chapter 5
Parenteral formulations

Overview

In this chapter we will:

- examine the types of parenteral formulations
- provide an overview of the advantages and disadvantages of parenteral formulations
- describe the formulation considerations for parenteral formulations
- briefly describe manufacturing consideration of parenteral formulations.

General description

Parenteral administration of drugs involves the injection of therapeutic agents, in the form of solutions, suspensions or emulsions, into the body. In so doing, one of the major barriers to drug entry (the skin) is breeched. Parenteral formulations have been officially recognised since the mid 19th century when morphine solution appeared in the 1874 addendum to the British Pharmacopoeia (1867). Currently many classes of drug are formulated as parenteral dosage forms and, indeed, the control of certain disease states is dependent on parenteral administration, e.g. type 1 diabetes mellitus. Parenteral products are therefore essential components of modern medicine.

KeyPoints

- Parenteral formulations are extensively used in the treatment and control of numerous disease states, e.g. diabetes, infection, pain.
- Parenteral formulations can be subdivided into three categories, namely solutions, suspensions and emulsions. Furthermore parenteral formulations may be defined as either large-volume or small-volume parenterals.
- Parenteral formulations are principally administered by three routes (intravenous, intramuscular and subcutaneous).
- The volume of injection and the requirements for onset of action primarily define the type of parenteral formulation (solution, suspension, emulsion) required.
- Parenteral formulations are *sterile* and therefore require specialist (and more expensive) manufacturing processes.
- Parenteral formulations are *pyrogen-free*.

Routes of parenteral administration

There are several different routes by which parenteral products may be administered and indeed there are very few, if any, organs into which parenteral dosage forms may not be injected. However, there are three routes by which parenterals are most frequently administered: (1) intravenous (IV); (2) intramuscular (IM); and (3) subcutaneous (SC). These sites are located beneath the epidermis/dermis within the skin.

Intravenous route

- This involves administration of the parenteral formulation into a vein, usually a large proximal vein. The veins are located beneath the subcutaneous tissue, embedded within the muscle.
- IV administration achieves a rapid and predictable response.
- It ensures 100% drug bioavailability.
- Both large- (up to 500 ml) and small- (up to 10 ml) volume formulations may be administered intravenously. Large volumes are infused into the vein at a controlled rate, e.g. total parenteral nutrition, infusion of solutions of electrolytes/nutrients either containing or devoid of drugs.
- Formulations are usually solutions or emulsions (in which the size of the disperse phase is small, <1 μm). Suspensions (or solutions that precipitate within the blood stream) must not be administered IV due to disruption of blood flow.
- Due to the subsequent dilution of the injected dose and the relative insensitivity of venous walls of veins, IV administration may be employed for the administration of drugs that would normally be too irritating if administered by other routes.
- Care must be taken regarding the rate of administration of the parenteral formulation. If the administration is performed too quickly, an excessive concentration of drug at the target organ may result, leading to drug-induced shock.
- Training is required to ensure that the dosage form is actually administered to the vein and that puncture of the vein is avoided.

Intramuscular route

- This involves administration into a muscle, usually the gluteal (buttocks), vastus lateralis (lateral thigh) or deltoid (upper arm) muscles. The musculature resides below the subcutaneous tissue (which itself lies beneath the epidermis and the dermis).
- The volume of injection is small, usually 1–3 ml or up to 10 ml in divided doses.
- Faulty injection technique may lead to local muscle damage.
- IM injection results in relatively rapid absorption, second only to IV with respect to the time taken for the onset of action. The nature of the formulation directly affects the rate of absorption of drugs administered by the IM route. Drug absorption from aqueous solutions is greater than from aqueous suspension or non-aqueous (oil-based) solutions of drugs.
- IM injections are usually used for controlled-release formulations.

Subcutaneous route

- This involves administration into the subcutaneous tissue, a layer of fat located below the dermis.
- There is a slower onset of action and sometimes less total absorption of therapeutic agents when compared to the IV or IM routes of administration. As before, the nature of the formulation directly affects the rate of drug absorption from this site: oily solutions or aqueous suspension of therapeutic agents exhibit slower drug absorption.
- The volume of injection is typically circa 1 ml; however, large-volume parenteral solutions (electrolyte or dextrose, up to 1000 ml) may be infused subcutaneously. This technique is termed hypodermoclysis and is only employed when there is difficulty in accessing a vein. On some occasions hyaluronidase may be administered to increase the available volume at the site by catalysing the temporary breakdown of the connective tissue at the site (hyaluronic acid).
- Viscous formulations are not generally administered subcutaneously.
- Typical sites of SC injection include the arms, legs and abdomen.
- SC administration is the route of choice for the administration of insulin.

Miscellaneous routes

In addition to the primary routes of administration cited above, there are other parenteral routes of administration that are not used as frequently as the IM, IV and SC routes but do play an important role in medicine. These include: (1) intradermal (ID); (2) intra-arterial (IA); (3) intrathecal (IT); (4) intradural and extradural; (5) and intracardiac (IC) routes.

Intradermal route

- This is the injection into the dermal layer of the skin.
- The ID route is generally used for diagnostic purposes, e.g. for the diagnosis of allergy and for the tuberculin test.
- Despite being a vascular site, absorption is slow and limited from this region.
- Only small volumes may be injected, circa 0.1 ml.

Intra-arterial route

- The parenteral formulation is injected into an accessible artery.
- This route requires specialist training to administer therapeutic agents as if the artery is missed, possible damage to adjacent nerves may result.

- The IA route is used to administer radiopaque media to visualise organs, e.g. heart, kidney.
- It is used to administer anticancer drugs to ensure that the highest possible concentration of drug reaches the target organ.

Intrathecal (IT) route

- This route is used to administer therapeutic agents to the cerebrospinal fluid to ensure that the appropriate concentration of drug is obtained at this site (e.g. for the treatment of infection).

Intradural and extradural routes

- Intradural and extradural administration is employed to achieve spinal anaesthesia.
- Intradural administration involves injection of the therapeutic agent within the dural membrane surrounding the spinal cord.
- Extradural administration involves injection of the therapeutic agent outside the dural membrane and within the spinal caudal canals.

Intracardiac (IC) route

- The intracardiac route involves injection of the formulation directly into the muscles of the heart.
- This route is normally used whenever there is a cardiac emergency.

Tip

The route of administration of the parenteral product directly affects the pharmacokinetic profile of the dosage form. Typically the intravenous route is employed for rapid onset of action whereas controlled-release formulations are administered by the intramuscular or subcutaneous routes.

Other more specialised routes are employed for the delivery of the therapeutic agent directly to the target site/region.

Advantages and disadvantages of parenteral formulations

Advantages

- An immediate physiological response may be achieved (usually by the IV route). This is important in acute medical situations, e.g. cardiac arrest, anaphylactic shock, asthma.
- Parenteral formulations are essential for drugs that offer poor bioavailability or those that are rapidly degraded within the gastrointestinal tract (e.g. insulin and other peptides).
- They offer a method to administer drugs to patients who are unconscious or uncooperative or for patients with nausea and vomiting (and additionally dysphagia).

- As trained medical staff primarily administer parenteral formulations, there is control of both the dosage and frequency of administration. The main exception to this is the administration of insulin, which, in the absence of complications (e.g. ketoacidosis), is performed exclusively by patients.
- Local effects may be achieved using parenteral formulations, e.g. local anaesthesia.
- Parenteral formulations provide a means by which serious imbalances in electrolytes may be corrected (using infusion solutions).
- Parenteral formulations may be readily formulated to offer a wide range of drug release profiles, including:
  - rapidly acting formulations (generally drug solutions that are administered IV)
  - long-acting formulations (generally drug suspensions, or solutions in which the drug is precipitated out of solution at the injection site, administered by the IM or SC routes). Examples of these include intermediate/long-acting insulin formulations and steroid injections.
- In patients who cannot consume food, total parenteral nutrition offers a means by which nutrition may be provided using specially formulated solutions that are infused into the patient.

Disadvantages

- The manufacturing process is more complicated than for other formulations due to the requirement for aseptic technique. The level of training of staff involved in the manufacture of parenteral formulations is high and often specialist equipment is required to ensure that the finished product specification is achieved.
- Skill of administration is required to ensure that the dosage form is administered by the correct route. If a parenteral suspension, which is designed for administration by the IM or SC route, is incorrectly administered by the IV route, a pulmonary microcapillary blockage may occur leading to a blockage in the flow of blood at that site.
- Parenteral formulations are associated with pain on administration.
- If the patient is allergic to the formulation (the therapeutic agents and/or the excipients), parenteral administration will result in both rapid and intense allergic reactions.
- It is difficult to reverse the effects of drugs that have been administered parenterally, even immediately after administration. This is not strictly the case with other routes of administration, e.g. oral, transdermal.

Formulation considerations for parenteral formulations

Parenteral formulations may be categorised as solutions (aqueous or oil-based), suspensions (aqueous or oil-based) or emulsions. For the most part, these formulations use similar (or indeed identical) excipients but, as may be expected, there are certain excipients that are unique to each category. Details of the key formulation excipients for each formulation type are provided below. In addition, the reader will observe a similarity in the excipients used for the formulation of solutions, suspensions and emulsions for parenteral administration and those used for non-parenteral use. The main formulation considerations for parenteral formulations are described below.

Type of preparation

The initial choice that must be made concerns the type of parenteral formulation required, a choice that is informed by the physicochemical properties of the therapeutic agent, the intended route of administration of the formulation, the volume to be administered and the general preference for a particular formulation based on the perceived pharmacological effect or onset of pharmacological effect. In some cases, the formulation scientist may be asked to formulate a specific preparation, e.g. an aqueous suspension for IM administration. However, in the absence of this information, several issues, detailed below, must be addressed.

Solubility of the therapeutic agent

With respect to the formulation of pharmaceutical products, therapeutic agents may be categorised into three groups:

1. Good solubility, in which the therapeutic agent is freely soluble in the chosen solvent (either aqueous or oil-based) at the concentration required in the parenteral product. In this case a parenteral solution is a possible formulation option.
2. Moderate solubility but insufficient to produce a solution in conventional solvents (e.g. water, oil). In this scenario, the use of co-solvents may sufficiently increase the solubility of the therapeutic agent in the vehicle to produce a parenteral solution containing the required drug concentration. This is generally the preferred strategy for therapeutic agents of moderate solubility. However, if required, the therapeutic agent may be formulated as a suspension, although one cautionary note regarding this approach is the potential recrystallisation of soluble drug during storage, a phenomenon that may affect the physical stability of the preparation.

3. Low solubility in the chosen vehicle. The preferred choice for therapeutic agents that exhibit low solubility in the chosen vehicle is a parenteral suspension formulation.

Preferred route of administration

If there is a preferred route of administration for the parenteral product, this will directly influence the nature of the parenteral product. In particular:

- IV products must be *aqueous solutions* and, furthermore, must not precipitate in the blood stream following administration. Emulsions may also be administered by this route provided the particle size of the internal phase is sufficiently small.
- Parenteral suspensions (aqueous or oil-based) and oil-based parenteral solutions must be administered either subcutaneously or intramuscularly. Aqueous solutions may also be administered intramuscularly or subcutaneously.
- There are other restrictions for those less commonly used routes of parenteral administration that are specific for each route.

Volume of dose to be administered

The volume of product to be parenterally administered will directly affect the type of formulated product.

- Large-volume parenterals (up to 500 ml) are administered intravenously (although the SC route of administration is infrequently used for this purpose).
- Small-volume parenterals may be administered by all routes (bearing in mind the restrictions of oil-based and suspension formulations).

Onset/duration of action

A wide range of predictable plasma drug concentration–time profiles may be obtained with parenteral formulations that are dependent on both the type of formulation and route of administration. Indeed, this is one of the major rationales for the use of parenteral administration of therapeutic agents. Whilst the pharmacokinetics of parenteral dosage forms is not under direct consideration in this book, it is important to summarise the effects of both formulation type and route of administration on such properties.

- Formulations administered intravenously will have an immediate pharmacological effect. The rates of drug absorption from the other main routes of administration (SC and IM) are slower.
- The absorption of therapeutic agents from aqueous solutions when administered by the IM or SC routes is faster than from

oil-based solutions, oil-based suspensions and aqueous suspensions. As a result, the slower absorption of therapeutic agents from oil-based solutions/suspensions and aqueous suspensions enables these formulations to offer a prolonged clinical effect whenever administered by the IM or SC routes. This may be illustrated by the following examples:

- When injected subcutaneously, the onset of action of soluble insulin (aqueous solution) is rapid (circa 30 minutes), peaks between 2 and 4 hours and has a duration of action of up to 8 hours. Conversely, intermediate/long-acting insulins (aqueous suspensions), when administered subcutaneously, have an onset of action of 1–2 hours, a peak action between 4 and 12 hours and a duration between 16 and 35 hours.
- Triamcinolone acetonide is administered intramuscularly or intra-articularly as an aqueous suspension to suppress inflammation. The duration of action of a single dose is approximately 21 days.

Physicochemical properties of the therapeutic agent

The physicochemical properties are important determinants of the stability and absorption of the therapeutic agents when formulated as parenteral suspensions (aqueous or oil-based). Conversely, when formulated as a parenteral solution the effects of the physicochemical properties of the therapeutic agent on the above properties are limited. In particular, the following properties directly affect the rate of dissolution (and hence the rate of absorption) of poorly soluble therapeutic agents following IM or SC administration.

Solid-state properties

In the solid state therapeutic agents may exist in either crystalline or amorphous states. In *crystalline* compounds the molecules are packed (bonded) in a defined, repeating order. Crystalline compounds exhibit a defined melting point, which occurs whenever there is sufficient energy applied to the crystal to overcome the attractive forces between the molecules in the lattice. As the strength of the interactive forces increases, so does the melting point of the crystal. *Polymorphism* refers to the ability of molecules to exist in more than one crystalline form. Usually one crystalline form is the stable form and the other(s) are less stable, being referred to as metastable. Over time the metastable form(s) will revert to the stable form. Importantly, different polymorphic forms of a particular therapeutic agent will exhibit different melting points and, as a result, will exhibit different dissolution rates. Polymorphic forms of a particular therapeutic agent will possess the same chemical structure; however, the different solubilities of the different polymorphs will lead to

different rates of dissolution after IM or SC administration and hence different rates of drug absorption.

Solubilities of insoluble salt forms

The reader will be aware that different salt forms of a particular therapeutic agent exhibit different aqueous solubilities. The rate of dissolution of poorly soluble therapeutic agents is directly proportional to the saturated solubility of the compound, as defined in the Noyes–Whitney equation:

$$\frac{\delta M}{\delta t} = \frac{DAC_s}{h}$$

where: $\frac{\delta M}{\delta t}$ refers to the rate of dissolution of the therapeutic agent; h refers to the thickness of the unstirred diffusion layer that surrounds each particle that is undergoing dissolution; D is the diffusion coefficient of the dissolved drug molecule through the unstirred diffusion layer; A is the surface area of the particle undergoing dissolution; C_s is the saturated solubility of the drug, i.e. the concentration that exists in solution adjacent to the dissolving particle.

Therefore, by altering the solubility of the salt form, the rate of dissolution of the drug particles following administration (IM or SC) may be modified. This approach has been successfully used commercially in the formulation of intermediate and long-acting insulin preparations. For example, the solubility of protamine insulin is dramatically lower than soluble insulin and this is reflected by the greater duration of action of the former system. The duration of action of insulin may be further enhanced by forming a salt with zinc or with protamine and zinc, which has lower solubility and hence a lower rate of dissolution.

Particle size

Particle size is a fundamental property that directly controls both the rate of dissolution and physical stability of parenteral suspensions. Referring to the Noyes–Whitney equation, it may be observed that the rate of dissolution of a poorly soluble drug increases as the surface area of the particle increases. In practice the surface area of the drug particle increases as the mean diameter of the particles decreases. Therefore, decreasing the particle size may increase the rate of dissolution of an insoluble therapeutic agent.

The role of particle size on the absorption of an insoluble drug may be illustrated in the following example, which relates to an aqueous testosterone suspension.

- A suspension of testosterone propionate (particle size range 40–100 μm) exhibits a duration of action of *8* days following IM administration.
- A suspension of testosterone propionate (particle size range 50–200 μm) exhibits a duration of action of *12* days following IM administration. Therefore, in this formulation the area of drug particle in contact with the biological fluids is less than in the previous example and, in accordance with the Noyes–Whitney equation, the longer duration may be explained by the slower rate of drug dissolution.
- Interestingly, a suspension of testosterone isobutyrate (particle size range 50–200 μm) exhibited a duration of action of *20* days following IM administration. The greater lipophilicity, and hence lower aqueous saturated solubility, of this testosterone ester would result in a slower rate of dissolution than for the more hydrophilic propionate ester of this drug.

In addition to the effect of particle size on the solubility and hence rate of dissolution of poorly soluble drugs, particle size plays an important role in the physical stability of parenteral suspensions. The reader will recall the Stokes' equation, in which the rate of particle sedimentation is related to particle size as follows:

$$\frac{\delta v}{\delta t} = \frac{2r^2 (\rho_s - \rho_l)g}{9\eta_l}$$

where: $\frac{\delta V}{\delta t}$ refers to the rate of particle sedimentation; r refers to the radius of the dispersed particles; $(\rho_s - \rho_l)$ refers to the density difference between the solid phase and the liquid phase; g refers to gravity; and η_l refers to the viscosity of the liquid phase.

It is accepted that reducing the rate of sedimentation of the dispersed drug particles will enhance the physical stability of suspensions. One method by which this may be achieved is to reduce the particle size of the drug particles. Increasing the particle size of the dispersed drug will both increase the rate of sedimentation (and possibly decrease the physical stability of the formulation) and decrease the rate of dissolution of the drug, the latter leading to a slower onset of activity but a prolonged duration of action following IM administration. The interplay between particle size and both the rate of dissolution (and hence absorption) and the physical stability of suspensions should be fully appreciated by students.

Vehicle

All parenteral formulations may be formulated using an aqueous vehicle, an oil vehicle or a hydroalcoholic vehicle, the choice being determined (in part) by the required solubility of the active agent in the formulation and the desired type of formulation.

Tip

The nature of the formulation directly affects the onset and duration of action of parenteral products. When administered by the same route, the onset of action of parenteral suspensions is slower than for solutions but the duration of action is markedly greater.

Aqueous vehicles

Water for injection is the major vehicle of choice for:

- freely soluble therapeutic agents (for the preparation of parenteral solutions)
- therapeutic agents of low aqueous solubility (for the preparation of parenteral suspensions)
- the external phase of parenteral emulsions.

Water for injection has specifications set regarding:

- appearance (clear, odourless and within a defined pH range, 5–7)
- purity (limits on the mass of ions, heavy metals and oxidisable compounds and also on the total amount of dissolved solids, <10 ppm)
- sterility:

– Water for Injections USP is non-sterile and is used in the preparation of parenterals that will be terminally sterilised (i.e. during or after the manufacture process).

– Sterile Water for Injections USP is available. This is water for injections that has been sterilised and which has been packaged in single units (1 litre in volume). It may contain a greater mass of dissolved solids due to leaching of solid matter from the containers during sterilisation. It is intended to be used as a vehicle for products that have been packaged and sterilised, e.g. for the reconstitution of antibiotic powders as solutions or suspensions.

- pyrogens:
  Water for injection must be free of pyrogens (fever-producing compounds) that are primarily associated with Gram-negative bacteria. It is important to have knowledge of the physicochemical properties of pyrogens as these properties directly influence the choice of methods that may be used to ensure removal of these compounds. In particular pyrogens are:

– thermostable, thereby invalidating their removal using simple heating cycles

– water-soluble, thereby invalidating their removal using conventional filtration techniques
– unaffected by bactericides.

In light of the above, pyrogens are effectively removed from water using either distillation or reverse osmosis. Following treatment, water for injection must be stored in *pyrogen-free containers* at a defined temperature (either 5°C or 60–90°C) if the period of storage exceeds 24 hours. Removal of pyrogens from the storage containers is typically performed by heating the container at either 250°C for 30–45 minutes or at 180°C for 3–4 hours.

As a variation on the above, *Bacteriostatic Water for Injections USP* is also available. Similar to Water for Injections USP, bacteriostatic water for injection is sterile and devoid of pyrogens. It additionally contains an antimicrobial agent, e.g. 0.9% w/v benzyl alcohol (a bacteriostatic preservative) and is commonly supplied in a multidose container (≤30 ml). Samples from this container may be repeatedly removed and used to dissolve or dilute therapeutic agents prior to injection. To prevent potential toxicity, Bacteriostatic Water for Injections USP is only used whenever the volume of formulation to be administered is less than 5 ml. Care must be given in the use of Bacteriostatic Water for Injections USP to ensure that the antimicrobial agent does not deleteriously interact with the therapeutic agent.

Non-aqueous vehicles

- Non-aqueous vehicles are employed for the production of:
  – non-aqueous parenteral solutions of therapeutic agents that are water-insoluble
  – non-aqueous parenteral suspensions of therapeutic agents that are water-soluble and/or exhibit aqueous instability
  – the internal phase of parenteral emulsions.
- Fixed oils are predominantly used as non-aqueous vehicles (e.g. corn oil, cottonseed oil, peanut oil, sesame oil); however, non-aqueous esters may be used, e.g. ethyl ethanoate:
  – Sesame oil is generally the oil of choice as it is more stable.
  – Oils must be free from rancidity and must not contain mineral oils or solid paraffins.
- Two major problems associated with the use of non-aqueous pharmaceutical solutions are:
  – Pain/irritation on injection. It should be noted that the viscosity of fixed oils increases at lower storage temperatures. This will, in turn, affect the ease of administration by injection and the pain/irritation at the site of injection. It is essential to ensure that the viscosities of oil-based solutions and suspensions are minimised both to reduce pain on injection and to enhance the ease of administration (injection).

- Patients may exhibit sensitivity to the oils and therefore the oil used in the formulation must be explicitly stated on the label/patient information.
- In some oily formulations, agents may be added to enhance the solubility of the therapeutic agent in the oil vehicle. Benzyl benzoate (itself a non-aqueous vehicle) may be used for this purpose.

Inclusion of co-solvents

- As highlighted in Chapter 1, co-solvents are employed whenever the solubility of the drug in water (or occasionally in oil-based vehicles) alone is insufficient for the required application. The types and choices of co-solvent that may be employed in parenteral formulations are generally similar to those used to formulate pharmaceutical solutions; however, when used in parenteral formulations, the potentially greater toxicity of these agents when administered parenterally should be carefully considered. Furthermore, the toxicity of co-solvents is dependent on the route of administration; toxicity is greater whenever administered by the IV in comparison to the IM and SC routes.
- Examples of co-solvents used in parenteral formulations include:
  - glycerol
  - ethanol (high concentrations of ethanol are known to produce pain on injection)
  - propylene glycol
  - polyethylene glycol 400.

  In veterinary formulations other co-solvents may be used, including 2-pyrrolidone and dimethyacetamide; however these co-solvents are not registered for use in parenteral formulations for humans.
- The concentration of co-solvent used should be sufficient to render the drug soluble within the formulation (over the shelf-life of the product) but should not be irritant or toxic to the patient.

Surface-active agents

The use of surface-active agents in solutions and suspensions designed for oral administration has been addressed in Chapters 1 and 2. In general the incorporation of surface-active agents within parenteral formulations is conceptually identical. In this section some of the basic concepts are revisited within the context of the specific use of these agents in parenteral formulations. In particular:

- Surface-active agents may be incorporated into parenteral solutions to enhance the solubility of the therapeutic agent to the required concentration. In this scenario, the concentration of surface-active agent employed will exceed the critical micelle concentration (CMC) of the surface-active agent. Surface-active agents may be incorporated into aqueous or non-aqueous (oil-based) vehicles for this purpose.
- When included in parenteral suspension formulations, surface-active agents act to enhance the physical stability of the formulation by adsorbing to the surface of the dispersed therapeutic agent and preventing caking of the solid particles. For this purpose concentrations of surface-active agents that are below the CMC may be used. It is extremely common for non-ionic surface-active agents to be used in this manner. Examples include:
  - polyoxyethylene sorbitan fatty acid esters (Tween series), within the concentration range of 0.1–0.5% w/v
  - poly(oxyethylene)-poly(oxypropylene) block co-polymers (Poloxamers), within the concentration range 0.01–5% w/v
  - lecithin, within the concentration range of 0.5–2.0% w/w.
- The choices of surface-active agent and the concentration to be used are dependent on the nature of the vehicle and the type of parenteral formulation (i.e. solution or suspension). Accordingly surfactants with low and high hydrophile–lipophile balance values will be used to stabilise oil-based and aqueous drug suspensions, respectively. Similarly, these surfactants are used to solubilise drugs in oil-based and aqueous vehicles, respectively; in this scenario higher concentrations (> CMC) are required.
- The use of surface-active agents to solubilise therapeutic agents is commercially employed. Examples of these formulated systems include:
  - Steroids have been solubilised for parenteral use using combinations of non-ionic surfactants, e.g. polyoxyethylene sorbitan fatty acid esters (Tween series) and sorbitan esters (Span series).
  - The poorly water-soluble vitamins (A, D, E and K) may be solubilised using surface-active agents as parenteral solution formulations. For example, phytomenandione is formulated as a colloidal solution in a mixed-micelles vehicle and is designed for administration either by slow IV injection or by IV infusion (after incorporation within a 5% glucose solution).
  - The poorly water-soluble antifungal agent amphotericin B is commercially available as a complex with sodium deoxycholate (Fungizone), L-α-dimyristoylphosphatidylcholine and

L-α-dimyristoylphosphatidylglycerol (Abelcet), sodium cholesteryl sulphate (Amphocil). These powders are constituted with water for injection to produce colloidal solutions prior to use as IV infusions.

Buffers

As highlighted in Chapter 1, buffers are commonly included in parenteral formulations to control the pH of the formulation. This is similarly the case for parenteral formulations where control of the pH of the formulation may:

- Maintain the solubility of the drug in the vehicle over the shelf-life of the preparation. Importantly, if there is precipitation of the therapeutic agent within a parenteral solution during storage, the preparation can no longer be referred to as a solution and thus the shelf-life of the product has been reached. Furthermore, the IV administration of a parenteral solution in which there is precipitated drug may lead to a blockage within the capillaries, with the associated deleterious effects on the organ to which the blood would normally be transported.
- Enhance the chemical stability of the therapeutic agent by maintaining the pH of the formulation within the range of optimum chemical stability of the therapeutic agent.

Examples of commonly used buffers include acetic acid/sodium acetate, citric acid/sodium citrate and sodium phosphate/disodium phosphate (see Chapter 1).

Tips

The preferred vehicle of choice for parenteral formulations is water.

In selecting a solubilisation strategy, consideration must be given to the toxicity of the solubilisation agent(s), e.g. co-solvent, surfactants, in the host (human or animal).

Polymers to modify formulation viscosity and/or drug solubility

The inclusion of polymers within parenteral suspensions occurs more frequently than in parenteral solutions. In parenteral solutions the inclusion of hydrophilic polymers will increase the viscosity of the formulations, which may in turn result in difficulties in administration. It must be remembered that during administration the formulation must flow through the narrow bore of the injection needle. Under these circumstances small changes in formulation viscosity will be amplified during the passage through the needle. In addition increased formulation viscosity may result in pain at the injection site. Whilst hydrophilic polymers may be added to solutions designed for oral administration to increase the viscosity, e.g. to aid the accurate measurement of a dose on the measuring spoon/cup, this requirement is unnecessary for parenteral solution formulations. Therefore, the inclusion of hydrophilic polymers in parenteral

solution formulations is restricted to aqueous solutions to enhance the solubility of the therapeutic agent by complexation. Poly(vinylpyrrolidone) (PVP) is an example of a polymer that may be used for this purpose; it is present in aqueous tetracycline and aqueous oxytetracycline injections for veterinary applications. Importantly, the molecular weight of PVP that is employed in the formulation of parenteral solutions is low (circa 12 000) and this, in conjunction with the linear nature of this polymer in aqueous solutions, ensures that large concentrations (up to 18% w/v) may be used without the viscosity of the resultant formulation being excessive for clinical use.

Lipophilic polymers are rarely, if ever, used to solubilise therapeutic agent in oil-based vehicles for parenteral administration. As stated previously, if required the solubility of drugs in the oil-based vehicle may be enhanced by the incorporation of surfactants (e.g. sorbitan esters, Span) or co-solvents, e.g. benzyl benzoate.

When used in aqueous suspensions, hydrophilic polymers maintain the physical stability of the formulation by a number of mechanisms.

Stearic stabilisation

In this the polymer chains adsorb on to the surface of the dispersed drug particles and, in so doing, the close approach of two particles is stearically inhibited. In terms of the DLVO theory (see Chapter 2), the presence of the adsorbed hydrophilic polymer is sufficient to prevent the two particles interacting at the primary minimum. In addition, if the polymer is a polyelectrolyte (e.g. sodium alginate), the polymer chains may effectively form a bridge between two particles when in the presence of an oppositely charged divalent or trivalent ion. The ion provides an effective charge on the surface of the particles, with which the charged polymer chain interacts. In so doing the two particles are maintained/stabilised at distances greater than the primary minimum.

Enhancement of the viscosity of the formulation

As previously defined, the physical stability of suspensions is dependent, at least in part, on the rate of sedimentation of the suspended particles (Stokes' equation). In addition the rate of sedimentation is inversely related to the viscosity of the formulation. The presence of hydrophilic polymers in parenteral suspensions will increase the viscosity of the formulation and will therefore act to stabilise the formulation. However it must be remembered that, as the viscosity of the formulation is increased, the ease of administration decreases and likelihood of pain upon injection increases. Therefore, the concentration of hydrophilic

polymer that may be used for this purpose (and hence the viscosity achieved) is limited by these potential clinical limitations.

The physical stabilisation of aqueous parenteral drug suspensions is usually achieved by the incorporation of surface-active agents and/or hydrophilic polymers. It should be noted that the range of surfactants and hydrophilic polymers that may be used in this fashion is lower than for comparator preparations designed for oral administration. This is primarily due to the potentially greater toxicity of excipients following parenteral administration.

The stabilisation of oil-based suspensions for parenteral administration is generally not performed using (lipophilic) polymers due to their limited availability. Instead the physical stability of oil-based systems may be effectively enhanced using salts of fatty acids or fatty acid esters, which primarily increase the viscosity of the formulation. Examples of these include:

- Aluminium salts of stearic acid (e.g. aluminium stearate, aluminium distearate, aluminium tristearate). These are normally prepared by dissolving the required concentration of aluminium salt (up to 5%, depending on the salt type) into the oil vehicle at high temperatures (circa 165°C). Upon cooling the drug may be dispersed into the rheologically structured vehicle.
- Trihydroxystearin (Thixcin). This may be dissolved in the oil-based vehicle without heating and, in a similar fashion to the example above, produces a rheologically structured vehicle into which the therapeutic agent may be dispersed.

Preservatives

Preservatives are incorporated into parenteral formulations whenever:

- The product is a multidose preparation. In this, several separate doses will be removed from the same container; the inclusion of preservatives is necessary to control microbial growth due to microbial introduction into the product.
- The product has not been terminally sterilised, e.g. by irradiation or heat. In this situation the preservative is required to guard against any possible breakdown in the aseptic manufacturing process.

In all other situations the presence of a preservative is deemed unnecessary.

Examples of preservatives employed in parenteral formulations include:

- esters of parahydroxybenzoic acid, e.g. methyl and propyl parahydroxybenzoic acid are often used in combination in a ratio of 9:1. The concentration is usually circa 0.2% w/v

- phenolic compounds, e.g. phenol (0.25–0.5% w/v) or chlorocresol (0.1–0.3% w/v).

Formulation considerations for the inclusion of preservatives into parenteral formulations include the following:

- In aqueous parenteral suspensions and in some aqueous parenteral solutions hydrophilic surfactants (included to enhance/maintain the solubility of the therapeutic agent or to ensure the physical stability of the formulation over the proposed shelf-life) may interact with esters of parahydroxybenzoate. In so doing the effective (free, unbound) concentration of preservative and hence the preservative efficacy are decreased. This problem is resolved by increasing the concentration of preservative (generally up to 0.25% w/v).
- Preservatives may similarly interact with the container and closure of the parenteral product, necessitating an increase in the concentration of preservative required or, preferably, a change in the type of container closure. For example, phenol has been shown to interact with rubber closures. In this situation, rather than increasing the concentration of phenol added, the rubber closure may be exchanged with a suitable replacement, e.g. nitrile closures.
- It is essential that the preservative does not adversely affect the chemical and physical stability of the parenteral product. For example, as insulin formulations are usually multidose preparations, preservatives are required to inhibit microbial contamination of the product. The physical stability of zinc insulin is compromised in the presence of phenol (but not methylparahydroxybenzoic acid).
- In the preservation of parenteral emulsions, the formulation scientist must be aware of the ability of the preservative to distribute between the inner oil phase and the outer aqueous phase. The preservative is required in the aqueous phase of the emulsion to exert the antimicrobial effect. Distribution between the two phases will therefore decrease the concentration of preservative in the aqueous phase and, accordingly, reduce the preservative efficacy. To overcome this, the concentration of preservative in the dosage form should be increased. This may be easily calculated by consideration of the partition coefficient of the preservative between the oil and aqueous phases and the solubility of the preservative in the two phases (Chapter 3).
- Oil-based parenteral products (solutions and suspensions) do not generally require the inclusion of a preservative due to the low water activity of this medium.

- The potential toxicity of preservatives must be considered when formulating parenteral products in light of the greater potential toxicity of preservatives when administered parenterally. It is therefore desirable to avoid the inclusion of preservatives whenever possible.

Agents to modify the osmolarity of parenteral products

Osmolarity refers to the mass of solute that, when dissolved in 1 litre of solution, will produce an osmotic pressure equivalent to that produced by a one-molar (1 mol) solution of ideal unionised substance. The units for osmolarity that are used in conjunction with parenteral preparations are mosmol/kg. An *isotonic* solution is one that exhibits the same effective osmotic pressure as blood serum, whereas hypotonic and hypertonic solutions refer to solutions in which the osmotic pressure exerted by the solution is less than and greater than blood serum, respectively. The tonicity of parenteral formulations is an important design criterion. In the presence of a hypotonic solution, red blood cells will swell (due to water entry into the cell) and eventually burst (termed haemolysis) whereas, in the presence of a hypertonic solution, water will leave the red blood cells, leading to crenation.

Ideally the administration of parenterals and in particular the IV administration of parenteral should be isotonic (circa 291 mosmol/l) to avoid potential damage. However, many parenteral products designed for IV administration are hypertonic. Products within the osmolarity range of 300–500 mosmol/l may be administered by the IV route rapidly (with care being taken with formulations at the higher extremes of this range to ensure that administration is slower). IV fluids may be profoundly hypertonic, e.g. the tonicity of Hyperamine 30 and Sodium Bicarbonate Intravenous Infusion BP (4.2% and 8.4% w/v) is 1450, 1000 and 2000 mosmol/l, respectively. Clinically this does not present any problems as these fluids will be administered to patients by a central venous line in which the infusion rate is slow and the infusion is rapidly diluted within the blood stream.

It is recommended that parenteral formulations designed for IV administration should not be hypotonic. Therefore, hypotonic solutions should be rendered isotonic by the addition of compounds that will increase the osmotic pressure of the solution. Typically sodium chloride or dextrose is used for this purpose. There are two methods by which the mass of these compounds required to render the solution isotonic may be calculated: (1) consideration of the gram-molecular concentration; and (2) consideration of the freezing-point depression of the solution. These are individually addressed below.

Gram-molecular concentration

- The gram-molecular concentration refers to the number of moles of substance in 100 grams of solvent.
- For example if 1 gram molecule (mole) of a non-ionic compound is dissolved in 100 grams of water, the gram-molecular concentration is 1%.
- As osmotic pressure is a colligative property, the number of moles of substance in solution is important. Therefore if 1 mol of NaCl is dissolved in water, 2 mol of ions are produced.
- A solution is isotonic whenever the gram-molecular concentration is 0.03%.
- The following three examples show how this may be used to produce isotonic solutions.

Worked examples

Example 5.1

Calculate the concentration (% w/v) of dextrose (molecular weight 180 g/mol) that should be added to water to produce an isotonic solution.

Dextrose is non-ionic and therefore 1 mol of dextrose when added to 100 grams of water will produce a gram-molecular concentration of 1%. Therefore:

$$0.03 \times 180 = 5.4\%\ w/v$$

Example 5.2

Calculate the concentration (% w/v) of sodium chloride (molecular weight 58.5 g/mol) that should be added to water to produce an isotonic solution.

Sodium chloride is ionic and therefore 1 mol of NaCl, when added to 100 grams of water, will produce a gram-molecular concentration of 2%. Therefore:

$$\left(\frac{0.03 \times 58.5}{2}\right) = 0.9\%\ w/v$$

Example 5.3

Calculate the concentration of sodium chloride that must be added to a 1% solution of lidocaine hydrochloride (molecular weight 270 g/mol) to render this isotonic.

Initially the gram-molecular concentration of the drug solution must be calculated (remembering that 1 mol of lidocaine hydrochloride dissociates to produce 2 mol of ions). The above

equations must be rearranged in terms of the gram-molecular concentration. Thus:

$$\left(\frac{2 \times 1}{270}\right) = 0.007\%$$

As this is less than 0.03%, the reader will observe that a simple solution of lidocaine hydrochloride (1% w/v) is hypotonic.

The gram-molecular percentage that must be added to correct this imbalance is therefore:

$$0.03 - 0.007 = 0.023\%$$

Therefore, the concentration of sodium chloride required to render this solution isotonic is:

$$\left(\frac{0.023 \times 58.5}{2}\right) = 0.67\%\ w/v$$

Freezing-point depression

- The inclusion of ions in a solvent will lower the freezing point of that solvent: the extent of the depression of the freezing point is dependent on the number of ions in solution. This is a basic colligative property.
- An isotonic solution exhibits a freezing-point depression of 0.52°C.
- Therefore the solution of drug should be adjusted to produce a freezing-point depression of 0.52°C to render the solution isotonic.
- Tables are available which provide the freezing-point depressions for various compounds.
- The following are two examples of the use of this technique.

Example 5.4

Calculate the concentration (% w/v) of sodium chloride that should be added to water to produce an isotonic solution.

The freezing-point depression of a 1% solution of NaCl is 0.576°C (derived from tables).

Therefore, the concentration of sodium chloride required to render a solution isotonic is:

$$\left(\frac{0.52}{0.576}\right) \times 1 = 0.9\%\ w/v$$

Example 5.5

Calculate the concentration of sodium chloride that must be added to a 1% solution of lidocaine hydrochloride (freezing-point depression of a 1% solution is 0.130°C) to render this isotonic.

Initially the freezing-point depression for the 1% solution of drug is calculated:

$$1 \times 0.130 = 0.130°C$$

Therefore the difference in freezing-point depressions of an isotonic solution and the described drug solution is:

$$0.52 - 0.13 = 0.39°C$$

The freezing-point depression of a 1% w/v solution of sodium chloride is 0.576°C. This allows the calculation of the required mass of sodium chloride to be added:

$$\left(\frac{0.39}{0.576}\right) = 0.677g$$

Antioxidants

As detailed in Chapter 1, many drugs are susceptible to degradation by oxidation, a process involving the addition of an electronegative atom or radical or the removal of an electropositive atom, radical or electron. Oxidation may occur due to the action of molecular oxygen; however, this is a slow process, especially in aqueous solution in which the concentration of dissolved oxygen is low. Alternatively oxidation may be facilitated by free radicals, with breakdown occurring via a chain reaction process. Radicals are formed due to the action of light, heat or transition metals (e.g. iron, copper) that are present in the formulation. Several important classes of therapeutic agents may undergo oxidative degradation, including phenothiazines, polyene antimicrobial agents, steroids, morphine and tetracyclines.

Antioxidants are included in parenteral formulations to slow down or inhibit oxidative degradation of therapeutic agents. These agents either act to prevent the formation of free radicals (e.g. butylated hydroxyanisole, butylated hydroxytoluene) or alternatively are strong reducing agents and are therefore oxidised in preference to the therapeutic agent (e.g. sodium metabisulphite, sodium formaldehyde sulphoxylate). Furthermore, chelating agents, e.g. ethylenediamine diacetic acid, may be added to extract dissolved transition metals, thereby reducing their ability to generate free radicals or to be involved in electron transfer reactions.

A further strategy that may be used to enhance the stability of the therapeutic agent is to flush the injection container/vial with nitrogen prior to closure. In so doing oxygen is removed from the headspace within the packaged product. Although successful, the

limitation of this approach is the availability of specialised filling equipment that will provide satisfactory gas purging prior to closure of the product.

Parenteral emulsions

The reader will be aware that the primary focus of this chapter has been the formulation of parenteral solutions and suspensions, due to the overwhelming majority of parenteral formulations being formulated as these dosage form types. However, under certain circumstances, emulsions are employed as parenteral formulations. As the reader will be aware, emulsions are disperse systems in which one immiscible liquid is dispersed in another liquid. Whilst two forms of emulsion exist, water in oil (w/o, in which water droplets are dispersed in an oil phase) and oil in water (o/w, in which oil droplets are dispersed in an aqueous phase), it is the latter type (o/w) that is usually administered parenterally. Examples of the parenteral use (past and present) of emulsions include:

Tips

The control of the osmotic properties of parenteral formulations for human use is an important formulation consideration, which should not be overlooked by the formulation scientist.

Parenteral formulations are sterile and therefore preservatives are only usually required whenever the preparation is a multidose formulation, e.g. veterinary parenterals.

Possible interactions between the preservative and viscosity-modifying agent must be considered in the selection of the type and concentration of preservative for parenteral formulations.

- The subcutaneous administration of allergenic compounds in a w/o emulsion was performed by Freund & McDermott (1942) to enhance the resultant antibody response.
- The IM administration of o/w emulsions to provide controlled drug release.
- The IV administration of o/w emulsions as total parenteral nutrition emulsions. In these, 10–20% oil is emulsified within an aqueous phase using phospholipids and lecithin surfactants to stabilise the emulsion. The emulsion is rendered isotonic by the addition of glycerol and glucose. The oils are subsequently broken down to triglycerides that provide essential fatty acids and act as a source of calories for patients who cannot consume food orally.

There are several problems associated with the use of parenteral emulsions that have restricted their pharmaceutical use:

- There is a limited list of surface-active agents that may be employed to stabilise parenteral emulsions (due to toxicity concerns).
- When administered intravenously it is essential that the droplet size is less than 1 μm to prevent blockage of blood flow within the capillaries. The physical instability of emulsions, which normally causes the droplets of the internal

phase to coalesce, is therefore a potential dangerous consequence of a poorly formulated emulsion.
- Emulsions are difficult to sterilise. Normal sterilisation methods, e.g. heat and filtration, are generally inappropriate.

Manufacture of parenteral formulations

As detailed previously, two essential requirements of parenteral formulations are sterility and the absence of pyrogens. It is of no surprise to the reader that these two requirements directly influence the methods by which parenteral formulations are manufactured. All raw materials must be of sufficient (injectable) grade and therefore are assured to be pyrogen-free. Furthermore, the methods used to remove pyrogens from both equipment (storage and manufacture) and water when used as a vehicle for parenterals have been detailed previously.

Before describing different strategies for the manufacture of sterile parenteral formulations, it is worth while briefly discussing the concept of sterility and the different methods by which the sterilisation of parenteral formulations may be achieved. Knowledge of these processes is important in the understanding of sterile product manufacture.

Sterilisation may be defined as the absence of viable microorganisms (either through the destruction of all living microorganisms or by their removal) in pharmaceutical preparations. There are five established methods by which pharmaceutical raw materials and pharmaceutical preparations may be sterilised: (1) moist-heat sterilisation; (2) dry-heat sterilisation; (3) filtration sterilisation; (4) sterilisation by exposure to ionising radiation; and (5) gas sterilisation.

Moist-heat sterilisation

- performed in an autoclave and employs steam under pressure
- offers efficient sterilisation at lower temperatures than dry-heat sterilisation, due to the presence of moisture
- mode of action is thought to be due to the denaturation/coagulation of microbial proteins
- at normal pressure the temperature of water cannot exceed 100°C. In moist-heat sterilisation the pressure in the autoclave is increased to enable an increase in the processing temperature
- exposure of the pharmaceutical product at the required temperature for the required time will result in efficient sterilisation. For example, at 103.4 kPa (i.e. 15 pounds per square inch) and 121°C sterilisation is achieved in 20 minutes whereas at 68.91 kPa (10 pounds per square inch) sterilisation

is achieved in 30 minutes. It must be remembered that the time of sterilisation must include a lag period, i.e. the temperature within the interior of the product

- moist-heat sterilisation is principally used to sterilise materials that are both thermostable (within the conditions of the sterilisation cycle) and through which moisture can perfuse. These include:
  - glassware
  - dressings
  - closures
  - aqueous solutions: the aqueous nature of these systems ensures that moist-heat sterilisation is an ideal method for terminal sterilisation (assuming that the therapeutic agent is thermostable). In this process the parenteral solution is either presented to the autoclave sealed in vials or sealed using a closure and aluminium cap. The temperature within the container is elevated to the designated sterilisation temperature at which it is held for the appropriate period.

Dry-heat sterilisation

- In this process microorganisms are destroyed following cellular dehydration and then pyrolysis/oxidation.
- Dry-heat sterilisation is performed in ovens.
- Due to the lower microbicidal efficiency of dry-heat sterilisation (in comparison to moist-heat sterilisation), dry-heat sterilisation is performed at higher temperatures and requires longer times of exposure of the microorganism to this temperature. Examples of dry-heat sterilisation cycles include:
  - 170°C for 1 hour
  - 160°C for 2 hours
  - 140°C for 4 hours.
- As with moist-heat sterilisation, the described sterilisation conditions refer to the time of residence of the product/article in the oven following attainment of the defined temperature. A lag time is therefore required to ensure that the article/container has achieved this temperature.
- Dry-heat sterilisation is employed to sterilise materials/products that cannot be readily sterilised by moist heat (and which are thermostable following exposure to the sterilisation cycle), e.g.:
  - oils and other aqueous vehicles (e.g. glycerin, propylene glycol)
  - heat-stable therapeutic agents/excipients
  - glassware (e.g. bottles).

Filtration sterilisation

- In this method microorganisms are removed (not destroyed) from solutions using sterilising filters of pore diameter 0.22 μm. This pore diameter is sufficient to entrap/retain bacteria and fungi. Following use, the filters (containing the entrapped/retained microorganisms) are then safely discarded.
- To maximise the lifetime of the filter (i.e. the volume that may be passed through the filter with blockage of fluid flow), the solution is passed through a series of clarifying filters of defined diameter, e.g. 1 μm, 0.45 μm, prior to passage through the sterilising filter.
- Filtration sterilisation is used to sterilise solutions of therapeutic agents that are thermolabile.
- This is an efficient, inexpensive technique.
- As the product is filtered prior to filling into the final container (e.g. vial/bottle), one concern with filtration sterilisation is the possible concern of the product being non-sterile due to a flaw in the manufacture (and hence function) of the sterilisation filter.

Sterlisation by exposure to ionising radiation

- involves exposure of the raw material/product to a defined dose of ionising radiation. Typically gamma radiation is employed, sterilisation occurring following exposure to 25–40 kGy
- requires specialist equipment and is therefore expensive for routine use
- used to sterilise therapeutic agents/excipients or the production of parenteral formulations that are manufactured and packaged under aseptic conditions but are neither terminally sterilised nor sterilised by filtration
- it must be noted that certain therapeutic agents and excipients are unstable in the presence of sterilising doses of ionising radiation. Therefore the effects of ionising radiation on the stability of formulation ingredients must be individually examined.

Gas sterilisation

- Gas sterilisation involves exposure of materials/products to mixtures of ethylene oxide or propylene oxide and an inert gas, e.g. carbon dioxide within a specially designed apparatus.
- Sterilisation efficiency increases in the presence of moisture (up to 60%) and elevated temperature (circa 55°C).
  A reduction in the operating temperature will result in an increased time required for sterilisation.

- Due to the highly penetrative nature of the gas medium, this technique is frequently used to sterilise medical devices (e.g. packaged catheters) and porous surgical accessories (e.g. blankets). However, this technique may also be employed for the sterilisation of therapeutic agents/excipients.
- Due to the toxicity of the gas mixture, sufficient time must be allowed after sterilisation to enable the sterilising gas to be desorbed from the product/ingredient.

Specific manufacturing requirements for parenteral products

The manufacture of parenteral products occurs under aseptic conditions, in an area that is only used for the preparation of sterile products. The large-scale manufacturing equipment within the facility must be capable of sterilisation in situ. For example, the manufacturing vessels in which the solutions are mixed are generally jacketed and may be sealed. Temperature can then be applied to these to render them sterile. In addition small-scale equipment (which has been previously sterilised and sealed) and raw materials (including the therapeutic agent) are entered into the aseptic manufacturing area through a special portal (with a positive airflow to prevent the ingress of microorganisms). The air supply to the manufacturing area is filtered. Operators within the manufacturing area must wear special (sterile) work clothing, ensuring that there is no operator contamination of the product and environment.

Whilst the manufacture of parenteral formulations is similar to that of non-sterile comparator formulations, the main difference (in addition to the points described in the paragraph above) is the means by which the product is rendered sterile. In this context the manufacture of parenteral solutions (aqueous and oil-based) and parenteral suspensions (aqueous and oil-based) will be briefly discussed separately.

Aqueous parenteral solutions

The main steps in the manufacture of aqueous parenteral solutions are as follows:

- The formulation components (including the therapeutic agent) are dissolved in the main mixing vessel within the manufacturing suite.
- If the active ingredient is thermostable, the formulation is filled into the final containers and sealed. Sterilisation is then performed using moist-heat sterilisation. Unless the preparation is a multidose product, the inclusion of a preservative is unnecessary.
- If the active ingredient is thermolabile, the product is sterilised using filtration and collected into a second mixing

vessel, from which filling into the final container is performed. In some cases it may be possible to fill the product into the final container immediately after filtration, obviating the need for a second mixing vessel. In this case preservatives are normally included.

Oil-based parenteral solutions

Moist-heat sterilisation cannot be used to sterilise oil-based solutions and therefore the manufacturing procedure must accommodate this limitation.

The main steps involved in the manufacture of oil-based parenteral solutions are as follows:

- Sterilisation of the oil-based vehicle (containing the various soluble excipients) within the mixing vessel in the aseptic manufacturing suite (performed using dry-heat sterilisation). If the therapeutic agent is stable under the conditions of dry-heat sterilisation, the drug may be incorporated (dissolved) at this stage. This product is then ready for filling into the final container (which is then sealed). Alternatively the product may be manufactured and terminally sterilised using dry-heat sterilisation.
- If the therapeutic agent is not stable under the above sterilisation conditions, sterile drug should be dissolved in the sterile oil-based vehicle using normal mixing facilities. This product is then ready for filling into the final container, which is subsequently sealed.

Aqueous parenteral suspensions

As suspensions contain drug that has been dispersed in the chosen vehicle, filtration cannot be performed to render the product sterile. Therefore, sterile drug must be added to the chosen vehicle and suitably dispersed under aseptic conditions. Typically, the main steps in the manufacture of aqueous parenteral suspensions are:

- dissolution of the formulation excipients in an aqueous (or hydroalcoholic) vehicle within the main vessel
- sterilisation of the vehicle by filtration and collection into a second vehicle, under aseptic conditions
- dispersal of the (sterile) therapeutic agent into the sterile vehicle. If required the particle size of the disperse phase may be reduced by, for example, passage through a ball mill (whose contents and packing material are both sterile)
- the formulation may then be filled into the final container, followed by sealing
- drug suspensions are often physically unstable if exposed to moist-heat sterilisation; however, if the suspension is stable under these conditions, then the formulation may be