

Box 11.3

Worked example

Imagine it is necessary to produce a tablet weighing 50 mg which contains 50 µg of a potent steroid, and that the product specification requires 99.7% of tablets to contain between 47.5 µg and 52.5 µg of the steroid. If the mean particle density of the components is 1.5 g/cm³ (1500 kg/m³), what particle size should the steroid and excipients be?

As there is 50 µg of the steroid in a 50 mg tablet, the proportion of active component (p) = 1×10^{-3} . The specification allows the content to vary by ± 2.5 µg, and so the % deviation allowed = $(2.5/50) \times 100 = 5\%$. Under these circumstances, the calculations described in the previous section show that, providing a random mix is achieved, the number of particles required in the tablet = 3.6×10^6 . The 50 mg tablet must therefore contain at least 3.6×10^6 particles and each particle must weigh less than:

$$50/3.6 \times 10^6 \text{ mg} = 1.39 \times 10^{-5} \text{ mg} = 1.39 \times 10^{-11} \text{ kg.}$$

Since the density of a particle = 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) = $4 \pi r^3/3$ and so:

$$r^3 \text{ must be } < 9.27 \times 10^{-15} \times 3/4\pi \text{ m}^3$$

$$\text{i.e. } r^3 < 2.21 \times 10^{-15} \text{ m}^3 \text{ and } r < 1.30 \times 10^{-5} \text{ m}$$

and therefore $d < 26 \mu\text{m}$.

calculates in a similar manner 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 in mixing potent (low-dose) substances and the importance of both the number of particles in the scale of scrutiny and 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 be to:

- indicate the degree/extent of mixing
- follow a mixing process
- indicate when sufficient mixing has occurred

- assess the efficiency of a mixer
- determine the mixing time required for a particular process.

One evaluation method involves the generation of a *mixing index* that compares the content standard deviation of samples taken from a mix under investigation (S_{ACT}) with the content standard deviation of samples from a fully random mix (S_{R}). Comparison with a random mix is made since 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:

$$M = \frac{S_{\text{R}}}{S_{\text{ACT}}} \quad (11.3)$$

At the start of the mixing process the value of S_{ACT} will be high so that M will be low. As mixing proceeds, S_{ACT} will tend to decrease as the mix approaches a random mix (see Fig. 11.3). If the mix becomes random, $S_{\text{ACT}} = S_{\text{R}}$ and $M = 1$. There is typically an exponential decrease in S_{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 utilization. Other more complicated equations for calculating the mixing index have been used but they 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

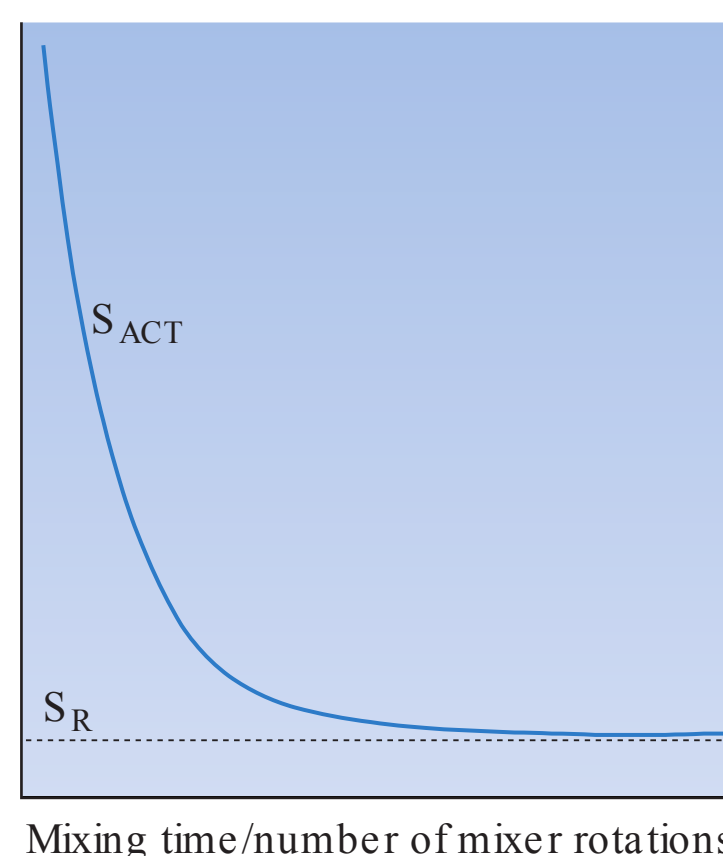


Fig. 11.3 • The reduction in content standard deviation as a random mix is approached. S_{ACT} represents the content standard deviation of samples taken from the mix and S_{R} the standard deviation expected from a random mix.