CHAPTER 17

STERILE FORMULATIONS

Author

Mrs. Jyoti Phogat
Assistant Professor, R. J. World College of Pharmacy Education and Technology, Jakhod, Rajasthan, India

Abstract

Sterile formulations are critical pharmaceutical products designed to be free from viable microorganisms, essential for parenteral administration and other applications requiring absolute sterility. This section covers various types of sterile products, including injections, ophthalmics, and large volume parenterals. The principles of sterilization, including terminal sterilization and aseptic processing, are examined in detail. Formulation considerations for sterile products, such as tonicity adjustment, pH control, and the use of preservatives in multi-dose formulations, are discussed. The manufacturing process for sterile products, including aseptic filling and lyophilization, is explored with emphasis on contamination control and validation. Clean room design and operation, including air classification and personnel gowning procedures, are addressed. Quality control measures specific to sterile formulations, such as sterility testing, endotoxin testing, and particulate matter analysis, are detailed. The challenges in developing and manufacturing sterile products, including stability issues and container-closure integrity, are discussed along with strategies to overcome them. Regulatory requirements and guidelines for sterile product manufacturing, including current Good Manufacturing Practices (cGMP), are highlighted to ensure compliance and product safety

Keywords: *Aseptic processing, Parenteral preparations, Clean room technology, Sterilization, Contamination control, Regulatory compliance*

Learning Objectives

After completion of the chapter, the student should be able to:

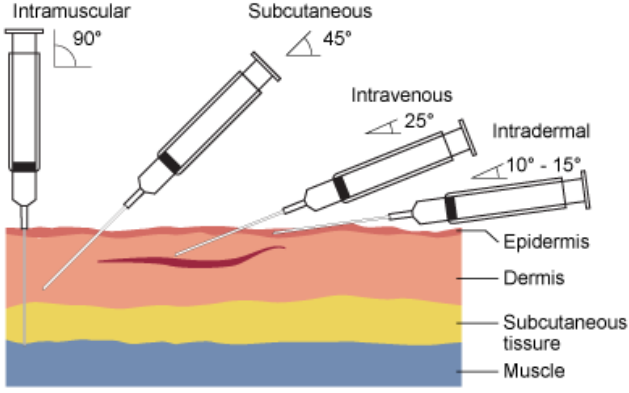
- Define sterile formulations and explain their importance in healthcare.
- Describe different types of parenteral preparations and their applications.
- Explain the principles of aseptic processing and sterilization methods.
- Discuss the formulation considerations for injectable products.
- Outline the manufacturing processes for different types of sterile formulations.
- Describe the quality control tests and regulatory requirements for sterile products.
- Analyze the challenges in maintaining sterility throughout the product lifecycle.

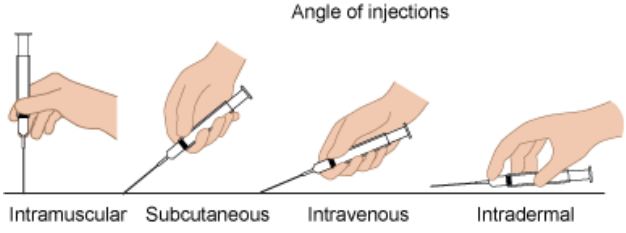
Injectables

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.

Routes of parenteral administration

There are several different routes by which Injectables 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 ml). 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.
Other more specialised routes are employed for the delivery of the therapeutic agent directly to the target site/region.

Advantages and disadvantages of Injectables

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.