Unit-4

Industrial Pharmacy-1

B.Pharma 5th Sem Notes

Unit: 4

Parenteral Products:

- Definition, types, advantages and limitations. Preformulation factors and essential requirements, vehicles, additives, importance of isotonicity
- Production procedure, production facilities and controls, aseptic processing
- Formulation of injections, sterile powders, large volume parenterals and lyophilized products.
- Containers and closures selection, filling and sealing of ampoules, vials and infusion fluids. Quality control tests of parenteral products.

Ophthalmic Preparations:

- Introduction, formulation considerations; formulation of eye drops, eye ointments and eye lotions; methods of preparation; labeling, containers; evaluation of ophthalmic preparations

PARENTERAL PRODUCTS

Definition

- The term 'parenteral' is derived from the Greek words 'para' (beside) and 'enteron' (intestine), meaning outside the intestine. Parenteral products are sterile preparations intended for administration by injection, infusion, or implantation into the body.
- They are introduced through the skin or mucous membranes by injection using needles or cannulas.
- According to the British Pharmacopoeia (BP), parenteral preparations are sterile liquid preparations or solid preparations to be dissolved or dispersed in an appropriate vehicle before use, intended for administration by injection, infusion, or implantation into the human or animal body.

Types of Parenteral Products

a) Based on Route of Administration

- **Intravenous (IV):** Administered directly into a vein. Provides rapid, complete bioavailability. Examples: IV fluids, blood products, anticancer drugs.
- **Intramuscular (IM):** Injected into muscle tissue. Volume: 2-5 mL. Allows depot formulations for sustained release.
- **Subcutaneous (SC/SQ):** Injected beneath the skin. Volume: up to 2 mL. Used for insulin, heparin, vaccines.
- **Intradermal (ID):** Injected into the dermis. Very small volume (0.1 mL). Used for tuberculin test, allergy testing.
- **Intrathecal:** Into the subarachnoid space of spinal cord. For anesthesia and CNS-specific drugs.
- **Intraperitoneal:** Into the peritoneal cavity. Used in dialysis and certain cancer treatments.
- **Intra-articular:** Into a joint cavity. Used for steroids in arthritis.
- **Intra-cardiac:** Emergency injection directly into heart muscle.

b) Based on Volume

- **Small Volume Parenterals (SVP):** Volume < 100 mL. E.g., ampoules, vials.
- **Large Volume Parenterals (LVP):** Volume ≥ 100 mL. E.g., IV infusions, dextrose, saline, TPN solutions.

c) Based on Physical Form

- Solutions (aqueous and non-aqueous)
- Suspensions
- Emulsions (oil-in-water for IV)
- Dry powders for reconstitution
- Lyophilized (freeze-dried) products

- Implants and depot preparations

Advantages of Parenteral Products

- **Rapid onset of action:** Direct entry into systemic circulation bypasses absorption barriers, producing immediate effects — crucial in emergencies.
- **100% bioavailability (IV):** Avoids first-pass metabolism and GI degradation, ensuring complete drug availability.
- **Suitable for unconscious patients:** Administered when patient cannot swallow or is uncooperative.
- **Suitable for drugs poorly absorbed orally:** E.g., proteins, peptides, insulin, heparin, aminoglycosides.
- **Controllable dosing:** Precise dose control, especially with infusion pumps.
- **Prolonged action possible:** Depot formulations (IM or SC) provide sustained release over days to months.
- **Nutritional support:** Total Parenteral Nutrition (TPN) provides complete nutrition via IV route.
- **Local effects:** Intra-articular or intrathecal injections provide localized drug action.

Limitations of Parenteral Products

- **Sterility requirements:** Must be absolutely sterile — contamination can cause severe infections, septicemia, or death.
- **Pain and discomfort:** Injections are invasive and may be painful.
- **Risk of adverse effects:** Rapid systemic entry increases risk of severe allergic reactions, embolism, or overdose.
- **Skilled administration:** Requires trained healthcare professionals; not suitable for self-administration in most cases.
- **Irreversibility:** Once injected, the drug cannot be retrieved (unlike oral forms that can be induced to vomit).
- **Expensive manufacturing:** Requires aseptic processing, special equipment, controlled environments — high production cost.
- **Short shelf life:** Many parenterals are aqueous solutions prone to hydrolysis, oxidation, and microbial growth.
- **Limited self-administration:** Exceptions include insulin pens and some SC injections.

Preformulation Factors and Essential Requirements

Preformulation Factors

Preformulation involves physicochemical characterization of a drug substance before formulation development. Key factors include:

a) Physicochemical Properties

- **Solubility:** Aqueous solubility determines vehicle choice. Poorly soluble drugs may need co-solvents, surfactants, or complexing agents like cyclodextrins.
- **pKa and Ionization:** Determines solubility at different pH values. Ionized forms are generally more water-soluble.
- **Partition Coefficient (log P):** Indicates lipophilicity. High log P drugs may need non-aqueous vehicles.
- **Stability:** Drug stability in aqueous/non-aqueous environments. Susceptibility to hydrolysis, oxidation, photodegradation, or polymerization must be studied.
- **Polymorphism:** Different crystal forms affect solubility and stability; must be characterized.
- **Protein binding:** Affects drug distribution and activity.
- **Osmolality:** Formulation must be compatible with physiological osmolality (~285–310 mOsm/kg).

b) Compatibility Studies

- Drug-excipient compatibility
- Drug-container/closure compatibility
- Drug-drug compatibility (for combination products)
- Drug-light compatibility (photostability)
- Drug-heat compatibility (autoclavability)

Essential Requirements of Parenteral Products

- **Sterility:** Absolute freedom from living microorganisms. Most critical requirement.
- **Freedom from pyrogens:** Pyrogen-free (endotoxin-free). Pyrogens cause fever, chills, hypotension. Tested by LAL (Limulus Amebocyte Lysate) test.
- **Freedom from particulate matter:** No visible particles (USP <790>) and sub-visible particles (USP <788>).
- **Isotonicity:** Preferably isotonic (285-310 mOsm/kg) to prevent hemolysis or crenation of red blood cells.
- **Correct pH:** Should be close to physiological pH (7.4). Acceptable range depends on route: IV (3-10.5), IM/SC (3-9).
- **Stability:** Chemically, physically, and microbiologically stable for declared shelf life.
- **Clarity:** Solution parenterals should be optically clear.
- **Safety:** Non-toxic; excipients and preservatives must be non-irritating at site of injection.
- **Compatibility:** Must be compatible with administration sets, IV fluids, and other co-administered drugs.
- **Accurate dosage:** Each container must deliver the correct labeled amount of active ingredient.

Vehicles, Additives, and Isotonicity

Vehicles

a) Aqueous Vehicles

- **Water for Injection (WFI):** Most commonly used vehicle. Prepared by distillation or reverse osmosis. Meets stringent pharmacopoeial standards for purity and endotoxin content.
- **Normal Saline (0.9% NaCl):** Isotonic aqueous vehicle. Widely used as diluent and IV fluid.
- **Dextrose solutions:** 5% dextrose in water (D5W) — isotonic. 10%, 50% dextrose for specific nutritional needs.
- **Ringer's solution:** Contains NaCl, KCl, CaCl2 — approximates plasma electrolyte composition.
- **Lactated Ringer's (Hartmann's):** Contains lactate which is metabolized to bicarbonate; used in fluid replacement.

b) Non-Aqueous Vehicles

- **Fixed oils:** Corn oil, sesame oil, arachis oil, cottonseed oil — used for oil-based depot injections (e.g., testosterone enanthate, progesterone).
- **Co-solvents:** Propylene glycol (up to 50% for IM/IV), polyethylene glycol 400, glycerin, ethanol — increase aqueous solubility.
- **Dimethyl sulfoxide (DMSO):** High penetration enhancer; limited parenteral use.
- **Benzyl benzoate:** Used in antibiotic and hormonal injections.

Additives / Excipients

Category	Examples	Purpose
Antimicrobial Preservatives	Benzalkonium chloride, Phenol, Cresol, Benzyl alcohol, Thiomersal, Chlorobutanol	Prevent microbial growth in multi-dose containers
Antioxidants	Sodium bisulfite, BHA, BHT, Ascorbic acid, Sodium metabisulfite, EDTA (chelating agent)	Prevent oxidative degradation of drug
Buffers	Phosphate buffer, Citrate buffer, Acetate buffer, Carbonate buffer	Maintain pH stability
Tonicity Agents	NaCl, KCl, Dextrose, Mannitol, Sorbitol, Glycerol	Adjust osmolality to isotonic range
Solubilizing Agents	Polysorbate 80, Cremophor EL, Cyclodextrins, Lecithin	Enhance drug solubility in aqueous media

Category	Examples	Purpose
Stabilizers	Human serum albumin, Gelatin, Sucrose, Trehalose	Stabilize proteins/peptides; used in lyophilized products
Chelating Agents	EDTA (disodium edetate)	Bind trace metals that catalyze oxidation
Bulking Agents	Mannitol, Lactose, Glycine, Sorbitol	Provide structure in lyophilized cakes
Surfactants	Polysorbate 20, Polysorbate 80, Lecithin	Emulsification and wetting

Importance of Isotonicity

Isotonicity refers to the property of a solution having the same osmotic pressure as blood plasma (~285-310 mOsm/kg or 0.9% NaCl equivalent).

Why Isotonicity is Important:

- **Prevention of hemolysis:** Hypotonic solutions (lower osmolality) cause water to enter RBCs by osmosis, leading to swelling and hemolysis (cell bursting).
- **Prevention of crenation:** Hypertonic solutions cause water to leave RBCs, causing cell shrinkage (crenation) and potential clumping.
- **Reduction of pain and irritation:** Isotonic solutions minimize pain at the injection site.
- **Tissue compatibility:** Isotonic preparations are compatible with body tissues and cause minimal damage.
- **Especially critical for:** Large volume IV infusions, ophthalmic preparations, intrathecal injections, and intravascular administration.

Methods of Adjusting Isotonicity:

- **Sodium Chloride Equivalent Method (E-value):** Amount of NaCl equivalent to 1g of drug. Sodium chloride needed = 0.9 - (E x drug concentration).
- **Freezing Point Depression Method:** Blood freezes at -0.52°C. Adjust solution to same freezing point depression.
- **Molecular Weight Method:** Calculate milliosmoles contributed by each component.

Production Procedure, Facilities and Controls

Production Facilities

Parenteral manufacturing requires highly specialized facilities to ensure sterility, freedom from pyrogens and particles:

a) Clean Room Classification (ISO / EU GMP)

Grade/Class	ISO Class	Max Particles ≥0.5µm/m³ (at rest)	Application
Grade A (EU)	ISO 5	3,520	Critical zone: filling, stopper placement, open containers
Grade B (EU)	ISO 5 (in operation)	3,520 (at rest)	Background for Grade A — aseptic preparation
Grade C (EU)	ISO 7	352,000	Less critical steps — solution preparation
Grade D (EU)	ISO 8	3,520,000	Less critical operations — washing, gowning
Class 100 (US)	ISO 5	100 particles ≥0.5µm/ft³	Equivalent to Grade A/B

b) HVAC (Heating, Ventilation, Air Conditioning) Systems

- HEPA filters (High-Efficiency Particulate Air) — >99.97% efficiency for 0.3µm particles
- Positive pressure differential between clean zones to prevent contamination entry
- Unidirectional (laminar) airflow in critical areas — Class 100/Grade A
- Air changes per hour (ACPH): Grade A = 100+; Grade C = 20+
- Temperature: 18-22°C; Relative Humidity: 45-55%

c) Utilities

- Water for Injection (WFI) system — distillation or reverse osmosis + ultrafiltration
- Clean Steam for sterilization
- Compressed air (filtered, oil-free)
- Nitrogen blanketing for oxidation-sensitive products

Production Procedure — General Steps

Step 1: Preparation of WFI and Equipment

- Depyrogenation of glassware at 250°C for 30 min (dry heat)
- Sterilization of equipment, containers, closures
- Preparation of WFI — validated and tested

Step 2: Compounding / Bulk Preparation

- Weighing and dispensing of API and excipients under Grade C/D conditions
- Dissolution in WFI with appropriate mixing

- pH adjustment using HCl or NaOH
- Volume adjustment with WFI
- In-process checks: pH, assay, appearance, osmolality

Step 3: Filtration

- Pre-filtration through 0.45µm filter (removes large particles)
- Sterilizing filtration through 0.22µm membrane filter (Millipore/Sartorius)
- Filter integrity test: Bubble point test / Forward flow diffusion test before and after filtration
- Filtration performed in Grade A/B environment

Step 4: Filling

- Filling under Grade A laminar airflow conditions
- Automated filling machines with in-process weight checks
- Fill volume must account for overfill as per pharmacopoeial requirements

Step 5: Stoppering / Sealing

- Stoppering of vials with pre-sterilized rubber stoppers under Grade A conditions
- Crimping of aluminum seals
- Ampoule fusion sealing using flame

Step 6: Terminal Sterilization (where applicable)

- Autoclaving: 121°C, 15 psi, 15-30 min for aqueous solutions
- Only if drug is thermostable

Step 7: Inspection and Release

- 100% visual inspection for particles, clarity, fill volume
- Sampling for QC testing
- Release by QA after review of batch records and QC results

Aseptic Processing

Aseptic processing is used when the product or container cannot withstand terminal sterilization. All components are sterilized separately and assembled under aseptic conditions.

Key Principles:

- **Environment:** Grade A/ISO 5 filling zone within Grade B/ISO 5 background room
- **Personnel:** Trained, gowned in sterile garments; minimized presence in critical zones; validated gowning procedures
- **Equipment:** Pre-sterilized by autoclave, dry heat, or gamma irradiation
- **Materials:** API and excipients sterilized by filtration (solutions) or dry heat/gamma irradiation (powders)

- **Containers/Closures:** Sterilized and depyrogenated separately
- **Monitoring:** Continuous environmental monitoring (particle count, viable and non-viable) during processing
- **Validation:** Process Simulation Tests (Media Fill Tests) performed at regular intervals using sterile growth medium to simulate actual process

Media Fill Test (Process Simulation):

- Performed using microbiological growth media (e.g., Soybean Casein Digest / Tryptic Soy Broth)
- Simulates all steps of aseptic processing
- Incubated at 20-25°C and 30-35°C for 14 days
- Acceptance criteria: zero contaminated units (for batches <5000 units)
- Frequency: minimum twice per year per shift per operator per process

Formulation of Specific Parenteral Products

Formulation of Injections (Solutions)

Injections are sterile aqueous or non-aqueous solutions, suspensions, or emulsions of medicaments for parenteral use.

General Formulation Approach:

- **Drug:** API with known purity, stability, and compatibility profile
- **Vehicle:** WFI, isotonic saline, or co-solvent system based on drug solubility
- **pH optimization:** Choose pH that maximizes both stability and solubility; consider physiological tolerance
- **Buffer:** Select appropriate buffer system (phosphate, citrate, acetate) at minimum capacity
- **Isotonicity adjustment:** Add NaCl, dextrose, or mannitol to achieve ~285-310 mOsm/kg
- **Antimicrobial preservative:** Only for multi-dose vials — e.g., benzalkonium chloride, phenol, benzyl alcohol
- **Antioxidant:** For oxygen-sensitive drugs — sodium metabisulfite, ascorbic acid, EDTA
- **Filter sterilization:** Through validated 0.22µm filter under Grade A conditions
- **Example:** Morphine Sulfate Injection: drug + NaCl (isotonicity) + sodium metabisulfite (antioxidant) + WFI; buffered to pH 3.0-4.0

Formulation of Sterile Powders

Sterile powders are intended for reconstitution with a suitable vehicle before administration. Used for drugs unstable in solution.

Types:

- **Aseptically manufactured powders:** Drug solution sterile filtered, then aseptically filled into vials and dried under aseptic conditions (rare).
- **Sterile bulk crystals:** Drug crystallized under aseptic conditions or terminally sterilized by ethylene oxide/gamma radiation, then aseptically filled.
- **Lyophilized powders:** Most common — see Section 5.4

Key Considerations:

- Reconstitution characteristics: rapid dissolution, no foaming, clarity
- Particle size of powder affects reconstitution time
- Overfill to account for losses during reconstitution
- Reconstitution vehicle compatibility: type, volume, resulting pH, osmolality
- Stability of reconstituted solution — in-use stability must be defined
- Example: Penicillin G sodium sterile powder for injection

Large Volume Parenterals (LVPs)

LVPs are sterile aqueous solutions packaged in containers of 100 mL or more, intended for IV infusion. They provide fluid, electrolyte, or nutritional replacement.

Types of LVPs:

Type	Composition	Use
Normal Saline (NS)	0.9% NaCl in WFI	Fluid/electrolyte replacement, drug vehicle
5% Dextrose (D5W)	5% glucose in WFI	Caloric support, drug vehicle
Lactated Ringer's (LR)	NaCl, KCl, CaCl2, Sodium lactate	Balanced crystalloid fluid replacement
Dextrose Saline	5% Dextrose + 0.9% NaCl	Combined glucose and electrolyte
Mannitol Solution	10-20% Mannitol	Osmotic diuretic, cerebral edema
TPN Solutions	Amino acids, lipids, glucose, electrolytes, vitamins	Total nutritional support
Plasma Expanders	Dextran, Hetastarch, Albumin	Volume replacement in shock

Manufacturing Considerations for LVPs:

- Manufactured in large batch sizes — tanks of 1000-5000 L
- Terminal sterilization by autoclaving (121°C, 15 min) preferred where product stability allows
- Containers: rigid glass or flexible plastic (PVC, non-PVC polypropylene)

- Must be pyrogen-free, particle-free, and isotonic
- In-line filtration before filling
- Clear labeling: concentration, volume, rate of administration, expiry

Lyophilized (Freeze-Dried) Products

Lyophilization (freeze-drying) is a drying process where water is removed from a product by sublimation under vacuum after freezing. It produces stable, sterile, dry products that can be reconstituted before use.

Process Steps in Lyophilization:

- **1. Formulation:** Drug + bulking agents (mannitol, sucrose, glycine) + stabilizers (albumin, trehalose) + pH adjustment in aqueous solution
- **2. Filling:** Sterile-filtered solution filled into vials under Grade A conditions; partially stoppered
- **3. Freezing:** Temperature lowered to -40 to -50°C to solidify the product. Rate of freezing affects ice crystal size and cake structure
- **4. Primary Drying (Sublimation):** Chamber pressure reduced (0.1-1 mbar); shelf temperature raised to -10 to -30°C. Ice sublimes directly to vapor, removing ~90-95% water
- **5. Secondary Drying (Desorption):** Temperature raised to +20 to +40°C to remove bound water. Residual moisture reduced to <1-3%
- **6. Stoppering:** Vials stoppered under nitrogen atmosphere at end of secondary drying within the lyophilizer

Formulation Considerations:

- Bulking agents: provide elegant cake structure — mannitol (crystalline), sucrose/trehalose (amorphous)
- Cryoprotectants/lyoprotectants: protect protein drugs during freezing and drying — sucrose, trehalose, sorbitol
- Collapse temperature: product must be kept below this temperature during primary drying
- Eutectic point: must be understood for formulation design
- Residual moisture: <1-3% typical; higher moisture reduces stability
- Reconstitution: rapid dissolution with clear solution upon adding WFI or diluent
- Examples: Lyophilized antibiotics (vancomycin), enzymes, vaccines, biologics (monoclonal antibodies)

Containers, Closures, Filling and Sealing

Containers and Closures — Selection Criteria

The container closure system must protect the product, maintain sterility, and not interact with the formulation.

a) Container Types

- **Ampoules:** Hermetically sealed glass containers. Single-dose only. No preservatives required. Volumes: 1-20 mL. Sealed by fusion.
- **Vials:** Glass or plastic containers closed with rubber stoppers + aluminum crimped seals. Single or multi-dose. Preservatives needed for multi-dose.
- **Infusion Bottles/Bags:** Glass bottles or flexible plastic bags (PVC, PP). Volumes 50 mL to several liters for LVPs.
- **Prefilled Syringes:** Ready-to-use with plunger and needle. Reduces preparation errors.
- **Cartridges:** Used in injection pens (e.g., insulin pens).

b) Glass Types for Parenteral Containers

Glass Type	Description	Hydrolytic Resistance	Use
Type I (Borosilicate)	Highly resistant borosilicate glass	Highest	All parenterals, especially biologics and blood products
Type II (Treated)	Soda-lime glass, surface treated with ammonium sulfate	High	Aqueous parenterals with pH < 7
Type III (Soda-Lime)	Regular soda-lime glass	Moderate	Non-aqueous parenterals, dry powders
Type NP (General)	Non-parenteral glass	Low	Oral and topical use only

c) Rubber Closures (Stoppers)

- Must be sterile, non-reactive, non-shedding, self-sealing upon needle withdrawal
- Materials: natural rubber, synthetic rubber (butyl, chlorobutyl, bromobutyl)
- Silicone coating to reduce friction and particle shedding
- Tested for: extractables/leachables, self-sealability, fragmentation, chemical resistance
- Pre-treatment: washing, siliconization, sterilization (autoclaving), depyrogenation

d) Plastic Containers

- PVC: flexible bags for IV fluids; risk of plasticizer leaching (DEHP) — now replaced by DEHP-free
- Polypropylene (PP): rigid or semi-rigid; excellent chemical resistance
- Polyethylene (PE): bottles and bags
- Must meet extractables/leachables standards — ICH Q3C, USP <661>

Filling and Sealing of Ampoules

Filling:

- Under Grade A laminar airflow; nitrogen blanketing for oxidation-sensitive products
- Measured volume fill using automatic piston or peristaltic filling machines
- Fill volume accounts for overfill (e.g., 1 mL nominal = 1.10 mL fill per USP)
- In-process weight/volume checks at defined intervals

Sealing — Pull Seal (Tip Seal):

- Neck of filled ampoule heated with gas-oxygen flame
- Top is pulled off while glass is molten, creating hermetic seal
- Faster process; risk of carbon deposits if not properly performed

Sealing — Tip Seal (Fusion Seal):

- Neck of ampoule heated until glass fuses shut
- More reliable hermetic seal; preferred for critical products
- Followed by annealing to relieve glass stress

Inspection after sealing:

- 100% visual inspection or automated inspection system for seal integrity, particles, fill volume
- Leak test using dye immersion or vacuum testing

Filling and Sealing of Vials

- Vials washed and depyrogenated (300°C, >30 min in tunnel depyrogenation oven)
- Filled under Grade A conditions — nitrogen overlay if needed
- Partially stoppered (for lyophilized products) or fully stoppered
- Aluminum crimp seal applied by crimping machine
- For lyophilized vials: stoppered automatically within the freeze-dryer at end of cycle
- Container closure integrity testing (CCIT): dye ingress, vacuum decay, headspace analysis

Filling and Sealing of Infusion Fluids (LVPs)

- Bottles: glass washed, sterilized; filled and sealed with rubber stopper + aluminum seal
- Flexible bags: aseptically filled in Grade A; port sealed by heat or aluminum crimp
- Ports fitted with administration set access and injection site
- Terminal sterilization by autoclaving: 121°C, 15-30 min
- After sterilization: cooled, inspected, labeled
- In-process checks: fill volume, pH, appearance, closure integrity

Quality Control Tests of Parenteral Products

Quality control tests for parenterals are mandated by pharmacopoeias (USP, BP, IP, EP) and regulatory guidelines (FDA, ICH).

a) Sterility Test (USP <71> / BP)

- Purpose: confirm absence of viable microorganisms
- Methods: (1) Direct Inoculation — product directly inoculated into thioglycollate medium (anaerobes) and Soybean Casein Digest medium (aerobes/fungi)
- (2) Membrane Filtration — preferred; product filtered through 0.45µm membrane, membrane transferred to media; avoids antimicrobial interference
- Incubation: 14 days at 30-35°C (bacteria) and 20-25°C (fungi)
- Interpretation: absence of growth = sterile; any growth = fail (investigate and retest if justified)
- Note: sterility test is retrospective; real assurance comes from validated aseptic process

b) Pyrogen / Bacterial Endotoxin Test

- **Rabbit Pyrogen Test (RPT):** 0.5 mL/kg IV injection in 3 rabbits; rectal temperature measured at 1, 2, 3 hours. Pass: total temperature rise < 1.15°C.
- **LAL Test (Limulus Amebocyte Lysate):** More sensitive and quantitative. Uses lysate of horseshoe crab blood cells which gels in presence of endotoxins. Methods: gel-clot, turbidimetric, chromogenic. Limit: typically < 0.25 EU/mL for IV products.
- **Recombinant Factor C (rFC) Test:** Newer alternative to LAL; does not require horseshoe crabs.

c) Particulate Matter Test (USP <788>, <790>)

- **Visible particles (USP <790>):** 100% visual inspection under standardized illumination; acceptance criteria: essentially free from particles.
- **Sub-visible particles (USP <788>):** Light obscuration method or microscopic method. Limits for LVP (>100 mL): ≤25 particles/mL at ≥10µm; ≤3 particles/mL at ≥25µm.

d) pH Measurement

- Using calibrated pH meter with appropriate electrodes
- Must be within the labeled pH range for the formulation

e) Clarity and Color

- Compare against turbidity standards (Formazin standard)
- Color comparison against color standards

f) Assay and Identification

- HPLC assay for drug content: typically 90-110% of labeled amount
- Identification by UV, IR, or MS
- Uniformity of content for unit dose containers

g) Osmolality / Tonicity

- Measured by freezing point osmometer
- Target: 285-310 mOsm/kg for isotonic products

h) Container Closure Integrity (CCI)

- Dye ingress test, vacuum/pressure decay, helium leak test
- Headspace oxygen/moisture analysis for sealed containers

i) Fill Volume / Weight

- Each container must deliver no less than the labeled volume (BP/USP overfill requirements)
- Gravimetric or volumetric check on statistically significant sample

j) Leaker Test for Ampoules

- Vacuum immersion in colored dye solution; dye entry indicates leakage
- Autoclave ampoules, then immerse in dye at atmospheric pressure

k) Abnormal Toxicity Test (Safety/General Safety Test)

- Inject product IV/IP into mice and guinea pigs; observe for 48-72 hours
- Detects unexpected toxic contamination

l) Uniformity of Dosage Units (USP <905>)

- Content uniformity or weight variation test
- Applicable to single-dose parenterals

OPHTHALMIC PREPARATIONS

Introduction to Ophthalmic Preparations

Ophthalmic preparations are sterile pharmaceutical products specifically formulated for application to the eye and its surrounding tissues. They are used for local therapeutic effects on the eye, in the treatment of ocular infections, inflammation, glaucoma, allergies, and dry eye syndrome, as well as for diagnostic and surgical purposes.

Unique Challenges of Ophthalmic Drug Delivery:

- **Precorneal drainage:** Only 1-7% of a topically applied dose is absorbed; rest drained through nasolacrimal duct.
- **Blood-ocular barrier:** Restricts drug entry from systemic circulation into the eye.
- **Tear dilution:** Normal tear volume ~7 µL; eye can hold ~30 µL; excess immediately drains.
- **Blink reflex:** Frequent blinking (15-20 times/min) rapidly removes instilled drops.
- **Lacrimation:** Irritating preparations cause excess lacrimation, washing drug away.
- **Conjunctival route:** More permeable than corneal route; preferred for posterior segment delivery.

Anatomy Relevant to Ophthalmic Drug Delivery:

- Cornea: main barrier; consists of epithelium, stroma, endothelium
- Conjunctiva: highly vascular; significant drainage via nasolacrimal duct
- Sclera: permeable to hydrophilic molecules
- Aqueous humor: bathes anterior chamber
- Vitreous: fills posterior chamber

Formulation Considerations

Formulation Parameters

a) Sterility

- Absolute requirement — the eye is extremely susceptible to infection
- Ophthalmic preparations must be sterile at the time of manufacture and during use
- Single-dose units: no preservative required
- Multi-dose containers: require antimicrobial preservatives

b) Isotonicity

- Normal tear fluid is isotonic (NaCl equivalent ~0.9%; osmolality ~300 mOsm/kg)
- Isotonic preparations cause no discomfort, stinging, or lacrimation
- Hypertonic solutions (e.g., 2-5% NaCl) used therapeutically to reduce corneal edema

- The eye can tolerate osmolality range of ~100-640 mOsm/kg without major discomfort

c) pH

- Normal tear pH: 7.4 (range 6.6-7.8); formulations ideally at this range
- pH affects drug solubility, stability, comfort, and corneal penetration
- pH < 3.5 or > 10.5 causes significant irritation
- pH stability buffer systems: phosphate (most common), borate, citrate, acetate
- Ionized (hydrophilic) drug: penetrates via aqueous pathway
- Unionized (lipophilic) drug: penetrates corneal lipid barrier better
- Most drugs have optimal corneal penetration at pH where both ionized and unionized forms exist

d) Viscosity

- Normal tear viscosity: ~1-3 mPa.s
- Increased viscosity prolongs precorneal residence time and improves bioavailability
- Viscosity agents: methylcellulose, hydroxypropylmethylcellulose (HPMC), carboxymethylcellulose, polyvinyl alcohol (PVA), carbopol
- Optimal range: 15-25 mPa.s — above this causes blurring and discomfort

e) Preservatives

Preservative	Concentration	Spectrum	Notes
Benzalkonium Chloride (BAK)	0.004-0.02%	Broad (bacteria, fungi)	Most widely used; may damage corneal epithelium with long-term use
Thiomersal (Thimerosal)	0.005-0.01%	Bacteria, fungi	Mercury-based; concerns over toxicity; use declining
Chlorobutanol	0.5%	Bacteria, fungi	Volatile; pH sensitive; used in acid preparations
EDTA (Disodium Edetate)	0.01-0.05%	Enhancer for BAK	Chelates Mg2+/Ca2+ in bacterial cell walls; potentiates BAK
Phenylmercuric Acetate/Nitrate	0.002-0.004%	Broad spectrum	Mercury compound; largely phased out
Sorbic Acid	0.1-0.25%	Bacteria, fungi	Milder; used in soft contact lens preparations
Polyquaternium-1 (Polyquad)	0.001%	Broad	Non-ionic polymer; better tolerated than BAK

Preservative	Concentration	Spectrum	Notes
Sodium Perborate	0.05%	Broad	Converts to H2O and O2 on contact with eye; self-preserved

f) Drug Absorption Enhancers

- Cyclodextrins: improve solubility and corneal permeation
- Penetration enhancers: EDTA, BAK, bile salts, surfactants — increase corneal permeability
- In situ gel systems: solution instilled as drops gels upon contact with tear fluid (triggered by pH, temperature, or ions)
- Colloidal systems: nanoparticles, nanosuspensions, liposomes, nanoemulsions

g) Drug Solubility and Stability

- Most ophthalmic drugs are hydrophilic salts for aqueous drop formulations
- Poorly soluble drugs: suspensions (e.g., prednisolone acetate suspension)
- pH-solubility profile determines buffer choice
- Light-sensitive drugs: amber glass or opaque containers

Formulation of Eye Drops

Eye drops (ophthalmic solutions and suspensions) are the most widely used dosage form for ocular drug delivery. They are sterile aqueous or oily solutions, suspensions, or emulsions for instillation into the conjunctival sac.

Composition of a Typical Eye Drop Formulation

Component	Example	Function
Active ingredient	Timolol maleate 0.5%	Therapeutic agent
Vehicle	Water for Injection / Sterile WFI	Solvent / carrier
Buffer	Sodium phosphate buffer pH 6.5-7.4	Maintain pH stability
Tonicity agent	NaCl, KCl, Dextrose	Achieve isotonicity
Preservative	Benzalkonium chloride 0.01%	Prevent microbial contamination
Viscosity agent	HPMC 0.5%	Increase retention time

Component	Example	Function
Antioxidant	Sodium metabisulfite, EDTA	Prevent oxidation, enhance preservation
Surfactant	Polysorbate 80	Wetting, solubilization

Manufacturing Procedure for Eye Drops

Manufacturing of eye drops follows stringent aseptic guidelines similar to parenterals.

Steps:

- Preparation: Dissolve buffers, tonicity agents, and preservatives in approximately 90% of WFI
- pH adjustment: Add buffering agents; verify pH with calibrated meter
- Dissolve API with mixing; adjust temperature if needed
- Add viscosity enhancers, antioxidants, and other excipients
- Make up to volume with WFI
- Check pH, appearance, and assay of bulk
- Filtration: through 0.22µm sterile membrane filter under Grade A conditions
- Filling: into previously sterilized bottles under Grade A laminar airflow
- Sealing: with tamper-evident dropper tips and screw caps
- Labeling and inspection: visual inspection for particles, color, fill volume

For Eye Drop Suspensions:

- Drug micronized to <10 µm particle size for comfort and ocular tolerability
- Sterilized separately (autoclave or filtration of vehicle; gamma irradiation of drug powder)
- Aseptically combined and filled under Grade A conditions
- Requires shaking before use — label accordingly
- Example: Prednisolone acetate 1% ophthalmic suspension

Formulation of Eye Ointments

Eye ointments are sterile semisolid preparations applied to the conjunctival sac. They provide prolonged contact time compared to drops, improving bioavailability. They are particularly useful for overnight treatment and for drugs requiring sustained activity.

Base Selection

- **Petrolatum (white soft paraffin):** Most common base; inert, non-irritating, does not absorb water; excellent ocular tolerance

- **Liquid paraffin (mineral oil):** Added to white petrolatum to adjust consistency and spreadability
- **Wool fat (lanolin):** Added (1-5%) to enable incorporation of aqueous solutions into the base
- **Polyethylene base:** Plastibase — used for water-soluble drugs
- **Standard formula:** White petrolatum 80%, liquid paraffin 10%, wool fat 10%
- **Water-soluble bases:** Macrogol (PEG) ointments — water washable, drug release into tear fluid; but may irritate

Manufacturing Procedure for Eye Ointments

- Melt petrolatum and liquid paraffin at 70-80°C in stainless steel vessel
- Add wool fat; mix until uniform and melted
- Cool to 50-55°C under aseptic conditions
- For suspensions: incorporate micronized (<75 µm, preferably <10 µm) sterile drug powder
- For solutions: dissolve drug in minimum vehicle and incorporate
- Pass through sterile ointment mill to ensure homogeneity and uniformity
- Fill into sterilized collapsible aluminum tubes (5 g tubes standard) using sterile filling machine
- Crimp-seal tubes under Grade A conditions
- Sterilization of base: dry heat 150°C for 2-3 hours (before drug addition) or gamma irradiation of finished product
- Alternatively: all components sterilized separately; aseptic compounding

Advantages of Eye Ointments

- Prolonged contact time — remains in eye 3-5x longer than drops
- Sustained drug release
- Suitable for water-insoluble drugs
- Less frequent dosing required
- Suitable for overnight application

Disadvantages

- Blurred vision upon application due to oil film on cornea
- Patient noncompliance — greasy feel
- Not suitable for daytime use in most patients
- Drug release may be incomplete from oily base

Formulation of Eye Lotions (Ophthalmic Washes / Collyria)

Eye lotions (also called eye washes, collyria, or ocular irrigating solutions) are sterile aqueous solutions used to cleanse, irrigate, or apply drugs to the external surface of the eye and conjunctiva. They are used in large volumes (100-200 mL) compared to drops.

Features and Formulation

- **Volume:** Typically 100-200 mL, applied with an eye bath
- **Sterility:** Must be sterile
- **Isotonicity:** Must be accurately isotonic — eye is in continuous contact
- **pH:** Must be physiological pH 7.4 or buffered close to it
- **Freedom from particles:** Must be particle-free — directly applied to ocular surface
- **Preservatives:** Required due to large-volume, multi-use nature: BAK, chlorobutanol

Examples of Eye Lotions

- Sodium Chloride eye lotion 0.9%: simple isotonic wash
- Balanced Salt Solution (BSS): isotonic solution with NaCl, KCl, CaCl2, MgCl2, sodium bicarbonate, and dextrose — used in ophthalmic surgery
- Boric acid eye lotion 1.9%: mildly antiseptic; isotonic; pH ~5
- Zinc sulfate lotion 0.25%: mildly astringent; conjunctivitis treatment

Methods of Preparation —

Preparation	Sterilization Method	Key Steps
Eye Drops (solutions)	Filtration (0.22µm membrane)	Dissolve, buffer, filter sterilize, aseptic fill
Eye Drops (suspensions)	Aseptic mixing of sterilized components	Micronize, sterilize powder, aseptically mix with sterile vehicle
Eye Ointments	Dry heat of base; gamma irradiation	Melt base, cool, aseptically incorporate sterile drug, mill, fill tubes
Eye Lotions	Filtration or terminal autoclave	Dissolve, adjust pH/tonicity, filter, fill
Eye Gels	Filtration or terminal autoclave	Prepare polymer gel, dissolve drug, sterilize by filtration, fill

Labeling and Containers for Ophthalmic Preparations

Containers

- **Eye drops:** Low-density polyethylene (LDPE) dropper bottles (5-15 mL). LDPE allows squeeze dispensing of calibrated drops (~50 µL/drop). Single-dose units in plastic vials (0.3-0.5 mL) — no preservative required.
- **Eye ointments:** Collapsible aluminum tubes (3.5-5 g) with ophthalmic applicator tip (fine, smooth, sterile). Tubes are flexible and maintain sterility.
- **Eye lotions:** Multi-dose glass or plastic bottles (100-200 mL) with secure, tamper-evident closure. Eye bath cup supplied separately.
- **Glass vs plastic:** Glass (Type I borosilicate): chemically inert, preferred for sensitive drugs. Plastic (LDPE/HDPE): lighter, less breakage risk, convenient.

Container Requirements:

- Sterile and non-reactive with the preparation
- Protect from light (amber or opaque containers where needed)
- Tamper-evident closure
- Easy to use without contamination — tip design critical
- Dropper: delivers consistent drop volume; does not allow reflux

Labeling Requirements

All ophthalmic preparations must carry specific labeling as per pharmacopoeial and regulatory requirements:

- Name of the preparation and active ingredient(s) with concentration
- 'Sterile' label — mandatory for all ophthalmic products
- Route of use: 'For ophthalmic use' or 'Eye drops' / 'Eye ointment'
- Batch number, manufacturing date, expiry date
- Manufacturer name and address
- Storage conditions (e.g., 'Store below 25°C', 'Protect from light')
- 'Discard 28 days after opening' — mandatory for multi-dose containers (prevents microbial contamination from opened bottles)
- Single-dose units: 'Use immediately after opening. Discard remaining contents.'
- Shake well before use — for suspensions
- Do not use if solution changes color or becomes cloudy
- Keep out of reach of children

Evaluation of Ophthalmic Preparations

Sterility Test

- As per USP <71> / BP — same as for parenterals
- Direct inoculation or membrane filtration method
- Incubated in thioglycollate and Soybean Casein Digest media for 14 days

Clarity / Appearance

- Solutions: must be clear and free from visible particles
- Suspensions: uniform, no caking, resuspendable
- Ointments: uniform, smooth, no gritty particles
- Tested by visual inspection under standard illumination

pH Determination

- Using calibrated pH meter with ophthalmic reference
- Acceptable range: typically 6.0-8.0 (product specific)
- Tear buffering capacity can neutralize mild pH differences

Particulate Matter

- Solutions: light obscuration or microscopic examination (USP <788>)
- Ointments: microscopic examination — USP <771> metal particle test
- Ointments: 10 µg of preparation examined under microscope; total metal particles ≥50 µm must not exceed 8

Uniformity of Content

- Assay of drug content — HPLC or UV spectrophotometry
- Typically 90-110% of labeled claim
- Uniformity of weight: for ointments and single-dose units

Viscosity

- Viscometers: Brookfield viscometer for solutions and gels
- Cone and plate rheometer for ointments
- Target: appropriate for the intended dosage form

Isotonicity

- Freezing point depression method — osmometer
- NaCl equivalent method (calculation)

- Target: 285-310 mOsm/kg for drops and lotions

Preservative Efficacy Test (Antimicrobial Effectiveness Test)

- USP <51> / BP Appendix XVIB — Antimicrobial Preservative Effectiveness Test
- Challenge test: inoculate with Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans, Aspergillus niger
- Monitor viable count reduction over 28 days
- Category 1 (aqueous eye preparations): log reduction from 2.0 at day 7; no increase from day 14 to 28

Leaker Test (for sealed ampoules and single-dose units)

- Methylene blue dye immersion under vacuum — dye entry indicates failure
- Electrical conductivity test

Stability Testing

- ICH Q1A(R2) guidelines — accelerated (40°C/75% RH) and long-term (25°C/60% RH or 30°C/65% RH) conditions
- Monitor assay, pH, clarity, particulate matter, preservative efficacy, container integrity

Squeeze Delivery Test (for LDPE Bottles)

- Drop volume test: each squeeze must deliver 25-50 µL per drop
- Drop count per bottle to confirm nominal volume claims

Particle Size (Suspensions)

- Laser diffraction (Malvern Mastersizer) or optical microscopy
- D90 < 10 µm for ophthalmic suspensions to ensure comfort

Corneal Cytotoxicity / Ocular Irritation Test

- HET-CAM (Hen's Egg Test on Chorioallantoic Membrane): predicts ocular irritation
- Draize Rabbit Eye Test: classical in vivo test; now largely replaced by in vitro alternatives
- BCOP (Bovine Corneal Opacity and Permeability): alternative in vitro method

Summary Comparison Table

Parameter	Parenteral Products	Ophthalmic Preparations
Sterility	Absolute requirement	Absolute requirement
pH	3-10.5 (route dependent)	6.0-8.0 (preferably 7.4)
Isotonicity	Critical, especially IV/intrathecal	Critical for comfort and safety
Preservatives	Multi-dose vials only; not ampoules	Multi-dose containers; not single-dose
Particle size	Must be particle-free (solutions)	<10 µm for suspensions
Viscosity	Low (solutions); moderate (gels/depots)	15-25 mPa.s (drops)
Sterilization	Terminal autoclave or aseptic fill	Filtration or aseptic; heat of ointment base
Containers	Ampoules, vials, bags, prefilled syringes	LDPE dropper bottles, Al tubes, glass bottles
QC Tests	Sterility, endotoxin, particles, assay	Sterility, clarity, pH, preservative efficacy
Volume	0.1 mL – several liters	Drops 5-15 mL; lotions 100-200 mL

🎓📄 Thank You for Reading! 📄🎓

👷 We hope this book helped you in your studies.

If you want to access 📱 complete notes, 📂 PDFs, and 📚 study material for your course, scan the QR code below. 🚀

📲✨ Scan & Download All Notes ✨📲

👉 **What You'll Get:**

📄 B.Pharm & D.Pharm Notes

📝 Exam-Oriented PDF Materials

🔔 Regular Updates & New Content

✨📣 **Stay Connected for More Updates** 📣✨

🌐 **Visit: https://noteskarts.com/**

📧 Contact: noteskartsconnect@gmail.com

✔ **One Scan = 📲 All Notes at Your Fingertips!** 🎯