Gray, J.B., Eds.; Academic Press: London, 1986; Vol. 3, 265–305.