concentrations between 0.3–2.0% w/v and derivatives of edetic acid (ethylenediaminetetraacetic acid; EDTA) at concentrations between 0.0005–0.01% w/v. Citric acid can also be used to adjust the pH of formulations and edetate compounds possess preservative properties.

If the primary mechanism of drug degradation in the product over time is hydrolysis rather than oxidation, then the shelf-life of the product will be improved by removal of all water from the product. Injectable products which are presented as freeze-dried powders (see Chapter 29 for the freeze-drying process and Chapter 17 for the sterilization of these powders) are usually formulated in this manner to improve the stability of a readily hydrolyzed drug substance.

pH adjustment and buffers

The physiological pH of plasma and extracellular fluid is 7.4; therefore ideally all injectable products should be formulated to this pH value. However, there is likely to be an optimum pH value at which the drug substance is most stable. The solubility of the drug in the vehicle may also be dependent on pH. Therefore, the pH chosen for a parenteral product is likely to be a compromise between the requirements for stability, solubility and physiological compatibility. Injectable products should have a pH value between 3.0 and 9.0 prior to administration. pH values above or below this range are too corrosive and will cause tissue damage at the site of injection. The pH of a parenteral formulation can be adjusted using acidifying or alkalizing agents. Acidifying agents include hydrochloric, citric and sulphuric acids. Alkalizing agents include sodium bicarbonate, sodium citrate and sodium hydroxide.

Buffers are included in parenteral products to maintain the pH of the product at the desired optimum value. Changes in pH may arise due to interactions between an ingredient in the formulation and the container, or from changes in storage temperature. Buffer ingredients commonly used in parenteral products include citric acid, sodium citrate, sodium acetate, sodium lactate and mono- and dibasic sodium phosphate.

Tonicity adjusting agents

An aqueous solution of sodium chloride at a concentration of 0.9% w/v or 9 g per L has a measured osmolarity of 286 mmol per L and is isotonic (meaning has the same osmotic pressure (see Chapter 3) with human plasma, which has an osmolality of between 280–295 mmol per kg.

Hypotonic solutions have a lower osmotic pressure than plasma. If mixed with blood they would cause the blood cells to swell and burst as water would be driven into the cells by osmosis. Hypertonic solutions have a higher osmotic pressure than plasma. If mixed with blood they would cause the blood cells to lose water by osmosis and shrink.

Hypotonic injection solutions are made isotonic by the addition of sodium chloride, dextrose or mannitol. Hypertonic injection solutions must be made isotonic by dilution prior to administration. Pharmacopoeias direct that intravenous infusions should be made isotonic with human plasma. Whilst not a pharmacopoeial requirement, it is considered desirable for subcutaneous, intradermal and intramuscular injections also to be isotonic. Intrathecal and intraocular injections should also be isotonic to avoid serious changes in osmotic pressure in the cerebrospinal fluid and the eye.

There are a number of methods available for calculating the amount of additional substance to be added to a hypotonic drug solution to render it isotonic, including freezing point depression, the use of sodium chloride equivalents, molar concentrations and calculations based on serum osmolarity. One method is demonstrated below:

Isotonicity calculation based on freezing point depression

The presence of solutes in water will increase osmolarity and depress the freezing point of water. These effects (colligative properties; Chapter 3) are dependent on the concentration of solute particles. Consequently, the freezing point of a solution can be used as a measure of its osmolarity. The freezing point of blood serum/plasma and tears is −0.52 °C. Therefore, an aqueous solution that freezes at −0.52 °C is isotonic. For high concentrations of electrolytes there may be a slight deviation in the direct relationship between concentration and freezing point depression, but in most cases the relationship holds true. Reference sources, such as the *Pharmaceutical Codex* give the freezing point depressions produced by a wide range of soluble materials.

The required amount of adjusting substance required to make a hypotonic solution isotonic is given by the equation: