**Unit-IV** **BP 502 T. (Industrial Pharmacy-I)** **Dr.Bijay Kumar Sahoo**

***Syllabus***

**Parenteral Products:**

1. Definition, types, advantages and limitations. Preformulation factors and essential requirements, vehicles, additives, importance of isotonicity.
2. Production procedure, production facilities and controls, aseptic processing
3. Formulation of injections, sterile powders, large volume parenterals and lyophilized products.
4. 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.

## Abbreviations: -

**LVP**: Large volume Parenteral

**SVP**: Small volume Parenteral

**P:** Partition coefficient

**HEPA:** High- efficiency Particulate Air

**LAL Test**: Limulus Amebocytes Lysate test

**BET**: Bacterial Endotoxin Test

**IPC:** In-Process Control

**WFI:** Water for Injection

**RH:** Relative Humidity

**FTM**: Fluid Thioglycolate Medium

**SCM**: Soyabean-casein digest Medium

**1. Definition:**

The term Parenteral has been derived from the Greek word **Para enteron**, which means outside the intestine**.** These are unique dosage forms as they are administered by injecting directly into the body tissues through skin and mucous membranes**.**

Parenteral products are sterile preparations containing one or more active ingredients intended for administration by injection, infusion or implantation into the body. They are packaged in either single-dose or multi dose containers.

**Types Parenteral Products:**

The types of Parenteral products are based on Volume and the state of product according to USP.

**Based on Volume:**

- SVP – An injection that is packed in containers labeled as containing 100 ml or less.
- LVP – These are parenterals designed to provide fluid, calories and electrolytes to the body and the volume is more than 100ml.

**Based on States of products:**

- Injection: Injections contain sterile solutions and are prepared by dissolving the active ingredient and other substances in Water for Injection or other suitable non-aqueous base or a mixture of both. The solution to be injected may show sediments which can be dispersed easily by shaking the container. The suspension should remain stable in order to deliver a homogenous dose whenever withdrawal is made from the container.
- Infusions**:** These parenteral preparations are composed of sterile aqueous solution with water as its continuous phase. The preparations are free from bacterial endotoxins or pyrogens and are made isotonic with blood. They do not contain any antimicrobial preservatives.
- Powder for Injection: These are sterile solid compounds that are distributed in their final volume when the vial or container is shaken to form a clear particle-free solution.
- Concentrated Solutions for Injections**:** The concentrated solutions are diluted with water for injection before they are administered through injection or through intravenous infusion.
- Implants: These solid sterile preparations are implanted in the tissue in order to release the active ingredient for long periods. They are stored in sterile containers individually.
- Injectable Emulsion: These are liquid preparations in which the drug substances are dissolved or dispersed in a suitable emulsion medium. These products provide essential fatty acid and vitamins.
- Oily Injection: These are used to prepare parenteral controlled release dosage forms.

**Advantages of Parenteral:**

a) Parenteral products can By passes pre systemic or first pass metabolism and the Onset of action is quick

b) The drugs, which cannot be administered orally, can be administered by this route.
c) The patients who are vomiting or unconscious cannot take drug by oral route. In such cases, the drug can be administered by this route.
d) The drug action can be prolonged by modifying the formulation.
e) This route can deliver transfusion fluids containing nutritives like glucose and electrolytes such as sodium chloride.

**Limitations:**

a) Injection causes pain at the site of injection.
b) The trained persons are required to administer the drug.
c) The administration of drug through wrong route of injection may prove to be fatal.
d) It is difficult to save a patient when over dose is given.
e) There are chances of sensitivity reaction or allergic reaction of a drug by an individual. These reactions are sometimes fatal and lead to death.

**Preformulation factors and essential requirements:**

Preformulation involves the study about physical & chemical properties of drug substance prior formulation. These studies are performed under stressed conditions of temperature, humidity; light and oxygen so that the reactions are accelerated and potential reaction are detected. A few physicochemical properties that affect a drug substance are discussed below.

- **Melting point:** It is the Temperature at which the solid and liquid phases are in equilibrium. Its determination is a primary indication of purity.
- **Solubility**: This property is essential for developing solution to be injected either intraveneously or intramuscularly. It is a function of chemical structure: salts of acid or bases are the drugs that can achieve the desired degree of water solubility.
- **Molecular structure and weight**: These are the basic characteristics of the drug from which the potential properties and reactivities of functional groups can be determined.
- **Particle Size and Shape**: Study of particle size give information about Solubility, dissolution rate and absorption etc.These charcterstics are determined by Scanning electron microscope or an optical microscope with polarizing attachments.
- **Ionisation constant**: This property is used to determine the $P^H$-dependent solubility of a compound.Potentiometric PH titration or PH-solubility analysis is used for determining the $P^{Ka}$ value.Ionisation constant of a compound also helps in determining the degree of ionization of an acid or base. Degree of ionization depends upon the $P^H$.
  For acidic drugs $P^{Ka}$ ranges from 3-7.5 and for basic drugs $P^{Ka}$ ranges from 7- 11.
- **Partition Coefficient (P);** It is a ratio of equilibrium concentration of drug in aqueous and oily phases in contact with each other at a constant temperature. Partition coefficient can be expressed as : $P = [C_{oil} / C_{water}]$,where, $C_{oil}$= organic phase concentration and $C_{water}$ = aqueous phase concentration.

- **Hygroscopicity:** The tendency of a solid to take up water from atmosphere, as it is subjected to a controlled RH programe under isothermal condition. A high degree of hygroscopicity can adversely affect the physical and chemical properties of a drug substance.

**Essential requirements for Formulation:** The formulations of parenteral preparations need careful planning, thorough knowledge of medicaments and additives to be used. The excess use of additives in parenteral products should be avoided as some of these may interfere with the drug. In the preparation of parental products, the following substances are added to make a stable preparation.

1. Vehicles
2. Additives

a) Solubilizing agents b) Stabilizers c)Buffering agents d) Antibacterial agents e) Chelating agents f)Suspending ,emulsifying and wetting agents g)Tonicity factors

1. **Vehicles:**

There are two types of vehicles, which are commonly used for the preparation of injections

**A) Aqueous vehicle** - water is used as vehicle for majority of injections because water is tolerated well by the body and is safest to administer .The aqueous vehicle used are ;-

1) Water for injections.
2) Water for injection free from CO2 (carbon dioxide)
3) Water for injection free from dissolved air, water for injection is sterile water, which is free from volatile, non- volatile impurities and from pyrogens.

Pyrogens are by-product of bacterial metabolism. pyrogens are Lyposaccharide, thermostable, soluble in water ,unaffected by bactericide and can pass through bacterial proof filters. pyrogens can be removed from water by simple distillation process using an efficient trap which prevents the pyrogen to enter into the condenser .immediately after the preparation of water for injection ,it is filled in to the final container, sealed and sterilized by autoclaving .

Water for injection, contaminated with pyrogens may cause rise in body temperature if injected .Hence, test for pyrogen is done to ensure that water for injection is free from pyrogens.

**B) Non -aqueous vehicles**:-The commonly used non-aqueous vehicles are oils and alcohols.

Fixed oil, such as arachis oil,cottonseed oil ,almond oil and sesame oil are used as vehicle .the oily vehicles are generally used when a depot effect of drug is required or the medicaments are insoluble or slightly soluble in water or the drug is soluble in oil example dimercaprol injection by using arachis oil as vehicle.

Ethyl alcohol is used in the preparation of hydrocortisone injection .hydrocortisone is insoluble in water, hence the solution is made in 50% alcohol .Alcohol causes pain and tissue damage at the site of injection. Therefore, it is not used commonly.

Propylene glycol is used as a vehicle in the preparation of digoxin injection .it is relatively non-toxic but it causes pain on S/C or I/M injection.

Sometime polyethylene glycol and glycerine usually diluted with sterile water are used to prepare solutions for injections .they are used as solvent as well as to increase the stability of certain preparations.

**2. <u>Additives:</u>**

These substances are added to increase the stability or quality of the product .These additives should be used only when it is necessary to use them. While selecting the additives, care must be taken that they should be compatible both physical and chemical with the entire formulation, .They should be added in minimum possible quantity .The following additives are commonly used in preparing stable parental preparations.

**a) Solubilising agents:-** These are used to increase the solubility of drugs which are slightly soluble in water .the solubility of drug is increased by using surface active agent like tweens and polysorbate or by using co solvents.

**b) Stabilizers:-** The drugs in the form of solution are more liable to deteriorate due to oxidation and hydrolysis .The stabilizers are added in the formulation to prevent this .the oxidation can be prevented by adding a suitable antioxidant such as, thiourea,ascorbic acid ,sodium metabisulphite ,or the product is sealed in an atmosphere of Nitrogen or Carbon dioxide. hydrolysis can be prevented by using a non-aqueous vehicle or by adjusting the pH of the preparation.

**Antioxidants:**

**Water soluble:** Sulfurous acid salts, Ascorbic acid isomers, Thiol derivatives

**Oil soluble;** Propyl gallate ,Butylated hydroxyanisole ,Ascorbyl palmitate, alpha Tocopherol

**c) Buffering agents:** -The degradation of the preparation, which is due to change in pH, can be prevented by adding a suitable buffer to maintain the desired $P^H$ .

| pH | Buffer system | Concentration (%) |
|---|---|---|
| 3.5-5.7 | Acetic acid-acetate | 1-2 |
| 2.5-6.0 | Citric acid- citrate | 1-5 |
| 6.0-8.2 | Phosphoric acid- phosphate | 0.8-2 |
| 8.2-10.2 | Glutamic acid- glutamate | 1-2 |

**d) Antibacterial agents**:- These substance are added in adequate quantity to prevent the growth of microorganism during storage. so these substances act as preservatives .antibacterial agents are added in single dose containers, where parenteral products are sterilized by filtration method and in multi dose containers to prevent microbial contamination .

Some typical preservative used in parenteral suspensions and their commonly used concentrations are as follows.-

Benzyl alcohol (0.9% to 1.5%)

Methylparaben (0.18% to 0.2%)

Propylparaben (0.02%)

Benzalkonium chloride (0.01% to 0.02%)

Thiomersal (0.001% to 0.01%)

f) **Chelating agent: -** Chelating agents such as EDTA (Ethylene diamine Tetra acetic acid) and its salts, sodium or pottasium salts of citric acid are added in the formulation,to chelate the metallic ions present in the formulation. They form a Complex which gets dissolved in the solvent.

| S. No. | Additives | Concentration range (%) |
|---|---|---|
| 1 | EDTA disodium | 0.00368-0.05 |
| 2 | EDTA calcium disodium | 0.04 |
| 3 | EDTAtetrasodium | 0.01 |

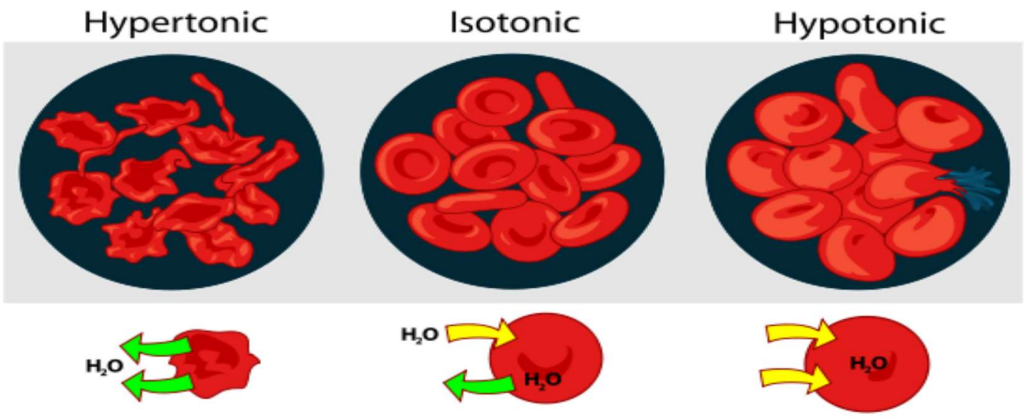
g) **Suspending, emulsifying and wetting agents:-** The suspending agents are used to improve the viscosity and to suspend the particles for a long time. Methyl cellulose, carboxy-methyl cellulose, gelatin and acacia are commonly used as suspending agents .Emulsifying agents are used in sterile emulsions .for this purpose lecithin is generally used .The wetting agents are used to reduce the interfacial tension between the solid particles and the liquid, so as to prevent the formulation of lumps. They also act as antifoaming agents to subside the foam produced during shaking of the preparation.

| **Additives** | **Concentration range (%)** |
|---|---|
| Polyethylene glycol 300 | 0.01-50.0 |
| Polysorbate 20 | 0.01 |
| Polysorbate 40 | 0.05 |
| Polysorbate 80 | 0.04-4.0 |
| Povidone | 0.2-1.0 |
| Propylene glycol | 0.2-50.0 |
| Sorbitan monopalminate | 0.05 |
| Dimethylacetamide | 0.01 |
| Lecithin | 0.5-2.3 |

h) **Tonicity factors:** - Parenteral preparation should be isotonic with blood plasma or other body fluids. The isotonicity of the solution may be adjusted by adding sodium chloride, dextrose and boric acid etc. in suitable quantities. These substances should be compatible with other ingredients of the formulation. Examples of Tonicity adjuster/modifier are Glycerin, lactose, mannitol, dextrose, NaCl, sodium sulfate and sorbitol

**Importance of Isotonicity:**

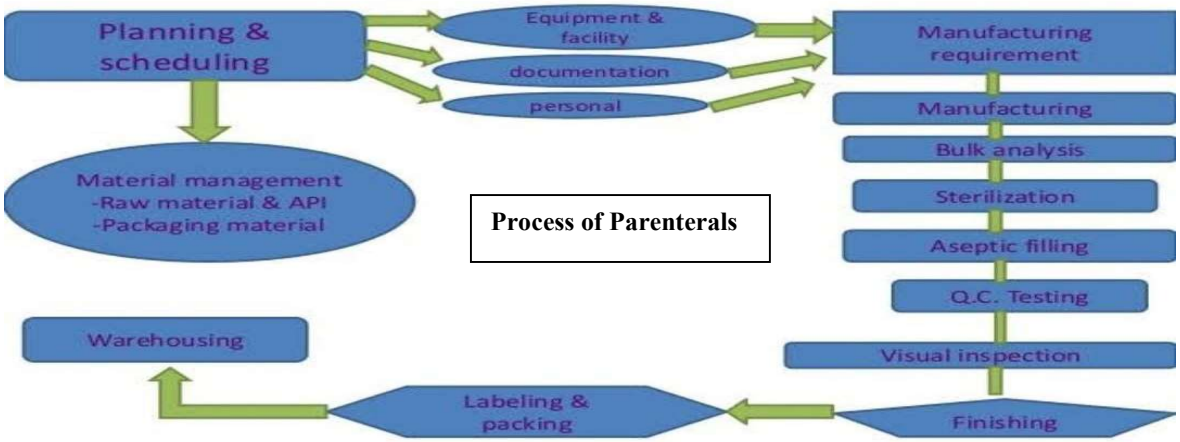
An isotonic solution is one that exhibits the same effective osmotic pressure as blood serum.Isotonicity is important for parenteral preparation because if the solution is isotonic with blood, the possibility of product penetrating the RBC and causing haemolysis is reduced. For hypertonic solution crenation and for hypotonic solution haemolysis will occur.




**Crenation** **Hemolysis**

**2. Production procedure - Aseptic processing:**

- The parenteral drug manufacturing (Drug Product Manufacturing) process includes compounding, mixing, filtration, filling, terminal sterilization, lyophilization, closing, and sealing, sorting, and inspection, labeling, and final packaging for distribution.
- The manufacturing process is complicated; requiring organization and control to ensure the product meets the quality and the specifications as shown in.
- Aseptic processing requirement adds more complication but assures that all dosage forms manufactured are free from any contamination of microbial, endotoxin, and visible particulate matter.
- The manufacturing process initiates with the procurement of approved raw materials (drug, excipients, vehicles, etc.) and primary packaging materials (containers, closures, etc.) and ends with the sterile product sealed in its dispensing package.




The manufacturing of parenterals involves the following steps;

1) Cleaning and washing of containers and closures
2) Preparation of solutions
3) Sterilization
4) Filling and sealing
5) Evaluation of parenterals
6) Packaging and labeling

1. **Cleaning of containers and closures:** - all the containers, closures and equipments which are required during the preparation of parental products are thoroughly cleaned with detergent and washing is done with tap water , followed by clean distilled water and finally rinsed with water for injection. Rubber closures are washed with hot solution of 0.5 % sodium pyrophosphate in water. The closures are then removed from the solution, washed with water followed by rinsing with filtered water for injection .on a small scale washing is done manually but on a large scale automatic washing machines are used.
2. **Preparation of Solution:-** The various ingredients of the formulation of parental preparations are weighed and collected in the preparation room. the raw materials required in the preparation of parenteral products should be pure. water for injection free from pyrogens and microorganisms are used in preparation of parenteral products. The Industrial pharmacist should decide the order of mixing and exact method of preparation to be followed before preparing the parenteral products . The parenteral preparation must be prepared under strict aseptic conditions . The ingredients are accurately weighed separately and dissolved in the vehicle as per method of preparation to be followed. The parenteral Solutions so formed is passed through bacteria proof filter ,such as ,filter candle, seitz filter, membrane filter, and sintered glass filters. the primary objective of filtration is to clarify the solution by removing foreign particles .if the parenteral preparations are required to be sterilized by means of bacteria proof filters, filtration should be done under strict aceptic condition to avoid contamination of filtered solution, before it is finally transferred into final container and sealed
3. **Sterilization**:-The parental preparations should be immediately sterilized after sealing in its final containers. The sterilization is done by any one of the methods of sterilization, which depends on the nature of Medicaments present in the parenteral preparations.

   For thermostable medicament ,the parenteral product are sterilised either by autoclaving at the temperature of 115°C to 116°C for 30 minutes or 121 degree centigrade for 20 minutes or in hot air oven at 160 degree centigrade for 2 hours. the thermolabile preparations are sterilized by filtration through a suitable bacteria proof filters. parenteral preparations which are sterilised by filtration method may contain a suitable bacteriostatic agent to prevent the growth of microorganisms .When the solutions are used for intravenous or intrathecal injection in doses exceeding 15 ml ,the bacteriostatic agent should not be used. The sterilised product is filled into the final containers and sealed .the process of filtration, filling and sealing are done under aseptic conditions.

4. **Filling and Sealing:-** The filtered product is filled into final container such as, ampoules, vials and transfusion bottles, which are previously cleaned and dried. ampoules are used for feeling single dose whereas , vials are used for filling multidoses .bottles are meant for filling transfusion fluids . On small scale feeling is done manually by using hypodermic syringe and needle .on the large scale feeling is done by automatic filling machine.The sterile Powders are filled into containers by individual weighing or by using automatic or semi automatic devices. The filling operation is carried out under strict aseptic precautions. During the filling of ampoules, the care should be taken that the solution should be filled below the neck of ampoules and the solution should not touch the neck of ampoules. this will prevent the cracking and stanining of the neck of ampoules at the time of Sealing. Sealing should be done immediately after filling .Ampoules are sealed manually on a small scale by rotating the neck of the ampoule in the flame of Bunsen burner but on a large scale ampoule sealing machine is used in which tip of ampoule is used to fused to seal it . The vials and transfusion bottles are sealed by closing its opening with rubber closures .The rubber closures are held in place by crimping the aluminium caps which is done manually or by mechanical means.

5. **Evaluation of Parenterals:-** The finished parenteral products are subjected to the following test ,in order to maintain quality control.

   a) Sterility test b) clarity test c) Leakage test d)Pyrogen test.

6. **Packaging and labeling:-** After evaluation of the parenteral preparation,the ampoules ,vials and transfusion bottles are properly labelled and packed. The label should state as :-

   a) Name of the preparation
   b) Quantity of the preparation
   c) Mfg.Lic .no.
   d) Batch no.
   e) Date of manufacture
   f) Date of expiry
   g) Storage condition
   h) Retail price
   i) Manufacturer's address

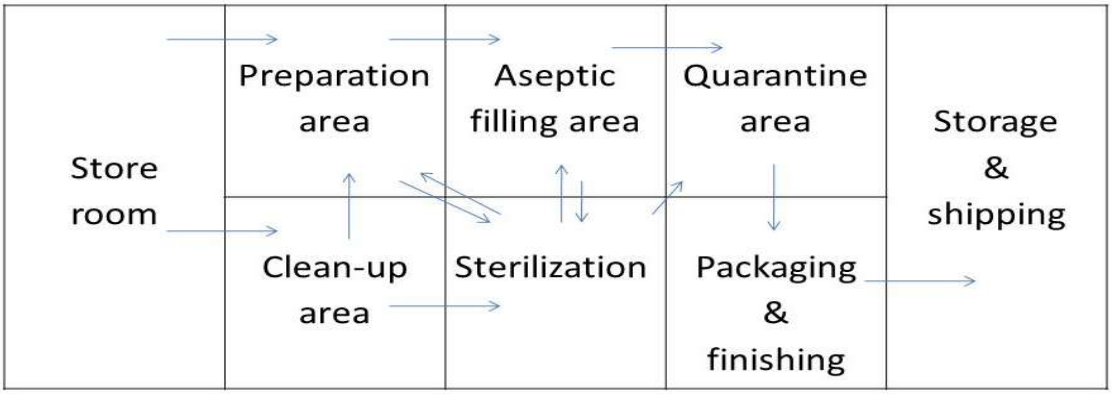
**Production facilities and controls:**

The production area where the parenteral preparations are manufactured can be divided into the following five sections.

1) Clean-up area
2) Preparation area
3) Aseptic area
4) Quarantine area
5) Finishing & packaging area

1. **Clean-up area:**
    - It is not aseptic area.
    - All the parenteral products must be free from foreign particles & microorganism.
    - Clean-up area should be withstand moisture, dust & detergent.
    - This area should be kept clean so that contaminants may not be carried out into aseptic area.

2. **Preparation area:**
    - In this area the ingredients of the parenteral preparation are mixed & preparation is made for filling operation.
    - It is not essentially aseptic area but strict precautions are required to prevent any contamination from outside.




3. **Aseptic area:**
    - The parenteral preparations are filtered, filled into final container & sealed in aseptic area.
    - The entry of personnel into aseptic area should be limited & through an air lock.
    - Ceiling, wall & floor of that area should be sealed & painted.
    - The air in the aseptic area should be free from fibers, dust and microorganism.
    - The High efficiency particulate air filters (HEPA) is used for air.
    - UV lamps are fitted in order to maintain sterility.

4. **Quarantine area:**
    - After filling, sealing & sterilization the parenteral product are held up in quarantine area.
    - Randomly samples were kept for evaluation.
    - The batch or product pass the evaluation tests are transfer in to finishing or packaging area.

5. **Finishing & packaging area:**
    - Parenteral products are properly labelled and packed.
    - Properly packing is essential to provide protection against physical damage.
    - The labelled container should be packed in cardboard or plastic container.
    - Ampoules should be packed in partitioned boxes

**Controlled environment required for parenteral preparation**:

Clean Room Classified Areas: Due to the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specifications for the environments (clean rooms) in which these products are manufactured. The Critical and General area of clean room: The clean room divides into

1. Critical Area
2. General Area.

The critical area is the area around the point of the production where contamination can gain direct access to the process. This area often protected by localized laminar flow clean benches and workstations. The General area is the rest of the clean room where contamination will not gain direct entry into the product but should be kept clean because of the transfer of contamination into the critical area. It is necessary that the critical area be cleaned most often with the best cleaning ability without introducing contamination.

**Classification of Clean Rooms**:-

The class is directly related to the number of particles per cubic foot of air equal to or greater than 0.5 micron.

1. Class 100,000: Particle count not to exceed a total of 100,000 particles per cubic foot of a size 0.5µ and larger or 700 particles per foot of size 5.0µ and larger.
2. Class 10,000: Particle count not to exceed a total or 10,000 particles per cubic foot of a size 0.5µ and larger or 65-70 particles per cubic foot of a size 5.0µ and larger.
3. Class 1,000: Particles count not to exceed a total of 1000 particles per cubic foot of a size 0.5µ and larger or 10 particles per cubic foot of a size 5.0µ and larger.
4. Class 100: Particles count not to exceed a total of 100 particles per cubic foot of a size 0.5µ and larger.

Class1: The particle count shall not exceed 3000 particles/m3 of a size 0.5µ.

Class 2: The particle count shall not exceed a total of 3000 particles/m3of a size of 0.5µ or greater; 2000 particles/m3of size 0.5µ or greater; 30 particles of a size 10µ.

Class 3: The particle count shall not exceed a total of 1,000,000 particles of a size of 1µ or greater; 20,000 particles/m3of size 5µ or greater; 4000 particles/m3of a size 10µ or greater; 300 particles of a size of 25µ or greater.

Class 4: The particle count shall not exceed a total of 200,000 particles of a size of 5µ or greater.

For the manufacture of sterile medicinal products normally 4 grades can be distinguished:

GRADE — 'A': The local zone for high risk operations. eg. filling zone, stopper bowls, open ampules and vials. GRADE — 'B': In case of aseptic preparation and filling, the back ground environment for grade — 'A' zone. GRADE — 'C' & 'D': Clean areas for carrying out less critical stages in the manufacture of sterile products.

**Aseptic processing:-**

The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which, whenever possible products intended to be sterile should be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal

sterilization by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g. plastic eye-dropper bottles), a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing. Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilization), by ethylene oxide (or other suitable gaseous sterilizing agents), or by filtration with subsequent aseptic filling of sterile final containers. In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to: the environment, personnel, critical surfaces, container/closure sterilization and transfer procedures, the maximum holding period of the product before filling into the final container and the sterilizing filter. Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 micron (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment. Filtration alone is not considered sufficient when sterilization in the final container is possible. Of the methods currently available, steam sterilization is preferred.

**3. Formulation of injections (Solution and suspension):-**

**Solutions:**

A range of excipients may be included in parenteral solutions, including antioxidants, antimicrobial agents, buffers, chelating agents, inert gases, and substances for adjusting tonicity. Antioxidants maintain product stability by being preferentially oxidized over the shelf life of the product.

Antimicrobial preservatives inhibit the growth of any microbes that are accidentally introduced while doses are being withdrawn from multiple-dose bottles and act as adjuncts in aseptic processing of products.

It is Prepared by dissolving the drug and preservative, adjusting the pH and sterile- filtering the resultant solution through a 0.22 μm membranes filter. Drug solutions that resist heat are terminally autoclave sterilized after filling; this assures product sterility and package.

**Suspension**

A **suspension** for injection consists of insoluble solid particles dispersed in a liquid medium, with the solid particles accounting for0.5-30% of the suspension. The vehicle may be aqueous, oil, or both.

- Caking of injectable suspensions is minimized through the production of flocculated systems, comprising clusters of particles (flocs) held together in a loose open structure.
- Excipients in injectable suspensions include antimicrobial preservatives, surfactants, dispersing or suspending agents, and buffers.
- Surfactants wet the suspended powders and provide acceptable syringeability while suspending agents modify the viscosity of the formulation.

**General steps in manufacturing:**

- Sterilization and milling of active ingredient (s).
- Sterilization of vehicle.
- Aseptic wetting and dispersion of the active ingredient (s).
- Aseptic milling of the bulk suspension.
- Aseptic filling of the bulk suspension in suitable containers

**Formulation of sterile powders:-**

Due to instability in water, many drugs are formulated as drug powders to be reconstituted prior to administration. eg.Penicillins, barbiturates, benzocain. Sterile water for injection is supplied with dry powders to make "solutions / or suspensions for injections". The obtained solution / suspension will meet with all the requirements of solution /suspension for parenteral. IV or IM route can give reconstituted solutions, however suspension is forbidden for IV administration.

Sterile powers are prepared by following methods.

1. Sterile recrystallization:
2. Lyophilization:
3. Spray drying

1. **Sterile Re-crystallization**: The drug is dissolved in a solvent and the obtained solution is sterilized through 0.22 μm membrane filter. A sterile anti-solvent is then added to crystalize the drug particles, which is filtered and dried aseptically.

   *Advantages:*

   This method is Flexible and economic.

   *Disadvantage:*

   This method represents variations from batch to batch and contamination.

2. **Lyophilization:** In this method, a solid substance is separated from solution by freezing the solvent and evaporating the ice under vacuum. The obtained drug solution is sterile filtered into sterile trays, which are aseptically loaded into a freeze dryer. The solution is then frozen at -50°C and then dried by vacuum to separate the drug powder.

   Advantage:

   This method involves removal of water at low temperatures.

   Disadvantage:

   i) In this method, the biological molecules are damaged by the stress associated with freezing, and drying.
   ii) This method is expensive and time consuming

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

Advantage:

i) This method is Simple, Economical, scalable and faster.
ii) This method involves Coating of particles during drying prolonged release.

Disadvantage:

i) In this method, the high processing temperatures and high shear forces can easily damage drugs.
ii) In this method, higher levels of drugs are lost in comparison to freeze-drying.
iii) This method has a limited solvent choice for a given drug.
iv) In this method, product cannot be prepared directly in vials or plates.

**Formulation of large volume parenterals: -**

Large volume injections are intended to be administered by IV Infusion Fluids & are included in the group of sterile products & are known as large volume Parenterals. These consist of single dose injecting a volume of 100 ml or more than 100 ml sometimes additional drugs are added to them by either injecting svp to the administration sets or by piggyback method(small volume infusion of an additional drug is added to the intravenous delivery system).large volume parenteral products include:

1) Infusion fluid(Basic nutrition -Dextrose inj, Fluid replacement therapy-Normal saline)
2) Total parenteral Nutrition solution(TPN)
3) Intravenous antibiotics
4) Dialysis fluid
5) Irrigation solutions

Large volume parenterals should be terminally heat sterilized. Apart from water for injection as the main component, other ingredients that should be included are carbohydrates (e.g. dextrose, sucrose and dextran), amino acids, lipid emulsion, electrolytes (Nacl) and glycerol, sorbitol and mannitol.The LVP are mostly clear solutions, except for the oil- in –water emulsions. The emulsions for infusion are produced by highly specialized method as they are destabilized by heat. This result in many difficulties during production, thus the size of oil droplets should be controlled during heat sterilization.

**Production of LVP**:

i) The manufacturing and filling of LVP fluids into containers are carried out in a a high standard clean room environment. High standards are required to prevent these products from getting contaminated with organisms, pyrogens and particulate matter.
ii) The fluids from a bulk container are filled into the product container using high speed filling machine. Before filling the fluid into the container, it is passed through an in-line membrane filter to remove the particulate matter.
iii) After filling, the neck of each glass bottle is immediately sealed with a tight fitting rubber closure held in place with a crimped aluminum cap.
iv) In case plastic bags are used, the pre-formed plastic bags are aseptically filled and heat-sealed immediately.
v) Blow –fill-seal system are adopted to minimizes the problems with product handling, cleaning and particulate contamination.

vi) The LVP products, including irrigation solution and dialysis fluids should be moist heat sterilized immediately after the containers are filled.

**Lyophilization or freeze-drying:-**

Lyophilization or freeze drying is a process in which water is removed from a product after it isfrozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. The process consists of three separate, unique, and interdependent processes like; Freezing, Primary drying (sublimation), and Secondary drying (desorption).

Advantages of Lyophilization

- Ease of processing a liquid, which simplifies aseptic handling.
- Enhanced stability of a dry powder.
- Removal of water without excessive heating of the product.
- Enhanced product stability in a dry state.
- Rapid and easy dissolution of reconstituted product

Disadvantages

- Increased handling and processing time.
- Need for sterile diluent upon reconstitution.
- Cost and complexity of equipment

**Steps involved in formulation of Lyophilized products:-**

- Dissolving the drug and excipients in a suitable solvent, generally water for injection (WFI).
- Sterilizing the bulk solution by passing it through a 0.22-micron bacteria-retentive filter.
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions.
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions.
- Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or pre-freezing in another chamber.
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state.
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers. There are many new parenteral products, including anti-infectives, biotechnology derived products, and in-vitro diagnostics which are manufactured as lyophilized products.

- Additionally, inspections have disclosed potency, sterility and stability problems associated with the manufacture and control of lyophilized products

**4. Selection of containers and closures:**

Selection of Containers & Closures should be such that it should ensure that the products must remain its purity, potency & quality during intimate contact with the container throughout its shelf life.

**Glass:-**

Glass is employed as the container material of choice for most SVIs. It is composed, principally, of silicon dioxide, with varying amounts of other oxides, such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron. Glass is preferred for clarity reasons

**Types:-**

The USP provides a classification of glass:

- Type I, a borosilicate glass;
- Type II, a soda-lime treated glass;
- Type III, a soda-lime glass; and
- NP, a soda-lime glass not suitable for containers for parenteral.

**Type I glass** will be suitable for all products, although sulfur dioxide treatment is sometimes used for even greater resistance to glass leach-ables. Because cost must be considered, one of the other, less expensive types may be acceptable.

**Type II glass** may be suitable, for example, for a solution that is buffered, has a pH below 7, or is not reactive with the glass.

**Type III glass** is usually suitable for anhydrous liquids or dry substances.

Types II and III glass compounds are composed of relatively high proportions of sodium oxide (~14%) and calcium oxide (~8%). This makes the glass chemically less resistant. Both types melt at a lower temperature, are easier to mold into various shapes.

Type II glass has a lower concentration of the migratory oxides than Type III. In addition, Type II has been treated under controlled temperature and humidity conditions, with sulfur dioxide or other de alkalizers to neutralize the interior surface of the container.

The glass types are determined from the results of two USP tests:

The Powdered Glass Test

The Water Attack Test.

The Powdered Glass Test challenges the leaching potential of the interior structure of the glass, whereas the Water Attack Test challenges only the intact surface of the container.

Selecting the appropriate glass composition is a critical facet of determining the overall specifications for each parenteral formulation. Glass can be the source / cause of leach-ables / extractable, particulates (glass deamination or glass lamellae formation), adsorption of formulation components, especially proteins, and cracks / scratches.

**Plastic:-**

Plastic packaging has always been important for ophthalmic drug dosage forms and is gaining in popularity for injectable dosage forms. Plastic bottles for large volume injectable (LVIs) have been used for many years. Plastic vials for SVIs may be a wave of the future plastic packing offers such advantages of cost savings elimination of the problems caused by breakage of glass and increase convenience of use. Plastics are light weight, less fragile & easy to handle but not clear as that of glass.

**Rubber:-**

Rubber formulations are used as rubber closures, rubber plungers and other applications. The most common rubber polymers used in SVIs closures are natural and butyl rubber. Silicone and neoprene also are used but less frequently in sterile products. Butyl rubber has great advantages over natural rubber in that butyl rubber requires fewer additives, has low water vapor permeation properties and has good characteristics with respect to gaseous permeation reactivity with the active ingredient.

Rubber permits the entry of hypodermic needle into injection vials & also provide resealing of the vial after needle is withdrawn.

**Filling and Sealing of Ampoules:-**

Ampoules are thin-walled glass containers, which after filling, are sealed by either tip sealing or pull sealing. The contents are withdrawn after rupture of the glass, or a single occasion only. These are great packaging for a variety of drugs. The filed – in product is in contact with glass only and the packaging is 100% tamper proof. The break system OPC(one –point cut) or the color break ring offer consistent breaking force. There are wide variety of ampoule types from 0.5 to 50ml volume.

- Here, the measured amounts of liquid deliver from the small orifice into the ampoule by filling machine.
- The size of the delivery tube is governed by opening in the container to be used, the viscosity and density of the liquid and the speed of delivery desired.
- The tube must free enter the neck of the container and deliver the liquid deep enough to permit air to escape without sweeping the entering liquid into the neck or out of the container.
- Filling machine parts should be constructed of non-reactive materials such as borosilicate glass or stainless steel.
- The solutions are usually filled in the bottle by gravity, pressure or vacuum filling device.
- Emulsion and suspension required specially designed filling equipment because of their high viscosity.
- Powders such as antibiotics, are more difficult to subdivide accurately and precisely into Individual dose containers than are liquid.
- Container should be sealed in the aseptic area in immediately adjacent to the filling machine.
- It is obvious that a sterile container that has been opened can no longer be considered to

be sterile. Therefore, temperature proof sealing is essential.

- Ampoules may be closed by melting a portion of the glass of neck to either form tip-seals or pull seals.
- **Tip-seals** are made by melting sufficient glass at the tip of the ampoule neck to form a bead of glass and close the opening. This is performed in a high temperature gas oxygen flame.
- **Pull-seals** are made by heating the neck of a rotating ampoule below the tip, then pulling the tip away to form a small, twisted capillary just prior to being melted closed. Pull sealing process is slower one, but the sealing done by this is more secure than that of tip sealing.
- Excessive heating of air and gasses in the neck causes expansion against the soft glass with the formation of fragile bubbles at the point of seal.

**Filling and Sealing of Vials and Infusion bottle:-**

The solutions, which sterilized through filtration, are to be filled under the aseptic conditions. During the filling of product to the containers, should be for the prevention of contamination, especially the product is sterilized by the filtration and will not be sterilized in to the final container. The second one is called as aseptic fill. A liquid is more easily exposed uniformly into the container having the narrow mouth than is used for solid. Liquids which are mobile are easier to transfer and subdivide than viscous or sticky fluids, since these require heavy-duty machinery for the rapid production filling. The filling of liquids into containers with high accuracy involves the following methods

i) Volumetric filling

ii) Time/pressure filling

Volumetric filling machines have pistons or peristaltic pumps. These are most common used method. Time-pressure filling is used for filling of sterile liquids. A filling system is connected by a production tank that equipped with a pressure sensor. The sensor is used for the measurement of pressure and transmits values PLC system that controls the product flow from the tank to the filling manifold. The product is driven by using pressure mainly uses nitrogen with no pump mechanism.

By closing the opening using the rubber closure (stopper) the glass or the plastic vials are sealed properly. This should be done by after filling with care, to prevent the contamination of the contents inside. Increased chances for contamination are the large opening in the vials than the ampoules. The open containers must be protected from contamination, especially with the blanket of HEPA filtered laminar airflow. By using the aluminum caps the rubber stoppers are held in appropriate place. Rubber closures that uses for the intravenous administration have a permanent hole through the closure. A 500ml of infusion bottle is considered suitable for preparation of parenteral solutions. It is assumed that the bottle has been stored with a double cap protecting the mouth. The outer cap is discarded and the inner cap is removed. After ensuring that the bottle neck is not chipped, the solution is poured in and immediately the inner cap is replaced.

**Quality Control Tests of Parenteral Products:-**

The following are the evaluation test for the parenteral. They are as follows.

1. Sterility test
2. Clarity test
3. Leakers test
4. Pyrogen test

**1. Sterility test:** It is a method carried out to detect confirm absence of any viable form of microbes in product. The method used for sterility tests are

a. Direct transfer method

b. Membrane filtration method.

**a. Direct transfer method**: Open each sample container and with draw the require amount of the sample. Inject one-half of sample in a test tube containing fluid Thioglycolate Medium (FTM). Inject another half in the test tube containing Soyabean-casein digest Medium(SCM). Volume of the medium must be sufficient to promote and expedite microbial growth. Adequate mixing between the sample inoculums and the culture medium must take place to maximize interaction and facilitate microbial growth. If the product to be tested contains any anti-microbial agent, using suitable reagent it should be neutralized before the test.

**b**. **Membrane filtration method (MF):** This method is employed in the following cases:

1. Oil & oily preparations
2. Alcoholic preparations
3. For preparations miscible with or soluble in aqueous or oily solvents.

The steps involved in MF sterility test method are

i). The filter unit must be properly assembled and sterilized prior to use.

Ii). The contents are transferred to the filter assembly under strict aseptic conditions.

iii) The membrane is removed aseptically.

iv). Membrane is cut in half.

iv) One half is place in suitable volume of FTM and another in an equal volume of SCM.

**Interpretation of results:**

i). If there is no visible evidence of microbial growth, it may be interpreted that the sample is without intrinsic contamination and the product complies the test for sterility.

ii). If microbial growth is found, the product does not complies the test for sterility and the sterility test may be repeated.

**2. Clarity test (particulate matter evaluation):-**

Particulate matter in parenteral solutions has been recognized as an acceptable. Since the user could be expected to conclude that the presence of visible dirt would suggest that, the product is of inferior quality.

a). ***In visual method***, the entire product should be inspected by human inspectors under good light baffled against reflection into the eye and against black and white background. Dark background detects light particles and light background detects dark particles. Any container with visible particle if seen is discarded.

b). ***In Coulter counter method***; the principle is based on that there will be an increase in the resistance as a particle approaches and passes through the orifice (2 electrodes).

c). This method require destruction of the product unit since an electrolyte is added to the preparation before its evaluation.

d). Some other methods of clarity testing can be listed as Filtration method, Light scattering method, Light absorption, Light blockage methods, etc...

e). Once the particles are detected, then they are identified by various methods like microscopy,X-ray powder diffraction, mass microscopy, micro-chemical tests, polarized light microscopy and scanning electron microscopy.

**3. Leakers test:-**

Leaker test for ampoules is intended to detect incompletely sealed ampoules so that they can be discarded in order to maintain sterile condition of the medicines. Open capillaries or cracks at the point of seal result in LEAKERS.

- The leaker test is performed by immersing the ampoules in a dye solution, such as 1% methylene blue, and applying at least 25 inches of vaccum for a minimum of 15 mins.
- Detection of leaker is prominent when ampoules are immersed in a bath of dye during autoclaving as this has advantage of acomplishing both leaker detection and sterilization in one operation.
- Another means of testing for leakers is a high frequency spark test system, which detect presence of pinholes in ampoules.
- Bottles and vials are not subjected to such a vaccum test because of the flexibility of the rubber closure.

**4. Pyrogen test:-**

Pyrogens are the metabolic products of microbes. Most bacteria, moulds and viruses produce Pyrogen. Most potent pyrogenic substance called endotoxins are produced by gram negative bacteria .Pyrogens when injected into a human, shows marked rise in the temperature , chills, body aches, cutaneous vasoconstriction and increased arterial blood pressure. The most likely source of pyrogens are water, contaminated solutes and containers.

- The test involves measurement of the rise in body temperature of rabbits following the IV injection of a sterile solution into ear vein of rabbit.
- Dose not exceeding 10 ml per kg injected intravenously within a period of not more than 10 mins.
- Selection of animals - healthy, adult, not less than 1.5kg.
- Equipment and material used in test - glassware, syringes, needles.
- Retaining boxes - comfortable for rabbits as possible.
- Thermometers - standardized position in rectum, precision of 0.1°C.

**Preliminary Test (Sham Test):**

If animals are used for the first time in a pyrogen test or have not been used during the 2 previous weeks, condition them 1 to 3 days before testing the substance by injecting IV 10ml per kg

pyrogen free saline solution warmed to about 38.5°c. Record the temperature of the animals, beginning at least 90 mins before injection and continuing for 3 hours after injection. Any animal showing a temperature variation of 0.6° or more must not be used in main test.

**Main Test:**

The main test is carried out by using a group of 3 Rabbits. Dissolve the substance in,or dilute with, pyrogen free saline solution. Warm the liquid to approximately 38.5° before injection.Inject the solution under examination slowly into the marginal veins of the ear of each rabbit over a period not exceeding 4 mins. Record the temperature of each animal at half hourly intervals for 3 hours after injection. The difference between the initial temperature and the maximum temperature which is the highest temperature recorded for a rabbit is taken to be its response.

**Interpretation of Result:**

a). The test is carried out on the first group of 3 rabbits; if necessary on further groups of 3 rabbits to a total of 4 groups, depending on the results obtained.

b). Intervals of passing or failing of products are on the basis of summed temperature response. If the difference is negative, the result is counted as zero response.

| **No. of Rabbits** | **Individual Temp. Rise($^{o}$C)** | **Temp. Rise in group ($^{o}$C)** | **Test** |
|---|---|---|---|
| 3 Rabbits | 0.6 | 1.4 | Passes |
| (If above not Passes)-: 3+5=8 Rabbits | 0.6 | 3.7 | Passes |
| If above Test not passes,the sample is said to Pyrogenic. | | | |

**Bacterial Endotoxin Test (BET) or Limulus Amoebocyte Lysate Test (LAL Test):-**

The bacterial endotoxin test (BET) is a test to detect or quantify endotoxins from gram negative bacteria using Amoebocyte lysate from the horse shoe crab (Limulus polyphemus or Tachypleustridentatus) .

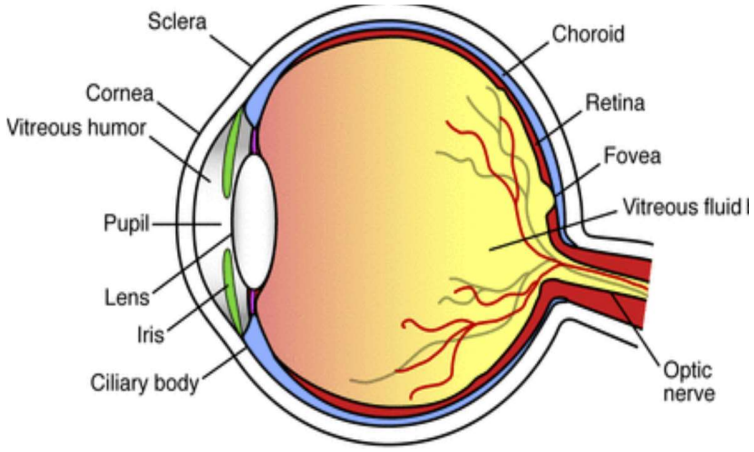
The endotoxins of gram-negative bacteria forms a firm gel within 60 mins in the presence of lysate of amebocytes of limulus polyphemus of horseshoe crab, when incubated at 37◦c. Hence, the test is only effective with gram-negative bacteria, which constitute the majority and the most potent of the pyrogens. The addition of a solution containing endotoxins to a solution of a lysate produces turbidity, precipitation or gelation of the mixture.

## Ophthalmic Preparations:-

**Introduction**;

Ophthalmic preparations (eye preparations) are sterile, liquid, semisolid, or solid preparations that may contain one or more active pharmaceutical ingredient(s) intended for application to the conjunctiva, the conjunctival sac or the eyelids. The choice of base and any excipients used for the preparation of ophthalmic preparations must be proven through product development studies not to affect adversely either the stability of the final product or the availability of the active ingredients at the site of action. The most commonly employed ophthalmic dosage forms are solutions, suspensions, and ointments. But these preparations when instilled into the eye are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage.

Eye is the most easily accessible site for topical administration of a medication. Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period. The newest dosage forms for ophthalmic drug delivery are: gels, gel-forming solutions, ocular inserts, intravitreal injections and implants**.**




Anatomy of the human eye.

## Formulation considerations:-

a) **Tonicity and Tonicity-Adjusting Agents:** The tonicity of aopthalmic solution should be adjust correctly(urge a osmotic pressure equal to that of tear fluids, generaly agreed to be equal to 0.9% NaCl) a range of 0.5-2.0% NaCl equvivalency does not cause a marked pain and range of about 0.2-0.7% sholud be acceptable for most persons. Common tonicity adjusting ingridient are:NaCl, Kcl, Buffer salt, dextrose, glycerine, propylene glycol and mannitol.

b) **pH Adjustment and Buffers:** pH adjustment is very important as pH affects:

- To render the formulation more stable
- The comfort, safety and activity of the product. Eye irritation→ increase in tear fluid secretion→Rapid loss of medication
- To enhance aqueous solubility of the drug.

- To enhance the drug bioavailability
- To maximize preservative efficacy Ideally every product buffered to a pH of 7.4(The normal physiological pH of tear fluid) If buffers are required, their capacity is controlled to be as low as possible.
- To enable the tears to bring the pH of the eye back to the physiological range
- To avoid effect of buffers on tonicity. Examples of buffer vehicles used:-Boric acid vehicle: pH ofslightly below 5-Isotonic phosphate vehicle: pH ranges from 5.9 -8.

c) **Viscosity-Imparting Agents:**
Polyvinyl alcohol, methylcellulose, hydroxyl propyl methylcellulose, hydroxylethylcellulose and carbomers are generally used in parentral preparation as viscosity imparting agent. They increase the ocular contact time thereby they decrease the drainage rate, increase the mucoadhessiveness and increase drug bioavilability.

d) **Stabilizers & Antioxidants:**
Stabilizers are the ingredients, which makes the preparation to decrease the rate of decomposition of active ingredient. Antioxidants are principle stabilizers added to some opthalmic preparation, primarily those containing epinephrine, and other oxidizable drugs.Example: Sodium bisulphite or metabisulphite are used in concentration up to 0.3% in epinephrine hydrochloride and bitartrate solution.

e) **Surfactants:**
The order of surfactant toxicity is anionic>cationic>>non-ionic. There are several non-ionic surfactant are used in low concentration to add in dispersing steroid in suspensions and to achieve or improve solution clarity. Some of the surfactant which are principally used are sorbiton ether esters of oleic acid (polysorbate or tween 20 and 80).

f) **Preservatives:**
Preservatives are included in multiple-dose eye solutions for maintaining the product sterility during use. Preservatives not included in unit-dose package. The use of preservatives is prohibited in ophthalmic products that are used at the of eye surgery because, if sufficient concentration of the preservative is contacted with the corneal endothelium; the cells can become damaged causing clouding of the cornea and possible loss of vision. The most common organism is Pseudomonas aeruginosa that grow in the cornea and cause loss of vision. Examples: benzalkonium chloride, 0.004% to 0.01%;benzethonium chloride, 0.01%; chlorobutanol,0.5%; phenylmercuric acetate, 0.004%; phenylmercuric nitrite, 0.004%; and, thimerosal, 0.005%to 0.01%.

**Formulation of eye drops:**

Ophthalmic solutions are sterile solutions intended for instillation in the eye.In addition to sterility, these dosage forms require the careful consideration of such other pharmaceutical factors as the need for antimicrobial agents, osmolarity, buffering, viscosity, and proper packaging.

An eye drop formulation comprises of the following:

a) Active ingredients to produce desired therapeutic effect.
b) Vehicle(Aquous or Oily).
c) Inert antimicrobial preservatives to prevent microbial contamination and to maintain sterility.
d) Inert adjuvants for adjusting tonicity, Viscosity and PH to increase the stability of active ingredients.
e) Suitable container to maintain the preparation in a stable form and provide protection against contamination during preparation, storage and use.
f) Multi dose eye drops are added with an effective antimicrobial preservative system(a single substance cannot be successfully used as a preservative in ophthalmic solution) that should pass the test for efficacy of antimicrobial preservative. This ensures that the eye drops are sterile and non-contaminated.

**Formulation of Eye Ointments:**

Ophthalmic ointments must be sterile. Like suspensions, ointments can be more difficult to manufacture in sterile form. They can be terminally sterilized, or, alternatively, they must be manufactured from sterile ingredients in an aseptic environment. Filtration through a suitable membrane or dry heat sterilization is often used.

- The ointment base selected for an ophthalmic ointment must be non-irritating to the eye and must permit the diffusion of the active ingredient throughout the secretions bathing the eye.
- Ointment bases utilized for ophthalmics have a melting or softening point close to body temperature.
- Ophthalmic ointments have a longer ocular contact time when compared to many ophthalmic solutions.
- Ointment base is sterilized by heat and filtered while molten to remove foreign particulate matter**.**
- It is then placed into a sterile steam jacketed to maintain the ointment in a molten state and excipients are added.
- One disadvantage to ophthalmic ointments is the blurred vision that occurs as the ointment base melts and spread across the lens.
- The bases like; yellow soft paraffin, liquid paraffin and wool fat can be used for the preparation of eye ointment.

**Formulation of Eye Lotions:-**

Eye lotions are undiluted aqueous solutions, applied to an eye bath, which for first aid purposes. It is may allow a large volume of fluid to flow quickly over the eye.

It is iso-osmotic to tears, because compared to eye drops, lotions cause much greater dilution of the lachrymal fluid, hence cause discomfort if not adjusted.e.g. Sodium chloride (NaCl) eye lotion B.P.C. is used to remove foreign substance from the eye.

Thus these preparations should be very simple as well as the most common eye lotion consists of sterile normal saline. This preparation demonstrate the requirements of an eye lotion which are:

- Sterile as well as usually containing no preservative.
- Isotonic to lachrymal fluid
- Natural pH
- Large volume but not greater than 200ml
- Non-irritant to ocular tissue.

**Methods of Preparation:**

1) Preparation of the Solution: The aqueous eye drops vehicle containing suitable preservative , antioxidant , stabilizer, tonicity modifier , viscosity modifier, or buffer should be prepared, and added with the active ingredient and the vehicle to make up the volume.
2) Clarification: sintered glass filters or membrane filters having 0.45-1.2 µm pore sizes should be used. The clarified solution is either fillied directly into the final containers which are sealed before heat sterilisation or is temporarily filled into a suitable container before filtration. Clarified containers vehicle is used to prepare eye drop suspensions filled into final containers and sealed before sterilisation.
3) Sterilisation: This can be achieved by autoclaving at 115$^{o}$C temperature for 30 minutes or 121$^{o}$C temperature for 15 minutes . Filtration into sterile containers through a membrane filter having 0.22µm pore size is also a suitable method for sterililisation.Dry heat sterilisation at 160$^{o}$C temperature for 2 hours is best suited for non-aqueous preparations such as liquid paraffin eye drops.
4) After sterilisation, the eye drop containers should be covered with a readily breakable seal to distinguish between opened and unopened containers.

**Labeling:-**

The label should include:

(1) The name of the pharmaceutical product;
(2) The name(s) of the active ingredient(s); International Nonproprietary Names (INN) should be used wherever possible;
(3) The concentration(s) of the active ingredient(s) and the amount or the volume of preparation in the container;
(4) The batch (lot) number assigned by the manufacturer;
(5) The expiry date, the utilization period, and, when required, the date of manufacture;
(6) Any special storage conditions or handling precautions that may be necessary;
(7) If applicable, the period of use after opening the container;
(8) Directions for use, warnings and precautions that may be necessary;
(9) The name and address of the manufacturer or the person responsible for placing the product on the market;

(10) If applicable, the name(s) and concentration(s) of antimicrobial agent(s) and/or antioxidant(s) incorporated in the preparation; and
(11) The statement "This preparation is sterile".

**Storage:**

Ophthalmic preparations should maintain their integrity throughout their shelf-life when stored at the temperature indicated on the label. Special storage recommendations or limitations are indicated in individual monographs.

**Containers:**

Traditionally, ophthalmic liquid products were packed in glass containers fitted with an eye dropper. Today, glass containers have limited use where product stability or compatibility issues exclude the use of flexible plastic containers made of polyethylene or polypropylene. Most liquid ophthalmic products on the market are packaged in plastic containers fitted with nozzles from which, by gentle squeezing, the contents may be delivered as drops.

- Plastic containers have several advantages over the glass-dropper combination such as minimizing the risk of the contents being contaminated with microorganisms by the replacement of the dropper which may have become contaminated by touching the infected eye or any other surfaces. Also, plastic containers are cheap, light in weight, more robust to handle and easier to use than glass-dropper type containers.
- Some plastic materials such as polyethylene can absorb some antimicrobial preservatives (e.g. benzalkonium chloride), or some drugs. They may also leach plasticizers into the product, or printing inks from the label can migrate through the plastic into the product.
- The challenge is to develop a packaging system for preservative-free products that maintains the sterility of the product throughout its shelf-life and during use.
- Unit-dose systems offer the easiest technical solution to this problem but have the disadvantage of higher cost of manufacture and of not being as compact as a multidose product containing equivalent doses.
- An alternative approach is to develop a multidose preservative free system. The container is required to be collapsible, and the suck-back of air, which could contain bacteria, has to be avoided. Containers are being developed that contain a valve mechanism to achieve this
- Plastic containers can also be permeable to water vapor and oxygen over prolonged periods of storage. This can lead to gradual loss of liquid product or oxidation of an unstable drug over time.
- Polyethylene containers are not able to withstand autoclaving and are usually sterilized by ethylene oxide or by irradiation before being filled aseptically with pre-sterilized product. Polypropylene containers can be autoclaved, but are not as flexible as polyethylene for eyedropper use.

- Semi-solid products have been traditionally packed in collapsible tin tubes. Metal tubes are a potential source of metal particles in ophthalmic products, and so the tubes have to be cleaned carefully prior to sterilization.
- Collapsible tubes made from laminates of plastic, aluminum foil and paper are good alternative to tin tubes. Laminate tubes fitted with polypropylene caps can be sterilized by autoclaving.

**Evaluation of ophthalmic preparations:-**

Ophthalmic preparations are evaluated as follows:

1) **Sterility:** The ophthalmic products should meet the standard requirements. If the ingredients used do not lend themselves to routine sterilization, ingredients that meet the sterility requirements should be used. The container for ophthalmic preparations should be sterilized at the time of filing and closing. They should be sealed and tamper-proof to maintain their sterility.
2) **Antimicrobial preservatives:** These should be added to multiple-dose containers, unless there are different directions provided in the individual monograph for multiple product withdrawal, the substance contains a radionuclide with a physical half of less than 24hours, he product itself is sufficiently microbicidal, or the added ingredients meet the requirements of antimicrobial agent content. Thus, acceptance criteria for the content of antimicrobial preservative in multiple-unit products should be established.
3) **Uniformity of Dosage Units**: This test should be performed for single-dose containers to evaluate the mass of dosage form as well as the content of the drug substance(s) in the dosages form. The test is performed by either content uniformity or weight variation.
4) **Uniformity in Containers:** Semisolid drug products undergo physical separation during manufacturing and /or during the storage period. To ensure the drug product integrity, the uniformity of the finished product at the time of batch release and throughout its shelf-life should be evaluated.
5) **Leachable and Extractables:** The packaging system and the preparation should not undergo any physical or chemical interaction to alter the strength, quality, or purity of the drug product. The packaging system should meet the requirements in elastomeric closures for injection, and glass or plastic containers.
6) **Container Closure Integrity:** The packaging system should be closed or sealed to prevent contamination or loss of contents. It should also be tamper-proof. Validation of container integrity should demonstrate no penetration of microbial, chemical or physical contaminants.

7) **Viscosity:** The residence time of the product in eyes increases in viscosity; but the diffusion of drug from the formulation in to the eye is inhibited. The ophthalmic ointments have a very high viscosity to prolong their residence time in the eyes.
8) **Antioxidant Content:** The content of antioxidants ( if added in the drug product) should be established unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should also be established based on the levels of antioxidant required to keep the product stable throughout its shelf-life.
9) **Particle Size and Particle Size Distribution:** The potential for any changes in the particle size of ophthalmic suspensions and emulsions should be evaluated through stability testing. the drop size for ophthalmic drops ranges from 20-70µm.However,the drop size should be controlled and maintained throughout the product shelf-life. Suitable substances should be added to the ophthalmic products to increase their stability, provided they do not cause any harm in the amounts administered and do not interfere with the therapeutic efficacy or responses to the specified assays and tests.

**References:**


1) Introduction to Pharmaceutical Dosage Forms. Ansel, HC— 4th ed. Philadelphia: Lea & Febiger; 1985:321–336.
2) Industrial pharmacy-I by KL Senthilkumar, AS Mundada and RS Kankate: Ist ed.Thakur Publication, pg. no.163-204.
3) Pharmaceutical dosage forms: parenteral medications of industrial pharmacy, Lachmann/ Lieberman's, 4th edition, pg.no. 864-871.

4). Dispensing pharmacy by R M Mehta, pg.no. 303-311.

5). The science & practice of pharmacy, Remington, 21st edition, pg.no. 1367-1374.