downwards, even if their particle sizes are similar. Trajectory segregation may also occur with particles of the same size but different densities due to their difference in mass. The effect of density on percolation segregation may be potentiated if the denser particles are also smaller. Often materials used in pharmaceutical formulations have similar densities and density effects are not generally too important. An exception to this is in fluidized beds, where density differences often have a greater adverse effect on the quality of the mix than particle size differences.

Particle shape effects

Spherical particles exhibit the greatest flowability and therefore are more easily mixed, but they also segregate more easily than non-spherical particles. Irregular or needle-shaped particles may become interlocked, decreasing 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 increase the likelihood of 'dusting out'.

It should be remembered that the particle size distribution and particle shape may change during processing (due 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 11.3. This may not, however, occur for segregating mixes, where there is often an optimum mixing time. This arises since the factors causing segregation generally require a longer time 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 where the two effects are balanced. This is illustrated in Figure 11.4 which demonstrates that, if factors exist which may cause segregation, then 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.

Approaches to minimize segregation

If segregation is a problem with a formulation there are a number of approaches that may be attempted

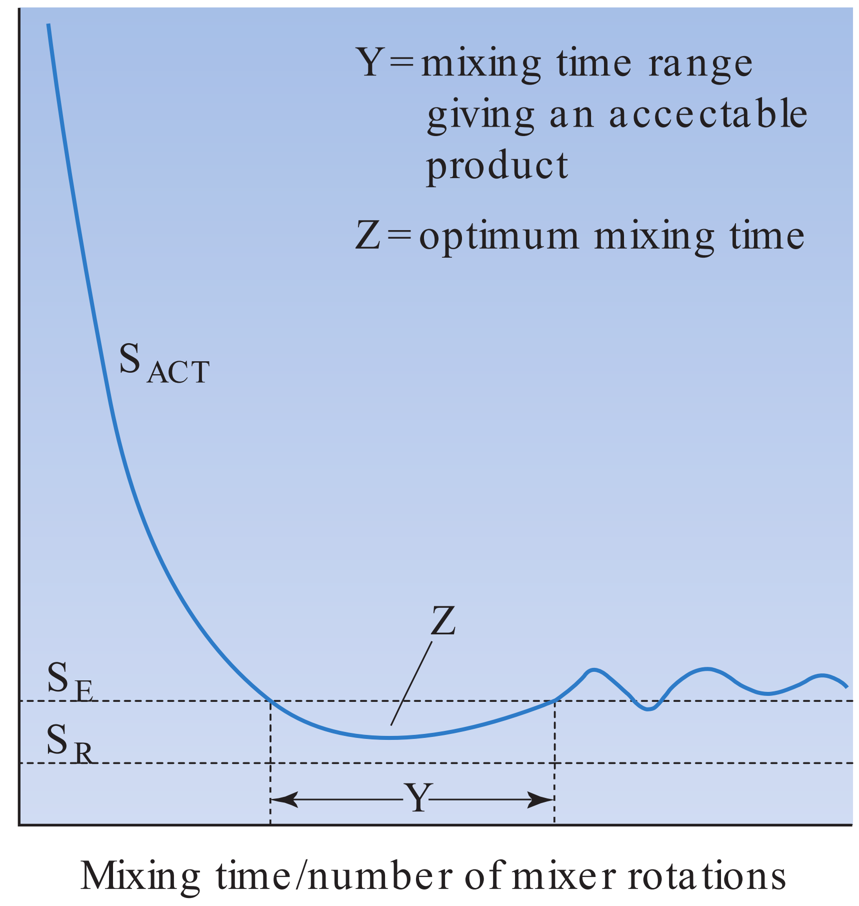

Fig. 11.4 • Possible effect of extended mixing time on the content standard deviation of samples taken from a mix prone to segregation. S_{ACT} represents the content standard deviation of samples taken from the mix, S_E the estimated acceptable standard deviation and S_R the standard deviation expected from a random mix.

to rectify the situation. These include the following:

- 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) to either reduce the particle size range (this may need to be followed by a sieving stage to remove fines) or to ensure all particles are below approximately 30 µm 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 which will produce a product of 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. 28.1)
- reducing the extent to which the powder mass is subjected to vibration or movement after mixing (e.g. avoid the use of pneumatic transfer systems)