Preservatives

Antimicrobial preservatives are added to injections which are designed for multiple use. Such products are usually packaged in glass vials or cartridges with a synthetic rubber septum that can be punctured on a number of occasions to withdraw a dose of the drug for administration (see the section below on containers). A preservative is included to inhibit the growth of any microorganisms that may be inadvertently introduced into the product during repeated use by the patient or healthcare professional.

Excipients such as ethanol, glycerol and propylene glycol which may be added to a formulation as co-solvents to aid drug dissolution also will provide an antimicrobial effect. Ethanol is effective at concentrations above 10% v/v, glycerol at 10–20% v/v and propylene glycol at 15–30% v/v. Some of the commonly used antimicrobial preservatives suitable for parenteral administration are given in Table 36.1. It should be noted that fatal toxic reactions in low birth-weight neonates have been linked to benzyl alcohol preserved injections. Thus, parenteral products preserved with benzyl alcohol should not be administered to neonates. Also, as noted above, preservatives should not be added to large volume parenterals (infusions), or products intended for intraspinal or intraocular injection. Preservation of pharmaceutical products, including injections is discussed in detail in Part 6 of this book.

Antioxidants

If the drug substance to be injected is prone to degradation by oxidation a number of formulation processes and excipients can be used to reduce the rate of drug degradation in the product and thus improve the shelf-life or expiry date.

It is common practice to use pharmaceutical grade compressed nitrogen gas (filtered through a 0.2 µm pore size filter) during the manufacturing process. Nitrogen is bubbled through the solution containing the drug prior to filling into the final packaging. The nitrogen gas displaces any dissolved oxygen from the drug solution. This process is known as 'sparging'. A nitrogen overlay may also be applied during the filling operation prior to sealing the final containers of the drug product. This will displace air from the headspace between the surface of the product and the top of the container (for example in a vial or ampoule) thereby removing oxygen.

An antioxidant may also be included in the formulation. Antioxidants are chemicals that have a lower oxidation potential than the drug substance and thus will react with any oxygen present in the product in preference to the drug. Vitamin C (ascorbic acid) and Vitamin E (alpha-tocopherol) can be used for this purpose, both in pharmaceutical products and in food. Alpha-tocopherol is highly lipophilic and can be used in oil-based parenteral products usually in the range of 0.001–0.05% v/v. Ascorbic acid is used in aqueous parenteral products at a concentration of 0.01–0.1% w/v. Ascorbic acid can also be used to adjust the pH of the formulation (see below). Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are structurally similar antioxidants used in parenteral preparations either separately or in combination. For intramuscular injections they are usually used at a concentration of 0.03% w/v and for intravenous injections 0.0002–0.002% w/v is used. The most commonly used antioxidants are the sulphite salts. Sodium metabisulphite is used at concentrations between 0.01–0.1% w/v and also has some preservative properties. It is used as an antioxidant for acidic parenteral products. If the product is of neutral pH sodium bisulphite is used, whereas sodium sulphite is used as an antioxidant in alkali parenterals.

The activity of an antioxidant can be enhanced by the inclusion of an antioxidant synergist, also referred to as chelating or sequestering agents. Antioxidant synergists reduce oxidation by removing trace levels of metal ions from the product by forming chelates with them. Metal ions, particularly copper, iron and manganese are believed to catalyse oxidation reactions between oxygen and drug substances. Examples of chelating agents used in parenteral products include: citric acid at

Table 36.1 Preservatives used in parenteral products

Preservative	Typical concentration (% w/v)
Benzalkonium Chloride	0.01
Benzoic Acid	0.17
Benzyl Alcohol	1–2
Chlorobutanol	0.1–0.5
Chlorocresol	0.1
Cresol	0.15–0.3