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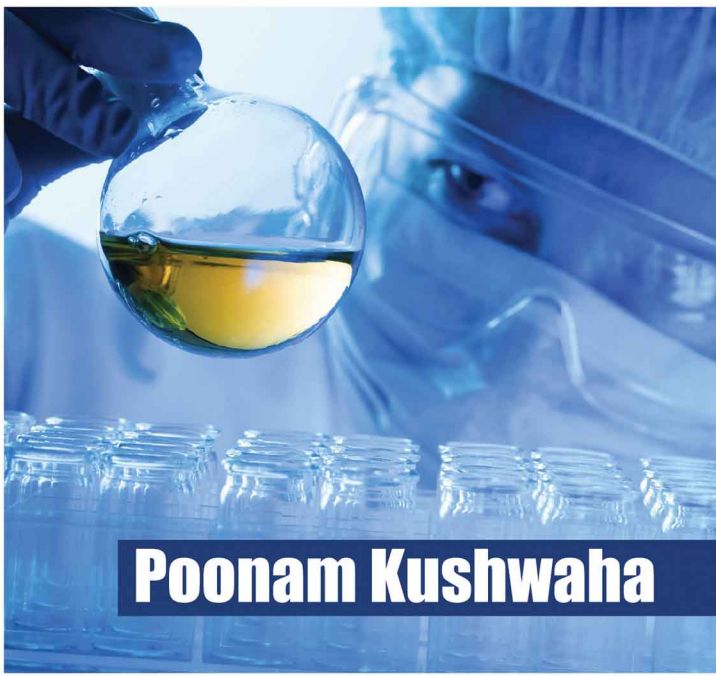
Handbook of Pharmaceutical Technology







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Chapter 4

Parenteral Products

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INTRODUCTION

Parenteral (Gk, para—beside and enteron—the intestine) dosage forms differ from all other drug dosage forms, because they are injected directly into body tissue through the primary protective systems of the human body, the skin, and mucous membranes. They must be exceptionally pure and free from physical, chemical and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and on pharmacists and other health care professionals to practice good aseptic practices (GAPs) in dispensing parenteral dosage forms for administration to patients.

Certain pharmaceutical agents, particularly peptides, proteins and many chemotherapeutic agents, can only be given parenterally, because they are inactivated in the gastrointestinal tract when given by mouth. Parenterally administered drugs are relatively unstable and generally highly potent drugs that require strict control of administration to the patient. Due to the advent of biotechnology, parenteral products have grown in number and usage around the world.

Advantages

1. Parenterals are unique among dosage forms of drugs because they are injected through the skin or mucous membranes into internal body compartments. Parenterals are useful for patients who cannot take drug orally and in emergency situation.

2. Drugs may be injected into the specialized area of the body, including joints (intra-articular), joint fluid area (intrasynovial), spinal column (intraspinal), spinal fluid (intrathecal), arteries (intra-arterial) and in emergency, even the heart (intracardiac).
3. Parenterals possess better and faster onset of action and bioavailability than other dosage forms (solid and liquid orals, etc.). Biologic products viz peptide hormones, vaccines, toxoids and antitoxins are best suited for parenteral route of administration.
4. Useful for delivering fluids, electrolytes or nutrients (total parenteral nutrition) to patients.
5. Useful for drugs that are inactivated in the GIT or susceptible first pass metabolism by liver.
6. Parenteral products could be administered as sterile solution during an irrigation procedure as these solutions can enter the blood stream directly through open blood vessels of wounds or abraded mucous membranes.
7. Sterile parenteral products could be administered even as solid pellets/tablets for tissue implantation and useful for providing sustained drug delivery (depot injection).
8. Parenterals as a dosage form scores better over other conventional dosage forms (solid/liquid orals) for administration of special categories of drugs like anticancer agents, immunosuppressants, hormones and peptides, radiopaque and diagnostic agents, etc.

Disadvantages

1. More expensive and costly to produce as compared to other formulations.
2. Potential for infection at the site of injection, thrombophlebitis, extravasation, fluid overload and air embolism.
3. Risk of needle stick injuries and exposure to blood borne pathogens by health care workers.
4. Disposal of needles, syringes and other infusion devices requires special consideration.
5. Improper injection procedures could cause damage to the patient's nerves, tissue, veins and other blood vessels.
6. The presence of traces of physical/chemical contaminants cause irritation to body tissues and also leads to degradation

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of product due to chemical change when thermal sterilization is employed.

Example: Minute traces of copper increases the rate of oxidation of ascorbic acid in solution. The contamination arises from water or chemical components or even the container.

Routes of administration

Intravenous route (IV) – IV injection of drugs provide rapid action compared with other routes of administration and because drug absorption is not a factor, optimum blood levels may be achieved with accuracy which is not possible by other routes.

In emergencies, IV administration of a drug may be life-saving because of placement of drug directly into the circulation and on the negative side, once a drug is administered intravenously, it cannot be retrieved.

Both small and large volumes of drug solutions may be administered intravenously. IV drugs must be in aqueous solution, they must mix with the circulating blood and not precipitate from solution.

Intramuscular route (IM)—IM injections of drugs provide effects that are less rapid but generally longer lasting than those obtained from IV administration. Aqueous or oleaginous solutions or suspensions of drug substances may be administered intramuscularly. IM injections are performed deep into skeletal muscles.

Subcutaneous route (SC)—This route may be used for injection of small amounts of medication. Injection of a drug beneath the skin is usually made in the loose interstitial tissue of the outer upper arm, the anterior thigh, or the lower abdomen. Prior to injection, the skin at injection site should be thoroughly cleansed. Irrigating drugs and those in thick suspension may produce induration, sloughing or abscess and may be painful. Such preparations are not suitable for SC injections.

Intradermal route—A number of substances may be effectively injected into the corium, the more vascular layer of skin just beneath the epidermis. These substances includes various agents for diagnostic detections, desensitization or immunization. The usual site for intradermal injection is the anterior forearm.

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FORMULATION REQUIREMENTS

Parenteral drugs are formulated as solutions, suspensions, emulsions and powders to be reconstituted as solutions. In general, there are two important aspects concerned with the development of these formulations:

- Vehicles and solvents for parenteral products
- Solutes.

1. Vehicles and solvents for parenteral products

The vehicle refers to a carrier or inert medium invariably being employed as a solvent (or diluents) in which a medicinally active ingredient is formulated and/or administered.

Some vehicles which are official in USP as follows:

- Aqueous vehicles
- Aqueous isotonic vehicles
- Nonaqueous vehicles.

a. Aqueous vehicles

Most commonly used vehicle for parenteral products is water, as it is the vehicle for all natural body fluids.

Types of water used in parenteral products:

- Water for injection, USP
  - Most frequently used for parenteral formulation.
  - Purified water underwent distillation or reverse osmosis.
  - Total dissolved solids not more than 1mg in 100 ml.
  - No added substances.
  - May not sterile.
  - Pyrogen free.
  - Used for manufacture of parenteral products to be sterilized after preparation.
  - Must store in tight container at suitable temperature.
  - Must be used within 24 hours.
  - Collected in sterile and pyrogen free container (glass or glass lined).
- Sterile water for injection
  - Water for injection which has been sterilized and packed in container of 1 L or less.

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- Pyrogen free.
- No antimicrobial preservation or added substances.
- Due to sterilization may contain slightly more solid content.
- Intended to be used to reconstitute sterile solids and dilute sterile solution.
- Must be added ascetically.

- Bacteriostatic water for injection
  - Sterile water for injection with suitable antimicrobial agent(s).
  - Filled in vials/syringe in volume not more than 30 ml.
  - Name and concentration of preservative must be stated.
  - Intended for small volume injectables (multidose vials).
  - Not to be used with large volume parenterals (usually with 5 ml or less).
- Sterile water for irrigation USP
  - Available as sterilized and packaged in a single dose container.
  - No added substances.
  - Packaged in container 1 L or larger.
  - Not intended for parenteral uses.
  - Labeled as "For Irrigation Only".

b. Aqueous isotonic vehicles

Isotonic relates to a solution which essentially has the same number of dissolved particles as the body fluids (e.g. blood, nasal secretions, tears). In general, the aqueous isotonic vehicles are employed quite often in parenteral products particularly.

Few typical examples are as follows:

- Sodium chloride injection, USP
  - Sterile, isotonic solution of sodium chloride in water for injection.
  - No antimicrobial agent.
  - Used as vehicle in preparing solutions/suspension for parenteral administration.
- Bacteriostatic sodium chloride injection, USP
  - Sterile, isotonic solution of sodium chloride in water for injection.

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- Contain one or more antimicrobial agents (specify in label).
- Volume not more than 30 ml (5 ml preferred).

- Miscellaneous
- Ringer's injection
  - Sterile solution of sodium chloride, potassium chloride and calcium chloride in water for injection.
  - Concentration as physiological concentrations.
  - Can be used as vehicle or electrolyte replenisher or fluid extender.
- Lactate Ringer's injection, USP
  - Sterile solution of sodium chloride, potassium chloride, calcium chloride and sodium lactate.
  - Intended to be used as fluid and electrolyte replenisher and systematic alkalyzer.

c. Nonaqueous vehicles

In formulation of sterile products, it is sometimes necessary to eliminate water entirely or in part from the vehicle, primarily because of solubility factors or hydrolytic reactions.

Nonaqueous solvents selected with great care:

- Must be nontoxic.
- Must be nonirritant.
- Must be nonsensitizing.
- Must not exert an adverse effect on ingredients of the formulation.

So that solvents are evaluated for its physical properties such as density, viscosity, miscibility, polarity, stability, solvent activity and toxicity.

i. **Solvents that are miscible with water and that are usually used in combination with water as vehicle**—Dioxalanes, butylenes glycol, polyethylene glycol 400 and 600, dimethyl-acetamide, propylene glycol, glycerine and ethyl alcohol.
ii. **Water immiscible solvents**—They include fixed oils (corn oil, cottonseed oil, peanut oil, and sesame oil), ethyl oleate, isopropyl myristate and benzyl benzoate.

Fixed oils are used as vehicles for certain hormone (e.g. progesterone, testosterone, deoxycorticosterone) and vitamin (e.g. Vitamin K, Vitamin E) preparations. The label of these

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preparations must state the name of the vehicle, so the user may beware in case of known sensitivity or other reactions to it.

2. Solutes

Solute represents a substance which is dissolved by a solvent. In other words, the solute designate the chemicals dissolved in vehicles, which must be best quality, because the presence of even small traces of contaminants may be detrimental to products. Obviously the solute may be the active ingredients (or drugs) which exerts a therapeutic effect.

Added substances or excipients: Apart from active ingredients, added substances are also added in the product (Table 4.1). They are added to enhance stability of the product. Such substances include:

- Buffers
- Tonicity contributors
- Antimicrobial agents
- Antioxidants
- Wetting, suspending and emulsifying agents
- Solublizers
- Stabilizers.

Desired characteristics

- It must be nontoxic in the quantity administered to the patients.
- They should not interfere with the therapeutic efficacy nor with the assay of the active therapeutic compound.
  a. **Buffers**: Buffers are added to maintain required pH of the product. Ideal pH for parenteral product is 7.4, the pH of blood. Extreme deviation can cause complications. Above pH 9, tissue necrosis often occur. If pH below 3, then extreme pain is experienced at the site of injection. Thus, the acceptable pH range is 3–10.5. For IV preparation pH is wider (pH 4–9) than the acceptable range for others. Buffers should not be used in intracardiac and intraocular injections. Acetate, phosphate, citrate and glutamate are most commonly used buffers.
  b. **Tonicity contributors**: These are the compounds contributing to the isotonicity of a product and reduces the pain of injection in the area with nerve endings. Injections

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should be made isotonic with blood by the addition of sodium chloride or dextrose. Buffers also acts as tonicity contributors.

c. **Antimicrobial agents**: Antimicrobial agents are included in multidose packaging, to prevent multiplication of any accidently introduced microbes in the products during the withdrawal of dosages. Some commonly used antimicrobial agents are: Benzyl alcohol, benzalkonium chloride, methylparaben, propylparaben, thiomersal, phenylmercuric nitrate.

d. **Antioxidants**: Antioxidants are included in formulation to protect therapeutic agents susceptible to oxidation, particularly under the accelerated conditions of thermal sterilization. Antioxidants acts by various ways, on the basis they are classified as:

   i. *Reducing agents*: These agents preferentially oxidized and gradually used up.
   For example: Ascorbic acid, sodium bisulfate, sodium metabisulfite, thiourea.

   ii. *Blocking agents*: They block oxidative chain reaction in which they are not usually consumed.
   For example: Ascorbic acid esters, BHT, tocopherol.

   iii. *Synergistic agents*: These compounds acts as synergists. They increases the effectiveness of antioxidants those block oxidative reactions.
   For examples: Ascorbic acid, citric acid, tartaric acid, phosphoric acid.

   iv. *Chelating agents*: These compounds forms complex with catalysts that otherwise accelerate the oxidative reaction.
   For example: EDTA salts.

e. **Wetting agents**: Wetting agent used in preparation of parenteral suspension to maintain particle size and to counteract caking. For examples: Tween 80, sorbitan trioleate.

f. **Suspending agents**: The improper formulation of suspension not only affects the dose uniformity but determines syringeability and injectability. The sedimentation of insoluble drugs makes it difficult to take accurate dose in the syringe (syringeability) and to inject in even row without clogging under given

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pressure (injectability). Sodium carboxymethylcellulose, methylcellulose, acacia, gelatin, polyvinylprollidone (PVP) may be used to prevent sedimentation of suspended particles.

g. **Emulsifying agents**: Emulsifying agents are used to prevent coalescence of dispersed globules and hence stabilizes the parenteral emulsion. For example: Lecithin.
h. **Stabilizers**: Drug in the solution form liable to undergo degradation through oxidation and hydrolysis. stabilizers are added to ensure the stability of drug compound in the preparation. For examples: Glycine, creatinine, sodium saccharin, sodium caprylate.
    i. *Solubilizing agents*: To enhance the solubility of drugs, parenteral formulation contains cosolvents such as alcohol, polyethylene glycol (PEG), nonionic surfactants. They are used to solubilize drugs such as vitamins, hormones and volatile oils.

Table 4.1: Common excipients used in parenterals

Excipients	*Concentration range (%)*
Antimicrobial preservatives	
a. Benzyl alcohol	0.5–10.0
b. Phenylmercuric nitrate	0.001
c. Thimerosal	0.001–0.02
d. Propylparaben	0.005–0.035
Solubilizers, wetting agents/emulsifiers	
a. Dimethylacetamide	0.01
b. Ethanol	0.61–49.0
c. Glycerol	14.6–25.0
d. PEG 300	0.01–50.0
Buffers	
a. Acetic acid	0.22
b. Citric acid	0.5
c. Maleic acid	1.6
d. Lactic acid	0.1
Tonicity modifiers	
a. Lactose	0.14–5.0
b. Mannitol	0.4–2.5
c. Sorbitol	2.0
d. NaCl	varies

Contd...

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Contd...

Excipients	*Concentration range (%)*
Suspending agents	
a. Gelatin	2.0
b. Pectin	0.2
c. PEG 4000	2.7–3.0
Antioxidants	
a. Ascorbic acid	0.02–0.1
b. Thiourea	0.005
c. BHT	0.005–0.002
Stabilizers	
a. Niacin	1.25–2.5
b. Sodium caprylate	0.4
c. Glycine	1.5–2.25

GENERAL MANUFACTURING PROCESS

The preparation of a parenteral product may encompass four general areas:

1. Procurement and accumulation of all components in a warehouse area, until released to manufacturing.
2. Processing the dosage form in appropriately designed and operated facilities.
3. Packaging and labeling in a quarantine area, to ensure integrity and completion of the product.
4. Controlling the quality of the product throughout the process.

Procurement encompasses selecting and testing according to specifications of the raw-material ingredients and the containers and closures for the primary and secondary packages. Microbiological purity, in the form of bioburden and endotoxin levels, has become standard requirements for raw materials.

Processing includes cleaning containers and equipment to validated specifications, compounding the solution (or other dosage form), filtering the solution, sanitizing or sterilizing the containers and equipment, filling measured quantities of product into the sterile containers, stoppering (either completely or partially for products to be freeze-dried), freeze-drying, terminal sterilization (if possible), and final sealing of the final primary container.

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Packaging normally consists of the labeling and cartoning of filled and sealed primary containers. Control of quality begins with the incoming supplies, being sure that specifications are met. Careful control of labels is vitally important, as errors in labeling can be dangerous for the consumer. Each step of the process involves checks and tests to ensure the required specifications at the respective step are being met. Labeling and final packaging operations are becoming more automated.

The quality control unit is responsible for reviewing the batch history and performing the release testing required to clear the product for shipment to users. A common FDA citation for potential violation of cGMP is the lack of oversight by the quality control unit in batch testing and review and approval of results.

Components

The components of parenteral products include the active ingredient, formulation additives, vehicle(s) and primary container and closure. Establishing specifications to ensure the quality of each of these components of an injection is essential. Secondary packaging is relevant more to marketing considerations, although some drug products might rely on secondary packaging for stability considerations, such as added protection from light exposure for light-sensitive drugs and antimicrobial preservatives.

The most stringent chemical-purity requirements will normally be encountered with aqueous solutions, particularly if the product is sterilized at an elevated temperature where reaction rates will be accelerated greatly. Dry preparations pose relatively few reaction problems but may require definitive physical specifications for ingredients that must have certain solution or dispersion characteristics when a vehicle is added.

Containers and closures are in prolonged, intimate contact with the product and may release substances into, or remove ingredients from, the product. Rubber closures are specially problematic (sorption, leachables, air and moisture transmission properties), if not properly evaluated for compatibility with the final product. Assessment and selection of containers and closures are essential for final product formulation, to ensure the product retains its purity, potency and quality during the intimate contact with the container throughout its shelf life.

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Administration devices (e.g. syringes, tubing, transfer sets) that come in contact with the product should be assessed and selected with the same care as are containers and closures, even though the contact period is usually brief.

1. Water for injection (WFI) preparation

The source water can be expected to be contaminated with natural suspended mineral and organic substances, dissolved mineral salts, colloidal material, viable bacteria, bacterial endotoxins, industrial or agricultural chemicals, and other particulate matter. The degree of contamination varies with the source and will be markedly different, whether obtained from a well or from surface sources, such as a stream or lake. Hence, the source water must be pretreated by one or a combination of the following treatments: chemical softening, filtration, deionization, carbon adsorption, or reverse osmosis purification.

Water for injection can be prepared by distillation or by membrane technologies (i.e. reverse osmosis or ultrafiltration). The EP (EUROPEAN PHARMACOPEIA) only permits distillation as the process for producing WFI. The USP and JP (JAPANESE PHARMACOPEIA) allow all these technologies to be applied.

i. **Distillation**: Distillation is a process of converting water from a liquid to its gaseous form (steam). Since steam is pure gaseous water, all other contaminants in the feed water are removed. A conventional still consists of a boiler (evaporator), containing feed water (distilland); a source of heat to vaporize the water in the evaporator; a headspace above the level of distilland, with condensing surfaces for refluxing the vapor, thereby returning nonvolatile impurities to the distilland; a means for eliminating volatile impurities (demister/separation device) before the hot water vapor is condensed; and a condenser for removing the heat of vaporization, thereby converting the water vapor to a liquid distillate.

ii. **Reverse osmosis (RO)**: As the name suggests, the natural process of selective permeation of molecules through a semipermeable membrane separating two aqueous solutions of different concentrations is reversed. Pressure, usually between 200 and 400 psig, is applied to overcome osmotic pressure and force pure water to permeate

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Handbook of Pharmaceutical Technology

Handbook of Pharmaceutical Technology articulates on the various pharmaco-technological concepts associated with industrial pharmacy, to introduce pharmacy students to the principles and technologies applied in the preparation of pharmaceutical dosages and drug delivery systems. An integrated presentation is used in this book to demonstrate the interrelationship between pharmaceutical and biopharmaceutical principles, formulation, manufacture and the application of various dosages forms in patient care.

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