Pharmaceutical Technology
Lecture- 6

Sterile Dosage Forms

By

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Sterile dosage forms

- Sterile dosage forms are pharmaceutical dosage forms with the common characteristic of sterility, that is, they are free from contaminating microorganisms.
- Among these sterile dosage forms are:

1. the various small- and large-volume injectable preparations
2. irrigation fluids intended to bathe body wounds or surgical openings, and dialysis solutions.
3. Biologic preparations, including vaccines, toxoids, and antitoxins.

- Sterility in these preparations is essential because they are placed in direct contact with the internal body fluids or tissues, where infection can easily arise.

4. Ophthalmic preparations, which are also prepared to be sterile, are discussed separately

Injections

- Injections are sterile, pyrogen-free preparations intended to be administered parenterally.
- The term parenteral refers to the injectable routes of administration.
- It derives from the Greek words para (outside) and enteron (intestine) and denotes routes of administration other than the oral route.
- Parentral preparations are either used alone or diluted.

Parenteral Routes of Administration

- Drugs may be injected into almost any organ or area of the body, including the joints (intraarticular), joint fluid area (intrasynovial), spinal column (intraspinal), spinal fluid (intrathecal), arteries (intra-arterial), and, in an emergency, even the heart (intracardiac).
- However, most injections go into a vein (intravenous, IV), into a muscle (intramuscular, IM), into the skin (intradermal, ID; intracutaneous), or under the skin (subcutaneous, , SC; sub-Q, SQ; hypodermic, hypo) (Fig. 15.1).

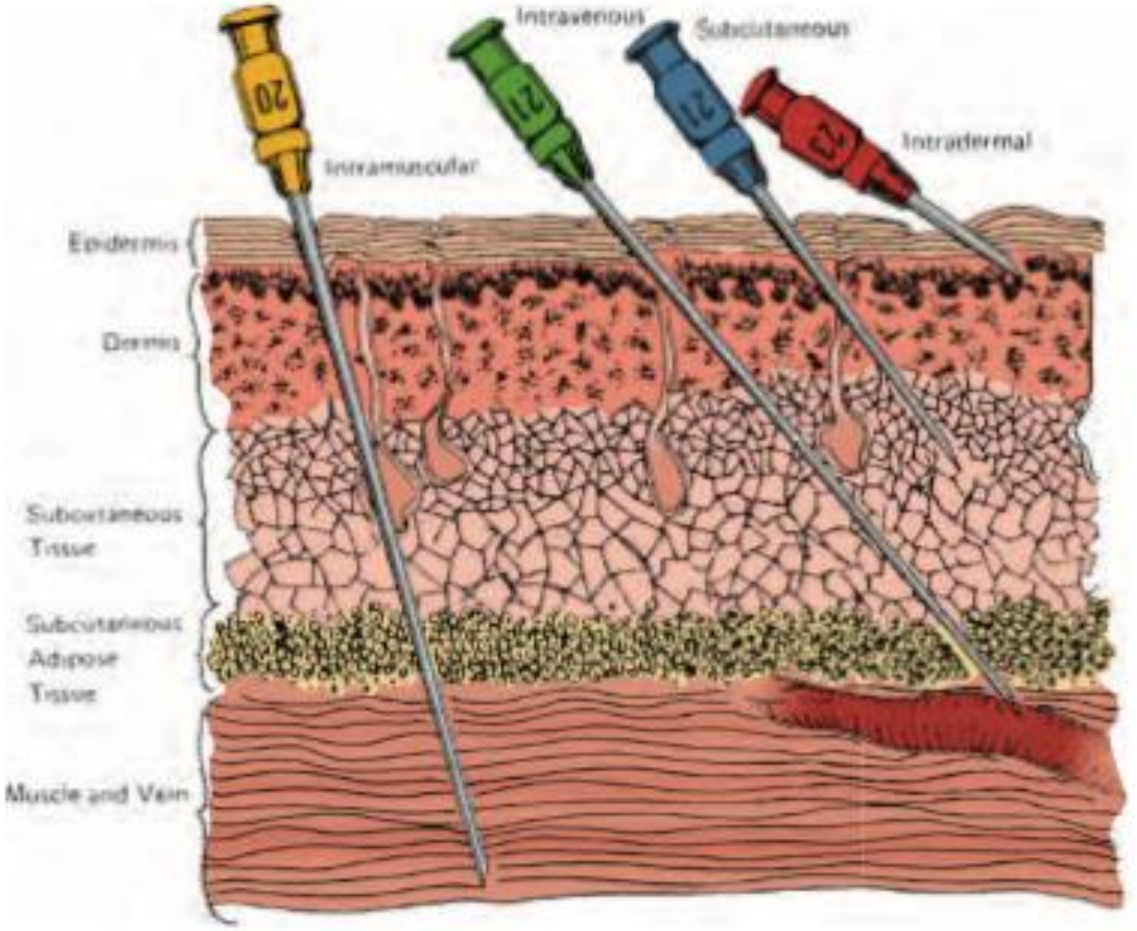


FIGURE 15.1 Routes of parenteral administration. Numbers on needles indicate gauge of the needles (outside diameter of shaft). (Reprinted with permission from Turco S, King RE. Sterile Dosage Forms: Their Preparation and Clinical Applications. 3rd Ed. Philadelphia, PA: Lea & Febiger, 1987.)

Intravenous Route

Advantages:

1. IV drugs provide rapid action compared with other routes of administration, and
2. because drug absorption is not a factor, optimum blood levels may be achieved with accuracy and immediacy not possible by other routes.
3. In emergencies, IV administration of a drug may be lifesaving because of the placement of the drug directly into the circulation and the prompt action that develops.
4. Both small and large volumes of drug solutions may be administered intravenously. The use of 1,000-mL containers of solutions for IV infusion is commonplace in the hospital.

Disadvantages :

1. Restricted to solution.
2. Once a drug is administered intravenously, it cannot be retrieved. In the case of an adverse reaction to the drug, for instance, the drug cannot be easily removed from the circulation, as it could, for example, by induction of vomiting after oral administration of the same drug.
3. It may cause haemolysis but can avoid by slow injection.

Intramuscular Route

1. IM injections of drugs provide effects that are less rapid but generally longer lasting than those obtained from IV administration .
2. The drug will stay in muscle and diffuse slowly so it has slower onset of action.
3. Aqueous or oleaginous solutions or suspensions of drug substances may be administered intramuscularly.
4. The absorption from this route depend on the release of drug and blood flow. Salt form of the drug absorb faster than free drug.
5. Depending on the type of preparation employed absorption may be in the following sequence: solution > aqueous suspension > oily solution > oily suspension > oily suspension with thickening agent.

Subcutaneous Route

1. The SC route may be used for injection of small amounts of medication. The maximum amount of medication that can be comfortably injected subcutaneously is about 1.3 mL, and amounts greater than 2 mL will most likely cause painful pressure
2. It has slow onset
3. It is simple to administered
4. Absorption from this route of injection is affected by concentration, Solubility and blood flow

- Example of drug given by this route is insulin of two types

1. Soluble insulin show fast absorption but short duration of action
2. Insoluble type protamine zinc insulin, which has slow response or onset but prolong action

- Irritating drugs and those in thick suspension may produce induration, sloughing, or abscess and may be painful. Such preparations are not suitable for SC injection.

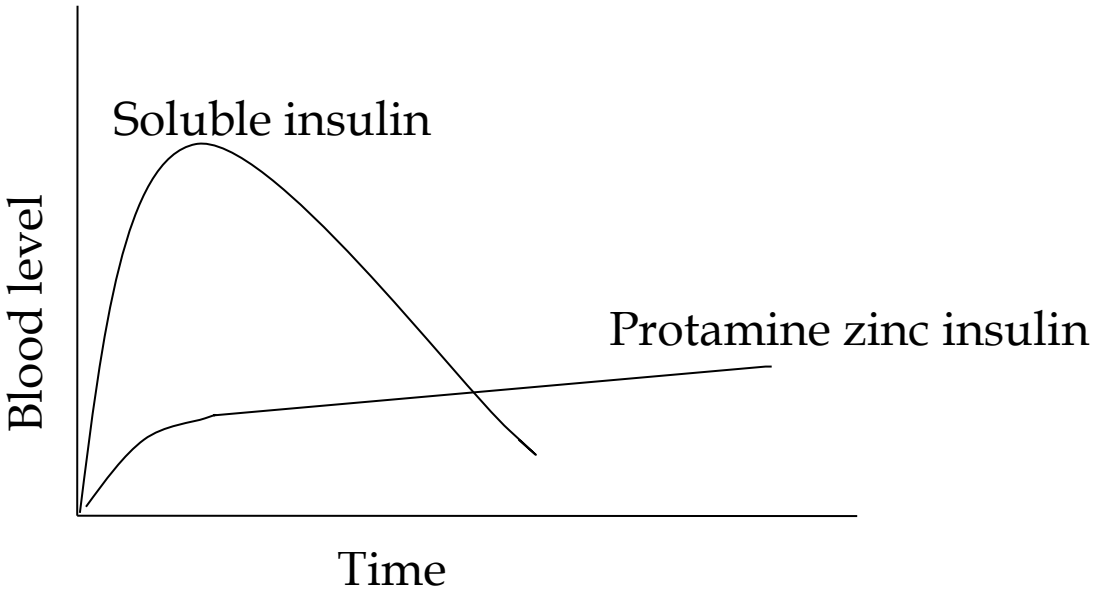


Figure 2. Plasma concentration time curve of two different types of insulin

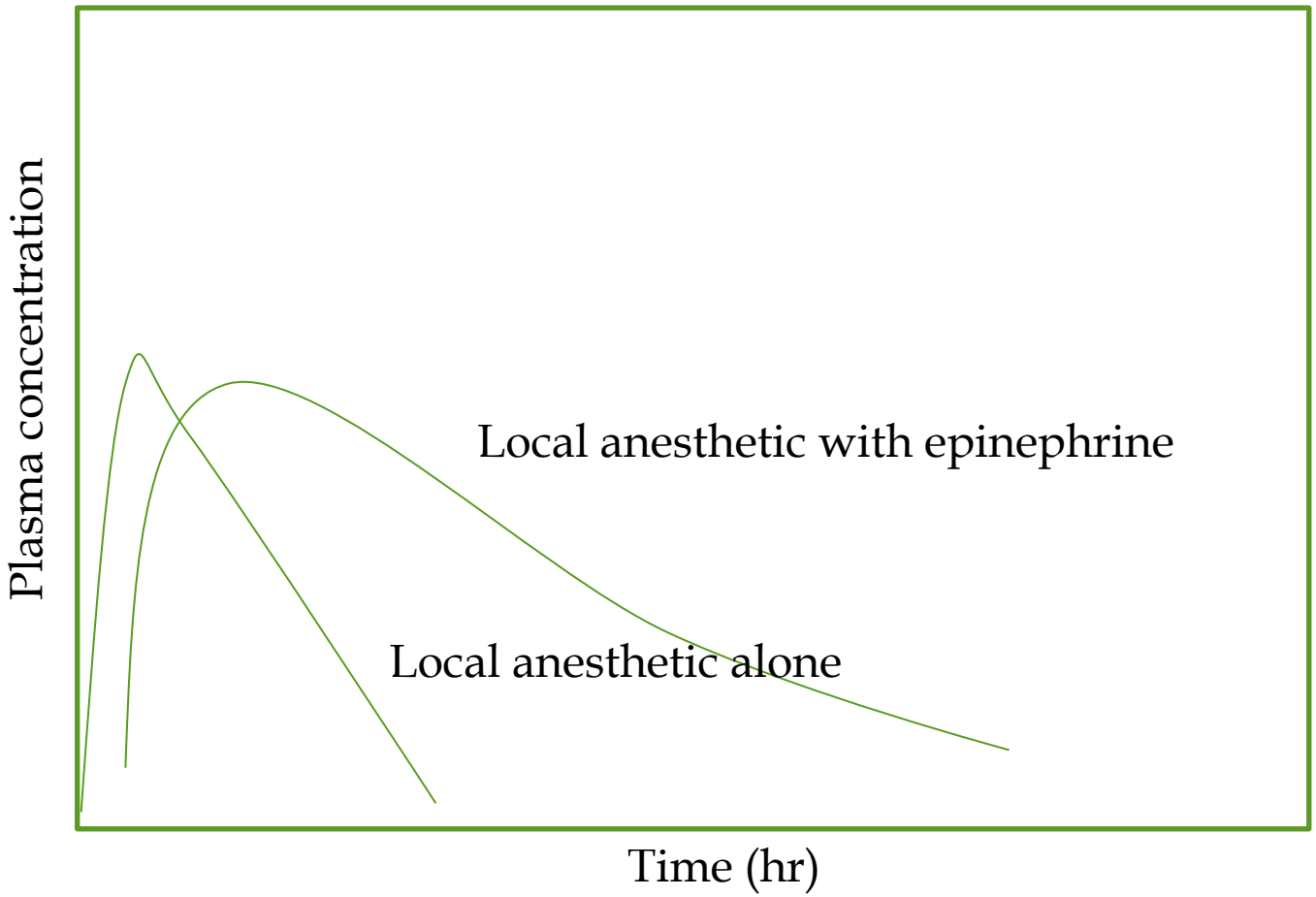
Intradermal Route

1. A number of substances may be effectively injected into the corium, the more vascular layer of the skin just beneath the epidermis.
2. These substances include various agents for diagnostic determinations, desensitization, or immunization.
3. The usual site for ID injection is the anterior forearm.
4. It has local distribution
5. Its absorption is slow
6. It is used for vaccines and for diagnostic test

Intraarterial Route

1. Need surgical operation
2. It is used for targeting a drug into organ for diagnostic test and
3. Anti-neoplastic drugs

To prolong the duration of action of local anesthetic, epinephrine is mixed with the local anesthetic.
Epinephrine is vasoconstrictor reduce blood flow and the absorption of the local anesthetic after intramuscular injection, thus prolong its duration as shown in the following figure.



The volume of injections for different types of injection is varying

Intravenous
Injected directly into a vein (major or peripheral vein)
Volume unlimited volume (infusion)
Intramuscular
Injected directly into skeletal muscle (pelvic)
Volume (2-5 ml)
Subcutaneous
Injected directly into alveolar region beneath the layer of the skin
Volume (2 ml)
Intradermal
Injected between the layers of the skin
Volume (0.2 ml)
Intraspinal
Injected into spinal canal
Volume (up to 10 ml)

Official Types of Injections

- According to the USP, injectable materials are separated into five general types. These may contain buffers, preservatives, and other added substances:

1. Injection: Liquid preparations that are drug substances or solutions thereof (e.g., Insulin Injection, USP)
2. For injection: Dry solids that, upon addition of suitable vehicles, yield solutions conforming in all respects to the requirements for injections (e.g., Cefuroxime for Injection, USP)
3. Injectable emulsion: Liquid preparation of drug substance dissolved or dispersed in a suitable emulsion medium (e.g., Propofol, USP)
4. Injectable suspension: Liquid preparation of solid suspended in a suitable liquid medium (e.g., Methylprednisolone Acetate Suspension, USP)
5. For injectable suspension: Dry solid that, upon addition of suitable vehicle, yields preparation conforming in all respects to the requirements for injectable suspensions (e.g., Imipenem and Cilastatin for Injectable Suspension, USP)

- The form in which the manufacturer prepares a given drug for parenteral use depends on the nature of the drug itself with respect to its physical and chemical characteristics and on certain therapeutic considerations.
- Generally, if a drug is unstable in solution, it may be prepared as a dry powder intended for reconstitution with a proper solvent at the time of administration, or it may be prepared as a suspension.
- If the drug is unstable in water, that solvent may be replaced in part or totally by a solvent in which the drug is insoluble.

- If the drug is insoluble in water, an injection may be prepared as an aqueous suspension or as a solution in a suitable nonaqueous solvent, such as a vegetable oil.
- If an aqueous solution is desired, a water-soluble salt form of the insoluble drug is frequently prepared.
- Aqueous or blood-miscible solutions may be injected directly into the blood stream.
- Blood-immiscible liquids, such as oleaginous injections and suspensions, can interrupt the normal flow of blood, and their use is generally restricted to other than IV administration.

- The onset and duration of action of a drug may be somewhat controlled by its chemical form, the physical state of the injection (solution or suspension), and the vehicle.

1. Drugs that are very much soluble in body fluids generally have the most rapid absorption and onset of action. Thus, drugs in aqueous solution have a more rapid onset of action than do drugs in oleaginous solution.
2. Drugs in aqueous suspension are also more rapid acting than drugs in oleaginous suspension because of the greater miscibility of the aqueous preparation with the body fluids after injection and the more rapid contact of the drug particles with the body fluids.

- Oftentimes, long action is desired to reduce the frequency of injections. These long-acting injections are called repository or depot preparations.

Preparation of injections

- The solutions and suspensions of drugs intended for injection are prepared in the same general manner as solutions and disperse systems, with the following differences:

1. Solvents or vehicles must meet special purity and other standards ensuring their safety by injection.
2. The use of added substances, such as buffers, stabilizers, and antimicrobial preservatives, falls under specific guidelines of use and is restricted in certain parenteral products. The use of coloring agents is strictly prohibited.
3. Parenteral products are always sterilized, must meet sterility standards, and must not exceed allowable endotoxin limits (ELs).
4. Parenteral solutions must meet compendial standards for particulate matt

5. Parenteral products must be prepared in environmentally controlled areas, under strict sanitation standards, and by personnel specially trained and clothed to maintain the sanitation standards.
6. Parenteral products are packaged in special hermetic containers of specific and high quality. Special quality control procedures are used to ensure hermetic seal and sterile condition.
7. Sterile powders intended for solution or suspension immediately prior to injection are frequently packaged as lyophilized or freeze-dried powders to permit ease of solution or suspension upon the addition of the solvent or vehicle.
8. Extemporaneously prepared parenteral preparations must be compounded in a USP <797> compliant facility.

Solvents and Vehicles for Injections

1. Water for Injection, USP, Sterile Water for Injection, USP, Bacteriostatic Water for Injection, USP.
2. Sodium Chloride Injection, USP, is a sterile isotonic solution of sodium chloride in water for injection.
3. Bacteriostatic Sodium Chloride Injection, USP, is a sterile isotonic solution of sodium chloride in water for injection.
4. Ringer's Injection, USP, is a sterile solution of sodium chloride, potassium chloride, and calcium chloride in water for injection. Ringer's is employed as a vehicle for other drugs or alone as an electrolyte replenisher and plasma volume expander.
5. Lactated Ringer Injection, USP, has different quantities of the three salts in Ringer injection, and it contains sodium lactate. This injection is a fluid and electrolyte replenisher and a systemic alkalizer.

- When solvent or vehicle contains bacteriostatic agent (i.e., benzyl alcohol), USP labeling requirements demand that the label state not for use in neonates.
- This statement was the result of problems encountered with neonates and toxicity of the bacteriostat, that is, benzyl alcohol.
- This toxicity results from the high cumulative amounts (milligrams per kilogram) of benzyl alcohol and the limited detoxification capacity of the neonate liver. This solution has not been reported to cause problems in older infants, children, or adults.

Nonaqueous Vehicles

- Although an aqueous vehicle is generally preferred for an injection, it may be precluded by the limited water solubility of a medicinal substance or its susceptibility to hydrolysis. When such physical or chemical factors limit the use of a wholly aqueous vehicle, the pharmaceutical formulator must turn to one or more nonaqueous vehicles.
- Among the nonaqueous solvents employed in parenteral products are fixed vegetable oils, glycerin, polyethylene glycols, propylene glycol, alcohol, and a number of less often used agents, including ethyl oleate, isopropyl myristate, and dimethylacetamide.

- These and other nonaqueous vehicles may be used provided they are safe in the amounts administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.
- The selected vehicle must be nonirritating, nontoxic in the amounts administered, and not sensitizing.
- Like water, it must not exert a pharmacologic activity of its own, nor may it adversely affect the activity of the medicinal agent.

- **The physical and chemical properties of the solvent or vehicle that must be considered are**

1. The solvent's physical and chemical stability at various pH levels
2. Viscosity, which must be such as to allow ease of injection (suitable for use in syringes)
3. Fluidity, which must be maintained over a fairly wide temperature range
4. Boiling point, which should be sufficiently high to permit heat sterilization;
5. Miscibility with body fluids
6. Low vapor pressure to avoid problems during heat sterilization; and
7. Constant purity or ease of purification and standardization.

General requirements for injections

1. **Safety:** The vehicle (solvent) and all the additive must undergo safety test (means all should be not toxic).
2. **Sterility**: It is very important, so the product and the container must be sterilized to prevent infection when there is injury. Five general methods are used to sterilize pharmaceutical products: 1. Steam 2. Dry heat 3. Filtration 4. Gas 5. Ionizing radiation.

- The method is determined largely by the nature of the preparation and its ingredients. However, regardless of the method used, the resulting product must pass a test for sterility as proof of the effectiveness of the method and the performance of the equipment and personnel.
- **Free from pyrogen:** pyrogen is fever producing organic substances arising from microbial contamination; they are a lipo-polysaccharide of the cell wall of microorganism and endotoxins.

4. **Clarity**: the parenterals should be free from particles specially which have a diameter 7.5 μ. Clarity test is done by taking parenteral solution and observe it at strong beam of light and the product will be observed for any foreign particle.
5. **Stability**: This is a standard requirement for all products not only for parenterals so the product should be stored at several temperatures for specific period of time then analyzed. They should not loss any amount of active constituents. should not loss its therapeutic activity
6. **Isotonicity**: Parenteral products should be isotonic with body fluids so should not change the morphology of RBCs (no shrinkage or hemolysis).