Box 36.1

Use of freezing point depression to adjust solutions to isotonicity

You are requested to make a solution containing 0.28% w/v potassium chloride isotonic by the addition of anhydrous glucose. From the literature: the freezing point depression of a 1% solution of potassium chloride is 0.439 and for anhydrous glucose it is 0.101.

Using Equation 36.1:

- 1% solution of potassium chloride depresses the freezing point of water by 0.439 °C. Thus, the freezing point depression of unadjusted solution = 0.28 × 0.439 = 0.123 °C.
- 1% solution of anhydrous glucose depresses the freezing point of water by 0.101 °C.

$$W = \frac{0.52 - 0.123}{0.101} = \frac{0.397}{0.101} = 3.93$$

Thus, you require the addition of 3.93% w/v (i.e. 3.93 g per 100 mL) anhydrous glucose to make the potassium chloride solution isotonic with plasma.

$$W = \frac{0.52 - a}{b} \qquad (36.1)$$

where W is the % w/v of adjusting substance in the final solution, a is the freezing point depression of unadjusted solution (i.e. freezing point depression of 1% solution × strength in % w/v) and b is the freezing point depression of water due to 1% w/v of adjusting substance, usually sodium chloride or glucose. A worked example is presented in Box 36.1.

Suspending agents

Drugs presented as suspensions for injection may require a suspending agent to ensure that the drug can be readily and uniformly resuspended prior to use. A water soluble cellulose derivative such as methylcellulose can be used in intramuscular and intra-articular injectable suspensions. Povidone has been used in the past for this purpose, but safety concerns about this compound when injected intramuscularly have led to it falling out of favour. A suitable non-ionic injectable surfactant such as a polysorbate may also be included in a suspension formulation to aid the uniform dispersion of the suspended drug substance.

Containers

As noted above (see pharmacopoeial requirements) the container or primary packaging of a parenteral product should ideally be transparent to allow the product to be examined prior to use. This is particularly important for injections supplied as powders for reconstitution, as the healthcare practitioner needs to be able to see that the drug substance has completely dissolved in the diluent prior to withdrawal of the dose. Large volume infusion fluids often have other drugs added to them, so again the clarity of the container is important to allow the proper mixing of the product to be assessed and to check that large particles (e.g. from the rubber closure) have not been inadvertently introduced.

Whatever type of container is used it must be tightly sealed to maintain the sterility of the injection prior to use and to prevent other contaminants entering the product which may lead to degradation of the drug substance (e.g. oxygen). The container should not interact with the drug product or other excipients it contains. It should also be robust enough to withstand the chosen sterilization process. In preference, parenteral products are manufactured and filled into the primary container which is then sealed and the product is then terminally sterilized inside the container, for example by using moist heat in an autoclave (see Chapters 16 and 17). If the drug substance cannot withstand this process then the containers will be sterilized first, the drug product sterilized by filtration and then filled under conditions of strict asepsis and the container sealed. This latter method of aseptic production obviously carries the risk of microbial contamination of the product during the filling and sealing process, hence the preference for sterilization of the drug product inside the sealed container after filling.

Ampoules

Small-volume parenteral products are often packaged in glass or plastic ampoules. The use of glass and plastics as packaging materials for pharmaceutical products is discussed in Chapter 47. Ampoules are used for single use, unpreserved products. Glass ampoules range in size typically from 1 mL up to 10 mL in volume, though larger sizes are available. The glass chosen is referred to as Type I or borosilicate glass which is less alkaline than the usual glass used for beverages and other purposes. Ampoules