indicates the average deviation as a percentage of the mean amount of active component in the samples. Thus, % CV = (content standard deviation/mean content) × 100. The value of % CV will increase as p decreases, as illustrated in Box 11.1.

Box 11.1

Worked example

Consider the situation where $n = 100\,000$ and $p = 0.5$. Using Equation 11.1, it can be calculated that the:

$$\text{SD} = 1.58 \times 10^{-3} \text{ and } \%\ \text{CV} = \left(1.58 \times 10^{-3}/0.5\right) \times 100 = 0.32\%$$

Thus on average, the content will deviate from mean content by 0.32% which is an acceptably low value for a pharmaceutical product.

If, however, p is reduced to 0.001 and n remains at 100 000 there is a reduction in SD to 9.99×10^{-5} but the

$$\%\ \text{CV} = \left(9.99 \times 10^{-5}/0.001\right) \times 100 = 10\%$$

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 unit dose size (increasing the scale of scrutiny), as this would increase the number of particles in each unit dose. The dose of a drug will, however, be fixed and any increase in the unit dose size will cause a reduction in the proportion of the active component in the unit dose. The consequence of increasing the unit dose size depends on the initial proportion of the active component. If p is relatively high initially, increasing the unit dose size causes the %CV in content to increase. If p is small, increasing the unit dose size has little effect. Inserting appropriate values into Equation 11.1 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 ± 1 SD of the overall proportion of the component (p), 95.5% will be within ± 2 SD of p and 99.7% of samples will be within ± 3 SD of p. For example, if $p = 0.5$ and the standard deviation in content = 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 samples would contain between 44% and 56% of drug (mean = 50%).

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

Box 11.2

Worked example

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 99.7% of samples contain within ± 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 ± 3 SD and ± 5% of p then Equation 11.2 can be used to calculate the standard deviation required:

$$3 \times \text{SD} = p \times (\%\ \text{acceptable deviation}/100) \qquad (11.2)$$

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

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

so

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

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 ± 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 3.6×10^{6}.

Estimation of the particle size required when formulating a dosage form

Using the preceding information, it is possible to estimate the particle size required so that a formulation may meet a desired specification.

The worked example in Box 11.3 indicates that in order to meet the product specification, the particle size of the components needs to be of the order of 26 μm. There would therefore be practical difficulties in making this product, as particles of this size tend to become very cohesive, flow poorly (see Chapter 12) and are difficult to mix.

In order to appreciate the effect of changing the scale of scrutiny, it is suggested that the reader