

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 mean 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 6). 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, an already formed random mix may change to a non-random mix, or a random mix may never be achieved. Care must be taken to avoid segregation occurring during handling after powders have been satisfactorily 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, i.e. it will result in a reduction in the quality of the mix and may cause a batch to fail a uniformity of content or uniformity of dosage units 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 in practice are not composed of monosized spherical particles but contain particles that differ in size, shape, density and surface properties. These variations in particle properties mean that they 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

Differences in the particle sizes of components of a formulation are the main cause of segregation in powder mixes in practice. Smaller particles tend to fall through the voids between larger particles and thus 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 small enough to 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 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* or *fluidization segregation*.

Particle density effects

If components are of different density, the more dense particles will have a tendency to move