INDUSTRIAL PHARMACY - I

UNIT 4 NOTES

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PARENTERAL PRODUCTS

- The term "Parenteral" comes from greek roots para (= beside) & enteron (= intestine) meaning outside the intestine.
- Parenteral products are sterile pharmaceutical preparations intended for administration by injection through the skin or mucus membrane using syringe & needle.
- They are given by routes that bypass the alimentary canal (e.g., intravenous, intramuscular, subcutaneous, etc.)

TYPES OF PARENTERAL PRODUCTS

Parenteral products can be classified on 3 basis:

① Based on Volume
② Based on Formulation type
③ Based on Route of Administration

① BASED ON VOLUME

ⓐ SMALL VOLUME PARENTERALS (SVP):

- Volume: Up to 100 mL
- Usually supplied in ampoules or vials.
- Commonly used for single-dose injections or multi-dose vials.
- Examples: Insulin injection, Adrenaline Injection, Ceftriaxone injection etc.
- Use: Given by IM, IV, SC or ID routes for therapeutic action.

ⓑ Large Volume Parentals (LVP)

- **Volume:** More than 100 mL, usually 100 mL to 1000 mL.
- Supplied in glass or plastic water bottles/bags.
- Must be free from preservation (since large volumes are infused directly into blood.
- Examples: - 5 % Dextrose Inj
  - Normal Saline (0.9% Sodium Chloride Injection)
  - Ringer's Lactate
  - Mannitol Injection
- **Use:** For fluid & electrolyte replacement, nutrition or blood volume expansion.

② Based On Formulation Type

ⓐ Solutions

- Clear, sterile liquids in which the drug is completely dissolved.
- Most common type of parenteral product.
- May be aqueous or non-aqueous (using oils).
- Examples: - Dextrose Injection IP
  - NaCl Injection
  - Vitamin K injection (oil-based)

ⓑ Suspensions

- Contain insoluble solid particles dispersed in a liquid medium.
- Require through making / shaking before use to ensure uniform dose.
- Must not be given IV (risk of embolism).
- Examples: - Procaine Penicillin Inj.
  - Hydrocortisone Suspension Inj.

③ Based On Route Of Administration

- Intravenous (IV) - Into the vein.
- Intramuscular (IM) - Into the Muscle.
- Subcutaneous (SC) - Under the skin.
- Intradermal (ID) - Into the skin layer.
- Other Specialized routes - Intra- articular, intrathecal etc.

ADVANTAGES

- Rapid onset of action due to direct entry into circulation.
- 100 % bioavailability (especially IV).
- Suitable for unconcious or vomiting patients.
- Useful for drugs unstable or poorly absorbed orally.
- Allows precise doing & controlled therapy.
- Can be used for depot or sustained - release formulations.

DISADVANTAGES

- Painful & invasive - requires skilled personnel.
- Risk of infection or contamination if sterility is compromised.
- Difficult to reverse in case of overdose or adverse reaction.
- More expensive due to strict sterile manufacturing & handling requirements.
- Requires trained personnel & special equipment for administration.

Preformulation Factors And Essential Requirements Of Parenteral Products

- Parenteral products are sterile pharmaceutical preparations intended for administration by injection or infusion, bypassing the GIT. Because they are introduced directly into tissues or blood, they must meet strict quality, safety & sterility standards.
- These are the physiochemical & biological properties studied before developing the parenteral formulation.

① Solubility And Vehicle Selection

- The drug must be sufficiently soluble in the chosen vehicle (water or oil) for uniform dosing.
- Aqueous vehicles (Water for inj.) are most common; non-aqueous oils are used for water-insoluble drugs or depot inj.

② Stability

- The drug must be chemically, physically & microbiologically stable throughout its shelf-life.
- Stability can be enhanced by buffers, antioxidants or suitable storage conditions.

③ pH And Isotonicity

- The formulation should have physiological pH (~7.4) to minimize tissue irritation.
- Solutions must be isotonic to prevent pain, hemolysis or tissue damag

④ **Sterility And Freedom From Pyrogens**

- Must be completely sterile and free from pyrogens (endotoxins that cause fever).
- Achieved using aseptic processing, filtration or sterilization techniques.

⑤ **Compatibility**

- Drug must be compatibility with excipients & container materials to prevent precipitation, degradation or chemical reactions.

⑥ **Container And Packaging**

- Must use sterile, non-reactive containers (glass vials, ampoules, plastic bags) with secure closures to maintain sterility.

Importance Of pH And Isotonicity In Parenteral Products

Parenteral products are injected directly into the bloodstream or tissues, so their pH & osmotic pressure must be carefully controlled to ensure safety, stability & patient comfort.

① Importance Of pH

pH is measure of the acidity or alkalinity of a solution.
The optimal range should be close to physiological pH (7.4).

Need For Control

- **Minimizes Tissue Irritation:** Highly acidic or alkaline solutions can cause pain, inflammation, or necrosis at the inj. site.
- **Enhances Stability:** Many drugs are stable only within a specific pH range; outside this range, they may degrade, precipitate or lose potency.
- **Prevents Drug Incompatibility:** Proper pH avoids reaction with excipients or container materials.

Methods To Control

Buffers like phosphate or citrate are often added to maintain the desired pH.

② Importance Of Isotonicity

Isotonicity means the sol^{n} has the same osmotic pressure as body fluids (~ 0.9 % NaCl).

Need For Control

- **Reduces Pain & Irritation:** Hypertonic or hypotonic solutions can cause cell shrinkage or swelling, leading to discomfort or tissue damage.
- **Prevent Hemolysis:** Especially critical for intravenous injections; red blood cells can rupture if the sol^{n} is not isotonic.
- **Improves Drug Acceptance:** Ensure safe & comfortable administration without adverse local effects.

Method To Control

Tonicity can be corrected using NaCl, dextrose or mannitol.

PRODUCTION PROCEDURE

- The basic steps for making parenterals include organizing equipment, managing materials & meeting manufacturing needs like ingredients & drugs.
- The product involves following general steps:

① PREPARATION OF FORMULATION

- Dissolve or disperse the active drug in a suitable vehicle (water/oil).
- Adjust pH, isotonicity & stability with buffers, tonicity agents & stabilizers.
- Filter the soln if required (for practical removal).

② STERILIZATION

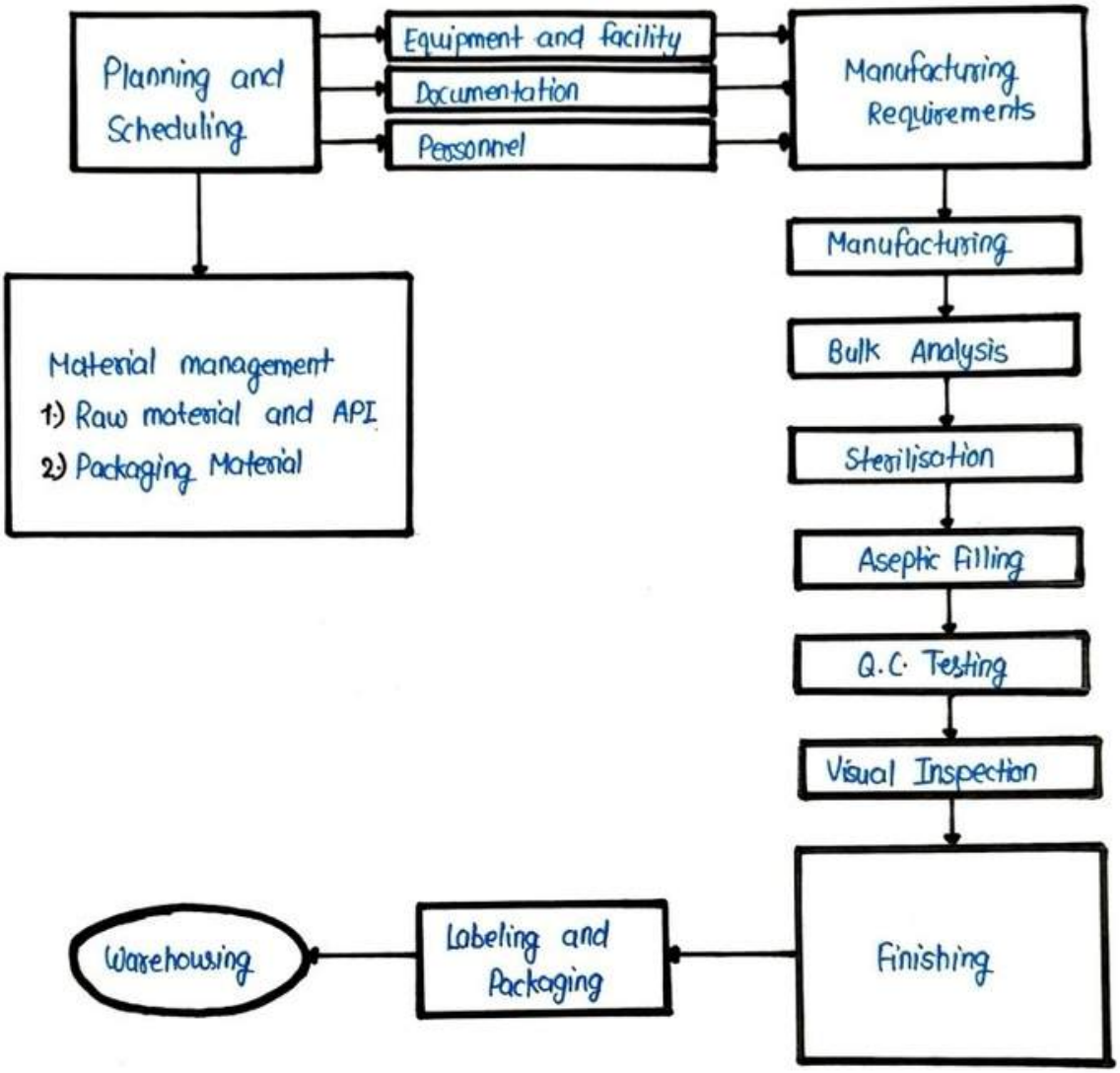
- Depending on the formulation, sterilization is done by:
  - Filtration (for heat-sensitive soln)
  - Autoclaving / Steam sterilization (for heat-stable soln)
  - Dry heat sterilization (for powders or glassware)
  - Radiation sterilization (rare, for specific products)

③ FILLING

- Under aseptic conditions, the sterile formulations is filled into sterile containers (vials, ampoules etc.)

④ SEALING AND PACKAGING

- Containers are sealed with sterile closures, labeled & stored under controlled conditions.



• Flow chart of Manufacturing Process of Parenterals

The process of making parenterals include these steps:

1.) Cleaning and washing of containers and closures.
2.) Preparation of solutions
3.) Sterilization

PRODUCTION FACILITIES

Production facilities & Controls :

FACILITIES

- Must be cleanroom-type areas with controlled air quality, temperature & humidity.
- Laminar airflow workbenches are used to maintain a sterile environment during filling.
- Separate areas are needed for :
  - Solution preparation
  - Sterilization
  - Filling & Sealing
  - QC testing

CONTROLS

- Environmental Control : Air quality, particle count, microbial contamination.
- Personnel control : Operators wear sterile gowns, gloves, masks & follow aseptic techniques.
- Equipment Control : Sterile & Validated equipment to prevent contamination.
- In-Process Control : pH , isotonicity , clarity , sterility checks.
- Finished Product Control : Sterility, Pyrogen test, particulate matter, labelling & packaging.

Aseptic Processing

Aseptic processing is the method of preparing, sterilizing & filling a parenteral product without using terminal sterilization, while maintaining sterility throughout.

Steps

- Sterilization of Formulation: Filtration through a 0.22 µm filter (for heat-sensitive drugs).
- Sterilization of containers & Closures: Autoclaving, dry heat, or gamma radiation.
- Sterile filling: Under Laminar airflow in an ISO-class cleanroom.
- Sealing: Using sterile stoppers, caps or seals.
- Environmental Monitoring: Continuous monitoring for airborne particles & micro-organisms.

Need / Importance

- Ensures that the product is sterile, safe & free from contamination.
- Essential for drugs that can't withstand heat sterilization (e.g. proteins, vaccines, some antibiotics).

Formulation Of Injections

- Injections are sterile preparations intended for administration by injection, infusion or implantation into the body. They are designed to deliver drugs directly into the bloodstream or tissues, bypassing the GIT.
- The formulations of injections requires careful selection of ingredients to ensure sterility, stability, safety & efficacy.

① Active Pharmaceutical Ingredients (API)

- The main therapeutic substances.
- It must be stable, soluble & compatible with other components.
- Poorly soluble drugs may require cosolvents, complexing agents or pH adjustments for solubilization.

② Vehicles

- Vehicles form the bulk of the injection & serve as solvents or dispersing media for the drug.
- They must be non-toxic, non-irritant, stable, sterile & compatible with the drug & container.

ⓐ Aqueous Vehicles:

- These are most commonly used because they are physiologically acceptable.

› Water for Injection – Pure, sterile water free from pyrogens. Used for preparing sol^{n} for immidiate used or for reconstitution of powders.

› Sterile water for injections - • Used when WFI is sterilized & filled into ampoules / vials.

› Bacteriostatic water for injections - • Contains a small amount of antimicrobial agent (e.g., benzyl alcohol) for use in multi-dose vials.
• Not for use in neonates or large volume injections.

› Non-aqueous Vehicles - • Fixed vegetable oils (e.g. sesame, peanut, castor oil) or co-solvents like propylene glycol.

› The vehicle must be non-toxic, non-irritant & compatible with the drug.

③ ADDITIVES

- Additives are pharmaceutical ingredients added to improve the stability, safety & acceptability of injections.
- Each additive must be non-toxic, non-irritant, non-reactive & used in the lowest effective concentration.

ⓐ Buffers : - Maintains the desired pH to ensure drug stability & patient comfort.
- Common buffers : Phosphate, Citrate, Acetate buffers.

(b) Antioxidants : - Prevent oxidation of drugs sensitive to air or light.
- Examples: Ascorbic drugs, Sodium metabisulfite, Thiourea.

(c) Preservatives : - Prevent microbial growth in multi-dose containers.
- Examples: Phenol, Benzyl alcohol, Benzalkonium Chloride.
- Note: Not used in large-volume parenterals (LVPs) or neonatal formulations.

(d) Chelating agents : - Bind trace metal ions that catalyze oxidation or degradation.
- Example : Disodium edetate (EDTA).

(e) Tonicity adjusters : - Maintain isotonicity with body fluids to avoid pain or hemolysis.
- Examples: NaCl, Dextrose, Mannitol.

(f) Solubilizing Agents / Surfactants : - Improve solubility of poorly soluble drugs.
- Examples : Polysorbate 80, Lecithin, Cremophor EL.

FACTORS TO BE CONSIDERED

- pH should be close to physiological pH (7.4) to reduce irritation.
- Formulation must be isotonic with body fluids to avoid pain, hemolysis, or tissue injury.
- The entire formulation must be sterile & pyrogen-free.
- Containers must be sterile, inert & compatible with the product.
- Closures must maintain sterility & prevent contamination.

STERILE POWDERS

- Sterile powder are dry, solid particles of one or more active ingredients which, when reconstituted with a suitable sterile solvent, from a solution or suspension for parenteral administration.
- They are used mainly for drugs that are unstable in aqueous solution during storage.

NEED FOR STERILE POWDERS

- Many drugs decompose rapidly in liquid form, losing potency over time.
- Formulating them as sterile dry powders improves stability, shelf life, & convenience.
- The product is reconstituted immediately before injection with sterile water or another suitable diluent.

METHODS OF PREPARING DRUG POWDER

① STERILE RE-CRYSTALLISATION

In this method, the drug is dissolved in a solvent, the solution obtained is sterilised by passing through a 0.22 μm membrane filter, and finally a sterile anti-solvent is added to crystalline the drug particles, which are filtered & dried aspetically.

② LYOPHILISATION

- In this method, a solid substances is separated from solution by freezing the solvent & evaporating the ice under vaccum.
- The obtained drug solution is sterile filtered into sterile trays, which're the aseptically loaded into a freeze layer.
- The solution is then frozen at -50°C and then dried by vaccum to separate the drug powder.

③ SPRAY DRYING

- In this method, the drug solution is sprayed into a dry chamber where it comes in contact with a hot steam of a sterile gas at 80 - 100°C temperature.

Formulation Of Large Volume Parenterals (LVPs)

- Large Volume Parenterals (LVPs) are sterile aqueous soln intended for parenteral administration in volumes greater than 100 mL.
- They are usually administered by IV infusion to supply fluids, electrolytes, nutrients or medications directly into the bloodstream.

Objectives / Uses

- To restore body fluids & electrolyte balance.
- To provide nutrition (glucose, amino acids, lipids).
- To act as vehicle for administration of drugs during infusion therapy.

Components Of LVP Formulation

① Active Ingredients

- Include electrolytes, nutrients, or therapeutic agents depending on the purpose.
- Examples: NaCl, Dextrose, Ringer's lactate, Amino acids, Fat emulsions.

② Vehicle

- Water for Injection (WFI) is the most commonly used vehicle.
- Must be pyrogen-free, sterile & non-reactive.

③ Additives

- **Electrolytes :** Maintain osmotic balance (e.g. Na^+, K^+, Cl^-, Ca^{2+}).
- **Nutrients :** For Parenteral nutrition (e.g. dextrose, amino acids, lipids, vitamins).
- **Buffers :** Maintain pH (e.g., phosphate, acetate buffers).
- **Antioxidants :** Prevent oxidation (e.g. Sodium metabisulfite, ascorbic acid).
- **Chelating agents :** Bind trace metals (e.g., disodium EDTA)
- **Note :** Preservatives are not used in LVPs because they may cause toxicity when infused in large volumes.

Factors To be Considered

- pH is usually adjusted near physiological pH (7.4).
- Solutions must be isotonic with body fluids to prevent irritation & hemolysis.
- LVPs are packed in single-dose plastic (PVC) or glass bottles of 250 - 1000 mL capacity.
- Containers must be sterile, non-toxic, non-reactive & leak-proof.
- Usually sealed with rubber closures & aluminium caps or welded plastic ports.

Formulation Of Lyophilized Products

- Lyophilized products (or freeze-dried products) are sterile dry powders obtained by removing water from a frozen solution or suspension under vaccum.
- They are reconstituted with a suitable sterile solvent before injection and are used mainly for heat- or moisture-sensitive drugs.

Purpose Of Lyophilization

- To enhance stability & shelf life of drugs unstable in liquid form.
- To produce a dry, prorous cake that reconstitutes quickly.
- To ensure sterility & product uniformity.
- To protect biological products like vaccines, hormones & enzymes from degradation.

Formulation Components

① Active Ingredient (API)

- The main drug which must remain stable during freezing & drying.
- Examples: Antibiotics (Ceftriaxone), Vaccines, Hormones, Enzymes.

② Additives

- These are added to maintain stability, appearance & isotonicity of the lyophilized product.

- **Bulking Agents:** Provide body & structure to dried cake (e.g. Mannitol)
- **Stabilizers / Protectants:** Prevent drug degradation during freezing & drying (e.g., Surrose, Trehalose, Gelatin).
- **Buffers:** Maintain pH within stable range (e.g., Phosphate, Citrate buffers).
- **Tonicity Adjusters:** Ensure isotonicity after reconstitution (e.g. NaCl etc.)
- **Chelating Agents:** Prevent metal ion-catalyzed degradation (e.g. EDTA)

③ Solvent (Vehicle)

- Usually Water for Injection (WFI) or sterile water.
- Must be pyrogen-free & compatible with all formulation components.

Stages Of Lyophilisation Process

① Freezing

- The sterile solution is frozen below its eutectic temperature (-40°C to -50°C).
- Water crystalline & separates from the solute.

② Primary Drying (Sublimation)

- Under high vaccum & low temperature, ice sublimes directly to vapor.
- About 90% of the water is removed in this step.

③ Secondary Drying (Desorption)

- The temperature is gradually raised to remove bound moisture.
- Final moisture content is usually below 1%.

Containers And Closures

- Typically filled into sterile glass vials before lyphilization.
- After drying, vials are partially stoppered with rubber closures & fully sealed under vaccum or inert gas (like nitrogen) after the process.

Advantages

- Greatly improves stability & Shelf-life.
- Produces lightweight, easily transportable products.
- Rapid reconstitution before use.
- Ideal for heat- & moisture-sensitive drugs.

DISADVANTAGES

- Expensive process & equipment.
- Time - consuming (can take several hours)
- Requires speciallized facilities & traind personnel.
- Some drugs may denature during freezing or drying.

EXAMPLES OF LYOPHILIZED PRODUCTS

- Ceftriaxone Sodium inj.
- Amikacin sulfate inj.
- Human insulin inj
- Vaccines & Monoclonal Antibodies.

Containers And Closures In Parenterals

- Parenteral preparations are sterile products that must remain free from contamination throughout their shelf life.
- Hence, their containers & and closures play a crucial role in maintaining sterility and compatibility of the product.

Types Of Containers

(A) Glass Containers

- Glass is the most traditional & widely used materials for parenterals because of its clarity, inertness & impermeability.

Types Of Glass (As Per USP/IP):

(1) Type I: Borosilicate Glass -

- High resistance to chemical attack & terminal attack.
- Used for all types of parenterals (acidic, neutral or alkaline solutions).
- Examples: Tubing glass used for ampoules & vials.

(2) Type II: Treated Soda-Lime Glass -

- Internally surface-treated with sulfur to reduce alkalinity.
- Used for acidic or neutral sols^{n}.

(3) Type III: Soda-Lime Glass -

- Moderate resistance; used for dry powders or non-aqueous preparations.

Forms

- **Ampoules:** Small, sealed glass containers for single-dose injections.
- **Vials:** Bottles with rubber closures, suitable for single or multi-dose use.
- **Bottles:** Used for large-volume parenterals (250 mL to 1000 mL).

(B) Plastic Containers

- Made from polyethylene (PE), polypropylene (PP) or polyvinyl Chloride (PVC).
- Lightweight, unbreakable, and compatible with most drugs.
- Used for large-volume parenterals, infusion fluids & IV sets.
- Must be leach-proof & not absorb drug components.

Closures For Parenteral Containers

- Closures are used to seal containers & protect the contents from contamination.
- They must maintain sterility & integrity throughout the product's shelf-life.

Types Of Closures

① Rubber Closures (Stoppers)

- Usually made from butyl, bromobutyl, or silicone rubber.
- Properties: - Must be elastic, non-reactive & resistant to chemicals.
  - Should withstand repeated needle punctures (for multi-dose vials).
- Coatings (e.g., Teflon, Silicone Oil) may be used to reduce adsorption or sticking.

② Aluminium Seals / Flip-Off Caps

- Used to hold rubber closures in place on vials & provide tamper evidence.
- Usually have a coloured flip-off disk for easy access during injection.

CHARACTERISTICS

- Must not adsorb or absorb the drug or leach chemicals into it.
- Must maintain airtight & microbial barrier properties.
- Should withstand sterilization methods (steam, dry heat, or radiation).
- Must allow easy withdrawl of contents & releasing (if multi-dose).
- Must be chemically inert, non-toxic, & compatible with the formulation.

Filling And Sealing Of Ampoules

- Ampoules are small, sealed glass containers (usually 1-20 mL) used for single-dose injections.
- They are preferred because they are airtight, tamper-proof & chemically inert.

Steps Involved

① Washing And Sterilization

- Ampoules are washed with detegent, purified water & finally Water for Injection (WFI).
- Dried in hot air oven & sterilized before filling.

② Filling

- Carried out aspetically using automatic ampoule-filling machines.
- Methods:
  - Tip Filling Method: Product is filled through the open neck.
  - Blow-fill-seal Method: Filling & Sealing are done simultaneously (in advanced systems).
- Filling accuracy is critical (±1% deviation).

③ Sealing

- Immediately after filling, ampoules are sealed by melting the neck using neck a gas-oxygen flame.
- Two main sealing types:
  - Tip-seal: Entire tip is melted & closed.
  - Pull-seal: Neck is heated & pulled to form a tight closure.

Filling And Sealing Of Vials

- Vials are glass or plastic containers with a rubber stopper & aluminium cap.
- They can be used for single-dose or multi-dose injections and are suitable for liquid or dry powder (lyophillized) formulations.

Steps Involved

① Washing & Sterilization

- Empty vials are washed with detergent, purified water & WFI, then sterilized in a dry heat oven (250°C for 30-60 min).
- Rubber closures & aluminium caps are sterilized separately.

② Filling

- Performed aseptically in a sterile are under laminar airflow (LAF).
- Automatic vial-filling machines ensure accurate filling.
- Filling methods: - Direct filling of sterile liquid solutions.
  - Filling of sterile powders (for dry injections or lyophillized products).

③ Partial Stoppering

- After filling, vials are partially stoppered with sterile rubber closures to allow vapor escape during sterilization or lyophillization.

④ SEALING

- After sterilization or freeze-drying, vials are fully stoppered & sealed with aluminium caps or flip-off seals.
- This ensures airtightness & tamper evidence.

Filling And Sealing Of Infusion Fluids

- Infusion fluids are large-volume sterile preparations (like 500 mL or 1000 mL) used for IV administration to supply water, electrolytes, or nutrients.
- They must be pyrogen-free, sterile and clear.

Steps Involved

① Preparation Of Containers

- Containers (usually glass bottles or plastic bags) are washed, rinsed with WFI & sterilized.
- All operations are done in clean or aseptic areas.

② Filling

- Filling is done automatically using volumetric filling machines under aseptic conditions.
- Product is filled out (for heat-stable fluids) or cold (for heat-labile fluids).
- The filling area is maintained under laminar airflow to prevent contamination.

③ SEALING

- After filling, bottles or bags are immediately sealed to maintain sterility.
- Sealing methods:
  - Glass bottles - Closed with butyl rubber closures & aluminium caps (crimped).
  - Plastic bottles / bags - Heat-sealed or fusion-sealed at the neck or port area.

Quality Control Tests For Parenterals

- Parenteral products bypass natural defense barriers hence strict quality control is essential to ensure sterility, safety, efficacy & uniformity of each batch.
- Following Quality Control test are performed for Parenterals:

① Sterility Testing
② Pyrogen Testing
③ Clarity Test
④ Leakage Test
⑤ pH Determination
⑥ Assay of Active Ingredients

① Sterility Test

- Purpose: To ensure the product is free from viable micro-organisms.
- Method: Performed under aseptic conditions using either:
  - ⓐ Membrane filtration method: product is passed through a sterile 0.45 um filter; filter is incubated in culture media.
  - ⓑ Direct Inoculation Method: small volumes of product are directly added to sterile culture media.
  - Media used:
    - Fluid thioglycollate Medium (For Anaerobic Bacteria)
    - Soybean - Casein Digest Medium (for aerobic bacteria & fungi).
  - Incubation: 14 days at 30 - 35°C & 20 - 25°C
- Acceptance: No microbial growth should appear.

② Pyrogen Test / Bacterial Endotoxin Test

- Purpose: To detect pyrogens (fever-producing substances), mainly bacterial endotoxins.

Ⓐ Rabbit Test

- Sample injected IV into healthy rabbits.
- Rise in body temperature above the specified limit indicates presence of pyrogens.

Ⓑ LAL Test (Limulus Amebocyte Lysate)

- Rapid in-vitro test using lysate from Limulus Polyphemus blood cells.
- Endotoxin causes gel formation or turbidity.
- Preferred method in modern QC (more sensitive & animal-free)

③ Clarity Test

- Checks for tubidity or foreign particles in the soln.
- Performed by visual inspection under good illumination against constrasting backgrounds.
- Product must appear clear, colourless & free from precipitates.

④ Leakage Test

- Ensures the container - closure system is propely sealed & airtight.
- Ampoules or vials are submerged in coloured dye under vaccum; if dye enters, it indicates leakage.
- Can also be done by pressure or vaccum decay methods.

⑤ pH Determination

- Measured using a pH meter.
- The pH must be within the physiological range and as specified in the monograph to ensure stability & safety.

⑥ Assay Of Active Ingredients

- Determines potency & uniformity of the drug using suitable analytical methods (titration, spectrophotometry, HPLC)
- Ensures the formulation contains the labeled amount of drug.

OPHTHALMIC PREPARATIONS

INTRODUCTION

- These are speciallized medicines applied topically, intraocularly or preocularly, and can also be used with eye devices.
- Eye medications typically come as solutions, lotions and ointments, with newer forms like gels, eye inserts, intravitreal injections and implants.

ADVANTAGE:

- Nurses can easily administer them, and patients can we them idependently.
- They are quickly absorbed for fast results.
- They have fewer side effects, longer shelf life, and better patient adherence.

DISADVANTAGES:

- They stay on the eye surface briefly and have low bioavailability.
- The dissolved medication is unstable and requires a preservative.

FORMULATION CONSIDERATIONS

① Clarity:

- Ophthalmic solutions must be clear and clean.
- Use rinsed tools for filteration to prevent contamination.
- Make clear solutions in clean areas with laminar- flow h
  non- shedding clothes.

- Clarity and stability are often achieved during filteration.
- If polymers are used, add a polishing filter step before final filtration.

② **Stability:**

- Drug stability in eye medications relies on the drug's properties, pH, preparation methods, additives and packaging.
- Achieving optimal stability often involves trade-offs and pH is crucial for longevity.
- Oxygen sensitivity can be managed with antioxidants or special packaging.
- Companies conduct stability test to ensure effectiveness until expiration, checking both chemical and physical stability.

③ **Buffer and pH:**

- Ophthalmic solutions should have a pH of 7.4 like tear fluid, but there is rare.
- Many eye care ingredients are weak base salts or stable in acidic conditions.
- Acidic pH typically doesn't cause discomfort, but excessive acidity can lead to stinging.
- Careful management of pH and buffer capacity is crucial for intraocular products.

④ **Tonicity:**

- Tonicity is a critical consideration in the formation of opthalmic preparations, as it directly impacts the compart, safety and effectiveness of the product, when applied to the eye.
- Tonicity refers to osmotic pressure exerted by a solution compared to that of body fluids such as teers.
- It is important to ensure that ophthalmic formulation have the appropriate tonicity to prevent irritation or damage to eye tissues.

- The outer eye can tolerant solutions equivalent to a range of 0.5 - 1.0% sodium chloride.

⑤ **Viscosity :**

- Viscosity is an important physical property in the formulations of ophthalmic preparations.
- It plays critical role in enhansing - ensuring the proper application, retention and effectiveness of ophthalmic products such as eye drops, gels and ointments.
- Higher viscosity formulations tend to remain on the surface of the eye for a longer time, which can improve duration of action of active ingredient.
- High viscosity formulations can create a smoother, more controlled drop, reducing the chances of irritation.

⑥ **Additives :**

- These substances are mainly inactive ingredients in eye medications for tissue compatibility.
- Purified water U.S.P. is for topical products, while water for injection U.S.P prevents pyrogen in intraocular products.
- Mineral oil and petroleum are used in ointments, but non-aqueous fluid are rarely in topical drops due to irritation.
- Some mineral and vegetable oils help moisture sensitive or poorly soluble drugs.

  Eg- Microbiological preservatives, Buffers, Antioxidants, Sufactants etc.

FORMULATION OF EYE DROPS

- An eye drop formulations contains therapeutic active ingredients, a vehicle (aqeous or oily), inert microbial-anti preservatives for sterility, and adjuvants to adjust tonicity, viscosity or pH, all in a stable container.

- Sterility is crucial to due to past Pseudomonas aeruginosa contamination, which can cause vision loss.

ANTI-MICROBIAL PRESERVATIVES:

- Multiple-dose eye drops need a strong preservatives system that passes sterility tests.
- Healthy eyes can fight infections, but damaged area at risk due to lack of blood supply.
- Preservatives should be avoided in surgical eye drops as they may damage internal surfaces.

Benzalkonium Chloride (0.01 %. w/v)	Chlorhexidine Acetate (0.01%. w/v)	Phenylmercuric Nitrate[a] (0.002%. w/v)
Atropin Sulphate	Cocaine	Tetracaine
Carbachol	Cocaine and Homatropine	Chloramphenicol
Cyclopentolate		Fluoroscien[b]
Homatropine		Hydrocortisone and Neomycin
Hyoscine		Lachesine
Hypromellose		Neomycin
Phenylephrine		Sulphacetamide
Physiostigmine		Zinc sulphate
Pilocarpine		Zinc sulpate and Adrenaline
Prednisolone		

- [a] The acetate may also be used.
- [b] This is a best used as a single dose.

FORMULATION OF EYE OINTMENTS

Different bases can be used to make eye ointments:

1.) Yellow soft Paraffin (80gm)
2.) Liquid Paraffin (10gm)
3.) Wool Fat (10gm)

White Soft Paraffin:

- White soft Paraffin is bleached yellow soft paraffin, not used directly.
- Wool fat emulsions help absorption, while liquid paraffin, lowers viscosity for easier application.

FORMULATION OF EYE LOTIONS

- Eye lotions are sterile products or solutions for quick eye washing.
- They match tear saltness but are thinner than drops.
- Improper recipes can cause discomfort, so use simple sterile normal saline.

Properties For Ideal Eye Lotions:

- It must be germ- and preservative-free, with osmotic pressure matching tears.
- It must have a neutral pH and not irritate eyes.
- It should be large, but no more than 200ml.

METHODS OF PREPARATION

① PREPARATION OF EYE DROPS:

i) Preparation for the solution-

- Prepare an eye drop solution with a preservative, antioxidant, stabilizer, tonicity modifier, viscoty modifier, or buffer, then add the active ingredient to achieve the desired volume.

ii) Clarification-

- Use filters with 0.45 to 1.2 micrometer pores. Pour clear solution into final containers for sealing and heat sterilization or store temporarily before filtration. The clarified liquid is for eye drop suspensions, which are then sealed for sterilization.

iii) Sterilization-

- Sterilization can be done by autoclaving at 115°C for 30 minutes or 121°C for 15 minutes, or by filtering through a 0.22 µm membrane filter into sterile containers. For non-aqueous products like liquid paraffin eye drops, use dry heat sterilization at 160°C for 2 hours.
- After sterilization, eye drop containers should have an easy-to-break seal to distinguish between opened and unopened ones.

② PREPARATION OF EYE OINTMENTS:

- Wool fat and yellow soft paraffin are melted in a heated water bath, mixed with liquid paraffin, and filtered through coarse filter paper in a heated funnel.

- The mixture is sterilized at 160°C for 2 hours, then combined with an eye ointment base and stored in a sterile container.

PREPAPAPARATIONS FOR EVE LOTIONS

- Preparation eye lotions involves the formulations of a sterile liquid solution intended for applications to the eyes.
- They are typically used to treat conditions such as dryness, irritation or inflammation.
- In older times, an eye lotions comprises of a solution which the patient had to dilute with an equal volume of water before applications.

Methods of Preparations :

To prepare and submit 1000 ml of sodium chloride lotion :-

- Sodium chloride - 9 gram
- Purified water - 1000 ml

Procedure :

- Dissolve sodium chloride in purified water.
- Made the final volume by addins more of purified water.
- Filter through sintered glass filter grade 4.
- The eye lotion is transferred to the bottle.
- Close & seal the bottles.
- Sterilize it by Autoclaving.

CONTAINERS

- Eye drop containers must protect against germs, moisture, air ensuring materials do not leak into the solution or absorb ingredients.
- All parts must be sterillized before final packaging.

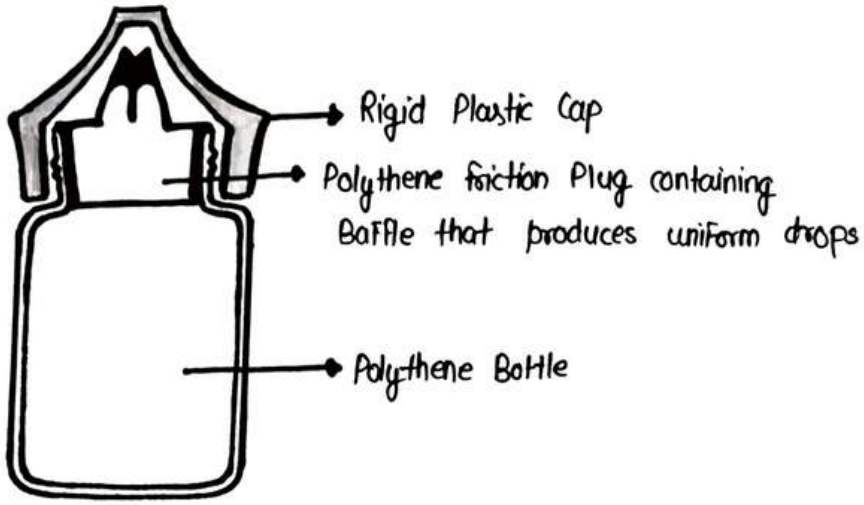
Eye drop containers can be glass or plastic, available in single-dose or multiple dose formats, with the latter holding up to 10ml:

① Single Dose Container:

- These containers are made of injection-moulded polypropylene with a sealed base and screw-cap nozzle, autoclaved in a heat-sealed pouch with a peal off backing.

② Plastic Container:

- Commercial age eye drops are usually packaged in sterillized plastic dropper bottles of polyethylene or polypropylene.

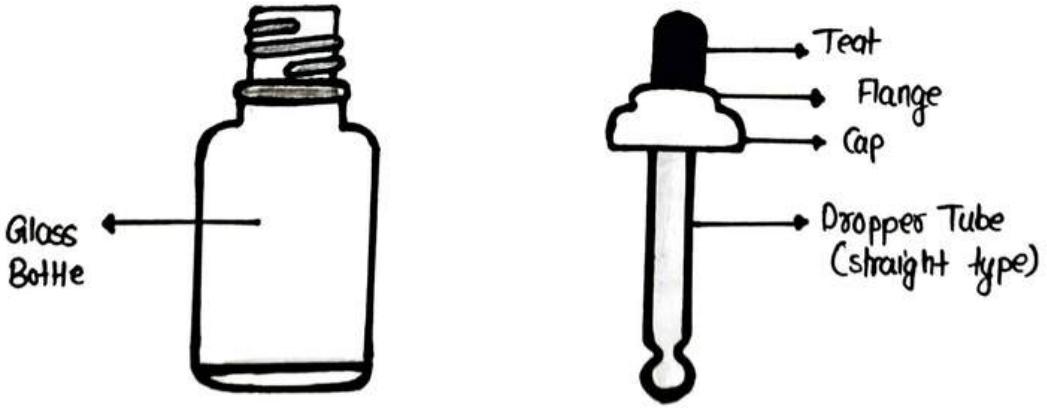


• Plastic Eye Drop Bottle

③ Glass Bottles:

Most on-site eye drops come in 10ml amber glass bottles, either neutral glass for multiple autoclaves or treated soda glass for single autoclaving.

- The teats are made of natural or synthetic rubber.
- Natural rubber teats can withstand autoclaving but not high dry heat.
- Silicone rubber teats resist dry heat and are suitable for only oily eye drops.
- However, silicone teats allow water vapor in, limiting the shelf-life of aqueous eye drops to 3 months.
- This shelf-life can be extended by using a screw cap with a sterilized silicone rubber dropper.



• Glass Type Eye Drops Bottles

Eye Ointments :

- Eye ointments should be in aluminium or plastic tubes or single-dose packages.
- Clear dust from metal tubes with filtered air before use.
- Some ointments come in flexible single-dose containers, opened by cutting the end with sterile scissors.
- Non-custom containers needs to be sealed in breakable packaging to indicate they haven't been opened.

Eye Lotions:

- Eye lotions should be in coloured, fluted bottles with metal or plastic screw caps.
- Avoid cork liners to prevent contamination, use rubber or plastic instead.
- If fluted bottles aren't available, uncoloured or non-fluted options are acceptable.

LABELING

① The label for eye care products must have:

- Product title, active ingredients and concentration
- Names and amounts of added agents, container volume and batch number
- Expiry Date
- Storage, handling and usage duration after opening
- Usage instructions, safety warnings, precautions and manufacture details.
- Notes : "This product is free from germs."

② Single-dose containers must include the following information:

- Names of the active ingredients and their amounts.
- Amount of preparation in container.
- Manufacture Name
- kind of Preparation

EVALUATION OF OPHTHALMIC PREPARATIONS

① **Sterility Test:**

- Perform sterility testing to ensure the absence of micro-organisms.
- Sterility test is using methods such as membrane filtration or the direct inoculation method.
- In addition, tests for endotoxins (pyrogens) are performed to ensure the absence of harmful bacterial products.

② **Physical and Chemical Testings:**

- **Appearance-** The preparation should be clear, free from particulate matter, and should not have any discoloration.
- **Viscosity-** This is measured to ensure the preparation has an appropriate consistency for easy application and retention in the eye.
- **pH-** Ophthalmic products should have a pH of about 7.4, like natural tears, to avoid irritation.
- **Preservatives-** A preservative must be safe for eye area, with attention to its concentration and stability.

③ **Microbial Limits Testing:**

- This involves evaluating the microbial contamination in the product, including tests for total aerobic microbial count and total yeast and mold count

④ Stability Testing:

- Ophthalmic preparations must retain their efficacy, safety and physiochemical properties over time.
- Stability testing involving assesing the formulation under various conditions (eg. temperature, humidity, light exposure) and is carried out throughout the shelf life of the product.
- Evaluating the effect of light on the stability of the formulation, particularly for products containing light-sensitive active ingredients.
- Testing the preparations' integrity at different temperatures and humidity levels.

⑤ Bioavailability:

- Ophthalmic drugs or preparations must penetrate the eye tissues to reach therapeutic levels at the target site.
- Human volunteers can measure the amount of drug that reaches the ocular surface and enters the eye.
- In some cases, pharmacokinetic studies are performed to assess how the drug is absorbed and distributed after instillation.

THANK YOU

FOR CHOOSING IMPERFECT PHARMACY AS YOUR STUDY PARTNER

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