

# **PARTICLE SCIENCE AND POWDER TECHNOLOGY**

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# 9

## Solid-state properties

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### CHAPTER CONTENTS

<b>The solid state</b>	<b>141</b>
<b>Crystallization</b>	<b>142</b>
<b>Polymorphism</b>	<b>142</b>
Polymorphism and bioavailability	144
<b>Hydrates and solvates</b>	<b>144</b>
<b>The amorphous state</b>	<b>145</b>
<b>Crystal habit</b>	<b>148</b>
<b>Surface nature of particles</b>	<b>149</b>
Dry powder inhalers	149
Surface energy	149
Vapour sorption	150
<b>References</b>	<b>151</b>
<b>Bibliography</b>	<b>151</b>

### THE SOLID STATE

The three states of matter are solid, liquid and gas (or vapour).

In a sealed container vapours will diffuse to occupy the total space, liquids will flow to fill part of the container completely, but solids will retain their original shape unless a compressive force is applied to them. From this simple consideration it becomes clear that solids are unique because their physical form (the packing of the molecules and the size and shape of the particles) can have an influence on the way the material will behave. At normal room temperature and pressure the majority of drugs and excipients exist as solids, and so the study of solid-state properties is of enormous pharmaceutical importance.

Solid particles are made up of molecules that are held in close proximity to each other by intermolecular forces. The strength of interaction between two molecules is due to the individual atoms within the molecular structure. For example, hydrogen bonds occur as a result of an electrostatic attraction involving one hydrogen atom and one electronegative atom, such as oxygen. For molecules that cannot hydrogen bond, attraction is due to van der Waal's forces. The term van der Waal's forces is generally taken to include dipole-dipole (Keesom), dipole-induced dipole (Debye) and induced dipole-induced dipole (London) forces. Here a dipole is where the molecule has a small imbalance of charge from one end to the other, making it behave like a small bar magnet. When the molecules pack together to form a solid, these dipoles align and give attraction between the positive pole of one and the negative pole on the next. Induced dipoles are where the free molecule does not have an imbalance of charge, but an imbalance is caused by bringing a second molecule into close proximity with the first.

## CRYSTALLIZATION

Materials in the solid state can be crystalline or amorphous (or a combination of both). Crystalline materials are those in which the molecules are packed in a defined order, and this same order repeats over and over again throughout the particle. In Figure 9.1(a) an ordered packing of a molecule is shown, here the shape of the molecule is represented by a 'hockey-stick' style image, illustrating a planar structure with a functional group pointing up at the end. (This is not a real molecule: it has been drawn to provide an easy representation of a possible crystal packing arrangement.) A characteristic property of a crystal is that it has a melting point. This is the temperature at which the crystal lattice breaks down, owing to the molecules having gained sufficient energy from the heating process to overcome the attractive forces that hold the crystal together. It follows that crystals with weak forces holding the molecules together (such as paraffins, which only have van der Waals interactions) have low melting points, whereas crystals with strong lattices (i.e. those held together with strong attractive forces, such as extensive hydrogen bonding) have high melting points.

Crystals are produced by inducing a change from the liquid to the solid state. There are two options: one is to cool a molten sample to below its melting point. Pharmaceutical examples of crystallizing through cooling include the formation of suppositories, creams and semisolid matrix oral dosage forms. The other method of crystallization is to have a solu-

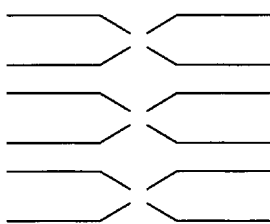
tion of the material and to change the system so that the solid is formed. At a given temperature and pressure, any solute (where the solute is the material that has been dissolved and the liquid is the solvent) has a certain maximum amount that can be dissolved in any liquid (called a saturated solution). If crystals are to be formed from a solution, it is necessary to have more solute present than can be dissolved at that temperature; this will eventually result in the formation of a solid in equilibrium with a saturated solution. In order to make a solid precipitate out of solution one can either:

- remove the liquid by evaporation (this is the way sea salt is prepared)
- cool the solution, as most materials become less soluble as the temperature is decreased
- add another liquid which will mix with the solution, but in which the solute has a low solubility. This second liquid is often called an antisolvent.

Many drugs are crystallized by adding water as an antisolvent to a solution of the drug in an organic liquid. For example, if a drug is almost insoluble in water but freely soluble in ethanol, the drug could be crystallized by adding water to a near-saturated solution of the drug in ethanol.

The processes by which a crystal forms are called **nucleation** and **growth**. Nucleation is the formation of a small mass on to which a crystal can grow. Growth is the addition of more solute molecules to the nucleation site. In order to achieve nucleation and growth, it is necessary to have a supersaturated solution, i.e. one where the amount of solute dissolved in the liquid is greater than the true solubility. Supersaturated solutions are not thermodynamically stable; in these circumstances the system will adjust in order to move back to the true solubility, and to do this the excess solute will precipitate. However, in some circumstances the process of nucleation can be slow. Most students will at some stage have a supersaturated solution which has not crystallized; then, simply by scratching the side of the beaker with a glass rod, crystallization can be induced. The scratching action produces a small amount of rough surface or glass spicule that acts as a nucleation site and causes the supersaturated solute to precipitate rapidly.

Polymorphism of molecule 



(a)



(b)

Fig. 9.1 Representation of two polymorphic forms of a crystal consisting of a molecule represented by a 'hockey-stick' shape.

## POLYMORPHISM

If the crystallization conditions are changed in any way, it is possible that the molecules may start to

form crystals with a different packing pattern from that which occurred when the original conditions were used. The change in conditions could be a different solvent, or a change in the stirring, or different impurities being present. Figure 9.1(b) shows an alternative packing arrangement from that which occurred for the same molecule in Figure 9.1(a). As both the packing arrangements in Figure 9.1 are repeating ordered systems, they are both crystals; these would be called polymorphic forms.

By looking at the packing arrangements in Figure 9.1 it can be seen that the molecules in (a) are more spaced out than those in (b), which means that the two crystal forms would have different densities (i.e. the same mass of material would be housed in different volumes). It looks as though it would be easier to physically pull a molecule off structure (a) than off (b), as the molecules in (b) are more interwoven into the structure. If this were the case then (a) would have a lower melting point than (b) and might dissolve more easily. Also, if an attempt were made to mill the two crystals, it appears that (a) would break easily, as there are natural break lines (either vertically or horizontally), whereas (b) does not seem to have an obvious weak line to allow easy breakage. This could mean that the milling and compaction (tableting) properties of the two forms will differ. In summary, a change in the packing arrangement of the same molecule, giving two different crystal forms, could result in significant changes in the properties of the solid.

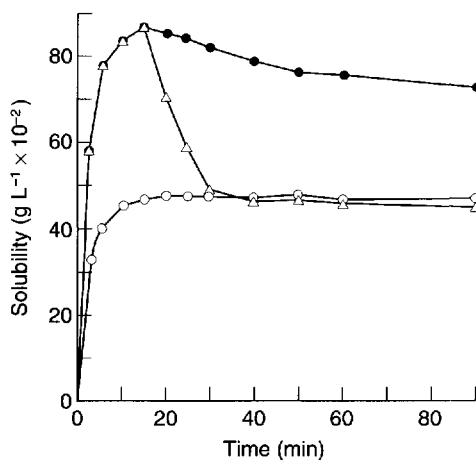
Many organic molecules, including drugs and excipients, exhibit polymorphism. Usually this is of a form known as monotropic, which means that only one polymorphic form is stable and any other polymorph that is formed will eventually convert to the stable form. However, some materials exhibit enantropic polymorphism, which means that under different conditions (temperature and pressure) the material can reversibly transform between alternative stable forms; however, this type of behaviour is less common and will not be considered further. Considering the more usual monotropic polymorphism, the true stable form has the highest melting point and all other forms are described as metastable. This means that the other forms exist for a period of time and thus appear stable, but given a chance they will convert to the true stable form. Different metastable forms can exist for very short times or for many months before they convert to the stable form, depending upon the conditions under which they are stored.

In general there will be a correlation between the melting point of the different polymorphs and the

rate of dissolution, because the one with the lowest melting point will most easily give up molecules to dissolve, whereas the most stable form (highest melting point) will not give up molecules to the solvent.

High melting point = strong lattice = hard to remove a molecule = low dissolution rate (and vice versa).

It is relatively easy to understand that changes in polymorphic form can cause changes in the rate at which a drug will dissolve. However, it is less easy to understand why this can lead to a change in the apparent solubility. None the less, it is true that when a metastable polymorphic form is dissolved it can give a greater amount of material in solution than the saturated solubility. In other words, metastable forms can dissolve to give supersaturated solutions. These supersaturated solutions will eventually return to the equilibrium solubility, owing to the stable crystal form precipitating from solution, but this process may not be instantaneous. In fact, the supersaturated solution can often exist long enough to cause an increase in bioavailability of a poorly soluble drug. Figure 9.2 shows the solubility of two different polymorphs of sulphamethoxydiazine. It can be seen that Form III has a higher solubility than Form II, and that this lasts throughout



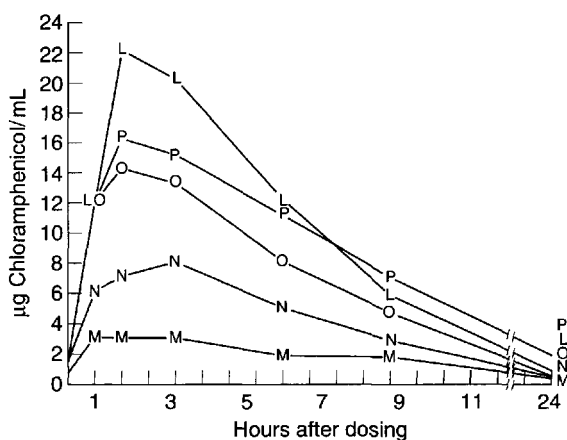
**Fig. 9.2** The solubility time relationship for sulphamethoxydiazine. ○, solubility of polymorphic Form III, which rises to the drug's equilibrium solubility and plateaus. ●, solubility of polymorphic Form II, which dissolves to twice the extent of Form III and then shows a gradual decline with time, as the stable form crystallizes from solution. △, the effect of adding crystals of Form III to the solution of Form II at the peak of solubility. It can be seen that the amount dissolved falls rapidly from the supersaturated level to the true equilibrium solubility because the added crystals of Form II act as nucleation sites. (Reproduced from Ebian et al 1973, with permission.)

the 90-minute experiment. However, if crystals of Form II are added to the solution of Form III, then the solubility reverts rapidly to that of Form II because the excess solute in the supersaturated solution will have seed crystals of Form II on which to precipitate.

### Polymorphism and bioavailability

Many drugs are hydrophobic and have very limited solubility in water. Owing to the limited aqueous solubility of such drugs the rate at which they dissolve (slow dissolution rate) can result in only a small percentage of the administered drug actually being available to the patient (low bioavailability). A classic example of the importance of polymorphism on bioavailability is that of chloramphenicol palmitate suspensions. In Figure 9.3 the blood serum level is plotted as a function of time after dosing. It can be seen that the stable  $\alpha$ -polymorph produces low serum levels, whereas the metastable  $\beta$ -polymorph yields much higher serum levels when the same dose is administered.

For drugs that are freely soluble in water the bioavailability is not likely to be limited by the dissolution, so it would be surprising for polymorphism to influence bioavailability in this way. However, for drugs with low aqueous solubility the polymorphic form must be well controlled to ensure that the bioavailability is the same each time the product is made, and throughout the shelf-life of the product. It would be risky to deliberately make a product using



**Fig. 9.3** Comparison of mean blood serum levels after the administration of chloramphenicol palmitate suspensions using varying ratios of the stable ( $\alpha$ ) and the metastable ( $\beta$ ) polymorphs. M, 100%  $\alpha$  polymorph; N, 25:75  $\beta$ : $\alpha$ ; O, 50:50  $\beta$ : $\alpha$ ; P, 75:25  $\beta$ : $\alpha$ ; L, 100%  $\beta$  polymorph. (Reproduced from Aguiar et al 1976, with permission.)

anything other than the stable form of a drug, as other polymorphic forms could convert to the stable form during the shelf-life of the product, which could result in a reduction in bioavailability and hence the therapeutic effect of the product.

In conclusion, the stable polymorphic form will have the slowest dissolution rate, and so there may be occasions when it would be desirable to speed the dissolution by using a metastable form. However, the risk associated with using the metastable form is that it will convert back to the stable form during the product's life, and give a consequent change in properties. As polymorphism can have such serious consequences for the bioavailability of drugs with low aqueous solubility, it is essential that manufacturers check for the existence of polymorphism and ensure that they use the same appropriate polymorphic form every time they make a product.

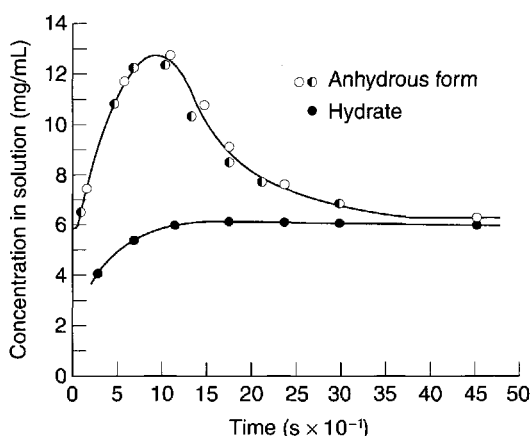
As mentioned above, many properties other than rate of solution can change when a material is in a different polymorphic form. For example, paracetamol is a high-dose drug with poor compression properties, which can make it difficult to form into tablets. Consequently, researchers have tried to use different polymorphic forms of paracetamol to find one that is more compressible.

### HYDRATES AND SOLVATES

It is possible for materials to crystallize and in so doing to trap molecules of the solvent within the lattice. If the solvent used is water, the material will be described as a hydrate. This entrapment is often in an exact molar ratio with the crystallizing material: for example, a monohydrate will have one molecule of water for each molecule of the crystallizing material. It is possible to have many different levels of hydrate: for example, some drugs can exist as a monohydrate, a dihydrate and a trihydrate (respectively one, two and three molecules of water to each molecule of drug). Morris (1999) notes that about 11% (over 16000 compounds) of all structures recorded on the Cambridge Structural Database exist as hydrates. Of the classes of hydrate materials that were similar to drugs, about 50% were monohydrates (one water molecule for each one of host), over 20% were dihydrates (two water molecules to one of host), 8% were trihydrates (three water molecules to one host) and 8% were hemihydrates (one water molecule to two of host); other hydrate levels (up to 10 water to one host) became progressively less common.

If solvents other than water are present in a crystal lattice the material is called a solvate. For example, if ethanol is present it would be an ethanolate. In general it is undesirable to use solvates for pharmaceuticals as the presence of retained organic vapours would be regarded as an unnecessary impurity in the product. If the organic vapour were toxic in any way it would obviously be inappropriate for pharmaceuticals. For this reason discussion will be limited to hydrates.

Hydrates often have very different properties from the anhydrous form, in the same way as two different polymorphs have different properties from each other. For this reason the difference between hydrates and anhydrous forms is described as pseudopolymorphism. With polymorphism the stable form has the highest melting point and the slowest dissolution rate (see above); however, with hydrates it is possible for the hydrate form to have either a faster or a slower dissolution rate than the anhydrous form. The most usual situation is for the anhydrous form to have a faster dissolution rate than the hydrate; an example of this is shown in Figure 9.4 for theophylline. In this situation, water could hydrogen bond between two drug molecules and tie the lattice together; this would give a much stronger, more stable lattice and hence a slower dissolution rate. It can be seen from Figure 9.4 that the anhydrous theophylline rises to a high concentration in solution and then falls again until the amount dissolved is the same as that recorded for the hydrate. The reason for this is that the hydrate has reached



**Fig. 9.4** The dissolution of theophylline monohydrate rising to an equilibrium solubility, compared with that for theophylline anhydrous which forms a supersaturated solution with a peak over twice that of the dissolving hydrate, before crystallizing to form the true equilibrium solubility. (Reproduced from Sheffer and Higuchi 1963, with permission.)

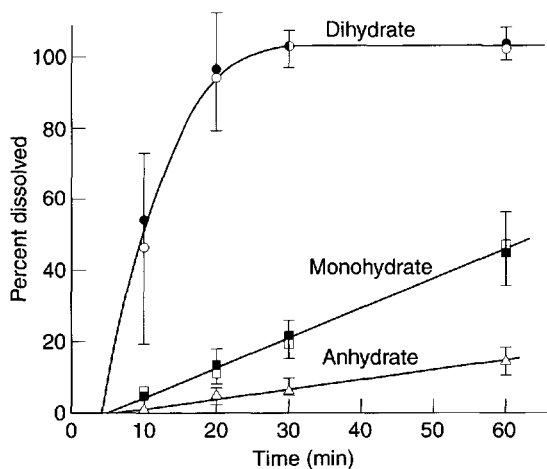
true equilibrium solubility, whereas the anhydrous form had initially formed a supersaturated solution (as has been described for metastable polymorphic forms above).

Although anhydrous forms are usually more rapidly soluble than the hydrate, there are examples of the opposite being true. In such circumstances one could think of water as a wedge pushing two molecules apart and preventing the optimum interaction between the molecules in the lattice. Here water would be weakening the lattice and would result in a more rapid dissolution rate. An example of the hydrate form speeding up dissolution is shown in Figure 9.5 for erythromycin.

## THE AMORPHOUS STATE

When a material is in the solid state but the molecules are not packed in a repeating long-range ordered fashion, it is said to be amorphous. Amorphous solids have very different properties from the crystal form of the same material. For example, crystals have a melting point (the break-up of the crystal lattice), whereas the amorphous form does not (as it does not have a crystal lattice to break).

Polymeric materials (or other large molecular weight species) have molecules that are so large and flexible that it is not possible for them to align perfectly to form crystals. For these materials it will be usual to have ordered regions within the structure



**Fig. 9.5** The dissolution behaviour for erythromycin as anhydrate, monohydrate and dihydrate, showing a progressively faster dissolution rate as the level of hydrate is increased. (Reproduced from Allen et al 1978, with permission.)

surrounded by disorder, so they are described as semicrystalline. For materials such as these it will not be possible to produce a completely crystalline sample; however, the degree of crystallinity can vary depending upon processing conditions. This can affect the properties of the material and hence how they function in pharmaceutical products.

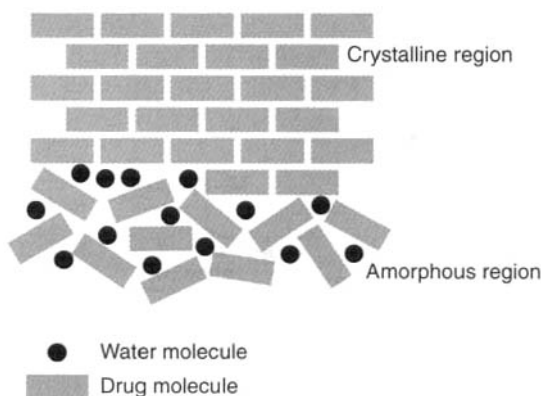
For low molecular weight materials the amorphous form may be produced if the solidification process was too fast for the molecules to have a chance to align in the correct way to form a crystal (this could happen when a solution is spray-dried). Alternatively, a crystal may be formed but then broken, for example if the crystal were exposed to energy, such as milling. A simple analogy that can be used here is that a crystal is like a brick wall, which has ordered long-range packing. If the wall is hit hard, perhaps during demolition, the bricks will separate (Figure 9.6). Unlike the brick wall, however, a disrupted crystal will be unstable and will revert back to the crystal form. This conversion may be rapid or very slow and, as with polymorphism, its pharmaceutical significance will depend on how long the partially amorphous form survives.

Amorphous forms have a characteristic temperature at which there is a major change in properties. This is called the glass transition temperature ( $T_g$ ). If the sample is stored below the  $T_g$  the amorphous form will be brittle and is described as the glassy state. If the sample is above its  $T_g$  it becomes rubbery. The  $T_g$ , although not well understood, is a point where the molecules in the glass exhibit a major change in mobility. The lack of mobility when the sample is glassy allows the amorphous form to exist for longer, whereas when  $T_g$  is below the

storage temperature the increased molecular mobility allows rapid conversion to the crystalline form.

The glass transition temperature of an amorphous material can be lowered by adding a small molecule, called a plasticizer, that fits between the glassy molecules, giving them greater mobility. Water is a good plasticizer for many materials, and so the glass transition temperature will usually reduce in the presence of water vapour. Most amorphous materials are able to absorb large quantities of water vapour. Absorption is a process whereby one molecule passes into the bulk of another material and should not be confused with adsorption, which is when something concentrates at the surface of another material. Figure 9.6 shows the way in which water can access amorphous regions. Figure 9.7 shows the amount of water that is adsorbed to a crystalline material (Figure 9.7(a)), compared to that absorbed into an amorphous form of the same material (Figure 9.7(b)). It can be seen that the amount absorbed is many times greater than that adsorbed. This large difference in water content at any selected relative humidity is important in many materials. For example, it is possible that certain drugs can degrade by hydrolysis when amorphous, but remain stable when crystalline. The extent of hydrolysis of an antibiotic which had been processed to yield different levels of crystalline:amorphous forms is shown in Table 9.1; the extent of degradation is greater when the amorphous content is increased.

In Figure 9.7 it can be seen that the amorphous form absorbs a very large amount of water until 50% RH, after which there is a weight loss, the reason for which is that the sample has crystallized. Crystallization occurs because the absorbed water has plasticized the sample to such an extent that the  $T_g$  has dropped below room temperature and allowed sufficient molecular mobility that the molecules are able to align and crystallize. The water is lost during this process, as absorption can only occur in the amorphous form and so cannot endure

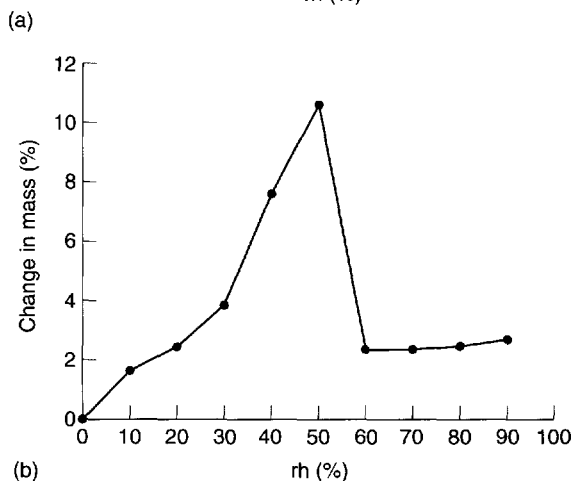
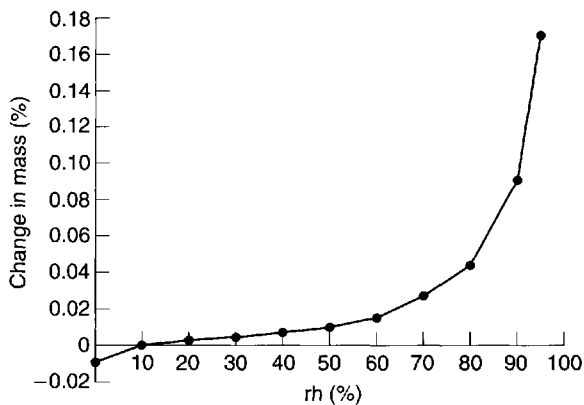


**Fig. 9.6** The disruption of a crystal (represented as a brick wall), giving the possibility for water vapour absorption in the amorphous region

**Table 9.1** The chemical stability of cephalothin sodium related to the amorphous content of the sample. Data derived from Pikal et al 1978

Sample	% amorphous	% stable drug after storage at 31%RH 50°C
Crystalline	0	100
Freeze dried	12	100
Freeze dried	46	85
Spray dried	53	44





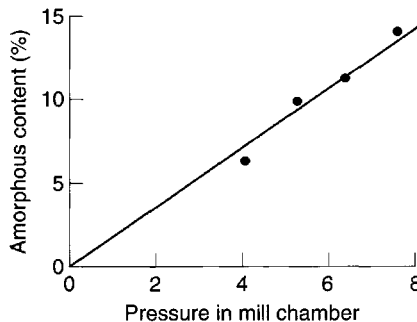
**Fig. 9.7** (a) A water sorption isotherm for crystalline lactose monohydrate. The quantity of water adsorbed to the crystal surface is small. (b) Water sorption isotherm for amorphous lactose, showing a rise to about 11% water content due to absorption, followed by water loss as the sample crystallizes and the absorbed water is expelled.

into the crystalline state. However, some water is retained in this example (Fig. 9.7(a) and (b)), because lactose is able to form a monohydrate. The amount of water required to form a monohydrate with lactose is 5% w/w (calculated from the molecular weight of lactose and water), which is much less than the 11% that was present in the amorphous form (Figure 9.7(b)).

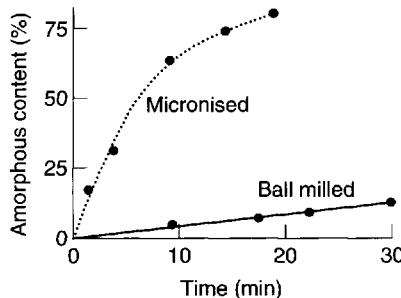
In Figure 9.8 the amorphous content of lactose is seen to increase in proportion to the length of time it was left in an air-jet mill (micronizer). In Figure 9.9 it can be seen that a drug substance became partially amorphous when treated in a simple ball mill, and extensively amorphous when micronized. Although the example in Figure 9.9 is an extreme behaviour it is not unusual for highly processed materials to become partially amorphous. Although milling does

not necessarily make all materials partially amorphous, the chance of seeing disruption to the crystalline lattice will increase with the amount of energy used in the milling.

The fact that processing can make crystalline materials partially amorphous means that it is possible for very complex materials to form that contain different metastable states. For example, in Figure 9.3 the plasma levels of two polymorphs of chloramphenicol palmitate were shown, however if the  $\beta$ -polymorph were milled it is possible that it might also become partially amorphous, which could make the plasma level even higher than when the crystalline form were used. However, milling the  $\beta$ -polymorph could also provide the necessary energy to convert it to the stable  $\alpha$ -polymorph, which would reduce the effective plasma level. Equally, milling could disrupt the  $\alpha$ -polymorph, giving a partially amorphous form that might have a higher bioavailability than the crystal. In other words, the effect of processing on the physical form can be very complicated, and often unpredictable. It is possible to produce a physical form that is partially amorphous and partially crystalline. The crystalline component could then be



**Fig. 9.8** The amorphous content induced in crystalline lactose as a consequence of milling in an air-jet mill at different air pressures. (Redrawn from Briggner et al 1994, with permission.)



**Fig. 9.9** The amorphous content of a model drug substance following milling in a ball mill and a micronizer. (Redrawn from Ahmed et al 1996, with permission.)

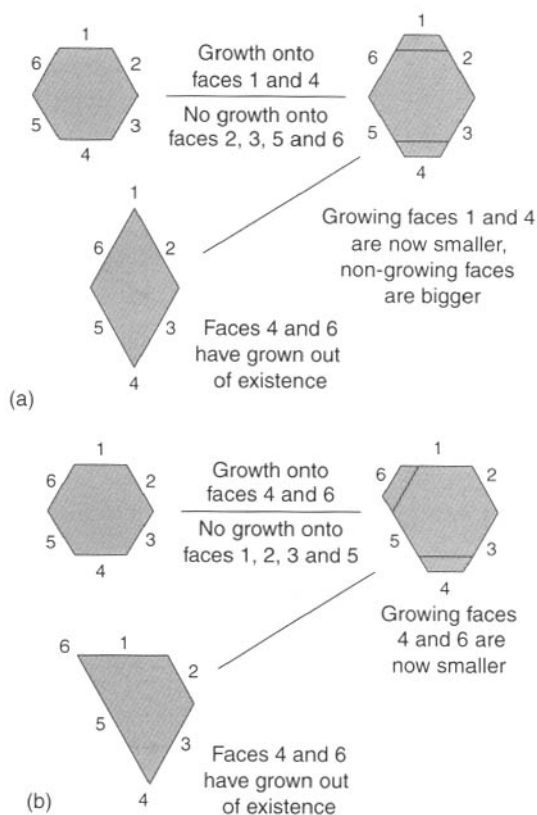
stable or metastable. Inevitably, with time (for low molecular weight species) the sample will revert to contain only the stable crystalline form, with no amorphous content and none of the metastable polymorph(s), but as this does not necessarily happen instantly the physical form and its complexity are of great importance.

## CRYSTAL HABIT

All of the above discussion relates to the internal packing of molecules. It has been shown that they may have no long-range order (amorphous), or have different repeating packing arrangements (polymorphic crystals), or have solvent included (solvates and hydrates). Each of these changes in internal packing of a solid will give rise to changes in properties. However, it is also possible to change the external shape of a crystal. The external shape is called the crystal habit and this is a consequence of the rate at which different faces grow. Changes in internal packing usually (but not always) give an easily distinguishable change in habit. However, for the same crystal packing it is possible to change the external appearance by changing the crystallization conditions.

With any crystalline material, the largest face is always the slowest growing. The reason for this is shown in Figure 9.10, where it can be seen that if drug is deposited on two faces of the hexagonal crystal habit, then the first consequence is that the face where drug is deposited actually becomes a smaller part of the crystal, whereas the other faces become larger. Eventually, the fastest growing faces will no longer exist (Figure 9.10). The growth on different faces will depend on the relative affinities of the solute for the solvent and the growing faces of the crystal. Every molecule is made up of different functional groups, some being relatively polar (such as carboxylic acid groups) whereas others are non-polar (such as a methyl group). Depending on the packing geometry of the molecules into the lattice, some crystal faces may have more exposed polar groups and others may be relatively non-polar. If the crystal were growing from an aqueous solution, drug would deposit on the faces that make the crystal more polar (i.e. the non-polar faces would grow, making the more polar faces dominate). If, however, the same crystal form were growing from a non-polar solvent, then the opposite would be true.

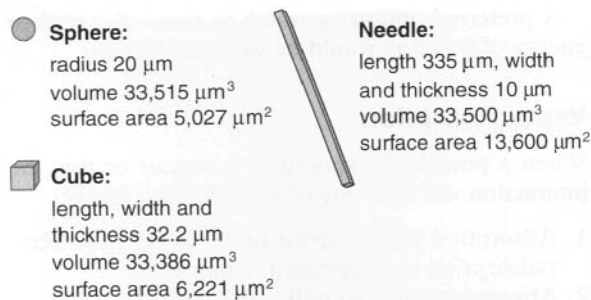
Obviously the external shape can alter the properties of drugs and excipients. For example, the disso-



**Fig. 9.10** (a) Demonstration of how growth on to faces 1 and 4 of a hexagonal crystal form result in the formation of a diamond. (b) Demonstration of how growth on to faces 4 and 6 of a hexagonal crystal result in the formation of a trapezium.

lution rate of a drug can change if the surface area to volume ratio is altered. An extreme difference would be between a long needle and a sphere (Figure 9.11). A sphere of 20  $\mu\text{m}$  radius has approximately the same volume (mass) as a needle of  $335 \times 10 \times 10 \mu\text{m}$ , but the surface area of the needle is 2.7 times greater than that of the sphere. As dissolution rate is directly proportional to surface area, the needle would dissolve much faster than the sphere. Crystals do not grow to make spheres, although through milling they can develop rounded geometries; the closest to a sphere would be a cube, which would still have under half the surface area of the needle shown in Figure 9.11.

As well as changes in dissolution rate, different crystal habits can cause changes in powder flow (which is important as, for example, the die of a tableting machine is filled by volume and requires good powder flow to guarantee content uniformity of the product) and sedimentation and caking of suspensions.



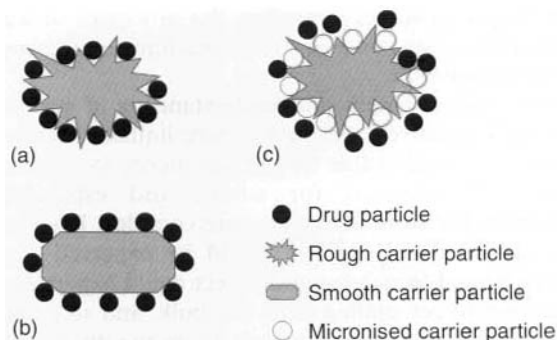
**Fig. 9.11** The relative surface areas of a sphere, a cube and a needle that each have similar volumes of material.

It is technically possible to engineer changes in crystal habit by deliberately manipulating the rate of growth of different faces of the crystal. This is done by intentionally adding a small amount of impurity to the solution. The impurity must interact preferentially with one face of the growing crystal, and in so doing it will stop growth on that face, causing the remaining face(s) to grow more rapidly. The impurity would either be a very similar molecule to that of the crystallizing material, so that part of the molecule is included in the lattice but the remainder blocks further layers from attaching, or it may be a surfactant that adsorbs to one growing face.

## SURFACE NATURE OF PARTICLES

### Dry powder inhalers

Dry powder inhalers (see Chapter 31) often have a micronized drug, which must be small enough to be inhaled, mixed with a larger carrier particle which is often lactose. The carrier particle is there to make the powder suitable for handling and dosing, as micronized particles have poor flow properties. The shape and surface properties of the drug and/or carrier particles can be critical in controlling the dose of drug that is delivered. It may be necessary to adjust the surface roughness of carrier particles. In Figure 9.12(a) there is a cartoon of a rough carrier particle: this would hold the micronized drug too strongly, essentially trapped within the rough regions of the carrier, and so the inhaled dose would be very low. In Figure 9.12(b) a smooth particle of the same carrier is seen: here the drug will be easily displaced from the carrier during inhalation, but it may not stay mixed with the carrier during filling of the inhaler and dosing. In Figure 9.12(c) a rough carrier particle has been mixed first with micronized carrier and then with micronized drug. Using this approach



**Fig. 9.12** A hypothesis that surface roughness may relate to dry release from carrier particles in dry powder inhalers. (a) Micronized drug trapped in the rough regions of the carrier particle, giving low inhaled dose. (b) Micronized drug can be readily removed from a smooth carrier particle. (c) Micronized drug may be removed readily (hence a high inhaled dose) if the carrier is first treated with micronized carrier particles in order to fill the rough voids.

the drug is free to detach, as the micronized carrier is trapped in all the crevices on the carrier surface. The hypothesis relating to the use of fine carrier particles to enhance the delivery of micronized drug from large carrier particles is not proved beyond doubt. It remains possible that interactions between the fine carrier and fine drug may be the reason for the enhanced delivery.

For products such as these it is becoming increasingly important first to measure the surface nature of samples and then to control the form in order to achieve the desired delivery of drug. The surface shape of the carrier is an important consideration for the design of this type of product. A further concern is the surface energy, as this can influence the way in which the drug and the carrier are attached to each other.

### Surface energy

Molecules at the surface of a material have a net inward force exerted on them from the molecules in the bulk: this is the basis of surface energy. Surface energy is important, as every interaction (except the mixing of two gases) starts with an initial contact between two surfaces. If this surface interaction is favoured then the process will probably proceed, whereas if it is not favoured then it will be limited. A good example of the role of surface energy is the wetting of a powder by a liquid, where the powder cannot dissolve until the liquid makes good contact with it. A practical example is instant coffee, where some brands are hard to wet and dissolve whereas others dissolve easily. Changes in the

wetting of powders can affect the processes of wet granulation, suspension formation, film coating and drug dissolution.

The measurement and understanding of surface energy is relatively simple for pure liquids, because there is a single value of surface energy (= surface tension). However, for solids, and especially powders, the situation is far more complex. Even on the same crystal form it would be expected that every crystal face, edge and defect could experience different forces pulling from the bulk, and so could have a different surface energy. From the discussion above, it would be reasonable to assume that different physical forms of the same drug could have quite different surface energies. Thus for the same drug it is possible that changes in habit and/or polymorphic form and/or the presence of a solvate or hydrate would change the surface energy. For amorphous forms the molecules at the surface have greater freedom to move and reorientate than do molecules in crystal surfaces, and so the amorphous form could have changes in surface energy with time (and with physical state in relation to  $T_g$ ).

The conventional way of determining the surface energy of a solid is to place a drop of liquid on to the solid surface and measure the contact angle. This is defined as the angle between the solid surface and the tangent drawn at the three-phase interface, measured through the liquid. Examples of contact angles are shown in Chapter 5. Perfect wetting of a solid by a liquid will result in a contact angle of  $0^\circ$ . Contact angles are the result of a balance of three interfacial forces  $\gamma_{LV}$  being the liquid surface tension,  $\gamma_{LS}$  between the liquid and the solid, and  $\gamma_{SV}$  between the solid and the vapour. The relative magnitude of these forces will determine whether the drop of liquid spreads on the solid or not, and consequently, by use of the contact angle ( $\theta$ ) it is possible to calculate the solid surface energy if the surface tension of the liquid is known:

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos \theta$$

This is known as Young's equation.

For smooth solid surfaces contact angles are an ideal way of assessing surface energy; however, powders present a problem as it is not possible to place a drop of liquid on their surface. Consequently, a compromise will always be required when measuring a contact angle for powdered systems. An example of such a compromise would be to make a compact of the powder so as to produce a smooth flat surface; the disadvantage of this is that the process of compaction may well change the surface energy of the powder.

A preferred option by which to assess the surface energy of powders would be vapour sorption.

## Vapour sorption

When a powder is exposed to a vapour or gas, the interaction will take one of the following forms:

1. Adsorption of the vapour to the powder surface (adsorption is described in Chapter 5)
2. Absorption into the bulk
3. Deliquescence
4. Hydrate/solvate formation.

Absorption into the bulk can occur if the sample is amorphous, whereas the interaction will be limited to adsorption if the powder is crystalline. The extent and energetics of interaction between vapours and powder surfaces allows the surface energy to be calculated. The other processes listed are deliquescence, which is where the powder dissolves in the vapour, and hydrate formation, which is discussed above.

It is therefore possible to use adsorption and/or absorption behaviour to determine powder surface energy. There are three basic approaches to this: gravimetric, calorimetric and chromatographic. Each of these techniques has found application in studies of batch-to-batch variability of materials. An example of a critical case could be that a certain drug shows extensive variability in respirable dose from a dry powder inhaler. Assuming that the size distribution was acceptable in all cases, it would be necessary to understand why some batches yielded unacceptable doses. These vapour sorption techniques could then be used to assess the surface energy and define values that would be acceptable in order to obtain good drug dosing, and equally to define batches of drug that will give unacceptable products.

Gravimetric methods use sensitive microbalances as a means of determining the extent of vapour sorption to a powder surface. The calorimetric approaches measure the enthalpy change associated with vapour-powder interaction, which gives clear information on the nature of the powder surface. Using the principles of gas chromatography it is possible to pack the powder for which the surface energy is required into a column, and then to inject different vapours into the column with a carrier gas. Obviously the time taken for the vapour to come out of the other end of the column is a measure of how favourable was the interaction between the powder and the vapour. It is then possible to calculate the surface energy of the powder from the retention time

of different vapours in the column. Gas chromatography is normally used with a column of known properties with unknown vapours; however, in this experiment the unknown is the solid column and the materials with known properties are the injected vapours. For this reason this technique is called inverse phase gas chromatography.

## REFERENCES

- Aguiar, A.J., Krc, J.Jr., Kinkel, A.W. and Sanyn, J.C. (1967) *J. Pharm. Sci.*, **56**, 847–853.
- Ahmed, H., Buckton, G. and Rawlins, D.A. (1996) *Int. J. Pharm.*, **130**, 195–201.
- Allen, P.V., Rahn, P.D., Sarapu, A.C. and Vanderwielen, A.J. (1978) *J. Pharm. Sci.*, **67**, 1087–1093.
- Briggner, L.-E., Buckton, G., Bystrom, K. and Darcy, P. (1994) *Int. J. Pharm.*, **105**, 125–135.

- Ebian, A.R., Moustafa, M.A., Khalil, S.A. and Motawi, M.M. (1973) *J. Pharm. Pharmacol.*, **25**, 13–20.
- Morris, K.R. (1999) Structural aspects of hydrates and solvates. In Brittain, H.G. (ed.) *Polymorphism in Pharmaceutical Solids*. Marcel Dekker, New York, pp. 125–181.
- Pikal, M.J., Lukes, A.L., Lang, J.E. and Gaines, K. (1978) *J. Pharm. Sci.*, **67**, 767–773.
- Shefter, E. and Higuchi, T. (1963) *J. Pharm. Sci.*, **52**, 781–791.

## BIBLIOGRAPHY

- Brittain, H.G. (ed.) (1999) *Polymorphism in Pharmaceutical Solids*. Marcel Dekker, New York.
- Buckton, G. (1995) *Interfacial Phenomena in Drug Delivery and Targeting*. Harwood Academic Press, Amsterdam.
- Florence, A.T. and Attwood, D. (1998) *Physicochemical Principles of Pharmacy*, 3rd edn. Macmillan, London.
- Mersmann, A. (ed.) (1994) *Crystallization Technology Handbook*. Marcel Dekker, New York.

# 10

## Particle-size analysis

John Staniforth

### CHAPTER CONTENTS

<b>Particle size and the lifetime of a drug</b>	<b>152</b>
<b>Particle size</b>	<b>153</b>
Dimensions	153
Equivalent diameters	153
Particle size distribution	154
Statistics to summarize data	155
Influence of particle shape	156
<b>Particle size analysis methods</b>	<b>156</b>
Sieve methods	156
Equivalent diameter	156
Range of analysis	157
Sample preparation and analysis conditions	157
Principle of measurement	157
Alternative techniques	157
Automatic methods	157
Microscope methods	157
Equivalent diameters	157
Range of analysis	157
Sample preparation and analysis conditions	157
Principle of measurement	158
Alternative techniques	158
Automatic methods	158
Electrical stream sensing zone method (Coulter counter)	159
Equivalent diameter	159
Range of analysis	159
Sample preparation and analysis conditions	159
Principle of measurement	159
Alternative techniques	160
Laser light scattering methods	160
Equivalent diameters	160
Range of analysis	160
Sample preparation and analysis conditions	160
Principles of measurement	160
Fraunhofer diffraction	161
Photo-correlation spectroscopy	161
Alternative techniques	162
Automatic methods	162
Sedimentation methods	162
Equivalent diameters	162
Range of analysis	162
Sample preparation and analysis conditions	162
Principles of measurement	162
Alternative techniques	163
Automatic methods	165
<b>Selection of a particle size analysis method</b>	<b>165</b>
<b>Bibliography</b>	<b>165</b>

### PARTICLE SIZE AND THE LIFETIME OF A DRUG

The dimensions of particulate solids are important in achieving optimum production of efficacious medicines. Figure 10.1 shows an outline of the lifetime of a drug; during stages 1 and 2, when a drug is synthesized and formulated, the particle size of drug and other powders is determined and influences the subsequent physical performance of the medicine and the pharmacological performance of the drug.

Particle size influences the production of formulated medicines (stage 3, Fig. 10.1) as solid dosage forms. Both tablets and capsules are produced using equipment that controls the mass of drug and other particles by volumetric filling. Therefore, any interference with the uniformity of fill volumes may alter the mass of drug incorporated into the tablet or capsule and hence reduce the content uniformity of the medicine. Powders with different particle sizes have different flow and packing properties, which alter the volumes of powder during each encapsulation or tablet compression event. In order to avoid such problems the particle sizes of drug and other powder may be defined during formulation so that problems during production are avoided.

Following administration of the medicine (stage 4, Fig. 10.1), the dosage form should release the drug into solution at the optimum rate. This depends on several factors, one of which will be the particle size of drug as predicted from the following theoretical considerations. Noyes and Whitney first showed that the rate of solution of a solid was related to the law of diffusion, and proposed that the following equations could be used to predict the rate of solution of a wide variety of solutes.

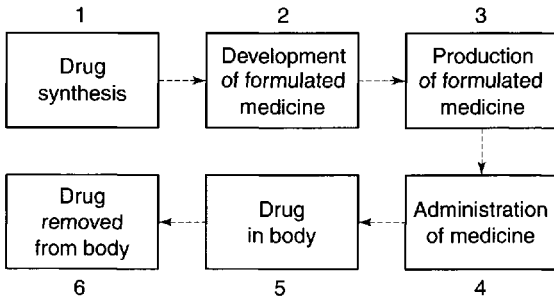


Fig. 10.1 Schematic representation of the lifetime of a drug.

$$\frac{dx}{dt} = c(C_s - C) \quad (10.1)$$

$$c = \frac{1}{t} \log_e \frac{C_s}{C_s - C} \quad (10.2)$$

where  $C$  is the concentration of solute in solution at time,  $t$ ,  $C_s$  is the solubility of solute and  $c$  is a constant which can be determined from a knowledge of solute solubility. The constant  $c$  was more precisely defined by Danckwerts, who showed that the mean rate of solution per unit area under turbulent conditions was given by:

$$\frac{dx}{dt} = D\sigma(C_s - C) \quad (10.3)$$

where  $D$  is a diffusion coefficient and  $\sigma$  is the rate of production of fresh surface.  $D\sigma$  can be interpreted as a liquid film mass transfer coefficient, which will tend to vary inversely with particle size as a reduction in size generally increases the specific surface area of particles. Thus particles having small dimensions will tend to increase the rate of solution. For example, the drug griseofulvin has a low solubility by oral administration but is rapidly distributed following absorption; the solubility of griseofulvin can be greatly enhanced by particle size reduction, so that blood levels equivalent to, or better than, those obtained with crystalline griseofulvin can be produced using a microcrystalline form of the drug. A reduction of particle size to improve rate of solution and hence bioavailability is not always beneficial. For example, small particle-size nitrofurantoin has an increased rate of solution which produces toxic side-effects because of its more rapid absorption.

It is clear from the lifetime of a drug outlined above that a knowledge and control of particle size is of importance both for the production of medicines containing particulate solids and in the efficacy of the medicine following administration.

## PARTICLE SIZE

### Dimensions

When determining the size of a relatively large solid it would be unusual to measure fewer than three dimensions, but if the same solid was broken up and the fragments milled, the resulting fine particles would be irregular with different numbers of faces and it would be difficult or impractical to determine more than a single dimension. For this reason a solid particle is often considered to approximate to a sphere which can then be characterized by determining its diameter. Because measurement is then based on a hypothetical sphere, which represents only an approximation to the true shape of the particle, the dimension is referred to as the *equivalent diameter* of the particle.

### Equivalent diameters

It is possible to generate more than one sphere which is equivalent to a given irregular particle shape. Figure 10.2 shows the two-dimensional projection of a particle with two different diameters constructed about it.

The projected area diameter is based on a circle of equivalent area to that of the projected image of a solid particle; the projected perimeter diameter is based on a circle having the same perimeter as the particle. Unless the particles are unsymmetrical in three dimensions then these two diameters will be independent of particle orientation. This is not true for Feret's and Martin's diameters (Fig. 10.3), the values of which are dependent on both the orientation and the shape of the particles. These are statistical diameters which are averaged over many different orientations to produce a mean value for each particle diameter. Feret's diameter is determined from the mean distance between two parallel

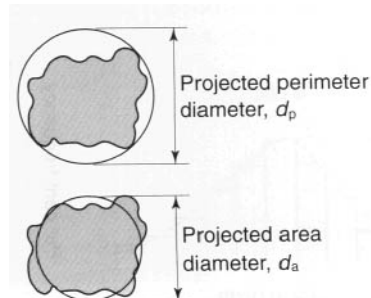
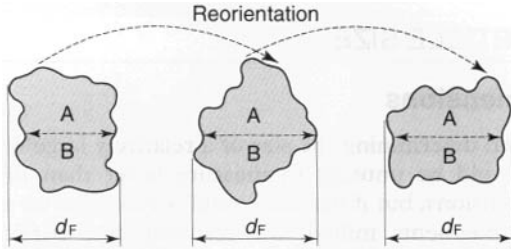


Fig. 10.2 Different equivalent diameters constructed around the same particle.



**Fig. 10.3** Influence of particle orientation on statistical diameters. The change in Feret's diameter is shown by the distances,  $d_F$ ; Martin's diameter  $d_M$  corresponds to the dotted lines in the midpart of each image.

tangents to the projected particle perimeter. Martin's diameter is the mean chord length of the projected particle perimeter, which can be considered as the boundary separating equal particle areas (A and B in Fig. 10.3).

It is also possible to determine particle size based on spheres of, for example, equivalent volume, sedimentation volume, mass or sieve mass of a given particle. In general, the method used to determine particle size dictates the type of equivalent diameter that is measured, although interconversion may be carried out and this is sometimes done automatically as part of the size analysis.

## Particle size distribution

A particle population which consists of spheres or equivalent spheres with uniform dimensions is monosized and its characteristics can be described by a single diameter or equivalent diameter.

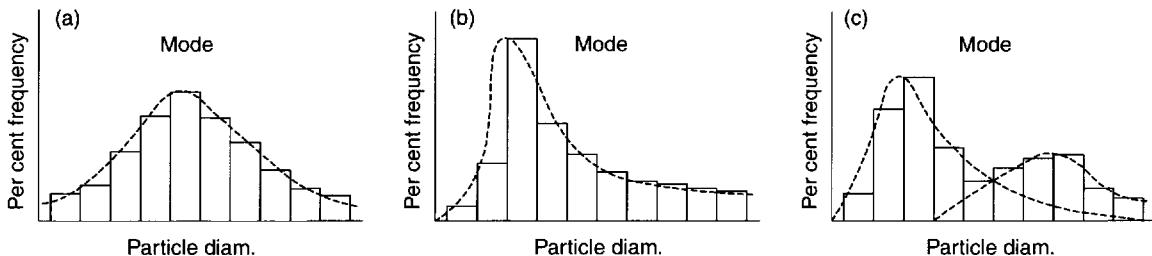
However, it is unusual for particles to be completely monosized: most powders contain particles with a large number of different equivalent diameters. In order to be able to define a size distribution or compare the characteristics of two or more powders consisting of particles with many different diameters, the size distribution can be broken down

into different size ranges, which can be presented in the form of a histogram plotted from data such as that in Table 10.1. Such a histogram presents an interpretation of the particle size distribution and enables the percentage of particles having a given equivalent diameter to be determined. A histogram representation allows different particle size distributions to be compared; for example, the size distribution shown in Fig. 10.4(b) contains a larger proportion of fine particles than the powder in Fig. 10.4(a) in which the particles are *normally distributed*. The peak frequency value, known as the *mode*, separates the *normal curve* into two identical halves, because the size distribution is fully symmetrical.

Not all particle populations are characterized by symmetrical normal size distributions and the frequency distributions of such populations exhibit skewness (Fig. 10.4(b)). A frequency curve with an elongated tail towards higher size ranges is *positively skewed* (Fig. 10.4(b)); the reverse case exhibits *negative skewness*. These skewed distributions can sometimes be normalized by replotting the equivalent particle diameters using a logarithmic scale, and are thus usually referred to as log normal distributions.

In some size distributions more than one mode occurs: Figure 10.4(c) shows bimodal frequency distribution for a powder which has been subjected to milling. Some of the coarser particles from the unmilled population remain unbroken and produce a mode towards the highest particle size, whereas the fractured particles have a new mode which appears lower down the size range.

An alternative to the histogram representation of a particle size distribution is obtained by sequentially adding the percent frequency values as shown in Table 10.2 to produce a cumulative percent frequency distribution. If the addition sequence begins with the coarsest particles, the values obtained will be cumulative percent frequency undersize; the



**Fig. 10.4** Frequency distribution curves corresponding to (a) a normal distribution, (b) a positively skewed distribution and (c) a bimodal distribution.



reverse case produces a cumulative percent oversize. Figure 10.5 shows two cumulative percent frequency distributions. Once again it is possible to compare two or more particle populations using the cumulation distribution representation. For example, the size distribution in Fig. 10.5(a) shows that this powder has a larger range or spread of equivalent diameters than the powder represented in Figure 10.5(b). The particle diameter corresponds to the point that separates the cumulative frequency curve into two equal halves, above and below which 50% of the particles lie (point *a* in Fig. 10.5(a)). Just as the median divides a symmetrical cumulative size distribution curve into two equal halves, so the lower and upper quartile points at 25% and 75% divide the upper and lower ranges of a symmetrical curve into equal parts (points *b* and *c*, respectively, in Fig. 10.5(a)).

**Statistics to summarize data**

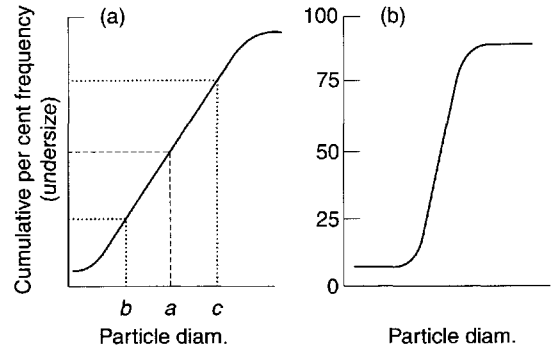
Although it is possible to describe particle size distributions qualitatively it is always more satisfactory to compare particle size data quantitatively. This is made possible by summarizing the distributions using statistical methods.

In order to quantify the degree of skewness of a particle population, the interquartile coefficient of skewness (IQCS) can be determined as follows:

$$IQCS = \frac{(c - a) - (a - b)}{(c - a) + (a - b)} \tag{10.4}$$

where *a* is the median diameter and *b* and *c* are the lower and upper quartile points (Fig. 10.5).

The IQCS can take any value between -1 and +1. If the IQCS is zero then the size distribution is practically symmetrical between the quartile points. To ensure unambiguity in interpreting values for IQCS a large number of size intervals are required.



**Fig. 10.5** Cumulative frequency distribution curves. Point *a* corresponds to the median diameter; *b* is the lower quartile point and *c* is the upper quartile point.

To quantify the degree of symmetry of a particle size distribution a property known as **kurtosis** can be determined. The symmetry of a distribution is based on a comparison of the height or thickness of the tails and the ‘sharpness’ of the peaks with those of a normal distribution. ‘Thick’-tailed ‘sharp’ peaked curves are described as **leptokurtic**, whereas ‘thin’-tailed ‘blunt’ peaked curves are **platykurtic** and the normal distribution is **mesokurtic**.

The coefficient of kurtosis, *k* (Eqn. 10.5), has a value of 0 for a normal curve, a negative value for curves showing platykurtosis and positive values for leptokurtic size distributions:

$$k = \frac{n \sum (x - \bar{x})^4}{(\sum (x - \bar{x})^2)^2} - 3 \tag{10.5}$$

where *x* is any particle diameter,  $\bar{x}$  is mean particle diameter and *n* is number of particles.

Again, a large number of data points are required to provide an accurate analysis.

The mean of the particle population referred to above in Eqn 10.5, together with the median (Fig. 10.5) and the mode (Fig. 10.4) are all measures

Table 10.1 Frequency distribution data		
Equivalent particle diameter (μm)	Number of particles in each diameter range (frequency)	Per cent particles in each diameter range (per cent frequency)
20	100	4.5
40	200	9.1
60	400	18.2
80	800	36.4
100	400	18.2
120	200	9.1
140	100	4.5

Table 10.2 Cumulative frequency distribution data			
Equivalent particle diameter (μm)	Per cent frequency (from Table 10.1)	Cumulative per cent frequency	
		Undersize	Oversize
20	4.5	4.5	100
40	9.1	13.6	95.5
60	18.2	31.8	86.4
80	36.4	68.2	68.2
100	18.2	86.4	31.8
120	9.1	95.5	13.6
140	4.5	100	4.5

of central tendency and provide a single value near the middle of the size distribution, which represents a central particle diameter. Whereas the mode and median diameters can be obtained for an incomplete particle size distribution, the mean diameter can only be determined when the size distribution is complete and the upper and lower size limits are known. It is also possible to define and determine the mean in several ways and, for log-normal distributions, a series of relationships known as Hatch-Choate equations link the different mean diameters of a size distribution (Table 10.3).

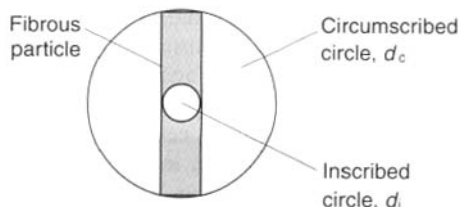
In a log-normal distribution the frequency,  $f$ , of the occurrence of any given particle of equivalent diameter  $d$  is given by:

$$f = \frac{\Sigma n}{2\pi \ln \sigma_g} \cdot \exp \left[ -\frac{(\ln d - \ln M)^2}{2 \ln^2 \sigma_g} \right] \quad (10.6)$$

where  $M$  is the geometric mean diameter and  $\sigma_g$  is the geometric standard deviation.

### Influence of particle shape

The techniques discussed above for representing particle size distribution are all based on the assumption that particles could be adequately represented by an equivalent circle or sphere. In some cases particles deviate markedly from circularity and sphericity, and the use of a single equivalent diameter measurement may be inappropriate. For example, a powder consisting of monosized fibrous particles would appear to have a wider size distribution according to statistical diameter measurements. However, the use of an equivalent diameter based on projected area would also be



**Fig. 10.6** A simple shape factor is shown which can be used to quantify circularity. The ratio of two different diameters ( $d_i/d_c$ ) is unity for a circle and falls for acicular particles.

misleading. Under such circumstances it may be desirable to return to the concept of characterizing a particle using more than one dimension. Thus, the breadth of the fibre could be obtained using a projected circle inscribed within the fibre ( $d_i$ ) and the fibre length could be measured using a projected circle circumscribed around the fibre  $d_c$  (Fig. 10.6).

The ratio of inscribed circle to circumscribed circle diameters can also be used as a simple shape factor to provide information about the circularity of a particle. The ratio  $d_i/d_c$  will be 1 for a circle and diminish as the particle becomes more acicular.

Such comparisons of equivalent diameters determined by different methods offer considerable scope for both particle size and particle shape analysis. For example, measurement of particle size to obtain a projected area diameter,  $a$ , and an equivalent volume diameter,  $v$ , provides information concerning the surface:volume ( $a/v$ ) ratio or bulkiness of a group of particles, which can also be useful in interpreting particle size data.

**Table 10.3 Hatch-Choate relationships**

$\ln d_n = \ln M + 0.5 \ln^2 \sigma_g$
$\ln d_s = \ln M + \ln^2 \sigma_g$
$\ln d_v = \ln M + 1.5 \ln^2 \sigma_g$
$\ln d_{sv} = \ln M + 2.5 \ln^2 \sigma_g k^1$
$\ln M = \ln d_g + 2.5 \ln^2 \sigma_g k^1$
$\ln d_n = \ln d_g - 2.5 \ln^2 \sigma_w$
$\ln d_s = \ln d_g - 2.0 \ln^2 \sigma_w$
$\ln d_v = \ln d_g - 1.5 \ln^2 \sigma_w$
$\ln d_{sv} = \ln d_g - 0.5 \ln^2 \sigma_w$

Key:  $M$ , geometric mean diameter by number (see Eqn 10.6);  $d_n$ , number mean diameter;  $d_s$ , surface mean diameter;  $d_v$ , volume diameter;  $d_{sv}$ , surface volume or surface weighted diameter;  $d_g$ , geometric mean diameter by weight

## PARTICLE SIZE ANALYSIS METHODS

In order to obtain equivalent diameters with which to interpret the particle size of a powder it is necessary to carry out a size analysis using one or more different methods. Particle-size analysis methods can be divided into different categories based on several different criteria: size range of analysis; wet or dry methods; manual or automatic methods; speed of analysis. A summary of the different methods is presented below based on the salient features of each.

### Sieve methods

#### Equivalent diameter

Sieve diameter,  $d_s$  – the particle dimension that passes through a square aperture (length =  $x$ ) as shown in Figure 10.7.

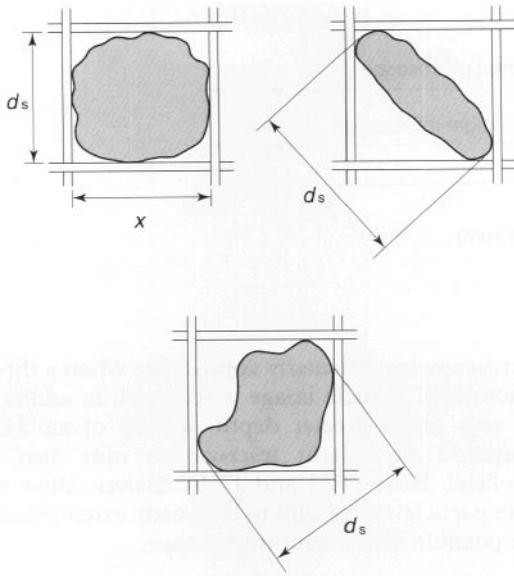


Fig. 10.7 Sieve diameter  $d_s$  for various shaped particles

### Range of analysis

The International Standards Organization (ISO) sets a lowest sieve diameter of  $45 \mu\text{m}$  and, as powders are usually defined as having a maximum diameter of  $1000 \mu\text{m}$ , this could be considered to be the upper limit. In practice sieves can be obtained for size analysis over a range from 5 to  $125\,000 \mu\text{m}$ . These ranges are indicated diagrammatically in Figure 10.8.

### Sample preparation and analysis conditions

Sieve analysis is usually carried out using dry powders, although for powders in liquid suspension or which agglomerate during dry sieving a process of wet sieving can be used.

### Principle of measurement

Sieve analysis utilizes a woven, punched or electroformed mesh, often in brass or stainless steel, with known aperture diameters which form a physical

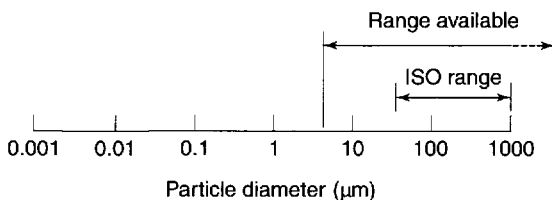


Fig. 10.8. Range of analysis for sieves

barrier to particles. Most sieve analyses utilize a series, stack or 'nest' of sieves, which has the smallest mesh above a collector tray followed by meshes that become progressively coarser towards the top of the series. A sieve stack usually comprises 6–8 sieves with an aperture progression based on a  $\sqrt{2}$  or  $2\sqrt{2}$  change in diameter between adjacent sieves. Powder is loaded on to the coarsest sieve of the assembled stack and the nest is subjected to mechanical vibration. After a suitable time the particles are considered to be retained on the sieve mesh with an aperture corresponding to the sieve diameter. Sieving times should not be arbitrary and it is recommended that sieving be continued until less than 0.2% of material passes a given sieve aperture in any 5-minute interval.

### Alternative techniques

Another form of sieve analysis, called air-jet sieving, uses individual sieves rather than a complete nest of sieves. Starting with the finest-aperture sieve and progressively removing the undersize particle fraction by sequentially increasing the apertures of each sieve, particles are encouraged to pass through each aperture under the influence of a partial vacuum applied below the sieve mesh. A reverse air jet circulates beneath the sieve mesh, blowing oversize particles away from the mesh to prevent blocking. Air-jet sieving is often more efficient and reproducible than using mechanically vibrated sieve analysis, although with finer particles agglomeration can become a problem.

### Automatic methods

Sieve analysis is still largely a non-automated process, although an automated wet sieving technique has been described.

### Microscope methods

#### Equivalent diameters

Projected area diameter,  $d_a$ ; projected perimeter diameter  $d_p$ ; Feret's diameter  $d_f$  and Martin's diameter  $d_M$  (see above).

### Range of analysis

This is shown diagrammatically in Figure 10.9.

### Sample preparation and analysis conditions

Specimens prepared for light microscopy must be adequately dispersed on a microscope slide to avoid

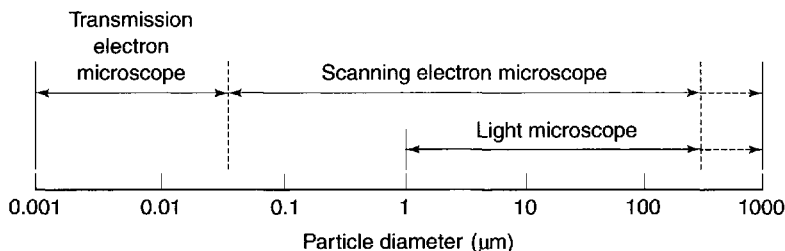


Fig. 10.9. Range of analysis for microscopy.

analysis of agglomerated particles. Specimens for scanning electron microscopy are prepared by fixing to aluminium stubs before sputter coating with a film of gold a few nm in thickness. Specimens for transmission electron microscopy are often set in resin, sectioned by microtome and supported on a metal grid before metallic coating.

### Principle of measurement

Size analysis by light microscopy is carried out on the two-dimensional images of particles which are generally assumed to be randomly oriented in three dimensions. In many cases this assumption is valid, although for dendrites, fibres or flakes it is very improbable that the particles will orient with their minimum dimensions in the plane of measurement. Under such conditions, size analysis is carried out accepting that they are viewed in their most stable orientation. This will lead to an overestimation of size, as the largest dimensions of the particle will be observed.

The two-dimensional images are analysed according to the desired equivalent diameter. Using a conventional light microscope, particle-size analysis can be carried out using a projection screen with screen distances related to particle dimensions by a previously derived calibration factor using a graticule. A graticule can also be used which has a series of opaque and transparent circles of different diameters, usually in a  $\sqrt{2}$  progression. Particles are compared with the two sets of circles and are sized according to the circle that corresponds most closely to the equivalent particle diameter being measured. The field of view is divided into segments to facilitate measurement of different numbers of particles.

### Alternative techniques

Alternative techniques to light microscopy include scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Scanning electron

microscopy is particularly appropriate when a three-dimensional particle image is required; in addition, the very much greater depth of field of an SEM compared to a light microscope may also be beneficial. Both SEM and TEM analysis allow the lower particle-sizing limit to be greatly extended over that possible with a light microscope.

### Automatic methods

Semiautomatic methods of microscope analysis use some form of precalibrated variable distance to split particles into different size ranges. One technique, called a particle comparator, utilizes a variable diameter light spot projected on to a photomicrograph or electron photomicrograph of a particle under analysis. The variable iris controlling the light spot diameter is linked electronically to a series of counter memories, each corresponding to a different size range (Fig. 10.10). Alteration of the iris diameter causes the particle count to be directed into the appropriate counter memory following activation of a switch by the operator.

A second technique uses a double-prism arrangement mounted in place of the light microscope eyepiece. The image from the prisms is usually displayed on a video monitor. The double-prism arrangement allows light to pass through to the monitor unaltered, where the usual single particle image is pro-

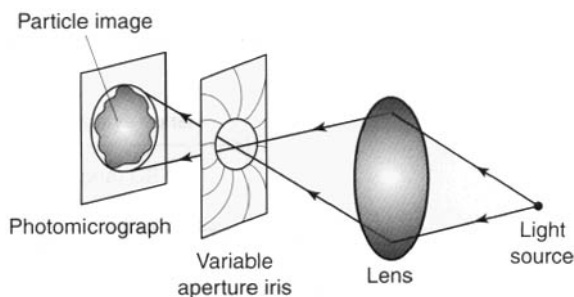


Fig. 10.10 Particle comparator.

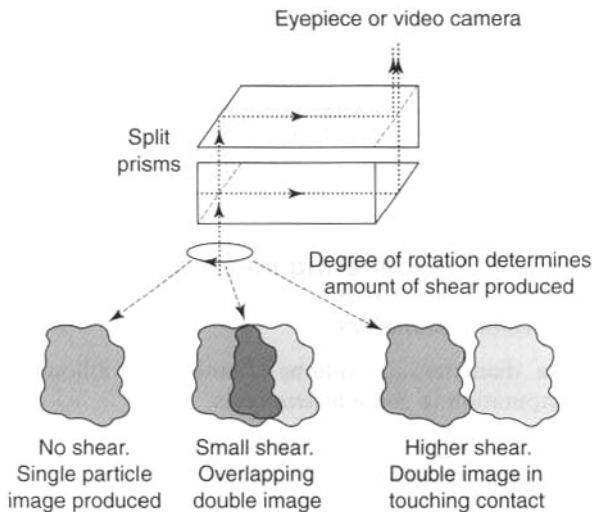


Fig. 10.11 Image-shearing eyepiece.

duced. When the prisms are sheared against one another a double image of each particle is produced and the separation of the split images corresponds to the degree of shear between the prisms (Fig. 10.11). Particle-size analysis can be carried out by shearing the prisms until the two images of a single particle make touching contact. The prism shearing mechanism is linked to a precalibrated micrometer scale from which the equivalent diameter can be read directly. Alternatively, a complete size distribution can be obtained more quickly by subjecting the prisms to a sequentially increased and decreased shear distance between two preset levels corresponding to a known size range. All particles whose images separate and overlap sequentially under a given shear range are considered to fall in this size range, and are counted by operating a switch which activates the appropriate counter memory. Particles whose images do not overlap in either shear sequence are undersize and particles whose images do not separate in either shear mode are oversize and will be counted in a higher size range.

Although semiautomatic size analysis methods remove some of the objectivity and fatigue associated with manual microscopic analysis, fully automatic size analysis has the advantage of being more objective, very much faster, and also enables a much wider variety of size and shape parameters to be processed.

Automatic microscopy is usually associated with microprocessor-controlled manipulation of an analogue signal derived from some form of video monitor used to image particles directly from a light microscope or from photomicrographs of particles.

Alternatively, the signal from an electron microscope can in some cases be processed directly without an intermediate video imaging system.

Automatic microscopy allows both image analysis and image processing to be carried out.

## Electrical stream sensing zone method (Coulter counter)

### Equivalent diameter

Volume diameter,  $d_v$ .

### Range of analysis

This is shown in Figure 10.12

### Sample preparation and analysis conditions

Powder samples are dispersed in an electrolyte to form a very dilute suspension, which is usually subjected to ultrasonic agitation for a period to break up any particle agglomerates. A dispersant may also be added to aid particle deagglomeration.

### Principle of measurement

The particle suspension is drawn through an aperture (Fig. 10.13) accurately drilled through a sapphire crystal set into the wall of a hollow glass tube. Electrodes situated on either side of the aperture and surrounded by an electrolyte solution, monitor the change in electrical signal that occurs when a particle

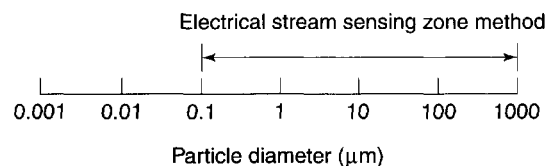


Fig. 10.12 Range of analysis for electrical stream sensing zone method.

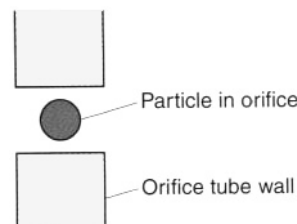


Fig. 10.13 Particle passing through the measuring aperture of an electrical stream sensing zone apparatus.

momentarily occupies the orifice and displaces its own volume of electrolyte. The volume of suspension drawn through the orifice is determined by the suction potential created by a mercury thread rebalancing in a convoluted U-tube (Fig. 10.14). The volume of electrolyte fluid which is displaced in the orifice by the presence of a particle causes a change in electrical resistance between the electrodes that is proportional to the volume of the particle. The change in resistance is converted into a voltage pulse which is amplified and processed electronically. Pulses falling within precalibrated limits or thresholds are used to split the particle size distribution into many different size ranges. In order to carry out size analysis over a wide diameter range it will be necessary to change the orifice diameter used, to prevent coarser particles blocking a small-diameter orifice. Conversely, finer particles in a large-diameter orifice will cause too small a relative change in volume to be accurately quantified.

### Alternative techniques

Since the Coulter principle was first described there have been some modifications to the basic method such as use of alternative orifice designs and hydrodynamic focusing, but in general the particle detection technique remains the same.

Another type of stream sensing analyser utilizes the attenuation of a light beam by particles drawn

through the sensing zone. Some instruments of this type use the change in reflectance, whereas others use the change in transmittance of light. It is also possible to use ultrasonic waves generated and monitored by a piezoelectric crystal at the base of a flowthrough tube containing particles in fluid suspension.

## Laser light scattering methods

### Equivalent diameters

Area diameter,  $d_a$ , volume diameter  $d_v$  following computation in some instruments.

### Range of analysis

This is shown in Figure 10.15.

### Sample preparation and analysis conditions

Depending on the type of measurement to be carried out and the instrument used, particles can be presented either in liquid or in air suspension.

### Principles of measurement

Both the large-particle and small-particle analysers are based on the interaction of laser light with particles.

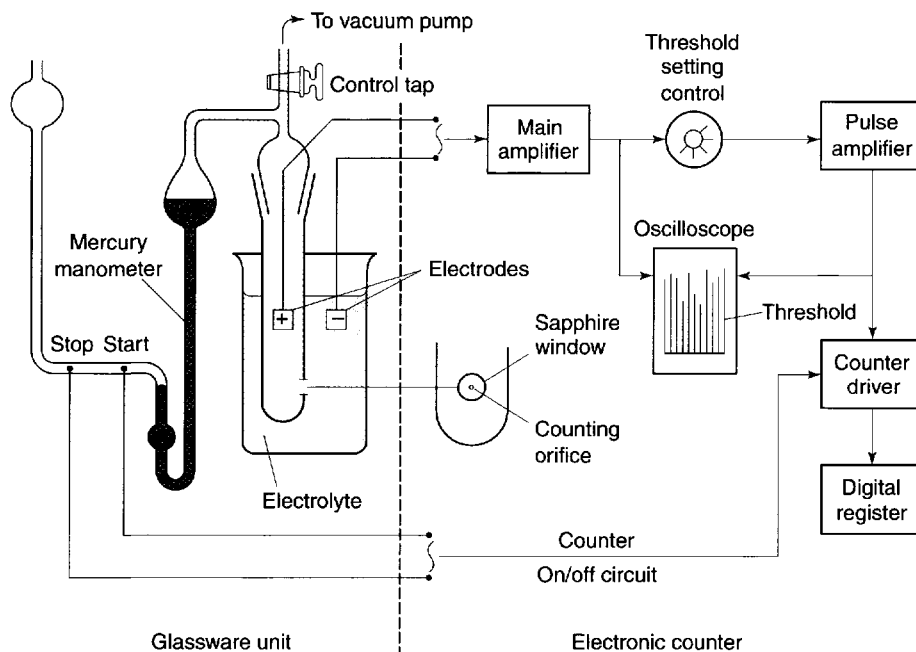


Fig. 10.14 Diagram of electrical stream sensing zone apparatus.

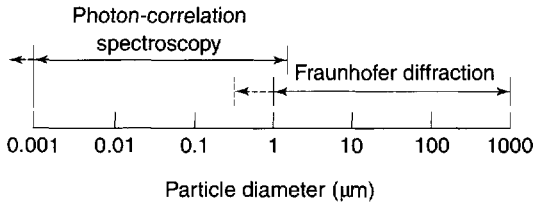


Fig. 10.15 Range of analysis for laser light scattering methods.

**Fraunhofer diffraction** For particles that are much larger than the wavelength of light, any interaction with particles causes light to be scattered in a forward direction with only a small change in angle. This phenomenon is known as Fraunhofer diffraction, and produces light intensity patterns that occur at regular angular intervals and are proportional to the particle diameter producing the scatter (Fig. 10.16). The composite diffraction pattern produced by different diameter particles may be considered to be the sum of all the individual patterns produced by each particle in the size distribution.

Light emitted by a helium–neon laser is incident on the sample of particles and diffraction occurs. In some cases the scattered light is focused by a lens directly on to a photodetector, which converts the signals into an equivalent area diameter. In other cases the scattered light is directed by a lens on to a rotating filter, which is used to convert equivalent area diameters into volume diameters which are quantified by final focusing on to a photodetector using a second lens. The light flux signals occurring on the photodetector are converted into electrical current, which is digitized and processed into size distribution data using a microprocessor (Fig. 10.17).

Small particle sizes can be analysed based on light diffraction or by photon correlation spectroscopy.

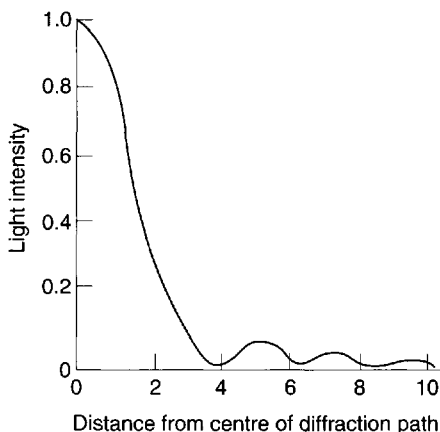


Fig. 10.16 Diffraction pattern intensity distribution.

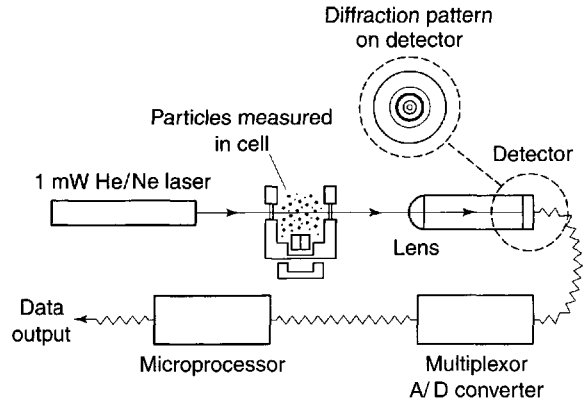


Fig. 10.17 Schematic diagram of laser diffraction pattern particle sizer.

In the former case Fraunhofer diffraction theory is still useful for the particle fraction that is significantly larger than the wavelength of laser light. As particles approach the dimension of the wavelength of the light, some light is still scattered in the forward direction, according to Mie scatter theory, but there is also some side scatter at different wavelengths and polarizations. Use of the Mie theory requires a knowledge of the refractive index of the sample material for calculation of particle size distributions.

**Photon-correlation spectroscopy** In the case of photon-correlation spectroscopy (PCS) the principle of Brownian motion is used to measure particle size. Brownian motion is the random movement of a small particle or macromolecule caused by collisions with the smaller molecules of the suspending fluid. It is independent of external variations except viscosity of fluid and temperature, and as it randomizes particle orientations any effects of particle shape are minimized. Brownian motion is independent of the suspending medium, and although increasing the viscosity does slow down the motion, the amplitude of the movements is unaltered. Because the suspended small particles are always in a state of motion, they undergo diffusion. Diffusion is governed by the mean free path of a molecule or particle, which is the average distance of travel before diversion by collision with another molecule. PCS analyses the constantly changing patterns of laser light scattered or diffracted by particles in Brownian motion and monitors the rate of change of scattered light during diffusion.

Particle movement during Brownian diffusion,  $D$ , is a three-dimensional random walk where the mean distance travelled,  $\bar{x}$ , does not increase

linearly with time,  $t$ , but according to the following relationship:

$$\bar{x} = \sqrt{Dt}$$

A basic property of molecular kinetics is that each particle or macromolecule has the same average thermal or kinetic energy,  $E$ , regardless of mass, size or shape:

$$E = kT$$

where  $k$  is Boltzmann's constant and  $T$  is absolute temperature (Kelvin).

Thus at  $T = 0$  K, molecules possess zero kinetic energy and therefore do not move.  $E$  can also be equated with the driving force,  $F$ , of particle motion:

$$F = \frac{E}{x}$$

At equilibrium

$$F = F_D$$

where  $F_D$  is the drag force resisting particle motion. According to Stokes' theory, discussed below,

$$F_D = 3\pi d_h \cdot \eta \cdot v_{st} \quad (10.7)$$

where  $d_h$  is the hydrodynamic diameter,  $v_{st}$  the Stokes velocity of the particle and  $\eta$  the fluid viscosity, i.e.

$$E = F\bar{x} = 3\pi d_h \cdot \eta \cdot v_{st}$$

but  $\bar{x}^2 = Dt$

and  $v_{st} = \bar{x}/t$

Substituting,  $E = 3\pi d_h \cdot \eta \cdot D$

Since  $E = kt$ ,

$$D = \frac{kT \times 10^7}{3\pi\eta d_h}$$

or

$$D = \frac{1.38 \times 10^{-12} T}{3\pi\eta d} \text{ m}^2 \text{ s}^{-1} \quad (10.8)$$

Equation 10.8 is known as the Stokes–Einstein equation and is the basis for calculation of particle diameters using photon-correlation spectroscopy.

### Alternative techniques

There is a wide variety of different instruments based on laser Doppler anemometry or velocimetry, and diffraction measurements. The instruments vary according to their ability to characterize different particle-size ranges, produce complete size distributions, measure both solid and liquid particles, and

determine molecular weights, diffusion coefficients, zeta potential or electrophoretic mobility.

### Automatic methods

Most of the instruments based on laser light scattering produce a full particle-size analysis automatically. The data are often presented in graphical and tabular form, but in some instruments only a mean diameter is produced.

### Sedimentation methods

#### Equivalent diameters

$d_{fd}$ , frictional drag diameter, a sphere having an equivalent drag force to a particle of the same diameter in the same fluid at the same velocity;  $d_{st}$ , Stokes diameter, the diameter of a particle measured during sedimentation at constant rate in laminar flow conditions.

#### Range of analysis

This is represented in Figure 10.18.

#### Sample preparation and analysis conditions

Particle-size distributions can be determined by examining the powder as it sediments out. In cases where the powder is not uniformly dispersed in a fluid it can be introduced as a thin layer on the surface of the liquid. If the powder is hydrophobic it may be necessary to add a dispersing agent to aid wetting. In cases where the powder is soluble in water it will be necessary to use non-aqueous liquids, or carry out the analysis in a gas.

#### Principles of measurement

Techniques of size analysis by sedimentation can be divided into two main categories according to the method of measurement used. One type is based on

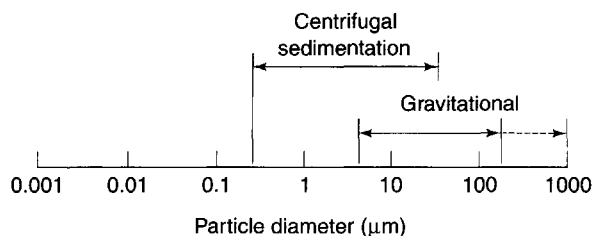


Fig. 10.18 Range of analysis for sedimentation methods.



measurement of particles in a retention zone; a second type uses a non-retention measurement zone.

An example of a non-retention zone measurement method is known as the pipette method. In this method, known volumes of suspension are drawn off and the concentration differences are measured with respect to time.

One of the most popular of the pipette methods was that developed by Andreasen and Lundberg and commonly called the Andreasen pipette (Fig. 10.19). The Andreasen fixed-position pipette consists of a 200 mm graduated cylinder which can hold about 500 mL of suspension fluid. A pipette is located centrally in the cylinder and is held in position by a ground-glass stopper so that its tip coincides with the zero level. A three-way tap allows fluid to be drawn into a 10 mL reservoir, which can then be emptied into a beaker or centrifuge tube. The amount of powder can be determined by weight following drying or centrifuging; alternatively, chemical analysis of the particles can be carried out. The largest size present in each sample is then calculated from Stokes' equation. Stokes' law is an expression of the drag factor in a fluid and is linked to the flow conditions characterized by a Reynolds number. Drag is one of three forces acting on a particle sedimenting in a gravitational field. A drag force,  $F_d$ , acts upwards, as does a buoyancy force,  $F_b$ ; a third force is gravity,  $F_g$ , which acts as the driving force of sedimentation. At the constant terminal velocity, which is rapidly achieved by sedimenting particles, the drag force becomes synonymous with particle motion. Thus for a sphere of diameter  $d$  and density  $\rho_s$ , falling in a fluid of density  $\rho_f$ , the equation of motion is:

$$F_d = \frac{\pi}{6}(\rho_s - \rho_f)F_g \cdot d^3$$

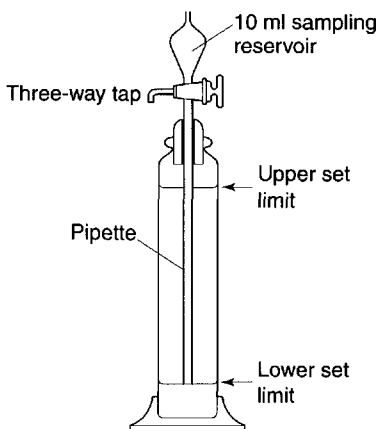


Fig. 10.19 Diagram of Andreasen pipette.

According to Stokes (Eqn. 10.7):

$$F_d = 3\pi d \eta v_{st}$$

where  $v_{st}$  is the Stokes terminal velocity, i.e. sedimentation rate. That is,

$$v_{st} = \frac{(\rho_s - \rho_f)F_g d^2}{18\eta} \quad (10.9)$$

as  $v_{st} = h/t$  where  $h$  is sedimentation height or distance and  $t$  is sedimentation time. By rearrangement, Stokes' equation is obtained:

$$d_{st} = \frac{18\eta h}{(\rho_s - \rho_f)F_g t} \quad (10.10)$$

Stokes' equation for determining particle diameters is based on the following assumptions: near-spherical particles; motion equivalent to that in a fluid of infinite length; terminal velocity conditions; low settling velocity so that inertia is negligible; large particle size relative to fluid molecular size, so that diffusion is negligible; no particle aggregation; laminar flow conditions, characterized by particle Reynolds numbers ( $\rho v d_{particle} / \eta$ ) of less than approximately 0.2.

The second type of sedimentation size analysis, using retention zone methods, also uses Stokes' law to quantify particle size. One of the most common retention zone methods uses a sedimentation balance. In this method the amount of sedimented particles falling on to a balance pan suspended in the fluid is recorded. The continual increase in weight of sediment is recorded with respect to time.

### Alternative techniques

One of the limitations of gravitational sedimentation is that below a diameter of approximately  $5 \mu\text{m}$  particle settling becomes prolonged and is subject to interference from convection, diffusion and Brownian motion. These effects can be minimized by increasing the driving force of sedimentation by replacing gravitational forces with a larger centrifugal force. Once again, sedimentation can be monitored by retention or non-retention methods, although the Stokes equation requires modification because particles are subjected to different forces according to their distance from the axis of rotation. To minimize the effect of distance on the sedimenting force, a two-layer fluid system can be used. A small quantity of concentrated suspension is introduced on to the surface of a bulk sedimentation liquid known as spin fluid. Using this technique of disc centrifugation, all particles of the same size are

**Table 10.4 Summary of particle size analysis instrument characteristics**

Analysis method		Sample measurement environment					Size data	Approximate size range ( $\mu\text{m}$ )				Initial cost		
		Gas	Aqueous liquid	Non-aqueous liquid	Replica	Other functions		Rapid analysis	printout available	0.001–10	1–10	10–100	100–1000	High
Sieve		√	√	√							√	√		√
Microscope	Light	Manual	√	√	√					√	√	√		√
		Semi-automatic	√	√	√					√	√	√		√
	Automatic	√	√	√			√	√		√	√	√	√	√
Electron					√	√	√	√	√	√	√	√	√	√
Electrical stream sensing zone			√	√			√	√		√	√	√	√	√
Laser light scattering	Diffraction Doppler anemometry	√	√	√		√	√	√		√	√	√	√	√
		√	√	√		√	√	√	√	√	√	√	√	√
Sedimentation	Gravitational	√	√	√			√	√		√	√			√
			√	√			×	×						
	Centrifugal		√	√			√	√	√	√		√		
							×	×						

in the same position in the centrifugal field and hence move with the same velocity.

### *Automatic methods*

In general, gravity sedimentation methods tend to be less automated than those using centrifugal forces. However, an adaptation of a retention zone gravity sedimentation method is known as a Micromerograph and measures sedimentation of particles in a gas rather than a fluid. The advantages of this method are that sizing is carried out relatively rapidly and the analysis is virtually automatic.

## **SELECTION OF A PARTICLE SIZE ANALYSIS METHOD**

The selection of a particle size analysis method may be constrained by the instruments already available in a laboratory, but wherever possible the limitations on the choice of method should be governed by the properties of the powder particles and the type of size information required. For example, size analysis over a very wide range of particle diameters may preclude the use of a gravity sedimentation method;

alternatively, size analysis of aerosol particles would probably not be carried out using an electric sensing zone method. As a general guide it is often most appropriate to determine the particle size distribution of a powder in an environment that most closely resembles the conditions in which the powder will be processed or handled. There are many different factors influencing the selection of an analysis method: these are summarized in Table 10.4 and may be used together with information from a preliminary microscopic analysis and any other known physical properties of the powder, such as solubility, density, cohesivity, in addition to analysis requirements such as speed of measurement, particle size data processing or the physical separation of different particle-size powders for subsequent processing.

## **BIBLIOGRAPHY**

- Allen, T. (1981) *Particle Size Measurement*, 3rd edn, Chapman and Hall, London and New York.
- Barnett, M.I. and Nystrom, C. (1982) Coulter counters and microscopes for the measurement of particles in the sieve range. *Pharm. Tech.*, 6 (Mar), 49–50.
- Kay, B.H. (1981) *Direct Characterization of Fine Particles*, John Wiley & Sons, New York and Chichester.

# 11

## Particle-size reduction

John Staniforth

### CHAPTER CONTENTS

#### Heat and heat transfer 586

- Introduction 586
- Methods of heat transfer 587
  - Conduction 587
  - Convection 587
  - Radiation 587
- Heat transfer by conduction and practical heat transfer 587
  - Illustrative calculation 589
- Heat transfer through multiple layers 589
- Film heat-transfer coefficient 590
- Overall heat-transfer coefficient 590

#### Steam as a heating medium 590

- Heat content of steam 591
- Effect of pressure on steam properties 592
  - Steam tables 592
- Adverse effects of air in steam 592
- Steam generation and use 593
  - Manufacturing installations for liquid and semisolid products 593
  - Steam traps 594
- Example calculations involving the use of steam 595

#### References 596

### Objectives of size reduction

The significance of particle size has been discussed in Chapter 10 and some of the reasons for carrying out a size-reduction operation will already have been noted. In addition, the function of size reduction may be to aid efficient processing of solid particles by facilitating powder mixing or the production of suspensions. There are also some special functions of size reduction, such as exposing cells prior to extraction or reducing the bulk volume of a material to improve transportation efficiency.

### INFLUENCE OF MATERIAL PROPERTIES ON SIZE REDUCTION

#### Crack propagation and toughness

Size reduction or comminution is carried out by a process of crack propagation, whereby localized stresses produce strains in the particles which are large enough to cause bond rupture and thus propagate the crack. In general, cracks are propagated through regions of a material that possess the most flaws or discontinuities, and is related to the strain energy in specific regions according to Griffith's theory. The stress in a material is concentrated at the tip of a crack and the stress multiplier can be calculated from an equation developed by Inglis:

$$\sigma_K = 1 + 2 \left( \frac{L}{2r} \right) \quad (11.1)$$

where  $\sigma_K$  is the multiplier of the mean stress in a material around a crack,  $L$  is the length of the crack and  $r$  is the radius of curvature of the cracks tip. For a simple geometric figure such as a circular discontinuity  $L = 2r$  and the stress multiplier  $\sigma_K$  will have a value of 3. In the case of the thin disc-shaped crack shown in cross-section in Figure 11.1, the crack was

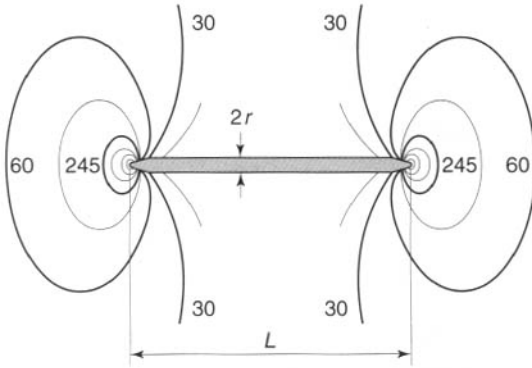


Fig. 11.1 Stress concentrations at the edges of a disc-shaped crack;  $r$  is the radius of curvature of the crack tip;  $L$  is the crack length.

considered to have occurred at molecular level between atomic surfaces separated by a distance of  $2 \times 10^{-10}$  m for a crack  $3 \mu\text{m}$  long, which gives a stress multiplier of approximately 245. The stress concentration diminishes towards the mean stress according to the distance from the crack tip (Fig. 11.1). Once a crack is initiated the crack tip propagates at a velocity approaching 40% of the speed of sound in the solid. This crack propagation is so rapid that excess energy from strain relaxation is dissipated through the material and concentrates at other discontinuities, where new cracks are propagated. Thus a cascade effect occurs and an almost instantaneous brittle fracture occurs.

Not all materials exhibit this type of brittle behaviour and can resist fracture at much larger stresses. This occurs because these tougher materials can undergo plastic flow, which allows strain energy relaxation without crack propagation. When plastic flow occurs, atoms or molecules slip over one another and this process of deformation requires energy. Brittle materials can also exhibit plastic flow and Irwin and Orowan suggested a modification of Griffiths' crack theory to take this into account; the new relationship has a fracture stress which varies inversely with the square root of crack length:

$$\sigma = \frac{E_p}{C} \quad (11.2)$$

where  $E_p$  is the energy required to form unit area of double surface.

It can therefore be seen that the ease of comminution depends on the brittleness or plasticity of the material and their relationship with crack initiation and propagation.

## Surface hardness

In addition to the toughness of the material described above, size reduction may also be influenced by surface hardness. The hardness of a material can be described by its position in a scale devised by a German mineralogist called Mohs. Mohs' scale is a table of materials, at the top of which is diamond with Mohs hardness  $>7$ , which has a surface so hard that it can scratch anything below it; at the bottom of the table with Mohs hardness  $<3$  is talc, which is soft enough to be scratched by anything above it.

A more quantitative measurement of surface hardness was devised by Brinell; such determinations of hardness may prove useful as a guide to the ease with which size reduction can be carried out: in general, harder materials are more difficult to comminute and can lead to abrasive wear of metal mill parts, which then cause product contamination. Conversely, materials with a large elastic component, such as rubber, are extremely soft yet difficult to size reduce.

Materials such as rubber which are soft under ambient conditions, waxy substances such as stearic acid which soften when heated, and 'sticky' materials such as gums are capable of absorbing large amounts of energy through elastic and plastic deformation without crack initiation and propagation. This type of polymeric material, which resists comminution at ambient or elevated temperatures, can be more easily size reduced by lowering the temperature below the glass transition point of the material. When this is carried out the material undergoes a transition from plastic to brittle behaviour and crack propagation is facilitated.

Other factors that influence the process of size reduction include the moisture content of the feed material. In general, a moisture content below 5% is suitable for dry grinding and greater than 50% if wet grinding is to be carried out.

## Energy requirements of size reduction process

Only a very small amount of the energy put into a comminution operation actually effects size reduction. This has been estimated to be as little as 2% of the total energy consumption, the remainder being lost in many ways, including elastic deformation of particles, plastic deformation of particles without fracture, deformation to initiate cracks that cause fracture, deformation of metal machine parts, inter-particle friction, particle-machine wall friction, heat, sound and vibration.

A number of hypotheses and theories have been proposed in an attempt to relate energy input to the degree of size reduction produced. Rittinger's hypothesis is usually interpreted according to the energy,  $E$ , used in a size-reduction process, which is proportional to the new surface area produced,  $S_n$ , or:

$$E = \kappa_R (S_n - S_i) \quad (11.3)$$

where  $S_i$  is the initial surface area and  $\kappa_R$  is Rittinger's constant of energy per unit area.

Kick's theory states that the energy used in deforming or fracturing a set of particles of equivalent shape is proportional to the ratio of the change in size, or:

$$E = \kappa_K \log \frac{d_i}{d_n} \quad (11.4)$$

where  $\kappa_K$  is Kick's constant of energy per unit mass,  $d_i$  is the initial particle diameter and  $d_n$  the new particle diameter.

Bond's theory states that the energy used in crack propagation is proportional to the new crack length produced, which is often related to the change in particle dimensions according to the following equation:

$$E = 2\kappa_B \left( \frac{1}{d_n} - \frac{1}{d_i} \right) \quad (11.5)$$

$\kappa_B$  is known as Bond's work index and represents the variation in material properties and size-reduction methods with dimensions of energy per unit mass.

Walker proposed a generalized differential form of the energy-size relationship which can be shown to link the theories of Rittinger and Kick, and in some cases that of Bond:

$$\partial E = -\kappa \frac{\partial d}{d^n} \quad (11.6)$$

where  $d$  is a size function that can be characterized by an integrated mean size or by a weight function,  $n$  is an exponent – when  $n = 1$  for particles defined by a weight function, integration of Walker's equation corresponds to a Kick-type theory; when  $n = 2$  a Rittinger-type solution results; and when  $n = 3/2$  Bond's theory is given.

When designing a milling process for a given particle, the most appropriate energy relationship will be required in order to calculate energy consumptions. It has been considered that the most appropriate values for  $n$  are 1 for coarse particles  $> 1 \mu\text{m}$  where Kick-type behaviour occurs, and 2 for Rittinger-type milling of particles  $< 1 \mu\text{m}$ . The third value of  $n = 3/2$  is the average of these two extremes and indicates a

possible solution where neither Kick's nor Rittinger's theory is appropriate.

Other workers have found that  $n$  cannot be assumed to be constant, but varies according to a particle size function, so that:

$$n = f(d)$$

or

$$E = -\kappa \frac{d}{d^{f(d)}} \quad (11.7)$$

As the particle size increases  $f(d)$  tends to 1, and as the size reduces  $f(d)$  tends to 2.

## INFLUENCE OF SIZE REDUCTION ON SIZE DISTRIBUTION

In Chapter 10, several different size distributions were discussed and these were based on either a normal or a log-normal distribution of particle sizes. During a size-reduction process the particles of feed material will be broken down and particles in different size ranges undergo different amounts of breakage. This uneven milling leads to a change in the size distribution, which is superimposed on the general movement of the normal or log-normal curve towards smaller particle diameters. Changes in size distributions that occur as milling proceeds were demonstrated experimentally by Heywood, who showed that an initial normal particle size distribution was transformed through a size-reduced bimodal population into a much finer powder with a positively skewed, leptokurtic particle population (Fig. 11.2) as milling continued. The initial, approximately normal, size distribution was transformed into a size-reduced bimodal population through

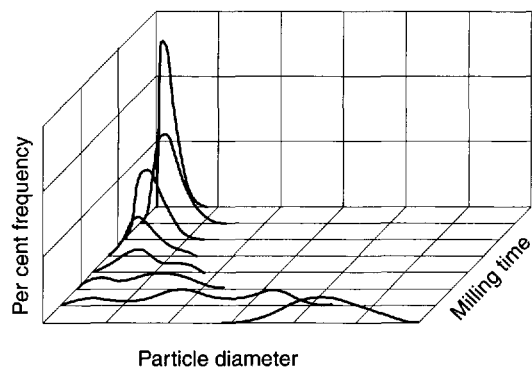
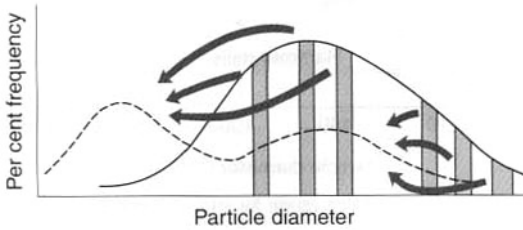
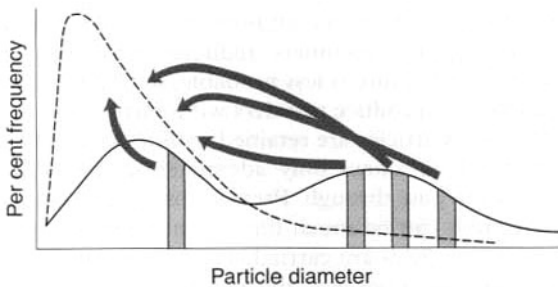


Fig. 11.2 Changes in particle size distributions with increased milling time.



**Fig. 11.3** Transformation of approximate normal particle size distribution into finer bimodal population following milling.



**Fig. 11.4** Transformation of a fine bimodal particle population into a finer unimodal distribution following prolonged milling.

differences in the fracture behaviour of coarse and fine particles (Fig. 11.3). If milling is continued a unimodal population reappears, as the energy input is not great enough to cause further fracture of the finest particle fraction (Fig. 11.4). The lower particle-size limit of a milling operation is dependent on the energy input and on material properties. Below particle diameters of approximately  $5 \mu\text{m}$ , interactive forces generally predominate over comminution stresses which are distributed over increasing surface areas, and particle agglomeration then opposes particle fracture and size reduction ceases. In some cases particle agglomeration occurs to such a degree that subsequent milling actually causes size enlargement.

## SIZE REDUCTION METHODS

There are many different types of size reduction techniques but the milling equipment used can be classified according to the principal method employed. Examples of each type will be given and the approximate size-reduction range provided, although it should be remembered that the extent of size reduction is always related to milling time.

## Cutting methods

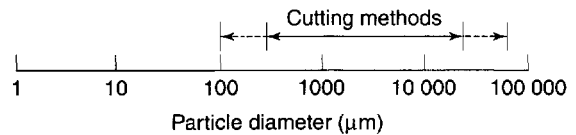
### Size reduction range

This is indicated in Figure 11.5.

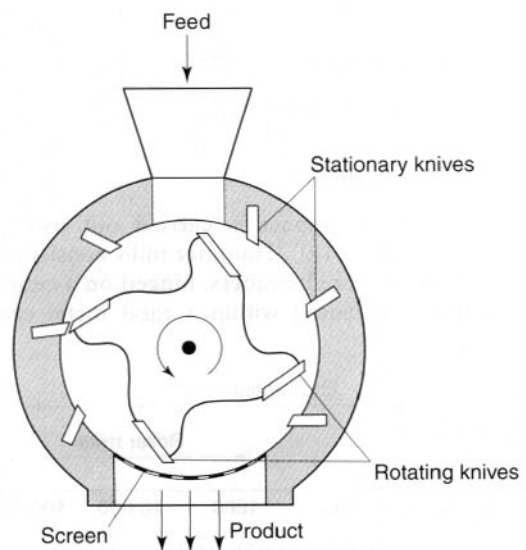
### Principle of operation

A cutter mill (Fig. 11.6) consists of a series of knives attached to a horizontal rotor which act against a series of stationary knives attached to the mill casing. During milling, size reduction occurs by fracture of particles between the two sets of knives, which have a clearance of a few millimetres. A screen is fitted in the base of the mill casing and acts to retain material in the mill until a sufficient degree of size reduction has been effected.

The high shear rates present in cutter mills are useful in producing a coarse degree of size reduction of dried granulations prior to tableting and of fibrous crude drugs such as roots, peels or barks prior to extraction.



**Fig. 11.5** Size reduction range for cutting methods.



**Fig. 11.6** Cutter mill.

## Compression methods

### Size reduction range

These are indicated in Figure 11.7.

### Principle of operation

Size reduction by compression can be carried out on a small scale using a mortar and pestle. End-runner and edge-runner mills are mechanized forms of mortar and pestle-type compression comminution (Fig. 11.7). In the end-runner mill a weighted pestle is turned by the friction of material passing beneath it as the mortar rotates under power; the edge-runner mill has the pestle equivalent mounted horizontally and rotating against a bed of powder, so that size reduction occurs by attrition as well as compression. Such techniques are now rarely used in pharmaceutical production.

### Alternative techniques

Another form of compression mill uses two cylindrical rolls mounted horizontally and rotated about their long axes. In roller mills, one of the rolls is driven directly while the second is rotated by friction as material is drawn through the gap between the rolls. This form of roller mill should not be confused with the type used for milling ointments, where both rolls are driven but at different speeds, so that size reduction occurs by attrition.

## Impact methods

### Size reduction range

These are shown in Figure 11.8.

### Principle of operation

Size reduction by impact is carried out using a hammer mill (Fig. 11.9). Hammer mills consist of a series of four or more hammers, hinged on a central shaft which is enclosed within a rigid metal case.

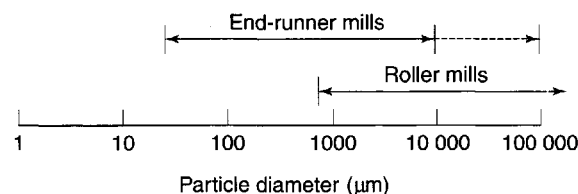


Fig. 11.7 Size reduction range for compression methods.

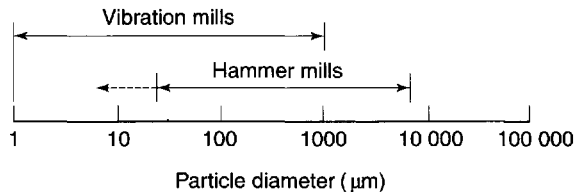


Fig. 11.8 Size reduction range for impact methods.

During milling the hammers swing out radially from the rotating central shaft. The angular velocity of the hammers produces strain rates up to  $80 \text{ s}^{-1}$ , which are so high that most particles undergo brittle fracture. As size reduction continues the inertia of particles hitting the hammers reduces markedly and subsequent fracture is less probable, so that hammer mills tend to produce powders with narrow size distributions. Particles are retained within the mill by a screen, which allows only adequately comminuted particles to pass through. Particles passing through a given mesh can be much finer than the mesh apertures, as particles are carried around the mill by the hammers and approach the mesh tangentially. For this reason square, rectangular or herringbone slots are often used. According to the purpose of the operation, the hammers may be square-faced, tapered to a cutting edge or have a stepped form.

### Alternative techniques

An alternative to hammer milling which produces size reduction is vibration milling (Fig. 11.10). Vibration mills are filled to approximately 80% total volume with porcelain or steel balls. During milling the whole body of the mill is vibrated and size reduction occurs by repeated impaction. Comminuted particles fall through a screen at the base of the mill.

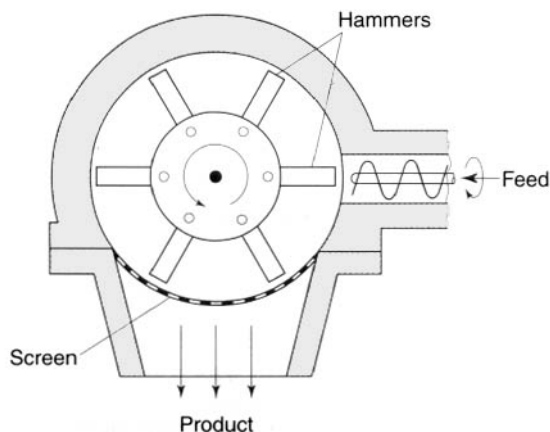


Fig. 11.9 Hammer mill.



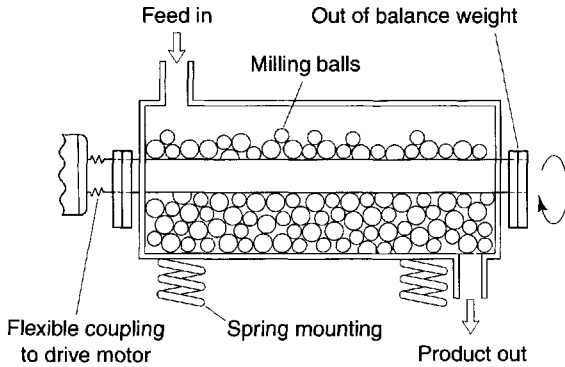


Fig. 11.10 Vibration mill.

The efficiency of vibratory milling is greater than that for conventional ball milling described below.

## Attrition methods

### Size reduction range

This is indicated in Figure 11.11.

### Principle of operation

Roller mills use the principle of attrition to produce size reduction of solids in suspensions, pastes or ointments. Two or three porcelain or metal rolls are mounted horizontally with an adjustable gap, which can be as small as  $20\ \mu\text{m}$ . The rollers rotate at different speeds so that the material is sheared as it passes through the gap and is transferred from the slower to the faster roll, from which it is removed by means of a scraper.

## Combined impact and attrition methods

### Size reduction range

This is indicated in Figure 11.12.

### Principle of operation

A ball mill is an example of a comminution method which produces size reduction by both impact and

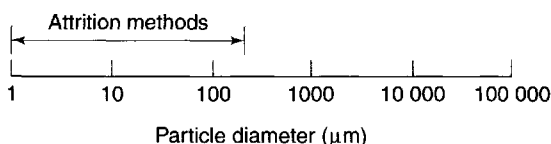


Fig. 11.11 Size reduction range for attrition methods.

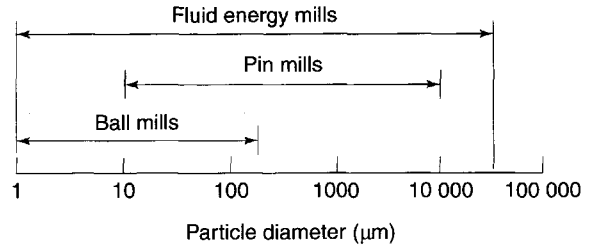


Fig. 11.12 Size reduction range for combined impact and attrition methods.

attrition of particles. Ball mills consist of a hollow cylinder mounted such that it can be rotated on its horizontal longitudinal axis (Fig. 11.13). Cylinder diameters can be greater than 3 m, although much smaller sizes are used pharmaceutically. The cylinder contains balls that occupy 30–50% of the total volume, ball size being dependent on feed and mill size; for example, a mill 1 m in diameter might contain balls with a diameter of 75 mm. Mills usually contain balls with many different diameters owing to self-attrition, and this helps to improve the product as the large balls tend to break down the coarse feed materials and the smaller balls help to form the fine product by reducing void spaces between balls.

The amount of material in a mill is of considerable importance: too much feed produces a cushioning effect and too little causes loss of efficiency and abrasive wear of the mill parts. The factor of greatest importance in the operation of the ball mill is the speed of rotation. At low angular velocities (Fig. 11.13(a)) the balls move with the drum until the force due to gravity exceeds the frictional force of the bed on the drum, and the balls then slide back *en masse* to the base of the drum. This sequence is repeated, producing very little relative movement of balls so that size reduction is minimal. At high angular velocities (Fig. 11.13(b)) the balls are thrown out on to the mill wall by centrifugal force and no size reduction occurs. At about two-thirds of the critical angular velocity where centrifuging occurs (Fig. 11.13(c)), a cascading action is produced. Balls are lifted on the rising side of the drum until their dynamic angle of repose is exceeded. At this point they fall or roll back to the base of the drum in a cascade across the diameter of the mill. By this means, the maximum size reduction occurs by impact of the particles with the balls and by attrition. The optimum rate of rotation is dependent on mill diameter but is usually of the order of  $0.5\ \text{s}^{-1}$ .

### Alternative techniques

Fluid energy milling is another form of size-reduction method which acts by particle impaction and

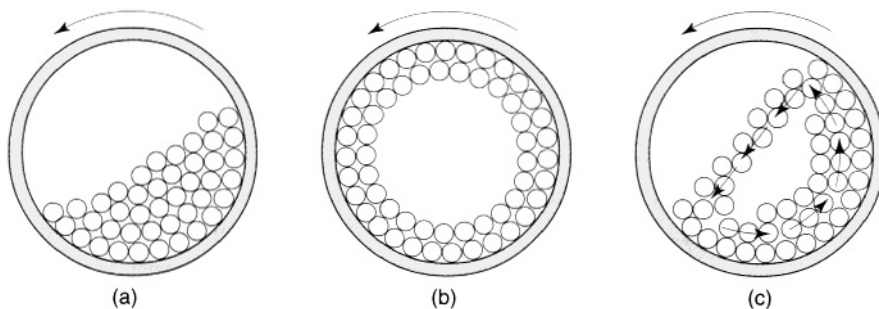


Fig. 11.13 Ball mill in operation, showing correct cascade action.

attrition. A typical form of fluid energy or jet mill is shown in Fig. 11.14. This type of mill or ‘micronizer’ consists of a hollow toroid which has a diameter of 20–200 mm, depending on the height of the loop, which may be up to 2 m. A fluid, usually air, is injected as a high-pressure jet through nozzles at the bottom of the loop. The high velocity of the air gives rise to zones of turbulence into which solid particles are fed. The high kinetic energy of the air causes the particles to impact *with other particles* with sufficient momentum for fracture to occur. Turbulence ensures that the level of particle–particle collisions is high enough to produce substantial size reduction by impact and some attrition. A particle-

size classifier is incorporated in the system so that particles are retained in the toroid until sufficiently fine and remain entrained in the air stream that is exhausted from the mill.

Other types of fluid energy mill replace the turbulence zone technique with horizontally opposed air jets through which the feed material is forced; alternatively, a single air jet is used to feed particles directly on to a target plate, where impaction causes fracture.

In addition to ball mills and fluid energy mills, there are other methods of comminution that act by producing particle impact and attrition. These include pin mills, in which two discs with closely spaced pins rotate against one another at high speeds (Fig. 11.15). Particle-size reduction occurs by impaction with the pins and by attrition between pins as the particles travel outwards under the influence of centrifugal force.

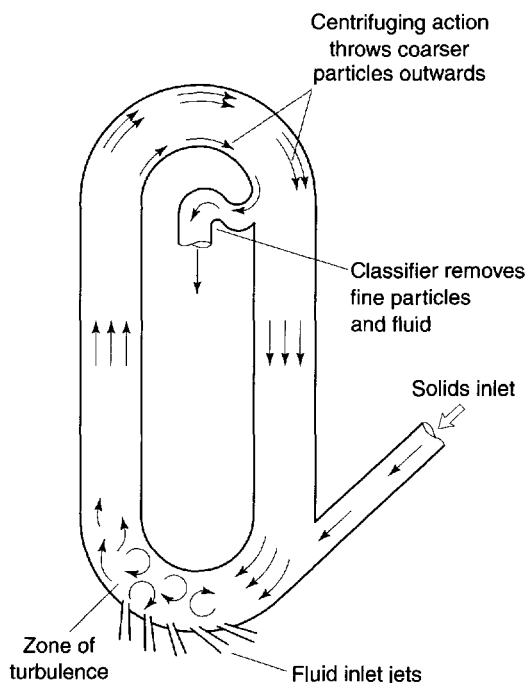


Fig. 11.14 Fluid energy mill.

### SELECTION OF PARTICLE SIZE-REDUCTION METHOD

Different mills give differing products from the same starting material; for example, particle shape may vary according to whether size reduction occurs as a

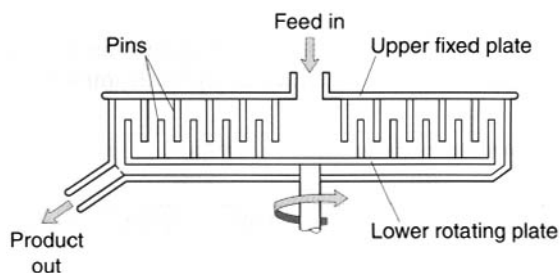


Fig. 11.15 Pin mill.

**Table 11.1 Selection of size reduction mills according to particle properties and product size required**

Mohs' 'hardness'	Tough	Sticky	Abrasive	Friable
<b>(a) Fine powder product (&lt; 50 <math>\mu\text{m}</math>)</b>				
1-3 (soft)	Ball, vibration (under liquid nitrogen)	Ball, vibration		Ball, vibration, pin, fluid energy
3-5 (intermediate)	Ball, vibration			Ball, vibration, fluid energy
5-10 (hard)	Ball, vibration, fluid energy		Ball, vibration, fluid energy	
<b>(b) Coarse powder product (50-1000 <math>\mu\text{m}</math>)</b>				
1-3 (soft)	Ball, vibration, roller, pin, hammer, cutter (all under liquid nitrogen)	Ball, pin		Ball, roller, pin, hammer, vibration
3-5 (intermediate)	Ball, roller, pin, hammer, vibration, cutter			Ball, roller, pin, vibration, hammer
5-10 (hard)	Ball, vibration		Ball vibration, roller	
<b>(c) Very coarse product (&gt; 1000 <math>\mu\text{m}</math>)</b>				
1-3 (soft)	Cutter, edge runner	Roller, edge runner, hammer		Roller, edge runner, hammer
3-5 (intermediate)	Edge runner, roller, hammer			Roller, hammer
5-10 (hard)	Roller		Roller	

result of impact or attrition. In addition, the proportion of fines in the product may vary, so that other properties of the powder will be altered.

The use to which a powder will be put usually controls the degree of size reduction, but in some cases the precise particle size required is not critical. In these circumstances the important factor is that, in general, the cost of size reduction increases as particle size decreases, so that it is economically undesirable to mill particles to a finer degree than necessary. Once the particle size required has been established the selection of mills capable of producing that size may be modified from a knowledge of the particle properties, such as hardness, toughness etc. The influences of various process and material variables on selection of a size reduction method are summarized in Table 11.1.

## BIBLIOGRAPHY

- Austin, L.G. and Brame, K. (1983) A comparison of the bond method for sizing wet tumbling ball mills with a size-mass balance simulation model. *Powder Technol.*, **34**, 261-274.
- Lachman, L., Lieberman, H.A. and Kanig, J.L. In *Theory and Practice of Industrial Pharmacy*, Lea and Febiger, Philadelphia.
- Mecham, W.J., Jardine, L.J., Reedy, G.T. and Steindler, M.J. (1983) General statistical description of the fracture particulates formed by mechanical impacts of brittle materials. *Ind. Engng. Chem. Fund.*, **22**, 384-391.
- Paramanathan, B.K. and Bridgwater, J. (1983) Attrition of solids, Pts I & II. *Chem. Engng Sci.*, **38**, 197-224.
- Voller, V.R. (1983) A note on energy-size reduction relationships in comminution. *Powder Technol.*, **36**, 281-286.
- Wheeler, D.A. (1982) Size reduction. *Processing* (Dec), 55-58.

# 12

## Particle-size separation

John Staniforth

### CHAPTER CONTENTS

<b>Objectives of size separation</b>	174
Size separation efficiency	174
<b>Size separation methods</b>	175
Size separation by sieving	175
Separation ranges	175
Principles of operation	176
Agitation methods	176
Brushing methods	176
Centrifugal methods	176
Standards for powders based on sieving	176
Size separation by fluid classification	176
Sedimentation methods	176
Separation ranges	176
Principles of operation	177
Alternative techniques	177
Standards for powders based on sedimentation separation	177
Elutriation methods	178
Separation ranges	178
Principles of operation	178
Alternative techniques	179
Cyclone methods	179
Separation range	179
Principle of operation	180
<b>Selection of a size separation process</b>	180
<b>Bibliography</b>	180

### OBJECTIVES OF SIZE SEPARATION

The significance of particle size and the principles involved in differentiating a powder into fractions of known particle size and in reducing particle dimensions have been considered in Chapters 10 and 11. In this chapter the methods by which size separation can be achieved will be discussed, together with the standards that are applied to powders for pharmaceutical purposes.

Solid separation is a process by which powder particles are removed from gases or liquids, and has two main aims:

1. to recover valuable products or byproducts;
2. to prevent environmental pollution.

Although size separation uses many similar techniques to those used in solid separation it has a different aim, which is to classify powders into separate particle size ranges or 'cuts', and is therefore linked to particle-size analysis. However, an important difference exists between size separation, and size analysis: following size separation, powder in a given particle size range is available for separate handling or subsequent processing. This means that whereas a particle-size analysis method such as microscopy would be of no use as a size-separation method, the principle of sieving could be used for both purposes.

### Size-separation efficiency

The efficiency with which a powder can be separated into different particle size ranges is related to the particle and fluid properties and the separation method used. Separation efficiency is determined as a function of the effectiveness of a given process in separating particles into oversize and undersize fractions.

In a continuous size-separation process the production of oversize and undersize powder streams

from a single feed stream can be represented by the following equation:

$$f_F = f_o + f_u \quad (12.1)$$

where  $f_F$ ,  $f_o$  and  $f_u$  are functions of the mass flow rates of the feed material, oversize product and undersize product streams, respectively. If the separation process is 100% efficient then all oversize material will end up in the oversize product stream and all undersize material will end up in the undersize product stream. Invariably, industrial separation processes produce an incomplete size separation, so that some undersize material is retained in the oversize stream and some oversize material may find its way into the undersize stream.

Considering the oversize material, a given powder feed stream will contain a certain proportion of true oversize material,  $\delta_F$ ; the oversize product stream will contain a fraction,  $\delta_o$ , of true oversize particles, and the undersize stream will contain a fraction,  $\delta_u$ , of true oversize material (Fig. 12.1)

The efficiency of the separation of oversize material, can be determined by considering the relationship between mass flow rates of feed and product streams and the fractional contributions of true size grade in the streams. For example, the efficiency  $E_o$

of a size-separation process for oversize material in the oversize stream is given by:

$$E_o = \frac{f_o \cdot \delta_o}{f_F \delta_F} \quad (12.2)$$

and the separation efficiency for undersize material in the undersize stream is given by:

$$E_u = \frac{f_u(1 - \delta_u)}{f_F(1 - \delta_F)} \quad (12.3)$$

The total efficiency,  $E_t$ , for the whole size separation process is given by:

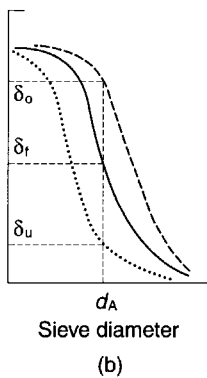
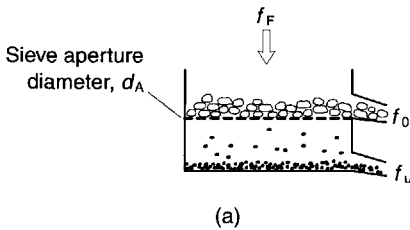
$$E_t = E_u \cdot E_o \quad (12.4)$$

Separation efficiency determination can be applied to each stage of a complete size classification and is often referred to as 'grade efficiency'. In some cases a knowledge of grade efficiency is insufficient, for example where a precise particle size cut is required. A 'sharpness index' can be used to quantify the sharpness of cut-off in a given size range. A sharpness index,  $S$ , can be determined in several different ways, for example by taking the percentage values from a grade efficiency curve at the 25 and 75% levels (L):

$$S_{25/75} = \frac{L_{25}}{L_{75}} \quad (12.5)$$

or at other percentile points, such as the 10 and 90% levels:

$$S_{10/90} = \frac{L_{10}}{L_{90}} \quad (12.6)$$



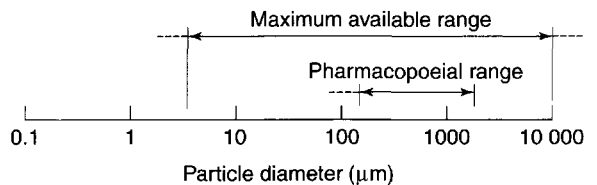
**Fig. 12.1** Size separation efficiency determination. (a) Separation operation; (b) size distributions of feed, oversize and undersize material to obtain values for  $\delta_o$ ,  $\delta_f$  and  $\delta_u$ .

## SIZE-SEPARATION METHODS

### Size separation by sieving

#### Separation ranges

These are shown in Figure 12.2.



**Fig. 12.2** Separation range for sieving.

### Principles of operation

The principles of sieving in order to achieve particle-size analysis were described in Chapter 10. There may be some differences in the methods used to achieve size separation rather than size analysis. The wire mesh used for the construction of British Standard sieves should be of uniform circular cross-section, and the sieve mesh should possess adequate strength to avoid distortion and should also be resistant to chemical action with any of the material to be sifted. Commonly used materials for the construction of test sieve meshes for size analysis are brass and bronze, but it is probably more common and more suitable to use stainless steel meshes in process sieves used for size separation.

The use of sieving in size separation usually requires processing of larger volumes of powder than are commonly found in size analysis operations. For this reason, the sieves used for size separation are often larger in area than those used for size analysis. There are several techniques for encouraging particles to separate into their appropriate size fractions efficiently. In dry sieving processes these are based on mechanical disturbances of the powder bed and include the following.

**Agitation methods** Size separation is achieved by electrically induced oscillation or mechanically induced vibration of the sieve meshes, or alternatively by gyration, in which sieves are fitted to a flexible mounting which is connected to an out-of-balance flywheel. The eccentric rotation of the flywheel imparts a rotary movement of small amplitude and high intensity to the sieve and causes the particles to spin, thereby continuously changing their orientation and increasing their potential to pass through a given sieve aperture. The output from gyratory sieves is often considerably greater than that obtained using oscillation or vibration methods.

Agitation methods can be made continuous by inclination of the sieve and the use of separate outlets for the undersize and oversize powder streams.

**Brushing methods** A brush is used to reorientate particles on the surface of a sieve and prevent apertures becoming blocked. A single brush can be rotated about the midpoint of a circular sieve or, for large-scale processing, a horizontal cylindrical sieve, is employed, with a spiral brush rotating about its longitudinal axis.

**Centrifugal methods** Particles are thrown outwards on to a vertical cylindrical sieve under the action of a high-speed rotor inside the cylinder. The current of air created by the rotor movement also

assists in sieving, especially where very fine powders are being processed.

Wet sieving can also be used to effect size separation and is generally more efficient than dry sieving methods.

### Standards for powders based on sieving

Standards for powders used pharmaceutically are provided in pharmacopoeiae, which indicate that 'the degree of coarseness or fineness of a powder is differentiated and expressed by reference to the nominal mesh aperture size of the sieves used'. Five grades of powder are specified and defined in, for example, the BP and these are shown in Table 12.1.

Some pharmacopoeiae define another size fraction, known as 'ultrafine powder'. In this case it is required that the maximum diameter of at least 90% of the particles must be no greater than 5  $\mu\text{m}$  and that none of the particles should have diameters greater than 50  $\mu\text{m}$ .

It should be noted that the term 'sieve number' has been used as a method of quantifying particle size in Pharmacopoeia. However, various monographs use the term differently and in order to avoid confusion it is always advisable to refer to particle sizes according to the appropriate equivalent diameters expressed in micrometres.

## Size separation by fluid classification

### Sedimentation methods

#### Separation ranges

These are shown in Figure 12.3.

**Table 12.1 Powder grades specified in British Pharmacopoeia**

Description of grade of powder	Coarsest sieve diameter ( $\mu\text{m}$ )	Sieve diameter through which no more than 40% of powder must pass ( $\mu\text{m}$ )
Coarse	1700	355
Moderately coarse	710	250
Moderately fine	355	180
Fine	180	—
Very fine	125	—

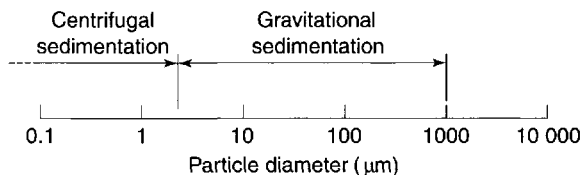


Fig. 12.3 Separation range for sedimentation techniques.

### Principles of operation

The principles of liquid classification using sedimentation methods are described in Chapter 10. Size separation by sedimentation utilizes the differences in settling velocities of particles with different diameters, and these can be related according to Stokes' equations, see Eqns 10.9 and 10.10.

One of the simplest forms of sedimentation classification uses a chamber containing a suspension of solid particles in a liquid, which is usually water. After predetermined times, particles less than a given diameter can be recovered using a pipette placed a fixed distance below the surface of the liquid. Size fractions can be collected continuously using a pump mechanism in place of a pipette.

Alternatively, a single separation can be carried out simply by removing the upper layer of suspension fluid after the desired time. Disadvantages of these simple methods are that they are batch processes and discrete particle fractions cannot be collected, as samples contain every particle diameter up to the limiting diameter and not specific size ranges.

### Alternative techniques

An alternative technique is to use a continuous settling chamber so that particles in suspension enter a shallow container, as shown in Figure 12.4. The particle Reynolds' number of the system ( $\rho u d_{\text{particle}}/\eta$ ) is below approximately 0.2, so that streamline flow occurs. Particles entering at the top of the chamber

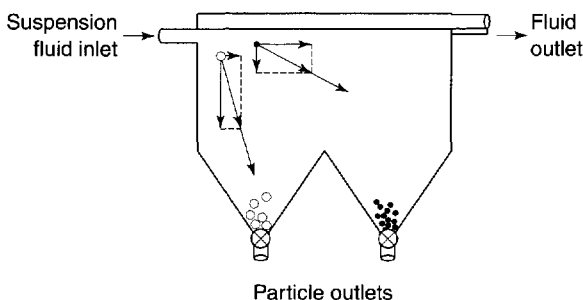


Fig. 12.4 Continuous settling chamber showing vectors of particle movement for different sizes.

are acted upon by a driving force which can be divided into two components: a horizontal component of particle velocity which is equal to the suspension fluid velocity, and a vertical component which corresponds to Stokes' settling velocity and is different for each particle size. These two components are constant for each particle, so that the settling path will be given by a curve whose slope depends on particle diameter. The coarsest particles will have the steepest settling paths and will sediment closest to the inlet, whereas the finest particles with low Stokes velocity component will have the shallowest settling paths and will sediment furthest from the fluid suspension feed stream (Fig. 12.4). Particles separated into the different hopper-type discharge points can be removed continuously.

Very fine particles will not sediment efficiently under the influence of gravity due to Brownian diffusion. In order to increase the driving force of sedimentation, centrifugal methods can be used to separate particles of different sizes in the submicrometre region.

Simple cylindrical centrifuges can be used to remove single size cuts from a fluid stream, but where separation is required over a wider number of size ranges multiple-chamber centrifuges can be used. In this type of centrifuge there are a number of spinning cylinders of different diameters set inside a closed chamber (Fig. 12.5). Fine particles in liquid suspension are fed in through the top of the inner or central cylinder. As in continuous-flow gravity sedimentation the particles are acted on by two component forces, one due to fluid flow and, in this case, one due to centrifugal force. The coarsest particles will have the shallowest trajectories and will be carried to the walls of the inner cylinder (Fig. 12.6); all other particles remain entrained in the liquid and flow out at the base of the cylinder and via a baffle or weir into the top of the next cylinder out, where the centrifugal force is higher. This sequence continues so that only the finest particles reach the outermost spinning cylinder.

Another type of sedimentation method is based on separation from particles dispersed in air and is known as **mechanical air classification**.

### Standards for powders based on sedimentation separation

There are no general pharmacopoeial standards for size separation based on sedimentation. However, tests are applied to Light Kaolin in order to limit the coarseness of the powder. Light Kaolin must consist of fine particles, partially because it is used in the

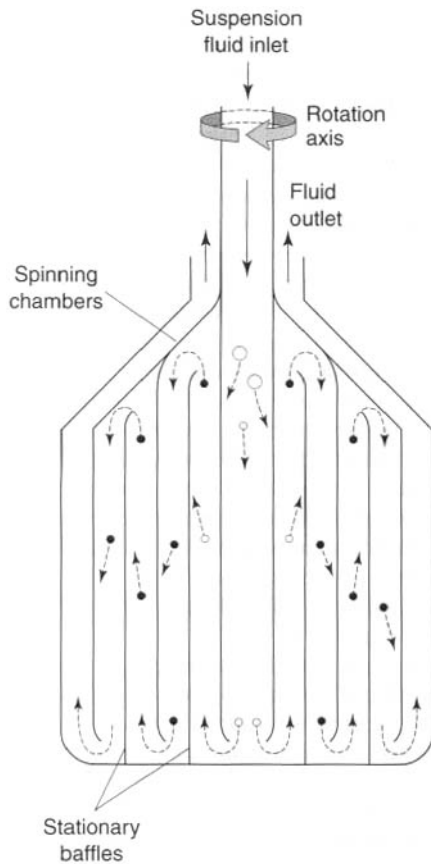


Fig. 12.5 Multiple-chamber separation centrifuge.

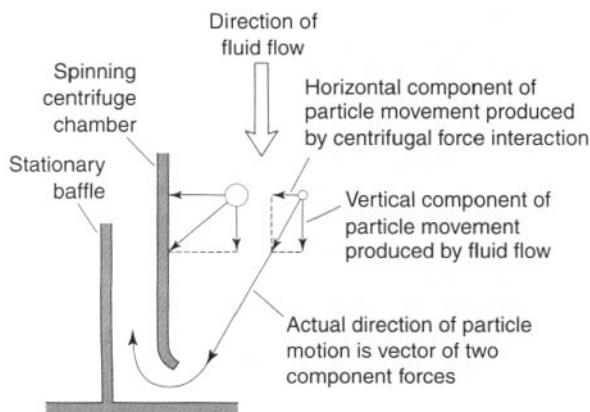


Fig. 12.6 Influence of particle size on particle movement in multiple-chamber centrifuge.

form of a suspension, but also because it is used therapeutically for its adsorptive properties, which are dependent on surface area and therefore on particle size. The test described in the *British Pharmacopoeia*,

for example, uses an adaptation of the batch sedimentation chamber method described above.

## Elutriation methods

### Separation ranges

These are shown in Figure 12.7.

### Principles of operation

In sedimentation methods the fluid is stationary and the separation of particles of various sizes depends solely on particle velocity. Therefore, the division of particles into size fractions depends on the *time* of sedimentation.

Elutriation is a technique in which the fluid flows in an opposite direction to the sedimentation movement, so that in gravitational elutriators particles move vertically downwards while the fluid travels vertically upwards. If the upward velocity of the fluid is less than the settling velocity of the particle, sedimentation occurs and the particle moves downwards against the flow of fluid. Conversely, if the settling velocity of the particle is less than the upward fluid velocity, the particle moves upwards with the fluid flow. Therefore, in the case of elutriation, particles are divided into different size fractions depending on the *velocity* of the fluid. Elutriation and sedimentation are compared in Figure 12.8, where the arrows are vectors, that is, they show the direction and magnitude of particle movement. This figure indicates that if particles are suspended in a fluid moving up a column, there will be a clear cut into two fractions of particle size. In practice this does not occur, as there is a distribution of velocities across the tube in which a fluid is flowing – the highest velocity is found in the centre of the tube and the lowest velocity at the tube walls. Therefore, the size of particles that will be separated depends on their position in the tube, the largest particles in the centre, the smallest towards the outside. In practice, particles can be seen to rise

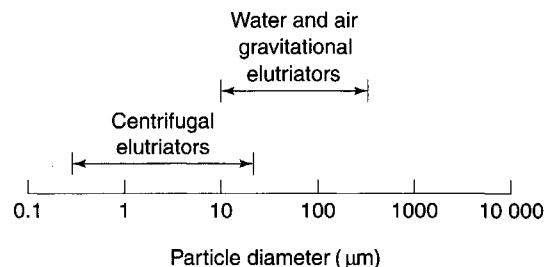


Fig. 12.7 Separation ranges for elutriation methods.



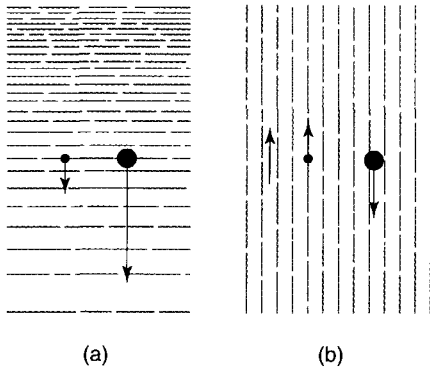


Fig. 12.8 Comparison of (a) sedimentation and (b) elutriation

with the fluid and then to move outwards to the tube wall, where the velocity is lower and they start to fall. A separation into two size fraction occurs, but the size cut will not be clearly defined. Assessing the sharpness of size cuts is discussed in more detail above.

Separation of powders into several size fractions can be effected by using a number of elutriators connected in series. The suspension is fed into the bottom of the narrowest column, overflowing from the top into the bottom of the next widest column and so on (Fig. 12.9). Because the mass flow remains the same, as the column diameter increases the fluid velocity decreases and therefore particles of decreasing size will be separated.

**Alternative techniques**

Air may be used as the counterflow fluid in place of water for elutriation of soluble particles into differ-

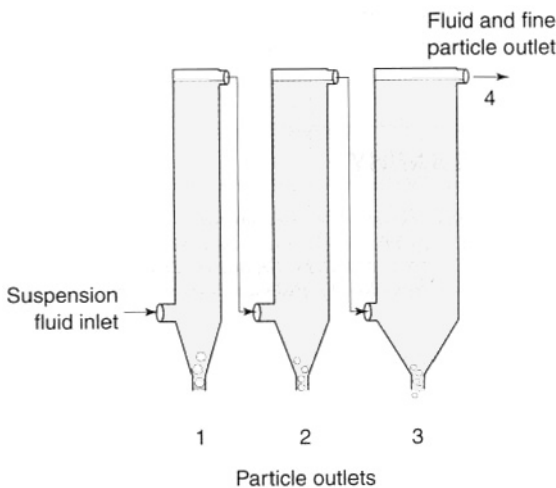


Fig. 12.9 Multistage elutriator. Particle outlets 1 to 4 collect fractions of decreasing particle size.

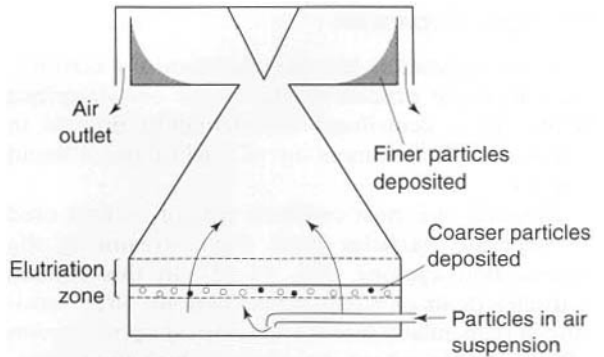


Fig. 12.10 Upward airflow elutriator.

ent size ranges. There are several types of air elutriator, which differ according to the airflow patterns used. An example of an upward airflow elutriator is shown in Figure 12.10. Particles are held on a supporting mesh through which air is drawn. Classification occurs within a very short distance of the mesh and any particles remaining entrained in the air stream are accelerated to a collecting chamber by passage through a conical section of tube. Further separation of any fine particles still entrained in the air flow may be carried out subsequently using different air velocities.

It may be required to separate finer particles than can be achieved using gravitational elutriation, and in these cases counterflow centrifugal methods can be used. Particles in air suspension are fed into a rotating hollow torus at high speed, tangential to the outer wall. Coarse particles move outwards to the walls against the inwardly spiralling air flow, which leaves the elutriator in the centre. The desired particle size fraction can be separated by selecting the appropriate airflow rate and rotor speed.

**Cyclone methods**

*Separation range*

This is shown in Figure 12.11.

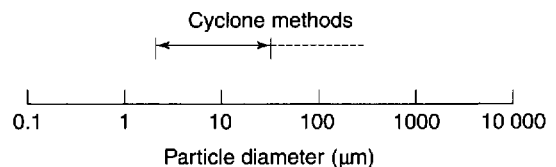


Fig. 12.11 Separation ranges for cyclone methods.

### Principle of operation

Cyclone separation can take the form of a centrifugal elutriation process similar to the one described above, or a centrifugal sedimentation process in which particles sediment out of a helical gas or liquid stream.

Probably the most common type of cyclone used to separate particles from fluid streams is the reverse-flow cyclone (Fig. 12.12). In this system, particles in air or liquid suspension are often introduced tangentially into the cylindrical upper section of the cyclone, where the relatively high fluid velocity produces a vortex that throws solid particles out on to the walls of the cyclone. The particles are forced down the conical section of the cyclone under the influence of the fluid flow – gravity interactions are a relatively insignificant mechanism in this

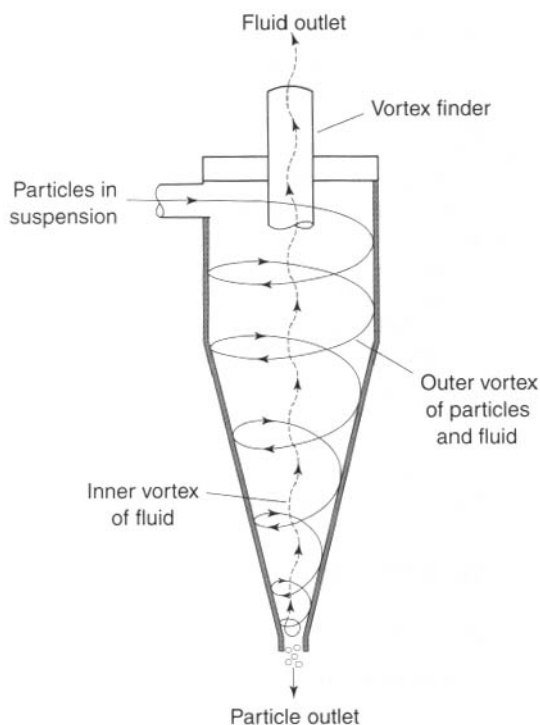


Fig. 12.12 Reverse-flow cyclone separation.

process. At the tip of the conical section the vortex of fluid is above the critical velocity at which it can escape through the narrow outlet and forms an inner vortex which travels back up the cyclone and out through a central outlet or vortex finder. Coarser particles separate from the fluid stream and fall out of the cyclone through the dust outlet, whereas finer particles remain entrained in the fluid stream and leave the cyclone through the vortex finder. In some cases, the outer vortex is allowed to enter a collector connected to the base of the cyclone, but the coarser particles still appear to separate from the fluid stream and remain in the collector. A series of cyclones having different flow rates or different dimensions could be used to separate a powder into different particle-size ranges.

## SELECTION OF A SIZE SEPARATION PROCESS

Selection of a specific size separation may be limited by pharmacopoeial requirements, but for general cases the most efficient method should be selected based on particle properties. Of these, size is particularly important as each separation method is most efficient over a particular size range, as indicated in the foregoing text.

Particles that have just undergone size reduction will already be in suspension in a fluid, whether air or water, and can be separated quickly by elutriation or cyclone separation methods, so that oversize material can be returned to the mill.

Alternatively, many powders used pharmaceutically are soluble in water and size separation may have to be restricted to air classification methods.

## BIBLIOGRAPHY

- Allen, T. (1981) *Particle Size Measurement*, 3rd edn, Chapman and Hall, London and New York.  
 Svarovsky, L. (1981) *Solid Gas Separation (Handbook of Powder Technology, Vol. 3)*, Elsevier, Amsterdam.

# 13

## Mixing

Andrew Twitchell

### CHAPTER CONTENTS

<b>Mixing principles</b>	<b>181</b>
The importance of mixing	181
Definition and objectives of mixing	181
Types of mixtures	182
Positive mixtures	182
Negative mixtures	182
Neutral mixtures	182
The mixing process	182
Scale of scrutiny	183
Mathematical treatment of the mixing process	185
Estimation of particle size required when formulating a dosage form	186
Evaluation of the degree of mixing	186
<b>Mechanisms of mixing and demixing</b>	<b>187</b>
Powders	187
Liquids	188
Powder segregation (demixing)	188
Particle-size effects	188
Particle-density effects	189
Particle-shape effects	189
Ordered mixing	190
Segregation in ordered mixes	190
<b>Mixing of powders</b>	<b>191</b>
Practical considerations	191
Powder mixing equipment	191
Tumbling mixers/blenders	191
High-speed mixer–granulators	192
Fluidized-bed mixers	193
Agitator mixers	193
Scale-up of powder mixing	193
<b>Mixing of miscible liquids and suspensions</b>	<b>194</b>
Propeller mixers	194
Turbine mixers	194
Inline mixers	195
<b>Mixing of semisolids</b>	<b>195</b>
Mixers for semisolids	195
Planetary mixers	195
Sigma-blade mixer	195
<b>References</b>	<b>196</b>
<b>Bibliography</b>	<b>196</b>

### MIXING PRINCIPLES

#### The importance of mixing

There are very few pharmaceutical products that contain only one component. In the vast majority of cases several ingredients are needed so that the required dosage form functions as required. If, for example, a pharmaceutical company wishes to produce a tablet dosage form containing a drug which is active at a dose of 1 mg, other components (e.g. diluents, binders, disintegrants and lubricants) will be needed both to enable the product to be manufactured and for it to be handled by the patient. Whenever a product contains more than one component a mixing or blending stage will be required in the manufacturing process. This may be in order to ensure an even distribution of the active component(s), to ensure an even appearance, or to ensure that the dosage form releases the drug at the correct site and at the desired rate. The unit operation of mixing is therefore involved at some stage in the production of practically every pharmaceutical preparation. This is illustrated below by the list of products that invariably utilize mixing processes of some kind:

- Tablets, capsules, sachets and dry powder inhalers – mixtures of solid particles (powder mixing)
- Linctuses – mixtures of miscible liquids
- Emulsions and creams – mixtures of immiscible liquids
- Pastes and suspensions – dispersions of solid particles.

This chapter considers the objectives of the mixing operation, how mixing occurs, and the ways in which a satisfactory mix can be produced and maintained.

#### Definition and objectives of mixing

Mixing may be defined as a unit operation that aims to treat two or more components, initially in an

unmixed or partially mixed state, so that each unit (particle, molecule etc.) of the components lies as nearly as possible in contact with a unit of each of the other components.

If this is achieved it produces a theoretical 'ideal' situation, i.e. a *perfect mix*. As will be shown, however, this situation is not normally practicable, is frequently unnecessary and is sometimes undesirable (e.g. mixing of lubricants with tablet granules; see Chapter 27).

How closely it is attempted to approach the 'ideal' situation depends on the product being manufactured and the objective of the mixing operation. For example, if a small amount of a potent drug is being mixed in a powder then the degree of mixing must be of a high order to ensure a consistent dose. Similarly, when dispersing two immiscible liquids, or dispersing a solid in a liquid, a well-mixed product is required to ensure product stability. In the case of mixing lubricants during tablet production, however, there is a danger of overmixing and the subsequent production of a weak tablet with an increased disintegration time.

## Types of mixtures

Mixtures may be categorized into three types.

### Positive mixtures

Positive mixtures are formed from materials such as gases or miscible liquids which mix *spontaneously* and *irreversibly* by diffusion, and tend to approach a perfect mix. There is no input of energy required with positive mixtures if the time available for mixing is unlimited, although it will shorten the time required to obtain the desired degree of mixing. In general materials that mix by positive mixing present no problems during product manufacture.

### Negative mixtures

With negative mixtures the components will tend to separate out. If this occurs quickly, then energy must be continuously input to keep the components adequately dispersed, e.g. with a suspension formulation, such as calamine lotion, where there is a dispersion of solids in a liquid of low viscosity. With other negative mixtures the components tend to separate very slowly, e.g. emulsions, creams and viscous suspensions. Negative mixtures are generally more difficult to form and maintain and require a higher degree of mixing efficiency than do positive mixtures.

### Neutral mixtures

Neutral mixtures are said to be static in behaviour, i.e. the components have no tendency to mix spontaneously or segregate spontaneously once work has been input to mix them. Examples of this type of mixture include mixed powders, pastes and ointments.

It should be noted that the type of mixture might change during processing. For example, if the viscosity increases the mixture may change from a negative to a neutral mixture. Similarly, if the particle size, degree of wetting or liquid surface tension changes the mixture type may also change.

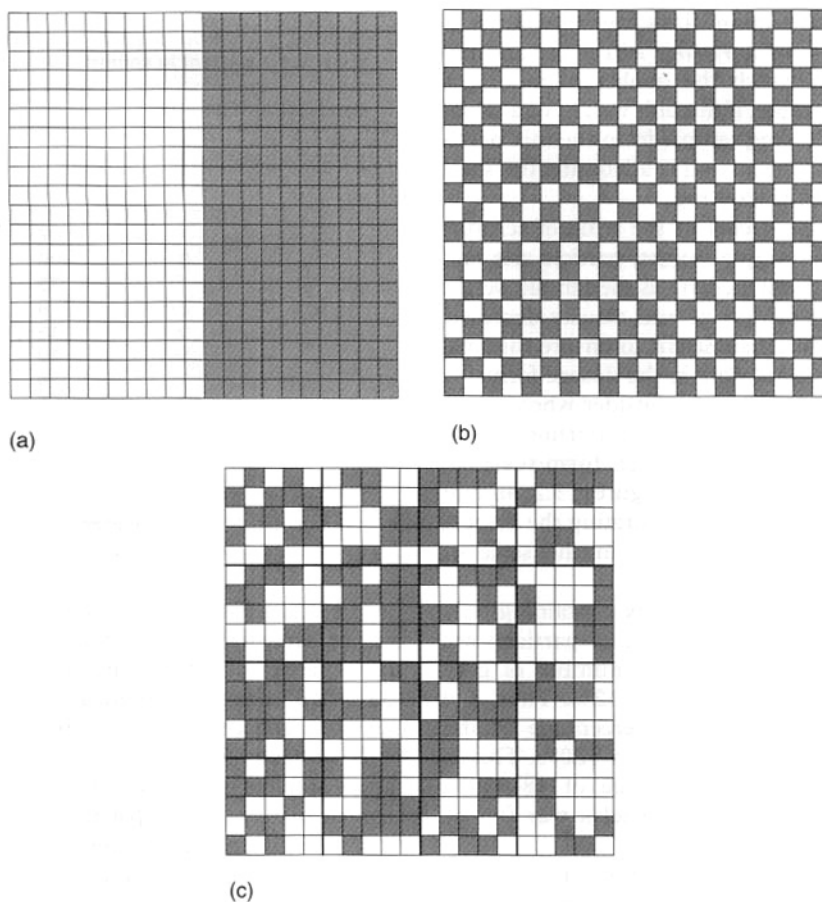
## The mixing process

To discuss the principles of the mixing process, a situation will be considered where there are equal quantities of two powdered components of the same size, shape and density that are required to be mixed, the only difference between them being their colour. This situation will not of course occur practically, but it will serve to simplify the discussion of the mixing process and allow some important considerations to be illustrated with the help of statistical analysis.

If the components are represented by coloured cubes, then a two-dimensional representation of the initial unmixed or completely segregated state can be produced, as shown in Figure 13.1(a).

From the definition of mixing, the ideal situation or '*perfect mix*' in this case would be produced when each particle lay adjacent to a particle of the other component (i.e. each particle lies as closely as possible in contact with a particle of the other component). This is shown in Figure 13.1(b), where it can be seen that the components are as evenly distributed as possible. If this mix were viewed in three dimensions then behind and in front of each grey particle would be a white particle, and vice versa.

Powder mixing, however, is a 'chance' process, and although the situation shown in Figure 13.1(b) could arise, the odds against it are so great that for practical purposes it can be considered impossible. For example, if there are only 200 particles present the chance of a perfect mix occurring is approximately 1 in  $10^{60}$  and is similar to the chance of the situation in Figure 13.1(a) occurring after prolonged mixing. In practice, the best type of mix likely to be obtained will have the components under consideration distributed as indicated in Figure 13.1(c). This is referred to as a *random mix*, which is defined as a mix where the *probability* of selecting a particular type of particle is the *same* at all positions in the mix, and is equal to the *proportion* of such particles in the total mix.



**Fig. 13.1** Different states of powder mixing. (a) Complete segregation. (b) An ideal or 'perfect' mix. (c) A random mix.

If any two adjacent particles are selected from the random mix shown:

the chance of picking two grey particles = 1 in 4 (25%)

the chance of picking two white particles = 1 in 4 (25%)

and the chance of picking one of each = 2 in 4 (50%).

If any two adjacent particles are selected from the perfect mix shown, there will always be one grey and one white particle.

Thus if the samples taken from a random mix contain only two particles, then in 25% of cases the sample will contain no white particles and in 25% it will contain no grey particles.

It can be seen that in practice the components will not be perfectly evenly distributed, i.e. there will not be full mixing. However, if an overall view is taken the components can be described as being mixed, as in the total sample (Fig. 13.1c) the amounts of each component are approximately similar (48.8% grey and 51.2% white). If, however, Figure 13.1(c) is con-

sidered as 16 different blocks of 25 particles, then it can be seen that the number of grey particles in the blocks varies from 6 to 19 (i.e. 24–76% of the total number of particles in each block). Careful examination of Figure 13.1(c) shows that as the number of particles in the sample increases then the closer will be the proportion of each component to that which would occur with a perfect mix. This is a very important consideration in powder mixing, and is discussed in more detail in the sections that follow.

### Scale of scrutiny

Often a mixing process produces a large 'bulk' of mixture that is subsequently subdivided into individual dose units (e.g. a tablet, capsule or 5 mL spoonful) and it is important that each dosage unit contains the correct amount/concentration of active component(s). It is the weight/volume of the *dosage unit* that dictates how closely the mix must be examined/analysed to ensure it contains the

correct dose/concentration. This weight/volume is known as the *scale of scrutiny* and is the amount of material within which the quality of mixing is important. For example, if the unit weight of a tablet is 200 mg then a 200 mg sample from the mix needs to be analysed to see if mixing is adequate; the scale of scrutiny is therefore 200 mg.

The number of *particles* in the scale of scrutiny will depend on the sample weight, particle size and particle density, and will increase as the sample weight increases and the particle size and density decrease. This number should be sufficient to ensure minimal deviation in the required dose in the dosage forms.

Another important factor to consider when carrying out a mixing process is the proportion of the active component in the dosage form/scale of scrutiny. This is illustrated in Figure 13.2 and in Table 13.1, the latter also demonstrating the importance of the number of particles in the scale of scrutiny.

Figure 13.2 shows a random mix containing only 10% grey particles. If the blocks of 25 particles are examined it can be seen that the number of grey particles varies from 0 to 8, or 0–32%. Thus, the number of grey particles as a percentage of the theoretical content varies from 0 to 320%. This is considerably greater than the range of 48–152% when the proportion of grey particles was 0.5 or 50% (Fig. 13.1(c)).

Table 13.1 shows how the content of a minor active constituent (present in a proportion of one part in a 1000, i.e. 0.1%) typically varies with the number of particles in the scale of scrutiny when sampling a random mix. In the example shown, when there are 1000 particles in scale of scrutiny three samples contain no active constituent and two have twice the amount that should be present. With 10 000 particles

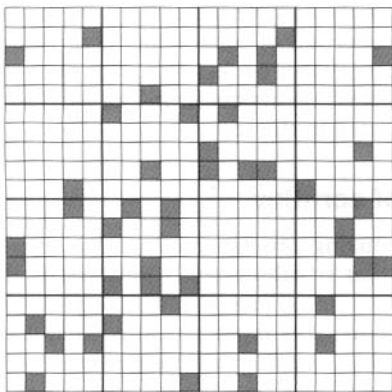


Fig. 13.2 Particle distribution in a representative random mix containing 10% active ingredient.

Table 13.1 Number of particles of a minor active constituent present in samples taken from a 1:1000 random powder mix with different numbers of particles in the scale of scrutiny

Sample number	Number of particles in scale of scrutiny		
	1000	10 000	100 000
1	1	7	108
2	0	10	91
3	1	15	116
4	2	8	105
5	0	13	84
6	1	10	93
7	1	6	113
8	2	5	92
9	0	12	104
10	1	13	90

The figures in the table are the numbers of particles of the minor constituent in the samples.

in the scale of scrutiny the deviation is reduced, but samples may still deviate from the theoretical content of 10 particles by  $\pm 50\%$ . Even with 100 000 particles deviation from the theoretical content may be  $\pm 15\%$ , which is unacceptable for a pharmaceutical mixture. The difficulty in mixing potent substances can be appreciated if it is realized that there may only be approximately 75 000 particles of diameter  $150 \mu\text{m}$  in a tablet weighing 200 mg.

The information in Figures 13.1 and 13.2 and Table 13.1 leads to two important conclusions:

1. The lower the proportion of active component present in the mixture the more difficult it is to achieve an acceptably low deviation in active content.
2. The more particles there are present in a unit dose/scale of scrutiny the lower the deviation in content.

One way of reducing the deviation, therefore, would be to increase number of particles in the scale of scrutiny by reducing particle size. This may, however, lead to particle aggregation owing to the increased cohesion that occurs with smaller particles, which in turn may reduce the ease of mixing.

It should be noted that with liquids even very small samples are likely to contain many million 'particles'. Deviation in content is therefore likely to be very small with miscible liquids, even if they are randomly mixed. Diffusion effects in miscible liquids arising from the existence of concentration gradients in an unmixed system mean they tend to approach a perfect mix.

## Mathematical treatment of the mixing process

It must be appreciated that there will always be some variation in the composition of samples taken from a random mix. The aim during formulation and processing is to minimize this variation to acceptable levels by selecting an appropriate scale of scrutiny, particle size and mixing procedure (choice of mixer, rotation speed etc). The following section uses a simplified statistical approach to illustrate some of the factors that influence dose variation within a batch of a dosage form, and demonstrates the difficulties encountered with drugs that are active in low doses (i.e. potent drugs).

Consider the situation where samples are taken from a random mix in which the particles are all of the same size, shape and density. The variation in the proportion of a component in samples taken from the random mix can be calculated from:

$$SD = \sqrt{\frac{p(1-p)}{n}} \quad (13.1)$$

where SD is the standard deviation in the proportion of the component in the samples (content sample deviation),  $p$  is the proportion of the component in the total mix and  $n$  is the total number of particles in the sample.

Equation 13.1 shows that as the number of particles present in the sample increases the content standard deviation decreases (i.e. there is less variation in sample content), as illustrated previously by the data in Figure 13.2 and Table 13.1. The situation with respect to the effect of the proportion of the active component in the sample is not as clear from Eqn 13.1. As  $p$  is decreased the value of the content standard deviation decreases, which may lead to the incorrect conclusion that it is beneficial to have a low proportion of the active component. A more useful parameter to determine is the percentage coefficient of variation (%CV), which indicates the average deviation as a percentage of the mean amount of active component in the samples. Thus, %CV = (content standard deviation/mean content)  $\times$  100. The value of %CV will increase as  $p$  decreases, as illustrated below.

Consider the situation where  $n = 100\,000$  and  $p = 0.5$ . Using Eqn 13.1, it can be calculated that  $SD = 1.58 \times 10^{-3}$  and %CV =  $(1.58 \times 10^{-3}/0.5) \times 100 = 0.32\%$ . Thus on average the content will deviate from the mean content by 0.32%, which is an acceptably low value for a pharmaceutical product.

However, if  $p$  is reduced to 0.001 and  $n$  remains at 100 000 there is a reduction in SD to  $9.99 \times 10^{-5}$ , but the %CV =  $(9.99 \times 10^{-5}/0.001) \times 100 = 10\%$ .

Thus in this latter case the content will deviate from theoretical content on average by 10%, which would be unacceptable for a pharmaceutical product.

It might be considered that the variation in content could be reduced by increasing the sample size (scale of scrutiny), as this would increase the number of particles in each sample. The dose of a drug will, however, be fixed, and any increase in the sample size will cause a reduction in the proportion of the active component. The consequence of increasing the sample size depends on the initial proportion of the active component. If  $p$  is relatively high initially, increasing the sample size causes the %CV in content to increase. If  $p$  is small, increasing the sample size has little effect. Inserting the appropriate values into Eqn 13.1 can substantiate this.

In a true random mix the content of samples taken from the mix will follow a normal distribution. With a normal distribution, 68.3% of samples will be within  $\pm 1$  SD of the overall proportion of the component ( $p$ ), 95.5% will be within  $\pm 2$  SD of  $p$ , and 99.7% of samples will be within  $\pm 3$  SD of  $p$ . For example, if  $p = 0.5$  and the standard deviation in content is 0.02, then for 99.7% of samples the proportion of the component will be between 0.44 and 0.56. In other words, if 1000 samples were analysed, 997 would contain between 44% and 56% of drug (mean = 50%).

A typical specification for a pharmaceutical product is that the active component should not deviate by more than  $\pm 5\%$  of the mean or specified content, i.e. the acceptable deviation =  $p \times (5/100)$  or  $p \times 0.05$ . (NB: this is not the same as a standard deviation of 5%.)

If a product contains an active component which makes up half of the weight of the dosage form ( $p = 0.5$ ) and it is required that the content of 99.7% of samples is within  $\pm 5\%$  of  $p$ , then the number of particles required in the product can be estimated as described below.

As 99.7% of samples will be within  $\pm 3$  SD and  $\pm 5\%$  of  $p$ , then Eqn 13.2 can be used to calculate the standard deviation required:

$$3 \times SD = p \times (\% \text{ acceptable deviation}/100) \quad (13.2)$$

In this case,  $3 \times SD = 0.5 \times 0.05$

$$\text{so} \quad \frac{0.5 \times 0.05}{3} = \sqrt{\frac{p(1-p)}{n}}$$

$$6.94 \times 10^{-5} = 0.5 (1 - 0.5)/n$$

and therefore  $n = 3600$ .

The above calculation indicates that 3600 particles are required in each sample or dosage form in order to be 99.7% sure that the content is within  $\pm 5\%$  of the theoretical amount.

If, however, the product contains a potent drug where  $p = 1 \times 10^{-3}$ , the number of particles needed to meet the same criteria can be estimated to be  $3.6 \times 10^6$ .

### Estimation of particle size required when formulating a dosage form

Using the above information it is possible to estimate the particle size required so that a formulation may meet a desired specification. For example, imagine a tablet weighing 50 mg which contains 50  $\mu\text{g}$  of a potent steroid needs to be produced, and that the product specification requires 99.7% of tablets to contain between 47.5  $\mu\text{g}$  and 52.5  $\mu\text{g}$  of steroid. If the mean particle density of the components is 1.5  $\text{g}/\text{cm}^3$  (1500  $\text{kg}/\text{m}^3$ ), what particle size should the steroid and the excipients be?

As there is 50  $\mu\text{g}$  of the steroid in a 50 mg tablet, the proportion of active component ( $p$ ) is  $1 \times 10^{-3}$ . The specification allows the content to vary by  $\pm 2.5 \mu\text{g}$ , and so the percentage deviation allowed is  $(2.5/50) \times 100 = 5\%$ . Under these circumstances the previous section showed that, provided a random mix is achieved, the number of particles required in the tablet is  $3.6 \times 10^6$ . The 50 mg tablet must therefore contain at least  $3.6 \times 10^6$  particles and each particle must weigh less than  $50/3.6 \times 10^6 \text{ mg} = 1.39 \times 10^{-5} \text{ mg} = 1.39 \times 10^{-11} \text{ kg}$ . Because the density of a particle is equal to particle mass/particle volume, the volume of each particle must be less than  $1.39 \times 10^{-11}/1500 \text{ m}^3 = 9.27 \times 10^{-15} \text{ m}^3$ .

The volume of a particle (assuming it is spherical) is  $4 \pi r^3/3$ , and so

$$\begin{aligned} r^3 &\text{ must be } < 9.27 \times 10^{-15} \times 3/4\pi, \\ r^3 &< 2.21 \times 10^{-15} \text{ m}^3 \text{ and} \\ r &< 1.30 \times 10^{-5} \text{ m } (d < 26 \mu\text{m}). \end{aligned}$$

This calculation therefore indicates that in order to meet the product specification, the particle size of the components needs to be of the order of 26  $\mu\text{m}$ . There would therefore be practical difficulties in making this product, as particles of this size tend to become very cohesive, flow poorly (see Chapter 14), and are difficult to mix.

In order to appreciate the effect of changing the scale of scrutiny, it is suggested that the reader calculates what particle size would be required if the tablet weight was increased to 250 mg. It should be remembered that the tablet weight or scale of scrutiny will affect both the number of particles present and the proportion of active component.

In summary, the above calculations illustrate the difficulty of mixing potent (low-dose) substances

and the importance of both the number of particles in the scale of scrutiny and the proportion of the active component.

## Evaluation of the degree of mixing

Manufacturers require some means of monitoring a mixing process for a variety of reasons; these could include:

- To indicate the degree/extent of mixing
- To follow a mixing process
- To indicate when sufficient mixing has occurred
- To assess the efficiency of a mixer
- To determine the mixing time required for a particular process.

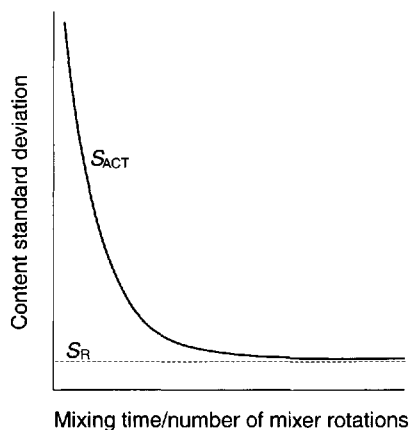
Many evaluation methods involve the generation of a **mixing index**, which compares the content standard deviation of samples taken from a mix under investigation ( $S_{\text{ACT}}$ ) with that of samples from a fully random mix ( $S_{\text{R}}$ ). Comparison with a random mix is made because this is theoretically likely to be the best mix that is practically achievable. The simplest form of a mixing index ( $M$ ) can be calculated as:

$$M = \frac{S_{\text{R}}}{S_{\text{ACT}}} \quad (13.3)$$

At the start of the mixing process the value of  $S_{\text{ACT}}$  will be high and that for  $M$  will be low. As mixing proceeds  $S_{\text{ACT}}$  will tend to decrease as the mix approaches a random mix (Fig. 13.3). If the mix becomes random,  $S_{\text{ACT}} = S_{\text{R}}$  and  $M = 1$ . There is typically an exponential decrease in  $S_{\text{ACT}}$  as the mixing time or number of mixer rotations increases, although the shape of the curve will depend on the powder properties and mixer design and use. Other more complicated equations for calculating the mixing index have been used, but all tend to rely on similar principles to those described.

In order to evaluate a mixing process in this way there are two basic requirements. First, a sufficient number of samples which are representative of the mix as a whole must be removed and analysed. A minimum of 10 samples is usually taken, these being removed from different depths into the mixer and from the middle and sides. Samples are often taken with a 'sampling thief', which is a device that can be inserted into the mix and samples withdrawn with minimum disruption to the powder bed. Second, a suitable analytical technique must be available so that the value of  $S_{\text{ACT}}$  is a true reflection of the variation in content in the samples and not due to variation arising from the method of analysis.





**Fig. 13.3** The reduction in content standard deviation as a random mix is approached.  $S_{ACT}$  represents the content standard deviation of samples taken from the mix and  $S_R$  the standard deviation expected from a random mix.

When mixing formulations where the proportion of active component is high it is possible to achieve an acceptably low variation in content without obtaining a random mix. Thus it may be possible to stop the mixing process before a random mix is achieved and thereby reduce manufacturing costs. Equation 13.2 can be used to generate an estimated acceptable standard deviation value ( $S_E$ ) that will allow the product to meet its specification. For example, if the proportion of active component present in the formulation is 0.5 and the acceptable variation from the mean content is  $\pm 5\%$  for 99.7% of samples, then:

$$S_E = \frac{0.5 \times (5 / 100)}{3} = 8.3 \times 10^{-3}$$

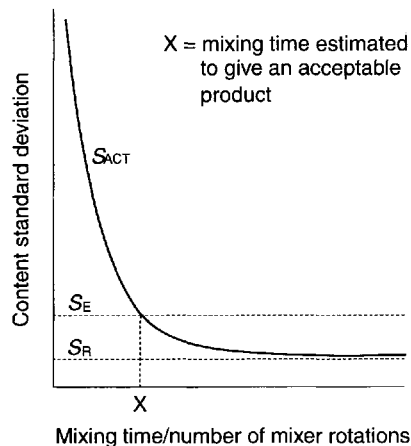
Therefore, if when the mix is analysed the content standard deviation in the proportion of the active component is  $< 8.3 \times 10^{-3}$  (%CV  $< 1.67$ ), the product should meet the specification. This approach is illustrated in Figure 13.4.

## MECHANISMS OF MIXING AND DEMIXING

### Powders

In order that powders may be mixed, the powder particles need to move relative to each other. There are three main mechanisms by which powder mixing occurs, namely *convection*, *shear* and *diffusion*.

Convective mixing arises when there is the transfer of relatively large groups of particles from one



**Fig. 13.4** The reduction in mixing time possible if a random mix is not required.  $S_{ACT}$  represents the content standard deviation of samples taken from the mix,  $S_E$  the estimated acceptable standard deviation and  $S_R$  the standard deviation expected from a random mix.

part of the powder bed to another, as might occur when a mixer blade or paddle moves through the mix, for example. This type of mixing contributes mainly to the macroscopic mixing of powder mixtures and tends to produce a large degree of mixing fairly quickly (as evidenced by a rapid drop in  $S_{ACT}$ ). Mixing does not, however, occur *within* the group of particles moving together as a unit, and so in order to achieve a random mix an extended mixing time is required.

Shear mixing occurs when a 'layer' of material moves/flows over another 'layer'. This might be due to the removal of a mass by convective mixing creating an unstable shear/slip plane, which causes the powder bed to collapse. It may also occur in high-shear mixers or tumbling mixers, where the action of the mixer induces velocity gradients within the powder bed and hence 'shearing' of one layer over another.

In order to achieve a true random mix, movement of individual particles is required. This occurs with diffusive mixing.

When a powder bed is forced to move or flow it will 'dilate', i.e. the volume occupied by the bed will increase. This is because the powder particles will become less tightly packed and there is an increase in the air spaces or voids between them. Under these circumstances there is the potential for the particles to fall under gravity, through the voids created. Mixing of individual particles in this way is referred to as diffusive mixing. Diffusive mixing, although having the potential to produce a random mix, generally results in a low rate of mixing.

All three mixing mechanisms are likely to occur in a mixing operation. Which one predominates and the extent to which each occurs will depend on the mixer type, mixing process conditions (mixer load, speed etc.) and the flowability of the powder components.

### Liquids

The three main mechanisms by which liquids are mixed are **bulk transport**, **turbulent mixing** and **molecular diffusion**.

Bulk transport is analogous to the convective mixing of powders and involves the movement of a relatively large amount of material from one position in the mix to another, e.g. due to a mixer paddle. It too tends to produce a large degree of mixing fairly quickly, but leaves the liquid within the moving material unmixed.

Turbulent mixing arises from the haphazard movement of molecules when forced to move in a turbulent manner. The constant changes in speed and direction of movement means that induced turbulence is a highly effective mechanism for mixing. Within a turbulent fluid there are, however, small groups of molecules moving together as a unit, referred to as eddies. These eddies tend to reduce in size and eventually break up, being replaced by new eddies. Turbulent mixing alone may therefore leave small unmixed areas within the eddies and in areas near the container surface which will exhibit streamlined flow (see Chapter 4). Mixing of individual molecules in these regions will occur by the third mechanism, which is molecular diffusion (analogous to diffusive mixing in powders). This will occur with miscible fluids wherever a concentration gradient exists and will eventually produce a well-mixed product, although considerable time may be required if this is the only mixing mechanism. In most mixers all three mechanisms will occur, bulk transport and turbulence arising from the movement of a stirrer or mixer paddle set at a suitable speed.

### Powder segregation (demixing)

Segregation is the opposite effect to mixing, i.e. components tend to separate out. This is very important in the preparation of pharmaceutical products, because if it occurs, a mix may change from being random to being non-random, or a random mix may never be achieved. Care must be taken to avoid segregation during handling after powders have been mixed, e.g. during transfer to filling machines, or in the hopper of a tablet/capsule/sachet-filling machine.

Segregation will cause an increase in content variation in samples taken from the mix and may cause a batch to fail a uniformity of content test. If segregation of granules occurs in the hopper of a filling machine an unacceptable variation in weight may result.

Segregation arises because powder mixes encountered practically are not composed of mono-sized spherical particles, but contain particles that differ in size, shape and density. These variations mean that particles will tend to behave differently when forced to move and hence, tend to separate. Particles exhibiting similar properties tend to congregate together, giving regions in the powder bed which have a higher concentration of a particular component. Segregation is more likely to occur, or may occur to a greater extent, if the powder bed is subjected to vibration and when the particles have greater flowability.

### Particle-size effects

A difference in the particle sizes of components of a formulation is the main cause of segregation in powder mixes in practice. Smaller particles tend to fall through the voids between larger ones and so move to the bottom of the mass. This is known as **percolation segregation**. It may occur in static powder beds if the percolating particles are so small that they can fall into the void spaces between larger particles, but occurs to a greater extent as the bed 'dilates' on being disturbed. Domestically, percolation segregation is often observed in cereal packets or jars of coffee, where the smaller 'particles' congregate towards the bottom of the container.

Percolation can occur whenever a powder bed containing particles of different size is disturbed in such a way that particle rearrangement occurs, e.g. during vibration, stirring or pouring.

During mixing, larger particles will tend to have greater kinetic energy imparted to them (owing to their larger mass) and therefore move greater distances than smaller particles before they come to rest. This may result in the separation of particles of different size, an effect referred to as **trajectory segregation**. This effect, along with percolation segregation, accounts for the occurrence of the larger particles at the edge of a powder heap when it is poured from a container.

During mixing, or when a material is discharged from a container, very small particles ('dust') in a mix may tend to be 'blown' upwards by turbulent air currents as the mass tumbles, and remain suspended in the air. When the mixer is stopped or

material discharge is complete, these particles will sediment and subsequently form a layer on top of the coarser particles. This is called *elutriation segregation* and is also referred to as 'dusting out'.

### Particle-density effects

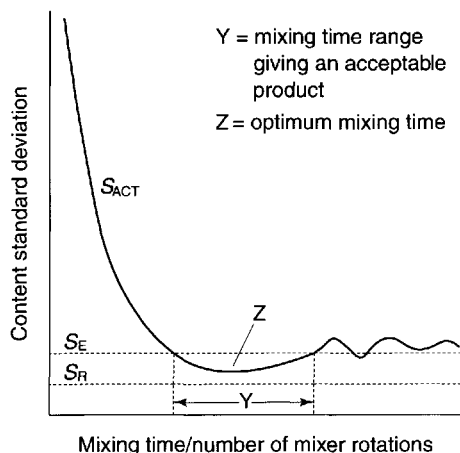
If components are of different density, the more dense material will have a tendency to move downwards even if the particle sizes are similar. Trajectory segregation may also occur with particles of the same size but different densities, owing to their difference in mass. The effect of density on percolation segregation may be potentiated if the more dense particles are also smaller. Alternatively, size and density effects may cancel each other out if the larger particles are more dense. Often materials used in pharmaceutical formulations have similar density values and density effects are not generally too important. An exception to this is in fluidized beds, where density differences are often more serious than particle size differences.

### Particle-shape effects

Spherical particles exhibit the greatest flowability and are therefore more easily mixed, but they also segregate more easily than non-spherical particles. Irregularly or needle-shaped particles may become interlocked, reducing the tendency to segregate once mixing has occurred. Non-spherical particles will also have a greater surface area to weight ratio (specific surface area), which will tend to decrease segregation by increasing any cohesive effects (greater contact surface area), but will also increase the likelihood of 'dusting out'.

It should be remembered that the particle size distribution and particle shape may change during processing (owing to attrition, aggregation etc.), and therefore the tendency to segregate may also change.

Non-segregating mixes will improve with continued increases in mixing time, as shown in Figure 13.3. This may not, however, occur for segregating mixes, where there is often an optimum mixing time. This is because the factors causing segregation generally require longer to take effect than the time needed to produce a reasonable degree of mixing. During the initial stages of the process the rate of mixing is greater than the rate of demixing. After a period of time, however, the rate of demixing may predominate until eventually an equilibrium situation will be reached



**Fig. 13.5** Possible effect of extended mixing time on the content standard deviation of samples taken from a mix prone to segregation.  $S_{ACT}$  represents the content standard deviation of samples taken from the mix,  $S_E$  the estimated acceptable standard deviation and  $S_R$  the standard deviation expected from a random mix.

where the two effects are balanced. This is illustrated in Figure 13.5, which demonstrates that, if factors exist that might cause segregation, a random mix will not be achieved and there may be both an optimum mixing time and a time range over which an acceptable mix can be produced.

If segregation is a problem with a formulation there are a number of approaches that may be attempted to rectify the situation. These include:

- Selection of particular size fractions (e.g. by sieving to remove fines or lumps) to achieve drug and excipients of the same narrow particle size range;
- Milling of components (size reduction) either to reduce the particle size range (this may need to be followed by a sieving stage to remove fines) or to ensure that all particles are below approximately  $30\ \mu\text{m}$  – at which size segregation does not tend to cause serious problems (but may give rise to aggregation);
- Controlled crystallization during production of the drug/excipients to give components of a particular crystal shape or size range;
- Selection of excipients which have a density similar to the active component(s); there is usually a range of excipients that will produce a product with the required properties;
- Granulation of the powder mix (size enlargement) so that large numbers of different particles are evenly distributed in each segregating 'unit'/granule; (see Fig. 25.1).

- Reduce the extent to which the powder mass is subjected to vibration or movement after mixing;
- Use filling machine hoppers designed so that powder residence time is minimized;
- Use equipment where several operations can be carried out without transferring the mix, e.g. a fluidized-bed drier or a high-speed mixer/granulator for mixing and granulating;
- Production of an 'ordered' mix.

This latter technique, which may also be referred to as *adhesive* or *interactive* mixing, is described in greater detail below.

## Ordered mixing

It would be expected that a mix comprised of very small and much larger particles would segregate because of the size differences. Sometimes, however, if one powder is sufficiently small (micronized) it may become adsorbed on to the 'active sites' on the surface of a larger 'carrier' particle and exhibit great resistance to being dislodged. This has the effect of minimizing segregation while maintaining good flow properties. It was first noticed during the mixing of micronized sodium bicarbonate with sucrose crystals, when the mixture was found to exhibit minimal segregation. The phenomenon is referred to as ordered mixing, as the particles are not independent of each other and there is a degree of order to the mix. If a carrier particle is removed then some of the adsorbed smaller particles will automatically be removed with it. Ordered mixing has also been used in the production of dry antibiotic formulations to which water is added before use to form a liquid or syrup product. In these cases the antibiotic in fine powder form is blended with, and adsorbed on to, the surface of larger sucrose or sorbitol particles (Nikolakakis and Newton 1989).

Ordered mixing probably occurs to a certain extent in every pharmaceutical powder mix, owing to interactions and cohesive/adhesive forces between constituents. It is most likely to occur when smaller particles exist, as these have a high specific surface area and so the attractive forces holding the particles to the adsorption site are more likely to be greater than the gravitational forces trying to separate the components.

Pharmaceutical mixes are therefore likely to be partly ordered and partly random, the extent of each depending on the component properties. With an ordered mix it may be possible to achieve a degree of mixing which is superior to that of a random mix, which may be beneficial for potent drugs.

Ordered mixing has been shown to be important in direct compression formulations (see Chapter 27) in preventing the segregation of drug from direct compression bases.

Dry powder inhaler formulations also use ordered mixing to deliver drugs to the lungs (see Chapter 31). In this case the drug needs to be in a micronized form in order to reach its site of action. By adsorbing the drug on to larger carrier particles (usually lactose) it is possible to manufacture a product that will provide an even dosage on each inhalation.

## Segregation in ordered mixes

Although ordered mixes can reduce or prevent segregation, it may still occur if:

1. ***The carrier particles vary in size.*** Different-sized particles will have different surface area to weight ratios and will contain different amounts of adsorbed material per unit mass. If the different-sized carrier particles separate (e.g. by percolation segregation), drug-rich areas where the smaller carrier particles congregate may result. This is referred to as ***ordered unit segregation***.
2. ***There is competition for the active sites on the carrier particle.*** If another component competes for sites on the carrier it may displace the original adsorbed material, which may then segregate owing to its small size. This is known as ***displacement segregation***, and has been shown to occur under certain circumstances with the addition of the lubricant magnesium stearate to tablet formulations.
3. ***There are insufficient carrier particles.*** Each carrier particle can only accommodate a certain amount of adsorbed material on its surface. If there is any excess small-sized material that is not adsorbed on to the carrier particles this may quickly separate. This is referred to as ***saturation segregation***, and may limit the proportion of the active component that can be used in the formulation.

With an ordered mix particles may be dislodged if the mix is subjected to excessive vibration. The extent to which this occurs depends on the forces of attraction between the components and therefore on how tightly the adsorbed particles are attached to the surface. The orientation of the particles is also important, those protruding from the surface being more likely to be dislodged than those lying parallel to it.

## MIXING OF POWDERS

### Practical considerations

When mixing formulations where there is a relatively low proportion of active ingredient(s) a more even distribution may be obtained by building up the amount of material in the mixer sequentially. This may be achieved by initially mixing the active component(s) with an approximately equal volume of diluent(s). Further amounts of diluents, equal to the amount of material in the mixer, can then be added and mixed, the process being continued until all material has been added. It may be more appropriate to pre-blend the active component with a diluent in a smaller mixer prior to transferring it to the main mixer in cases where the amount of active ingredient is very small.

Care must be taken to ensure that the volume of powder in the mixer is appropriate, as both over and underfilling may significantly reduce mixing efficiency. In the case of overfilling, for example, sufficient bed dilation may not take place for diffusive mixing to occur to the required extent, or the material may not be able to flow in a way that enables shear mixing to occur satisfactorily. Similarly, underfilling may mean the powder bed does not move in the required manner in the mixer, or that an increased number of mixing operations may be needed for a batch of material.

The mixer used should produce the mixing mechanisms appropriate for the formulation. For example, diffusive mixing is generally preferable for potent drugs, and high shear is needed to break up aggregates of cohesive materials and ensure mixing at a particulate level. The impact or attrition forces generated if too-high shear forces are used may, however, damage fragile material and so produce fines.

The mixer design should be such that it is dust-tight, can be easily cleaned, and the product can be fully discharged. These reduce the risk of cross-contamination between batches and protect the operator from the product.

In order to determine the appropriate mixing time, the process should be checked by removing and analysing representative samples after different mixing intervals. This may also indicate whether segregation is occurring in the mixer, and whether problems occur if the mixing time is extended.

When particles rub past each other as they move within the mixer, static charges will be produced. These tend to result in 'clumping' and a reduction in diffusive mixing, and cause material to adhere to

machine or container surfaces. To avoid this, mixers should be suitably earthed to dissipate the static charge and the process should be carried out at a relative humidity greater than approximately 40%.

### Powder mixing equipment

#### Tumbling mixers/blenders

Tumbling mixers are commonly used for the mixing/blending of granules or free-flowing powders. There are many different designs of tumbling mixer, e.g. double-cone mixers, twin-shell mixers, cube mixers, Y-cone mixers and drum mixers, some of which are shown diagrammatically in Figure 13.6. It is now common to use *intermediate bulk containers* (IBCs) both as the mixer bowl and to either feed the hopper of a tablet or capsule machine or as the hopper itself. The shape of an IBC used for this purpose is illustrated in Figure 13.7.

Mixing containers are generally mounted so that they can be rotated about an axis. When operated at the correct speed, the tumbling action indicated in Figure 13.8 is achieved. Shear mixing will occur as a velocity gradient is produced, the top layer moving with the greatest velocity and the velocity decreasing as the distance from the surface increases. When the bed tumbles it dilates, allowing particles to move

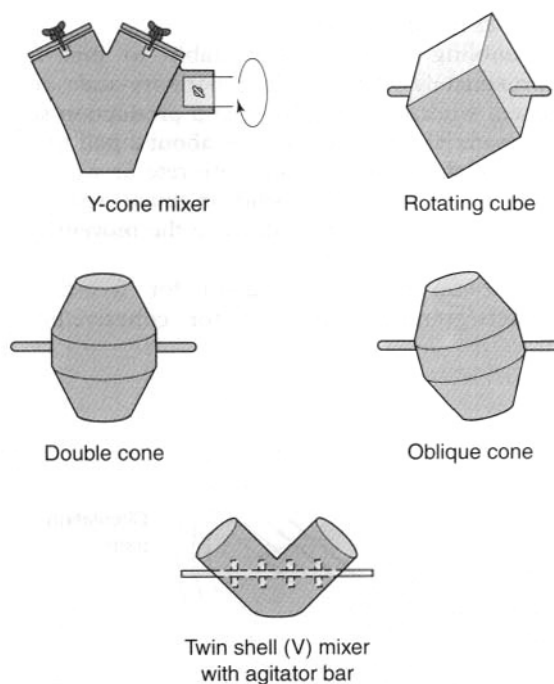


Fig. 13.6 Different designs of tumbling mixers.

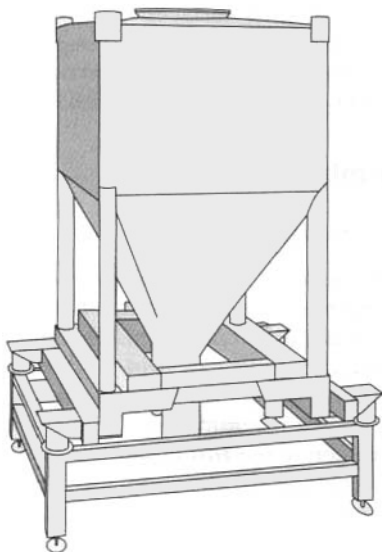


Fig. 13.7 Typical intermediate bulk container.

downwards under gravity, and so diffusive mixing occurs. Too high a rotation speed will cause the material to be held on the mixer walls by centrifugal force, and too low a speed will generate insufficient bed expansion and little shear mixing. The addition of 'prongs', baffles or rotating bars will also cause convective mixing, for example the V-mixer with agitator bar in Figure 13.6.

Tumbling mixers are available to mix from approximately 50 g, e.g. for laboratory-scale development work, to over 100 kg at a production scale. The material typically occupies about a half to two-thirds of the mixer volume. The rate at which the product is mixed will depend on mixer design and rotation speed, as these influence the movement of the material in the mixer.

Tumbling mixers are good for free-flowing powders/granules but poor for cohesive/poorly

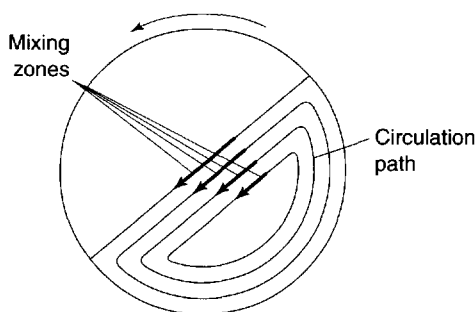


Fig. 13.8 Movement of the powder bed in a tumbling mixer.

flowing powders, because the shear forces generated are usually insufficient to break up any aggregates. Care must also be taken if there are significant differences in particle size present, as segregation is likely to occur. A common use of tumbling mixers is in the blending of lubricants, glidants or external disintegrants with granules prior to tableting.

Tumbling mixers can also be used to produce ordered mixes, although the process is often slow because of the cohesiveness of the adsorbing particles.

The Turbula shaker-mixer (WAB, Switzerland) is a more sophisticated form of tumbling mixer that uses inversional motion in addition to the rotational and translational motion of traditional tumbling mixers. This leads to more efficient mixing and makes it less likely that materials of different sizes and densities will segregate.

### High-speed mixer-granulators

In pharmaceutical product manufacture it is often preferable to use one piece of equipment to carry out more than one function. An example of this is the use of a mixer-granulator (one design of which is shown diagrammatically in Figure 13.9). As the name suggests, it can both mix and granulate a product, thereby removing the need to transfer the product between pieces of equipment and so reducing the opportunity for segregation to occur.

The centrally mounted impeller blade at the bottom of the mixer rotates at high speed, throwing the material towards the mixer bowl wall by centrifugal force. The material is then forced upwards before dropping back down towards the centre of the mixer. The particulate movement within the bowl tends to mix the components quickly owing to high shear forces (arising from the high velocity) and the expansion in bed volume that allows diffusive mixing. Once mixed, granulating agent can be added and granules formed in situ using a slower impeller speed and the action of the side-mounted chopper blade. Further details of granule production using this method can be found in Chapter 25.

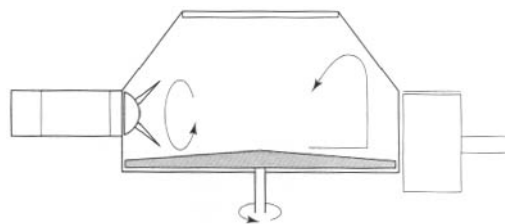


Fig. 13.9 Diagrammatic representation of a high-speed mixer-granulator.

Because of the high-speed movement within a mixer–granulator, care must be taken if material fractures easily. This, and the problems associated with overmixing of lubricants, means that this type of mixer is not normally used for blending lubricants.

### Fluidized-bed mixers

The main use of fluidized-bed equipment is in the drying of granules (Chapter 26) or the coating of multiparticulates (Chapter 28). Fluidized-bed equipment can, however, be used to mix powders prior to granulation in the same bowl. This is discussed in detail in Chapter 25.

### Agitator mixers

This type of mixer depends on the motion of a blade or paddle through the product, and hence the main mixing mechanism is convection. Examples include the ribbon mixer (Fig. 13.10), the planetary mixer (Fig. 13.11) and the Nautamixer (Fig. 13.12). In the first, mixing is achieved by the rotation of helical blades in a hemispherical trough. ‘Dead spots’ are difficult to eliminate in this type of mixer and the shearing action caused by the movement of the

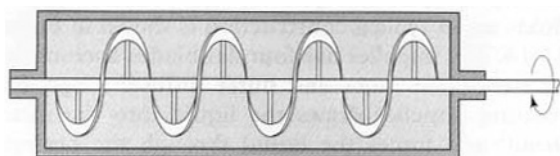


Fig. 13.10 Ribbon agitator powder mixer.

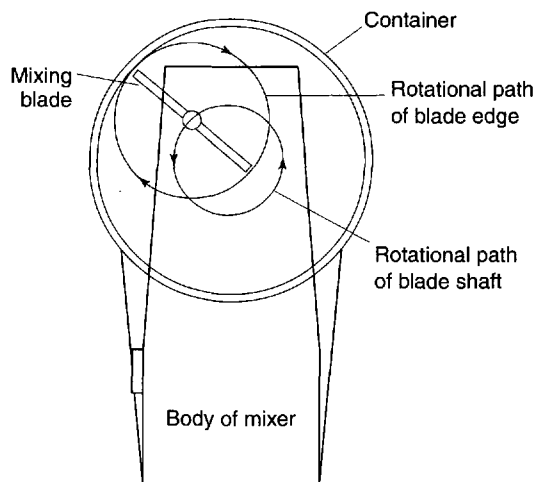


Fig. 13.11 Planetary mixer – top view, showing path of paddle.

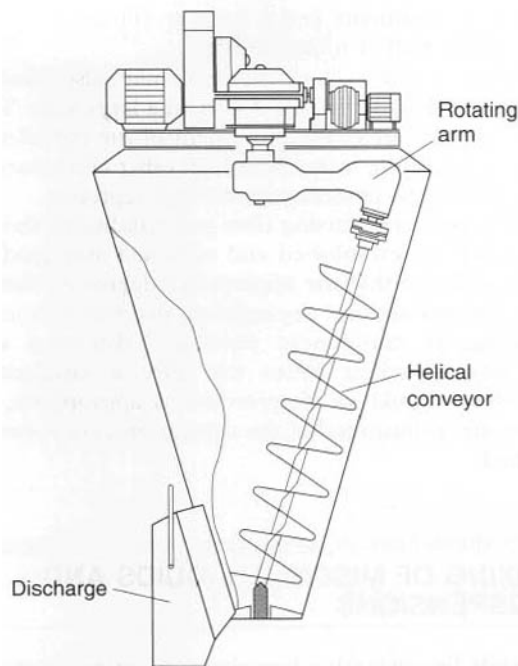


Fig. 13.12 Nautamixer (courtesy of Nautamixer Ltd).

blades may be insufficient to break up drug aggregates. The mixer does, however, mix poorly flowing material and is less likely to cause segregation than a tumbling mixer. The Nautamixer consists of a conical vessel fitted at the base with a rotating screw, which is fastened to the end of a rotating arm at the upper end. The screw conveys the material to near the top, where it cascades back into the mass. The mixer thus combines convective mixing (as the material is raised by the helical conveyor) and shear and diffusive mixing (as the material cascades downwards).

### Scale-up of powder mixing

The extent of mixing achieved at a small laboratory scale during development work may not necessarily be mirrored when the same formulation is mixed at a full production scale, even if the same mixer design is used for both. Often, mixing efficiency and the extent of mixing is improved on scale-up owing to increased shear forces. This is likely to be beneficial in most cases, although when blending lubricants care is needed to avoid overlubrication, which may for example lead to soft tablets and delayed disintegration and dissolution.

Problems associated with a deficiency of some of the components of a formulation, which have been encountered at a production scale but not in development work, have been traced to adsorption of a

minor constituents (e.g a drug or colourant) on to the mixer wall or mixing blade.

Drug particle characteristics may also change when the drug is manufactured on a large scale. This may in turn affect the movement of the particles in the mixer or the interaction with other components, and hence the tendency to mix and segregate.

The optimum mixing time and conditions should therefore be established and validated at a production scale, so that the appropriate degree of mixing is obtained without segregation, overlubrication or damage to component particles. Minimum and maximum mixing times that give a satisfactory product should be determined if appropriate, so that the 'robustness' of the mixing process is established.

## MIXING OF MISCIBLE LIQUIDS AND SUSPENSIONS

Mobile liquids with a low viscosity are easily mixed with each other. Similarly, solid particles are readily suspended in mobile liquids, although the particles are likely to settle rapidly when mixing is discontinued. Viscous liquids are more difficult to stir and mix, but they reduce the sedimentation rate of suspended particles (see Chapter 23).

### Propeller mixers

A common arrangement for medium-scale fluid mixing is a propeller-type stirrer which may be clamped to the edge of a vessel. A propeller has angled blades, which cause the fluid to circulate in both an axial and a radial direction. An off-centre mounting discourages the formation of a vortex, which may occur when the stirrer is mounted centrally. A vortex forms when the centrifugal force imparted to the liquid by the propeller blades causes it to back up around the sides of the vessel and create a depression at the shaft. As the speed of rotation is increased air may be sucked into the fluid by the formation of a vortex; this can cause frothing and possible oxidation (Figure 13.13(a)). Another method of suppressing a vortex is to fit vertical baffles into the vessel. These divert the rotating fluid from its circular path into the centre of the vessel, where the vortex would otherwise form (Figure 13.13(b)).

The ratio of the diameter of a propeller stirrer to that of the vessel is commonly 1:10–1:20, and it typically operates at speeds of 1–20 rps. The propeller

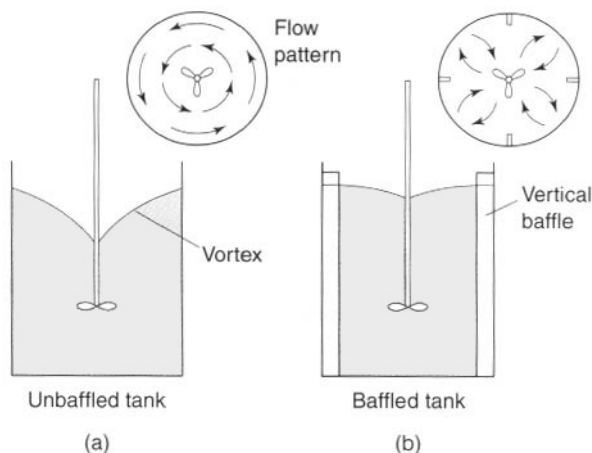


Fig. 13.13 Propeller mixer with (a) un baffled tank and (b) baffled tank.

stirrer depends for its action on a satisfactory axial and radial flow pattern, which will not occur if the fluid is sufficiently viscous. There must be a fast flow of fluid towards the propeller, which can only occur if the fluid is mobile.

### Turbine mixers

A turbine mixer may be used for more viscous fluids and a typical construction is shown in Figure 13.14. The impeller has four flat blades surrounded by perforated inner and outer diffuser rings. The rotating impeller draws the liquid into the mixer 'head' and forces the liquid through the perforations with considerable radial velocity, sufficient to overcome the viscous drag of the bulk of the fluid. One drawback is the absence of an axial component, but a different head with the perforations pointing upwards can be fitted if this is desired.

As the liquid is forced through the small orifices of the diffuser rings at high velocity large shear forces are produced. When mixing immiscible liquids, if the orifices are sufficiently small and velocity sufficiently high, the shear forces produced enable the generation of droplets of the dispersed phase which are small enough to produce stable dispersions (water-in-oil or oil-in-water). Turbine mixers of this type are therefore often fitted to vessels used for the large-scale production of emulsions and creams.

Turbine-type mixers will not cope with liquids of very high viscosity, as the material will not be drawn into the mixer head. These liquids are best treated as semisolids and handled in the same equipment as used for such materials.



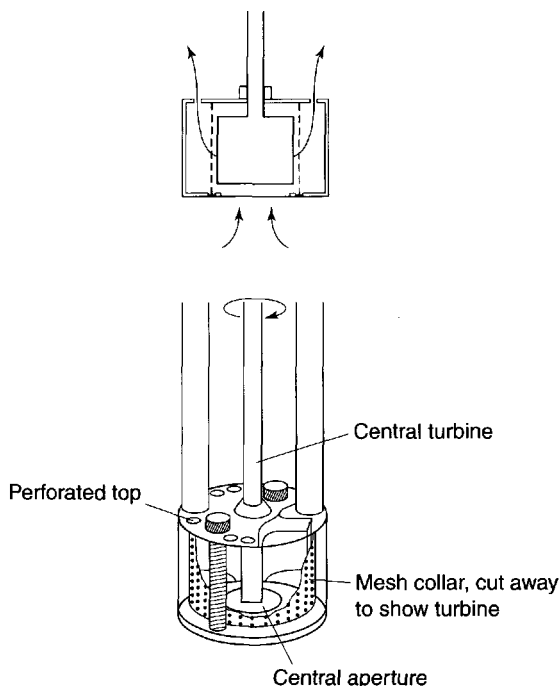


Fig. 13.14 Turbine mixer.

### *Inline mixers*

As an alternative to mixing fluids in batches in vessels, mobile miscible components may be fed through an 'inline' mixer designed to create turbulence in a flowing fluid stream. In this case a continuous mixing process is possible.

## MIXING OF SEMISOLIDS

The problems that arise during the mixing of semisolids (ointments and pastes) stem from the fact that, unlike powders and liquids, semisolids will not flow easily. Material that finds its way to 'dead' spots will remain there. For this reason, suitable mixers must have rotating elements with narrow clearances between themselves and the mixing vessel wall and they must produce a high degree of shear mixing, as diffusion and convection cannot occur.

### Mixers for semisolids

#### *Planetary mixers*

This type of mixer is commonly found in the domestic kitchen (e.g. Kenwood-type mixers) and larger

machines which operate on the same principle are used in industry.

The mixing blade is set off-centre and is carried on a rotating arm. It therefore travels round the circumference of the mixing bowl while simultaneously rotating around its own axis (as Fig. 13.11). This is therefore a double rotation similar to that of a spinning planet rotating around the sun – hence the name.

A small clearance between the vessel and the paddle gives shear, but 'scraping down' several times is necessary to mix the contents well as some materials are forced to the top of the bowl. Planetary mixers are also sometimes used to mix powders, particularly if a wet mass for granulation is required (see Chapter 25).

#### *Sigma-blade mixer*

This robust mixer will deal with stiff pastes and ointments and depends for its action on the close intermeshing of the two blades which resemble the Greek letter  $\Sigma$  in shape. The clearance between the blades and the mixing trough is kept small by the shape shown in Figure 13.15.

It is very difficult using primary mixers to completely disperse powder particles in a semisolid base so that they are invisible to the eye. The mix is usually subjected to the further action of a roller mill or colloid mill, so as to 'rub out' these particles by the intense shear generated by rollers or cones set with a very small clearance between them.

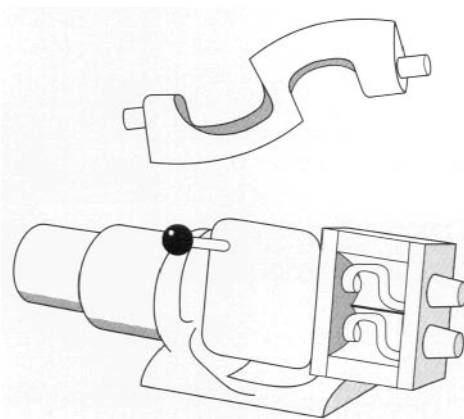


Fig. 13.15 Sigma blade mixer.

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**REFERENCE**

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Nikolakis, N. and Newton, M. (1989) *J. Pharm. Pharmacol.*, **41**, 145.

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**BIBLIOGRAPHY**

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Kaye, B.H. (1997) *Powder Mixing*. Chapman & Hall, London.

Miyunami, K. (1991) Mixing. In: Linoya, K., Gotoh, K. and Higashitani, K. (eds) *Powder Technology Handbook*. Marcel Dekker, New York, p 595–612.

Rothman, H. (1981) High speed mixing in the pharmaceutical industry. *Manuf. Chemist Aerosol News*, **52(4)**, 47–49.

Rumpf, H. (1990) *Particle Technology*. Chapman & Hall, London.

Staniforth, J.N. (1982) Advances in powder mixing and segregation in relation to pharmaceutical processing. *Int. J. Pharmaceut. Tech. Product Manuf.*, **3(Suppl)**, 1–12.

Williams, J.C. (1990) Mixing and segregation of powders. In: Rhodes, M.J. (ed) *Principles of Powder Technology*. John Wiley, Chichester, Ch 4, p 71–90.

# 14

## Powder flow

John Staniforth

### CHAPTER CONTENTS

#### Particle properties 198

- Adhesion and cohesion 198
- Measurement of adhesive/cohesive properties 198
- Shear strength 198
- Tensile strength 199
- Angle of repose 200

#### Particle properties and bulk flow 200

- Particle size effects 200
- Particle shape 201
- Particle density (true density) 201

#### Packing geometry 201

- Characterization of packing geometry by porosity and bulk density 201
- Factors affecting packing geometry 202

#### Process conditions: hopper design 202

- Flow through an orifice 202
- Factors affecting flow rates through orifices 204
- Orifice diameter 204
- Hopper width 204
- Head size 204
- Hopper wall angle 204
- Mass flow and funnel flow 205
- Mass flow rate 205

#### Characterization of powder flow 205

- Indirect methods 205
- Angle of repose 205
- Shear cell determinations 207
- Bulk density measurements 207
- Critical orifice diameter 208
- Direct methods 208
- Hopper flow rate 208
- Recording flowmeter 208

#### Improvement of powder flowability 208

- Alteration of particle size and size distribution 208
- Alteration of particle shape or texture 209
- Alteration of surface forces 209
- Formulation additives: flow activators 209
- Alteration of process conditions 209
- Use of vibration-assisted hoppers 209
- Use of force feeders 209
- Caution! 209

#### Bibliography 210

Powders are generally considered to be composed of solid particles of the same or different chemical compositions having equivalent diameters less than 1000  $\mu\text{m}$ . However, the term 'powder' will also be used here to describe groups of particles formed into granules which may have overall dimensions greater than 1000  $\mu\text{m}$ .

The largest use of powders pharmaceutically is to produce tablets and capsules. Together with mixing and compression properties, the flowability of a powder is of critical importance in the production of pharmaceutical dosage forms. Some of the reasons for producing free-flowing pharmaceutical powders include:

1. uniform feed from bulk storage containers or hoppers into the feed mechanisms of tableting or capsule-filling equipment, allowing uniform particle packing and a constant volume-to-mass ratio which maintains tablet weight uniformity;
2. reproducible filling of tablet dies and capsule dosators, which improves weight uniformity and allows tablets to be produced with more consistent physicommechanical properties;
3. uneven powder flow can result in excess entrapped air within powders, which in some high-speed tableting conditions may promote capping or lamination;
4. uneven powder flow can result from excess fine particles in a powder, which increase particle-die-wall friction, causing lubrication problems, and increase dust contamination risks during powder transfer.

There are many industrial processes that require powders to be moved from one location to another and this is achieved by many different methods, such as gravity feeding, mechanically assisted feeding, pneumatic transfer, fluidization in gases and liquids and hydraulic transfer. In each of these examples powders are required to flow and, as with other operations described earlier, the efficiency with which

they do so is dependent on both process design and particle properties.

## PARTICLE PROPERTIES

### Adhesion and cohesion

The presence of molecular forces produces a tendency for solid particles to stick to themselves and to other surfaces. Adhesion and cohesion can be considered as two parts of the same phenomenon: cohesion occurs between like surfaces, such as component particles of a bulk solid, whereas adhesion occurs between two unlike surfaces, for example between a particle and a hopper wall.

Cohesive forces acting between particles in a powder bed are composed mainly from short-range non-specific van der Waals forces which increase as particle size decreases and vary with changes in relative humidity. Other attractive forces contributing to interparticle cohesion may be produced by surface tensional forces between adsorbed liquid layers at the particle surfaces and electrostatic forces arising from contact or frictional charging, which may have short half-lives but increase cohesion through improving interparticle contacts and hence increasing the quantity of van der Waals interactions. Cohesion provides a useful method of characterizing the drag or frictional forces acting within a powder bed to prevent powder flow.

#### Measurement of adhesive/cohesive properties

Adhesive/cohesive forces acting between a single pair of particles or a particle and substrate surface can be accurately determined using a specially adapted ultracentrifuge to apply very high forces strong enough to separate the two surfaces.

However, it is more usual when studying powder flow to characterize adhesion/cohesion in a bed of powder.

**Shear strength** Cohesion can be defined as the stress (force per unit area) necessary to shear a powder bed under conditions of zero normal load. Using this criterion, the shear strength of a powder can be determined from the resistance to flow caused by cohesion or friction and can be measured using a shear cell.

The shear cell (Fig. 14.1) is a relatively simple piece of apparatus which is designed to measure shear stress,  $\tau$ , at different values of normal stress,  $\sigma$ . There are several types of shear cell, such as the

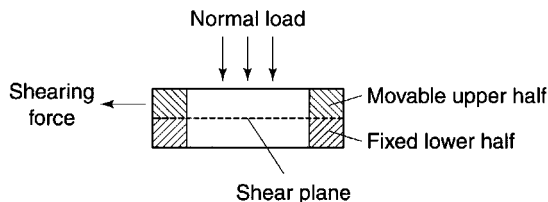


Fig. 14.1 Diagrammatic representation of Jenike shear cell.

Jenike and the Portishead, which use different methods of applying the stresses and measuring the shear strengths. In order to carry out a shear strength determination, powder is packed into the two halves of the cell. Weights are placed on the lid of the assembled cell, or some other method may be used to apply the normal stress. A system of a cord connected from the lid of the cell, by a pulley, to weights, or other means are used to apply a shearing stress across the two halves of the cell. The shear stress is found by dividing the shear force by the cross-sectional area of the powder bed and will increase as the normal stress increases. One of the most convenient, informative and widely used methods of presenting this stress interrelationship is provided by plotting a Mohr diagram.

A Mohr diagram is constructed by plotting the normal stress,  $\tau$ , as the ordinate and the stress,  $\sigma$ , as the abscissa. For two values of shear stress on the abscissa, at which failure occurs and the cell is sheared,  $\sigma_1$  and  $\sigma_2$  are used as the diameter of a Mohr circle with radius  $\frac{\sigma_1 + \sigma_2}{2}$  (Fig. 14.2). A series of Mohr semicircles can be constructed in this way with different pairs of shear stresses causing failure (Fig. 14.3). A line is constructed to touch all of the Mohr semicircles and define the critical combinations of normal and shearing stresses at which failure occurs. The line is called the yield locus and is a characteristic of the powder under given conditions. Several different properties of the powder can be obtained from the complete Mohr diagram, and some of these are shown in Table 14.1.

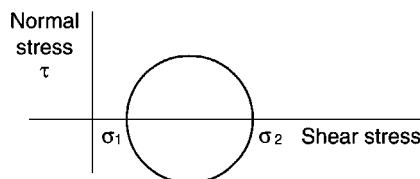


Fig. 14.2 Mohr circle

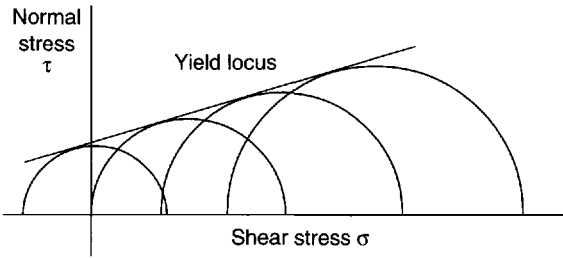


Fig. 14.3 Mohr diagram

In order to calculate the cohesion in a powder bed using the shear cell method, the yield locus is extrapolated back to zero normal stress; the shear stress at zero normal stress is, by definition, equal to the cohesion of the powder. For a non-cohesive powder the extrapolated yield locus will pass through the origin, equivalent to zero shear stress. In rheological terms the stress due to cohesion along the yield locus may be called the yield stress and the powder termed a plastic solid.

**Tensile strength** The tensile strength of a powder bed is a characteristic of the internal friction or cohesion of the particles, but unlike shear strength determinations, the powder bed is caused to fail in tension

by splitting, rather than failing in shear by sliding. The powder is packed into a split plate, one half of which is fixed and the other half free to move by means of small wheels or ball bearings that run in tracks in a table (Fig. 14.4). The table is then tilted towards the vertical until the angle is reached at which the powder cohesion is overcome and the mobile half-plate breaks away from the static half-plate. The tensile strength,  $\sigma_t$ , of the powder can then be determined from Eqn 14.1.

$$\sigma_t = \frac{M \sin \theta}{A} \times 10^5 \text{ Pa} \quad (14.1)$$

where  $M$  is the mass of the mobile half plate + powder,  $\theta$  the angle of the tilted table to the horizon-

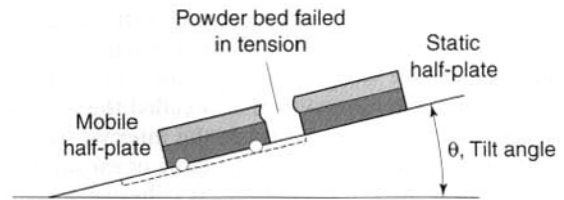
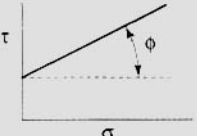
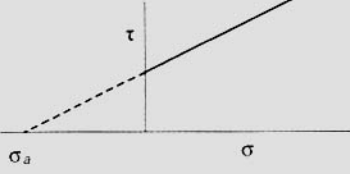


Fig. 14.4 Measurement of tensile strength of a powder bed using tilting table method

Table 14.1 Some properties relating to powder cohesion and flowability which can be obtained from Mohr diagrams

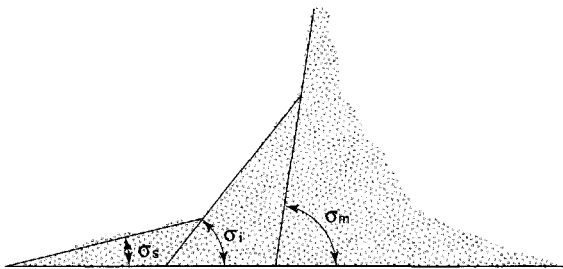
Measurement	Property measured	Powder characteristics
1 Acute angle of the extrapolated yield locus at the shear stress axis 	Angle of internal friction, $\phi$	Difficulty of maintaining constant volume flow
2 Tan $\phi$ or slope of the yield locus	Coefficient of friction	Indirect measurement of powder flowability
3 Diameter of circle with tangent to $t$ linking minor stress at $\sigma = 0$ to major unconfined yield stress $\sigma_u$	Stress equilibrium in powder arch when no flow occurs	Minimum opening dimensions to prevent arching
4 Extrapolation of yield locus to cut normal stress axis 	$\sigma_a$ , apparent tensile strength of powder bed	Resistance to failure in tension
5 Shear stress, $t_0$ , at zero normal stress, $\sigma_0$	Cohesion coefficient	Cohesion, when powder is non-cohesive, yield locus passes through origin and shear stress = 0

tal at the point of failure, and  $A$  is the cross-sectional area of the powder bed.

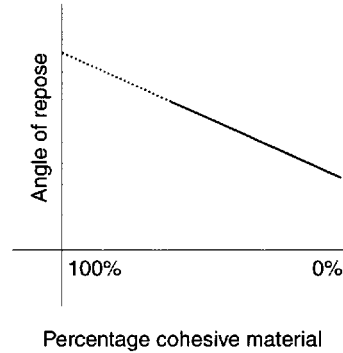
The tensile strength values of different powders have been found to correlate reasonably well with another measurement of powder cohesion, angle of repose.

**Angle of repose** From the previous discussion it will be realized that an object, such as a particle, will begin to slide when the angle of inclination is large enough to overcome frictional forces. Conversely, an object in motion will stop sliding when the angle of inclination is below that required to overcome adhesion/cohesion. This balance of forces causes a powder poured from a container on to a horizontal surface to form a heap: initially the particles stack until the approach angle for subsequent particles joining the stack is large enough to overcome friction, and they slip and roll over each other until the gravitational forces balance the interparticle forces. The sides of the heap formed in this way make an angle with the horizontal which is called the angle of repose and is a characteristic of the internal friction or cohesion of the particles. The value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. If the powder is very cohesive the heap may be characterized by more than one angle of repose. Initially the interparticle cohesion causes a very steep cone to form, but on the addition of further powder this tall stack may suddenly collapse, causing air to be entrained between particles and partially fluidizing the bed, making it more mobile. The resulting heap has two angles of repose: a large angle remaining from the initial heap and a shallower angle formed by the powder flooding from the initial heap (Fig. 14.5).

In order to overcome this problem, it has been suggested that determinations of angles of repose be carried out using different concentrations of very



**Fig. 14.5** Cohesive powder poured in a heap and showing different angles of repose:  $\sigma_m$  maximum angle formed by cohesive particles  $\sigma_s$  shallowest angle formed by collapse of cohesive particle heap, resulting in flooding. In some cases a third angle,  $\sigma_i$  is identifiable as an intermediate slope produced by cohesive particles stacking on flooded powder.



**Fig. 14.6** Determination of angle of repose for very cohesive powders.

cohesive powders and non-cohesive powders. The angles of repose are plotted against mixture concentration and extrapolated to 100% cohesive powder content so as to obtain the appropriate angle of repose (Fig. 14.6).

### Particle properties and bulk flow

In the discussion concerning adhesion/cohesion it has become clear that an equilibrium exists between forces responsible for promoting powder flow and those preventing powder flow, i.e. at equilibrium:

$$\Sigma f(\text{driving forces}) = \Sigma f(\text{drag forces}) \quad (14.2)$$

that is,

$$\Sigma f(\text{gravitational force, particle mass, angle of inclination of powder bed, static head of powder, mechanical force ...}) = \Sigma f(\text{adhesive forces, cohesive forces, other surface forces, mechanical interlocking...}). \quad (14.3)$$

Some of these forces are modified or controlled by external factors related to particle properties.

### Particle-size effects

Because cohesion and adhesion are phenomena that occur at surfaces, particle size will influence the flowability of a powder. In general, fine particles with very high surface to mass ratios are more cohesive than coarser particles which are influenced more by gravitational forces. Particles larger than  $250 \mu\text{m}$  are usually relatively free flowing, but as the size falls below  $100 \mu\text{m}$  powders become cohesive and flow problems are likely to occur. Powders having a particle size less than  $10 \mu\text{m}$  are usually extremely cohesive and resist flow under gravity, except possibly as large agglomerates.

### Particle shape

Powders with similar particle sizes but dissimilar shapes can have markedly different flow properties owing to differences in interparticle contact areas. For example, a group of spheres has minimum interparticle contact and generally optimal flow properties, whereas a group of particle flakes or dendritic particles has a very high surface-to-volume ratio and poorer flow properties.

### Particle density (true density)

Because powders normally flow under the influence of gravity, dense particles are generally less cohesive than less dense particles of the same size and shape.

### Packing geometry

A set of particles can be filled into a volume of space to produce a powder bed which is in static equilibrium owing to the interaction of gravitational and adhesive/cohesive forces. By slight vibration of the bed, particles can be mobilized so that if the vibration is stopped, the bed is once more in static equilibrium but occupies a different spatial volume than before. The change in bulk volume has been produced by rearrangement of the packing geometry of the particles. In general, such geometric rearrangements result in a transition from loosely packed particles to more tightly packed ones, so that the equilibrium balance moves from left to right in Eqn 14.2 and cohesion increases. This also means that more tightly packed powders require a higher driving force to produce powder flow than more loosely packed particles of the same powder.

### Characterization of packing geometry by porosity and bulk density

A set of monosized spherical particles can be arranged in many different geometric configurations. At one extreme, when the spheres form a cubic arrangement, the particles are most loosely packed and have a porosity of 48% (Fig. 14.7(a)). At the other extreme, when the spheres form a rhombohedral arrangement, they are most densely packed and have a porosity of only 26% (Fig. 14.7(b)). The porosity used to characterize packing geometry is linked to the bulk density of the powder. Bulk density,  $\rho_B$ , is a characteristic of a powder rather than individual particles and is given by the mass,  $M$ , of powder occupying a known volume,  $V$ , according to the relationship:

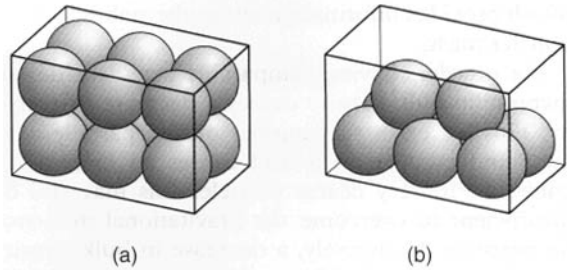


Fig. 14.7 Different geometric packings of spherical particles: (a) cubic packing; (b) rhombohedral packing.

$$\rho_B = \frac{M}{V} \text{ kg m}^{-3} \quad (14.4)$$

The bulk density of a powder is always less than the true density of its component particles because the powder contains interparticle pores or voids. This statement reveals that whereas a powder can only possess a single true density it can have many different bulk densities, depending on the way in which the particles are packed and the bed porosity. However, a high bulk density value does not necessarily imply a close-packed low-porosity bed, as bulk density is directly proportional to true density.

bulk density  $\propto$  true density

i.e. 
$$\text{bulk density} = k \text{ true density} \quad (14.5)$$

or

$$k = \frac{\text{bulk density}}{\text{true density}} \quad (14.6)$$

The constant of proportionality,  $k$ , is known as the **packing fraction** or **fractional solids content**. For example, the packing fraction for dense, randomly packed spheres is approximately 0.63, whereas the packing fraction for a set of dense, randomly packed discs is 0.83.

Also:

$$1 - k = e \quad (14.7)$$

where  $e$  is the fractional voidage of the powder bed, which is usually expressed as a percentage and termed the bed porosity. Another way of expressing fractional voidage is to use the ratio of particle volume  $V_P$  to bulk powder volume  $V_B$ , i.e.

$$e = \frac{1 - V_P}{V_B} \quad (14.8)$$

A simple ratio of void volume  $V_v$  to particle volume  $V_P$  represents the voids ratio:

$$\frac{V_v}{V_P} = \frac{e}{(1 - e)} \quad (14.9)$$

which provides information about the stability of the powder mass.

For powders having comparable true densities an increase in bulk density causes a decrease in porosity. This increases the number of interparticle contacts and contact areas and causes an increase in cohesion. In very coarse particles this may still be insufficient to overcome the gravitational influence on particles. Conversely, a decrease in bulk density may be associated with a reduction in particle size and produce a loose-packed powder bed which, although porous, is unlikely to flow because of the inherent cohesiveness of the fine particles. The use of porosity as a means of characterizing packing geometries can sometimes be misleading. For example, monosize cubic crystals could be considered to be loosely packed with a porosity of 20%, as the closest packed cubic arrangement would have a porosity close to 0%. By comparison, a system of spheronized crystals of the same size with a porosity of 30% could be considered to be more closely packed, as the closest packed spherical arrangement has a porosity of 26%. In this example the powder with the higher porosity is relatively more closely packed than that with the lower porosity.

In powders where the particle shape or cohesiveness promotes arch or bridge formation, two equilibrium states could have similar porosities but widely different packing geometries. In such conditions, interparticle pore-size distributions can be useful for comparing packing geometry.

For example, Fig. 14.8(a) shows a group of particles in which arching has occurred and Fig. 14.8(b) shows a similar group of particles in which arch formation is absent. The total porosity of the two systems can be seen to be similar but the pore size distributions (Fig. 14.9) reveal that the powder in which arch formation has occurred is generally more tightly packed than that in which arching is absent.

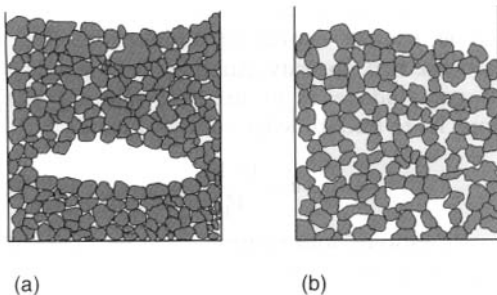


Fig. 14.8 Two equidimensional powders having the same porosity but different packing geometries.

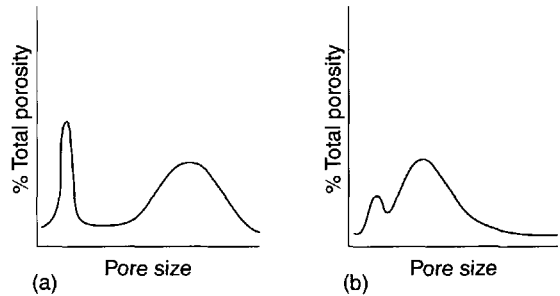


Fig. 14.9 (a) Interparticle pore size distribution corresponding to close-packed bed containing a powder arch. (b) Interparticle pore size distribution corresponding to loosely packed bed.

### Factors affecting packing geometry

- 1 *Particle size and size distribution*: void spaces between coarse particles may become filled with finer particles in a powder with a wide size range, resulting in a more closely packed cohesive powder.
- 2 *Particle shape and texture*: these influence the minimum porosity of the powder bed. Arches or bridges within the powder bed will be formed more readily through the interlocking of non-isometric, highly textured particles. This tendency for irregular particles to produce open structures supported by small or large powder arches causes them to have a larger difference in porosity between loose packing and tight packing geometries than more regularly shaped particles.
- 3 *Surface properties*: the presence of electrostatic forces can add to interparticle attractions and promote closer particle packing, resulting in increased cohesion.
- 4 *Handling and processing conditions*: the way in which a powder has been handled prior to flow or packing influences the type of packing geometry.

## PROCESS CONDITIONS: HOPPER DESIGN

### Flow through an orifice

There are many examples of this type of flow to be found in the manufacture of pharmaceutical solid dosage forms, for example when granules or powders flow through the opening in a hopper or bin used to feed powder to tableting machines, capsule-filling machines or sachet-filling machines. Because of the importance of such flow in producing unit



doses containing the same or very similar powder masses, and the importance of flow behaviour in other industries, the behaviour of particles being fed through orifices has been extensively studied.

A hopper or bin can be modelled as a tall cylindrical container having a closed orifice in the base and initially full of a free-flowing powder which has a horizontal upper surface (Fig. 14.10(a)). When the orifice at the base of the container is opened, flow patterns develop as the powder discharges. (Fig. 14.10(a)–(f)).

The observed sequence is as follows:

- 1 On opening the orifice there is no instantaneous movement at the surface, but particles just above the orifice fall freely through it (Fig. 14.10(b)).
- 2 A depression forms at the upper surface and spreads outwards to the sides of the hopper (Fig. 14.10(c) and (d)).
- 3 Provided that the container is tall and not too narrow, the flow pattern illustrated in Fig. 14.10(e) and shown schematically in Figure 14.11 is rapidly established. Particles in zone A move rapidly over the slower moving

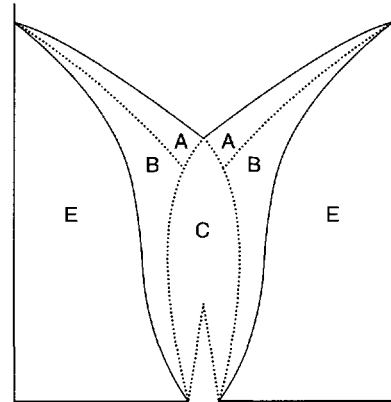


Fig. 14.11 Fully developed flow of a free-flowing powder through an orifice.

- particles in zone B, whereas those in zone E, remain stationary. The particles in zone A feed into zone C, where they move quickly downwards and out through the orifice. The more slowly moving particles in zone B do not enter zone C.
- 4 Both powder streams in zones B and C converge to a 'tongue' just above the orifice, where the

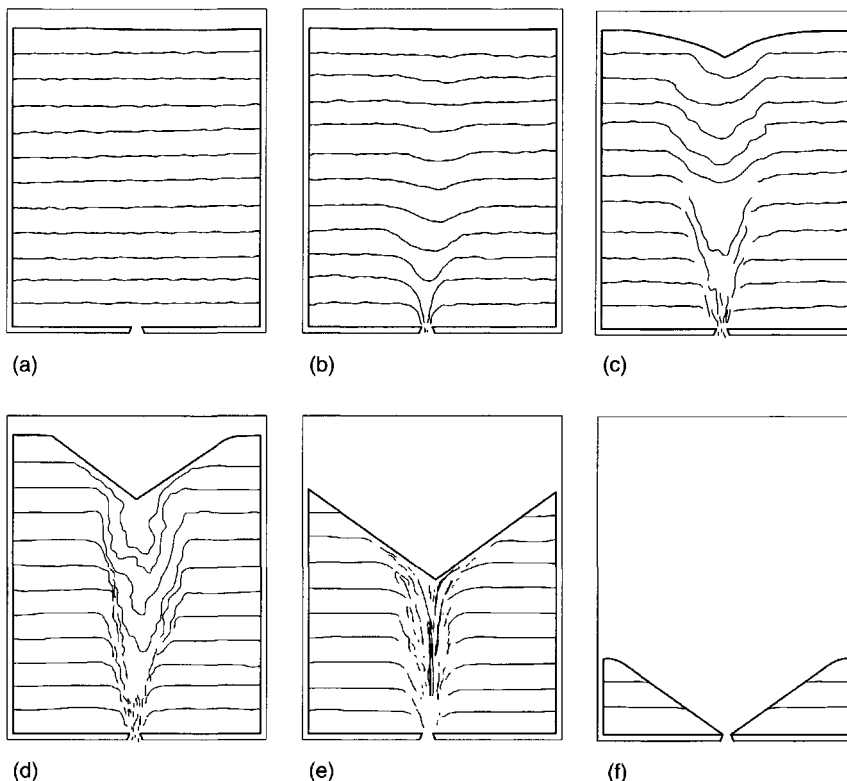


Fig. 14.10 Development of flow through an orifice. The horizontal lines are formed by indicator particles to show the course of the discharge.

movement is most rapid and the particle packing is least dense. In a zone just above the orifice, the particles are in free flight.

Important practical consequences of this flow pattern are that if a square-bottomed hopper or bin is repeatedly refilled and partially emptied, the particles in a zone towards the base and sides of the container (Fig. 14.10(f)) will not be discharged and may degrade; alternatively, this static zone may provide a segregation potential for previously homogeneous powders.

### Factors affecting flow rates through orifices

The flow patterns described above, together with powder flow rates through orifices, are dependent on many different factors, some of which are particle related and some process related. Particle-related effects, notably particle size, are discussed above. Process-related effects include the following.

**Orifice diameter** Flow rate  $\propto D_o^A$ . The rate of powder flow through an orifice is proportional to a function of orifice diameter,  $D_o$  ( $A$  is a constant with a value of approx. 2.6). Provided that the height of the powder bed, called the head of powder, remains considerably greater than the orifice diameter, flow rate is virtually independent of powder head. This situation is unlike that relating to liquid flow through an orifice, where the flow rate falls off continuously as the head diminishes. The constant rate of flow for powders is a useful property as it means that if a bulk powder is filled into dies, sachets, capsules or other enclosures, they will receive equal weights if filled for equal times.

**Hopper width** At different positions within a powder bed the consolidating stresses and shear or tensile strengths are different (Fig. 14.12(b)). If the

bed strength at a given point in the hopper is great enough to resist the driving forces promoting flow, then a stable arch will be formed. At all other points in the powder the bed strength will not be high enough to support an arch against the stresses within it, and flow will occur. The stresses acting on a stable arch are proportional to the width of the container and vary with diameter, as exemplified in Figure 14.12(a) and (b). The relationship between the stress on the arch and the arch strength, resulting in part from consolidating pressures at different points in the hopper (Fig. 14.12(c)), shows that with the exception of a region close to the hopper outlet and another at the point where the cylindrical section meets the conical section of the hopper, powder arches are weaker than the stresses on them. This suggests that powder flow will occur in all other regions (Fig. 14.12(d)) and allows the hopper design to be adjusted so that the minimum hopper widths are always large enough to produce arch stresses greater than arch strengths, and thereby ensure continuous, uniform powder flow.

**Head size** Figure 14.12(b) shows the way in which solids' pressure changes with powder head size (powder depth). The pressure below the upper free surface increases to a constant governed by frictional factors. The pressure again falls off towards the hopper outlet and drops below atmospheric at the orifice, causing air to be drawn up into the region close to the base so as to equalize this negative pressure and allow flow to continue.

**Hopper wall angle** It was noted above in the description of flow through an orifice, that a flat-bottomed bin retains a certain volume of powder in the form of a drained cone centred on the orifice. In order to prevent this behaviour and to ensure that all the powder is discharged from a hopper, the walls are frequently angled inwards as the outlet is

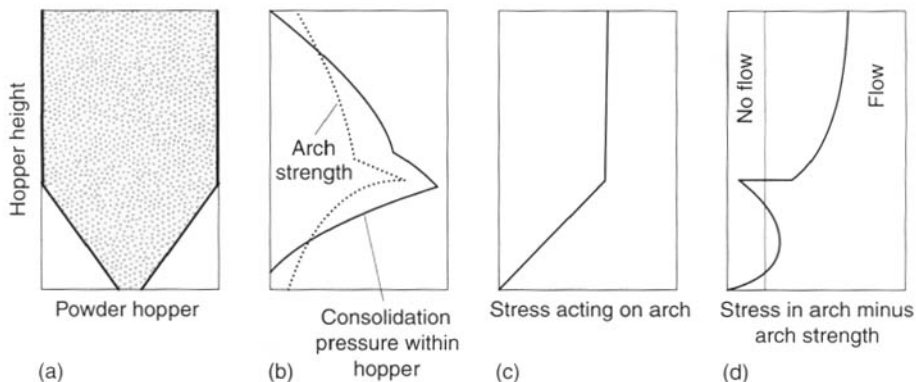


Fig. 14.12 Influence of stress interactions within a hopper on powder flow.

approached. The wall angle that is required to ensure that powder empties freely is determined by the particle-wall adhesion component of friction within powders, and is characterized by a wall-friction angle,  $\phi$ . Powders with very low wall-friction angles will empty freely, even from hoppers with very shallow slopes, whereas powders with very high wall-friction angles will empty poorly even from steep-walled hoppers. In between these two extremes powder discharge characteristics will be determined by the relationship between wall friction and hopper angle, as shown in Figure 14.13.

**Mass flow and funnel flow**

Powder that discharges freely from a hopper is said to undergo mass flow when particles that enter the hopper first leave it first. This first-in-first-out sequence holds throughout the bed, so that powder can be considered to leave in near-horizontal bands which move down the hopper *en masse* (Fig. 14.14(a)).

Powders which do not discharge freely, due either to high adhesion/cohesion or to hopper angles which are too shallow, may undergo funnel flow (Fig. 14.14(b)). Particles which are loaded into the hopper last are among the first to leave, forming a ‘pipe’, ‘rat-hole’ or ‘funnel’, extending from the upper free powder surface to the hopper outlet and producing uneven erratic flow. Another problem associated with funnel flow may occur when the rat-hole collapses. This produces a sudden rapid discharge of powder which can entrain relatively large volumes of air, causing the particles to partially fluidize and flood out of the hopper. This ‘flooding’ or ‘flushing’ may be succeeded by periods when the bed is quiescent and flow is slow or interrupted.

In general, most powders will discharge by mass flow from hoppers with  $\theta$  angles of about 20°, and by

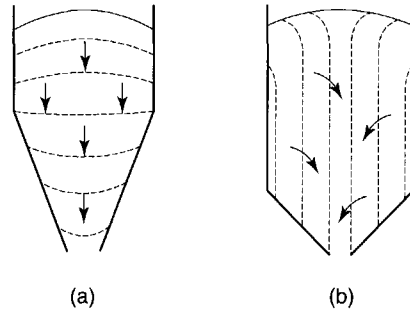


Fig. 14.14 (a) Mass flow hopper, (b) funnel flow hopper.

funnel flow from hoppers with angles of approximately 50°.

**Mass flow rate**

Throughout this section it has been shown that specific particle properties and individual design criteria influence powder flow. However, in a given practical situation powder flowability is the resultant of the relative influences of all these factors. An equation has been derived which relates some particulate properties, such as bulk density,  $\rho_B$ , and angle of repose,  $\alpha$ , and hopper design criteria such as orifice diameter,  $D_o$ , and a discharge coefficient,  $C$ , to mass flow rate of powder,  $M$ :

$$M = \pi/4 C \rho_B \rho [(g D_o^5)/2 \tan \alpha]^{1/2} \quad (14.10)$$

where  $g$  is acceleration due to gravity.

**CHARACTERIZATION OF POWDER FLOW**

When examining the flow properties of a powder it is useful to be able to quantify the type of behaviour and many different methods have been described, either directly using dynamic or kinetic methods, or indirectly, generally by measurements carried out on static beds.

**Indirect methods**

**Angle of repose**

Angles of repose have been used as indirect methods of quantifying powder flowability, because of their relationship with interparticle cohesion. There are many different methods of determining angles of repose and some of these are shown in Table 14.2.

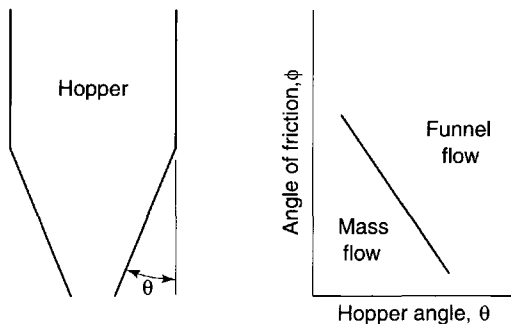
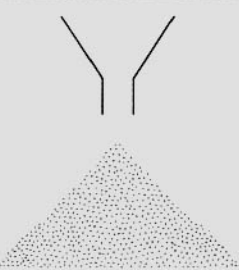
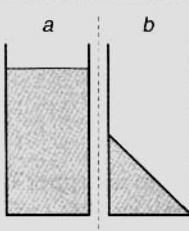
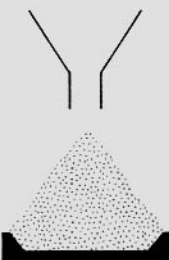
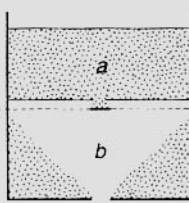
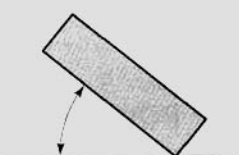
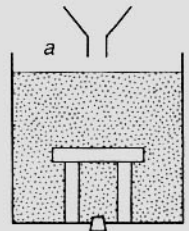
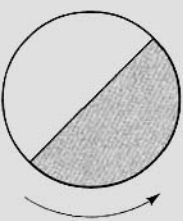
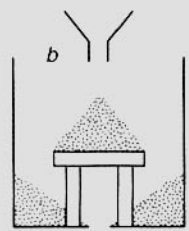


Fig. 14.13 Influence of hopper wall angle and particle-wall friction on powder flow.

The different methods may produce different values for the same powder, although these may be self-consistent. It is also possible that different angles of repose could be obtained for the same powder, owing

to differences in the way the samples were handled prior to measurement. For these reasons, angles of repose tend to be variable and are not always representative of flow under specific conditions.

**Table 14.2 Methods of measuring angle of repose**

Apparatus	Method	Angle defined	Apparatus	Method	Angle defined
	Fixed height cone	Angle of repose		Ledge	Drained angle of repose
	Fixed base cone	Angle of repose		Crater	Drained angle of repose
	Tilting table	Angle of repose		Platform	Drained angle of repose
	Rotating cylinder	Dynamic angle of repose			

As a general guide, powders with angles of repose greater than  $50^\circ$  have unsatisfactory flow properties, whereas minimum angles close to  $25^\circ$  correspond to very good flow properties.

### Shear cell determinations

It is possible to characterize flowability indirectly from the behaviour of powder in a shear cell. A flow factor, f.f., can be obtained by determining the reciprocal slope of a curve or tangent to a curve of unconfined yield stress  $\sigma_u$ , plotted against the maximum normal stress on a yield locus,  $\sigma_m$  (Fig. 14.15(a)). The unconfined yield stresses are those in Mohr semi-circles constructed through the origin; the maximum normal stresses have a semicircle passing through the largest normal stress (Fig. 14.15(b)). By plotting a series of different yield loci, several values can be obtained for  $\sigma_u$  and  $\sigma_m$ .

The relationship between flow factors and powder flowability is shown in Table 14.3.

### Bulk density measurements

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and may therefore be more resistant to powder flow. The ease with which a powder consolidates can be used as an indirect method of quantifying powder flow.

Figure 14.16 shows a mechanical tapping device or jolting volumeter which can be used to follow the change in packing volume that occurs when void space diminishes and consolidation occurs. The powder contained in the measuring cylinder is mechanically tapped by means of a constant velocity rotating cam and increases from an initial bulk

f.f. value	Flow descriptor
>10	Free flowing
4–10	Easy flowing
1.6–4	Cohesive
<1.6	Very cohesive

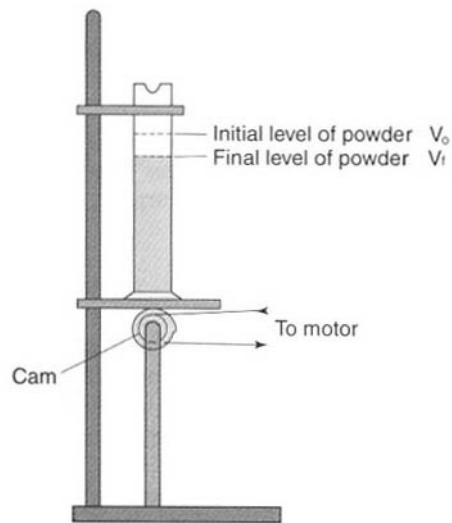


Fig. 14.16 Mechanical tapping device (Jolting Volumeter).

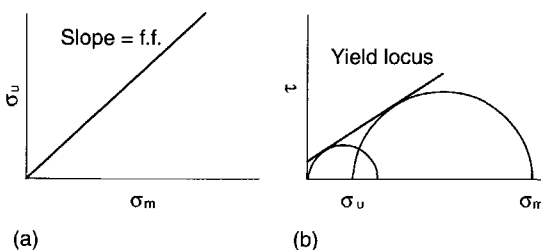


Fig. 14.15 (a) Plot of unconfined yield stress,  $\sigma_u$ , against maximum stress,  $\sigma_m$ , with a slope corresponding to the flow factor, f.f. (b) Example of Mohr diagram used to obtain one pair of values for  $\sigma_u$  and  $\sigma_m$ .

density  $D_0$  (also known as fluff or poured bulk density) to a final bulk density  $D_f$  (also known as equilibrium, tapped or consolidated bulk density) when it has attained its most stable, i.e. unchanging arrangement.

Hausner found that the ratio  $D_f/D_0$  was related to interparticle friction and, as such, could be used to predict powder flow properties. He showed that powders with low interparticle friction, such as coarse spheres, had ratios of approximately 1.2, whereas more cohesive, less free-flowing powders such as flakes have Hausner ratios greater than 1.6.

Another indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability and is calculated according to Eqn 14.11.

$$\% \text{ compressibility} = \frac{D_f - D_0}{D_f} \times 100 \quad (14.11)$$

**Table 14.4 Relationship between powder flowability and % compressibility**

% Compressibility range	Flow description
5–15	Excellent (free-flowing granules)
12–16	Good (free flowing powdered granules)
18–21	Fair (powdered granules)
23–28	Poor (very fluid powders)
28–35	Poor (fluid cohesive powders)
35–38	Very poor (fluid cohesive powders)
>40	Extremely poor (cohesive powders)

Table 14.4 shows the generalized relationship between descriptions of powder flow and percent compressibility, according to Carr.

### Critical orifice diameter

In order to carry out measurements of critical orifice diameter, powder is filled into a shallow tray to a uniform depth with near-uniform packing. The base of the tray is perforated with a graduated series of holes, which are blocked either by resting the tray on a plane surface or by the presence of a simple shutter. The critical orifice diameter is the size of the smallest hole through which powder discharges when the tray is lifted or the shutter removed. Sometimes repetition of the experiment produces different critical orifice diameters, and in these cases maximum and minimum values are sometimes quoted.

Critical orifice diameter is a direct measure of powder cohesion and arch strength since:

$$\tan \alpha = \frac{r}{x} \quad (14.12)$$

where  $r$  is the particle radius and  $x$  is the orifice radius, and

$$\tan F' = \frac{\tan \phi}{1 - \tan \phi \frac{r}{x} - \frac{r^2}{x^2}} \quad (14.13)$$

where  $F'$  is the angle of form, which is the obtuse angle between the contracting powder dome and the horizontal, and  $\tan \phi$  is a coefficient of friction.

An alternative critical orifice method for determining powder flowability uses a cylinder with a series of interchangeable base plate discs having different diameter orifices. Using this system, flowability indices related to orifice diameter have been

used as a method of specifying materials for use in filling given capsule sizes or producing particular tablet sizes at a specified rate.

## Direct methods

### Hopper flow rate

The simplest method of determining powder flowability directly is to measure the rate at which powder discharges from a hopper. A simple shutter is placed over the hopper outlet and the hopper filled with powder. The shutter is then removed and the time taken for the powder to discharge completely is recorded. By dividing the discharged powder mass by this time, a flow rate is obtained which can be used for quantitative comparison of different powders.

Hopper or discharge tube outlets should be selected to provide a good model for a particular flow application. For example, if a powder discharges well from a hopper into a tablet machine feed frame, but does not flow reproducibly into the tablet die, then it is likely that more useful information will be generated by selecting experimental conditions to model those occurring in flow from the feeder to the die rather than those in flow from the hopper to the feeder.

### Recording flowmeter

A recording flowmeter is essentially similar to the method described above except that powder is allowed to discharge from a hopper or container on to a balance.

In the case of analogue balances a chart recorder is used to produce a permanent record of the increase in powder mass with time. In some systems the signal from the balance is digitized and processed by a microcomputer. Recording flowmeters allow mass flow rates to be determined and also provide a means of quantifying uniformity of flow.

## IMPROVEMENT OF POWDER FLOWABILITY

### Alteration of particle size and size distribution

Because coarse particles are generally less cohesive than fine particles and an optimum size for free flow exists, there is a distinct disadvantage in using a finer grade of powder than is necessary.

The size distribution can also be altered to improve flowability by removing a proportion of the fine particle fraction or by increasing the proportion of coarser particles, such as occurs through granulation.

### **Alteration of particle shape or texture**

In general, for a given particle size more spherical particles have better flow properties than more irregular particles. The process of spray-drying can be used to produce near-spherical excipients, such as spray-dried lactose. Under certain circumstances, drug particles that are normally acicular can be made more spherical by temperature-cycling crystallization.

The texture of particles may also influence powder flowability, as particles with very rough surfaces will be more cohesive and have a greater tendency to interlock than smooth-surfaced particles. The shape and texture of particles can also be altered by control of production methods, such as crystallization conditions.

### **Alteration of surface forces**

Reduction of electrostatic charges can improve powder flowability and this can be achieved by altering process conditions to reduce frictional contacts. For example, where powder is poured down chutes or conveyed along pipes pneumatically, the speed and length of transportation should be minimized. Electrostatic charges in powder containers can be prevented or discharged by efficient earth connections.

The moisture content of particles is also of importance to powder flowability, as adsorbed surface moisture films tend to increase bulk density and reduce porosity. In cases where moisture content is excessive powders should be dried and, if hygroscopic, stored and processed under low-humidity conditions.

### **Formulation additives: flow activators**

Flow activators are commonly referred to pharmaceutically as 'glidants', although some also have lubricant or antiadherent properties. Flow activators improve the flowability of powders by reducing adhesion and cohesion.

Some commonly used glidants include talc, maize starch and magnesium stearate, which may have their effect by reducing or altering electrostatic interactions. A flow activator with an exceptionally high specific surface area is colloidal silicon dioxide, which may act by reducing the bulk density of tightly packed powders. Colloidal silicon dioxide also improves flowability of formulations, even those containing other glidants, although in some cases it can cause flooding.

Where powder flowability is impaired through increased moisture content, a small proportion of very fine magnesium oxide may be used as a flow activator. Used in this way, magnesium oxide appears to disrupt the continuous film of adsorbed water surrounding the moist particles.

The use of silicone-treated powder, such as silicone-coated talc or sodium bicarbonate, may also be beneficial in improving the flowability of moist or hygroscopic powder.

### **Alteration of process conditions**

#### *Use of vibration-assisted hoppers*

In cases where the powder arch strength within a bin or hopper is greater than the stresses in it, due to gravitational effects, powder flow will be interrupted or prevented. If the hopper cannot be redesigned to provide adequate stresses and if the physical properties of the particles cannot be adjusted or the formulation altered, then extreme measures are required. One method of encouraging powder flow where arching or bridging has occurred within a hopper, is to add to the stresses due to gravitational interactions by vibrating the hopper mechanically. Both the amplitude and the frequency of vibration can be altered to produce the desired effect, and may vary from a single cycle or shock produced by a compressed-air device or hammer, to higher frequencies produced, for example, by out-of-balance electric motors mounted on a hopper frame.

#### *Use of force feeders*

The flow of powders that discharge irregularly or flood out of hoppers can be improved by fitting vibrating baffles, known as live-bottom feeders, at the base of the conical section within a hopper.

The outflowing stream from a hopper can be encouraged to move towards its required location using a slightly sloping moving belt, or in the case of some tableting machines, the use of mechanical force feeders. Force feeders are usually made up of a single or two counter-rotating paddles at the base of the hopper just above the die table in place of a feed frame. The paddles presumably act by preventing powder arching over dies, and thereby improve die filling especially at high turret speeds.

### **Caution!**

In most pharmaceutical technology operations it is difficult to alter one process without adversely

influencing another. For example, increasing compression pressure to produce stronger tablets may also impair disintegration and prolong dissolution; increasing mixing times of drugs with excipients in the presence of magnesium stearate, to improve homogeneity, may also impair tablet strength.

In the case of alterations made in order to improve powder flow, relative particle motion will be promoted and can lead to demixing or segregation. *In extremis*, improving powder flow to improve weight uniformity may reduce content uniformity through increased segregation.

## BIBLIOGRAPHY

- Gioia, A. (1980) Intrinsic flowability. A new technology for powder-flowability classification. *Pharm. Techn.*, 4 (Feb.), 65-68.
- Lieberman, H.A. and Lachman, L. (eds) (1981) *Pharmaceutical Dosage Forms*, Volume 2, Marcel Dekker Inc., New York and Basel.
- McNaughton, K. (ed.) (1981) *Solids Handling*, McGraw-Hill Publications Co., New York.
- Sadek, H.M., Olsen, J.L., Smith, H.L. and Onay, S. (1982) A systematic approach to glidant selection. *Pharm. Tech.*, 6 (Feb.), 42-44, 46, 50, 52, 54, 56, 59, 60, 62.
- Shahinpoor, M. (ed.) (1983) *Advances in the Mechanics and the Flow of Granular Materials*, Volumes 1 and 2. Gulf Publishing Co., Houston and London.
- Singley, M.E. and Chaplin, R.V. (1982) Flow of particulate materials, *Trans. ASAE*, 25, 1360-1373.
- Taubmann, H.J. (1982) The influence of flow activators on the flow behaviour of powders. *Aufbereitungs-Technik*, 23, 423-428.