Table 11.1 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.

appreciated if it is realized that there may only be approximately 75 000 particles of diameter 150 μm in a tablet weighing 200 mg.

The information in Figure 11.1, Figure 11.2 and Table 11.1 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 likely deviation in content.

One way of reducing the deviation, therefore, would be to increase the number of particles in the unit dose by decreasing the particle size. This may, however, lead to particle agglomeration due to the increased cohesion and adhesion that occurs with smaller particles, which in turn may reduce the ease of mixing.

It should be noted that with liquid solutions, 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 that they tend to approach a perfect mix.

Mathematical treatment of the mixing process

It should be appreciated that there will always be some variation in the composition of samples taken from a pharmaceutical mix or 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 (the latter involving the correct 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 (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 Equation 11.1:

$$\mathrm{SD} = \sqrt{\frac{p(1-p)}{n}} \tag{11.1}$$

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

Equation 11.1 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 11.2 and Table 11.1. The situation with respect to the effect of the proportion of the active component in the sample is not as clear from Equation 11.1. As p is decreased, the value of content standard deviation decreases, and this 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