INDUSTRIAL PHARMACY-I

UNIT IV-PARENTERALS

CLASS:35

TOPIC Labeling, containers; evaluation of ophthalmic preparations

Container-eye drops

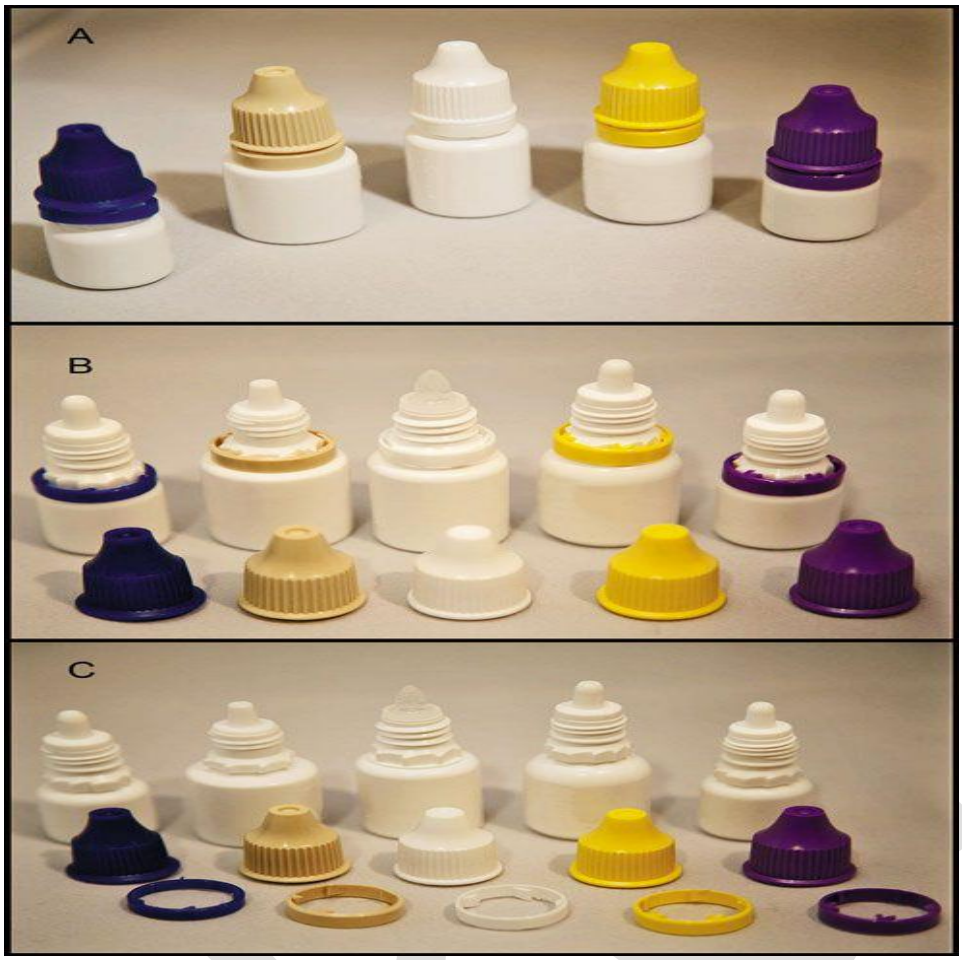
- The commonly used container for opthalmic solutions or suspension is multi-dose container (5ml, 10ml).
- Glass container is supplied with sterile plastic dropper.
- Plastic bottles are with built-up nozzle

Label

- Not for injection.
- For external use only.
- Shake well before use (if it is suspension)

The eye drops should be packed in neutral glass containers or in suitable plastic containers.

- neutral glass small bottles having capacity of 4ml to 8ml are used.
- It has **two poly propylene screw caps**, one for attaching a silicone rubber teat to the container and the other for covering the teat.
- The plastic squeeze bottles having ridged plastic cap and polythene friction plug containing baffle that produces uniform drops are also used these days.
- These are very handy. These bottles are sterilized by gaseous sterilization method.



Label requirements-EYE LOTIONS

label must include

- Title identifying the product
- Conc. of contents
- Sterile until open
- Not to be taken
- Use once & discard the remaining solution
- Expiry date

Preserved eye lotions would need additional label which includes

- Avoid contamination of contents during use

- Discard remaining solutions not more than four weeks after first opening
- Lotions should be supplied in coloured fluted bottles & sealed

Opthalmic preparation -evaluation tests

In vitro tests include-

- Sterility
- pH
- Clarity of solutions
- Visual assessment
- Size of the particles,
- Tonicity/osmolarity
- Viscosity
- Amount of substance
- Amount of preservative
- Stability

In vitro releas

In vivo tests include-

- Draize eye test
- In vivo release

Specified (Other) tests include-

- Analysis of ions (for contact lenses)
- Oxygen permeability (for contact lenses)
- Determination of encapsulation efficiency (for multicompartment drug delivery systems and emulsions)

Draize eye test

- The test subject for this test should be rabbits, as their vision organ anatomy and physiology are well described in the literature.
- Susceptibility of the eye to irritating compounds is higher in case of rabbits in comparison with humans.
- Rabbits are taken into the group of 3 to 6 and placed in cages, adapted explicitly for them.
- The site of administration of the drug for this test is either conjunctival sac or applied directly on the cornea.

Sterility

- **Sterility** Examination is the primary type of in-vitro test.
- It involves inoculation of the sample at aseptic conditions.
- The sample can be examined on one of the two microbiological media,
- 1)Thioglycolate medium for aerobic and anaerobic bacteria. It is also known as fluid sodium mercapto acetate or sodium thioglycolate.
- 2) Medium with hydrolysate of casein and soy for aerobic bacteria and fungi. It is also called soya-bean casein digest media.

Direct Inoculation Method

- This process involves the transfer of the prepared sample to the medium.
- A limitation of sterility testing is that product containing antimicrobial properties should be neutralized for such effects these properties may interfere with results.
- The diluted solution of ointment formulation with a sterile solvent containing the chosen surface active agent is necessary before the test

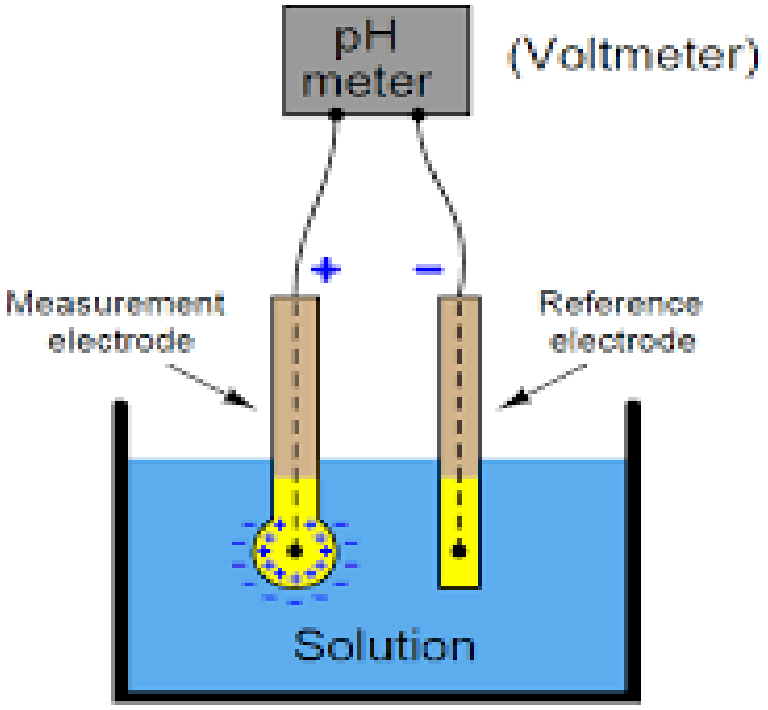
Membrane Filtration Method

- For water and oil solutions, cellulose nitrate filters are used for this test having a size of pores less than 0.45 μm.
- Specialized adjusted filter is used for specific products like antibiotics.

- In the case of testing products with antimicrobial effects The membrane should be washed with a chosen sterile solvent at least three times limiting with not exceeding the fivefold cycle of filter washing for each 100ml of the solvent sample
- The indirect method can also be used for ointments.
- Isopropyl myristate is used to dilute the fatty base ointments at the temperature not more than 40°C.
- The product is filtered as quickly as possible.
- For every drug form, after filtration and washing, the membrane is either transferred to the medium, or the medium introduced to the filtration set on the membrane.

pH Testing

- A suitable formulation for pH testing are solutions, drops, suspensions and in situ gels.
- The test is performed by using a potentiometer using the potential difference measurement principle.
- In this method, the sample is kept separately at the sample electrode, and a reference of known pH is used on the other electrode.
- Another method which can be used for this purpose is by measuring the potential difference between measurement (glass) electrode and reference (calomel or silver chloride) electrode, both placed in examined preparation



Clarity Testing (Visual Method)

- It involves the visual assessment of formulation in suitable lighting on white and black background.
- The test is performed for liquid forms but not for the suspensions.
- Eye drops are tested for clarity while in situ gels are tested two times, one before and one after gelling.

Clarity Testing by UV Transmittance

- Another method of testing for clarity by transmittance measurement using a UV-Vis spectrophotometer.
- This method employed on contact lenses filled with active ingredients where the formulation is of solid type.
- The lenses are hydrated in physiological saline at the initial stage of the test followed by placing on the surface of a quartz cuvette.

- In the final step, the transmittance is measured afterwards from 200 to 1000 nm wavelength

Content of Substance or Preservative Analysis

- The examination of drug or preservative content should be done by testing parameters given as per the label with relevant analytical technique, i.e. Spectrophotometric method, HPLC
- **Viscosity Analysis** This test is done by using viscometer. Choice of viscometer is based on the type and amount of sample.
- **Tonicity Analysis** Three primary methods are used to assess the tonicity of any ophthalmic formulation.

➢ Freezing point depression method

➢ Electrical impedance method

➢ Vapour pressure method

Stability Analysis

- This test provides the information on changes in the quality of active ingredient or medicinal product over the time due to the environmental factors.
- **In vitro drug release**

➢ Bottle method

➢ Modified rotating basket method

➢ Diffusion with franz cells

➢ Modified rotaing paddle apparatus

➢ Flow through device

Draize eye test

- The initial amount of the formulation being applied on the eyeball was set about 0.1ml, but varies after attempts pointed to reducing the amount. The left eyeball is used as a control.

- The eyeball condition is observed using a magnifying glass before and after administering the formulation.
- The eyeball is monitored for the blinking or rubbing of the eye as an indication of the discomfort level after application. The evaluation takes place usually after one h, 24 h, 48 h, and 72 h.

Transcorneal Permeation Test

- Transcorneal Permeation Test This test includes healthy albino rabbits as test subjects.
- The formulation is applied Using a syringe with needle, after intramuscular or intravenous anaesthetic injection a sample of aqueous humor is taken (150–200 μL) Stored at negative temperature (−20∘C) before HPLC analysis

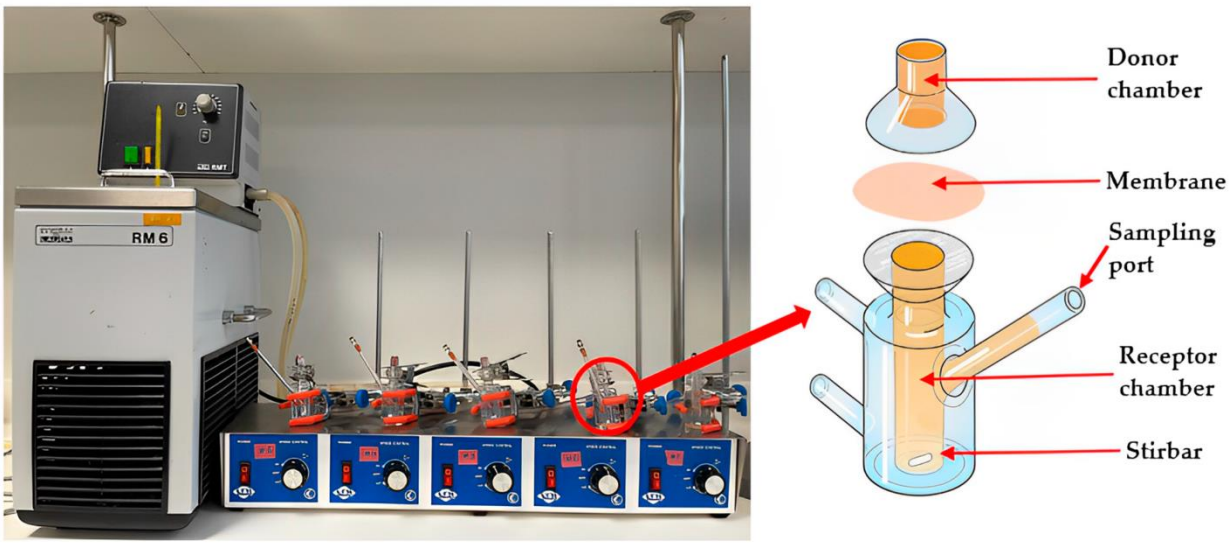
In Vitro Analysis

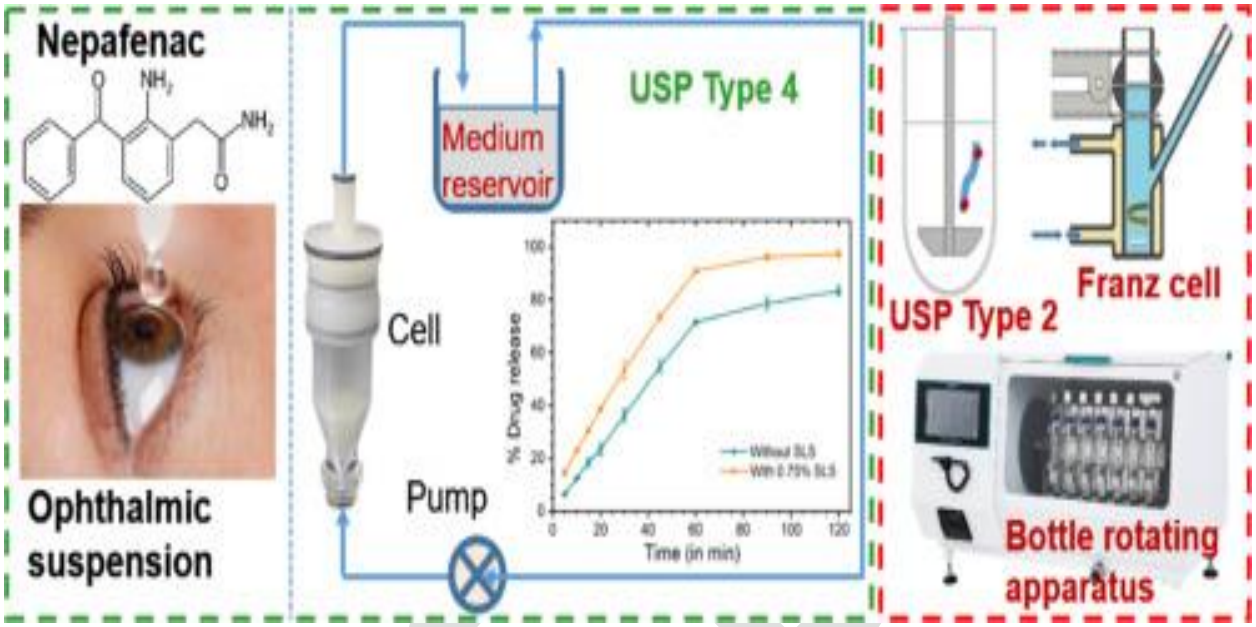
Bottle method

- In this method, the formulations are placed in culture bottles or vials containing phosphate buffer at pH 7.4 or artificial isotonic tear fluid. The bottles and vials are shaken in water baths or incubated under magnetic stirring at 37°C.
- The samples are withdrawn at specified time intervals and afterwards examined for drug amount.

Franz diffusion cell method

- The test requires equipment consisting of two separate compartments, one donor and one receiver.
- The formulation is placed in a donor compartment of Franz cell, and a thermostated (37∘C ± 0.5∘C) the receiver compartment contains dissolution medium.
- Continuous stirring is applied in the receiver compartment using a magnetic stirrer (50 rpm).
- Both the compartments are separated with a dialysis membrane (cellophane).
- Samples are taken from the receiver compartment at specified time intervals, and the drug is marked using a suitable analytical technique.





Rotating basket method

- In this test, the formulation is placed in a set of baskets or substitutes cylindrical glass pipes.
- These pipes are connected with a stirrer on one side and the other side is attached to shafts of the apparatus, covered with a dialysis membrane.
- The components are put in a beaker with a water

Preservatives

- The selection of a preservative for ophthalmic solutions is not an easy task, with very few candidates to choose from:
- The following criteria are important for selection of preservative:
- Board spectrum of activity against both Gram-positive and Gram-negative organisms and fungi.
- The agent should rapidly kill virulent organisms.
- Satisfactory chemical and physical stability over a wide range of pH and temperature.
- Compatibility with formulation components and container materials.
- Nontoxic and non irritating during use.

- . Preservatives Conc. Range
- 1 Quaternary ammonium compounds 0.004-0.02 0.01 most common
- 2 Organic mercurials 0.001-0.01
- 3 Parahydroxy benzoates 0.1 maximum
- 4 Chlorobutanol n 0.5

METAL PARTICLES IN OPTHALMIC OINTMENT

- Extrude as completely as practicable the content of 10 tubes individually into separate, clear, flat-bottom, 60-mm petri dishes that are free from scratches.
- Cover the dishes and heat at 85°c for 2 hours, increasing the temperature slightly if necessary to ensure that a fully fluid sate is obtained.
- Taking precautions against disturbing the melted sample, allow each to cool to room temperature and to solidify.
- Remove the covers and invert each petri dish on the stage of suitable microscope adjusted to furnish 30 times magnification and equipped with an eye pieces micrometer disk that has been calibrated at the magnification being used.

METAL PARTICLES IN OPTHALMIC OINTMENT

- Examine three entire bottom of the petri dish for metal particles.
- Count the number of metal particles that are 50um on larger in any dimension.
- The requirements are met if the total number of such particles in all 10 tubes does not exceed 50 and if not more than 1 tube is found to contain more than 8 such particles. If these results are not obtained, repeat the test on 20 additional tubes. 8.
- The requirements are met if the total number of metal particles that are 50um on larger in any dimension does not exceed 150 in all 30 tubes tested and if not mote than 3 of the tubes are found to contain more than 8 such particles each

Packaging of ophthalmic products

- The plastic bottles for packaging of ophthalmic products are generally made of Low Density Polyethylene(LDPE), either with or without any colorants or with opacifying

agents. Polypropylene(PP) or high density polyethylene(HDPE) are also used to meet specific product requirements.

- **Eye drops** (Single-dose containers): Plastic bottles(LDPE) are widely used.
- **Eye drops(Multiple- dose containers**): Traditionally, glass bottles with rubber teat dropper were widely used. Now- a-days, plastic bottles(LDPE) are widely used.
- **Eye ointments**: Flexible plastic or collapsible metal tubes are used. Caps or closures are generally made from Polypropylene(PP) and basically seal the container to prevent contamination or leakage of the product.

Glass container

- Neutral,Boro-silicate type glass(Type 1 glass) were widely used as a container for ophthalmic preparations, Plastic container
- Thermoplastic polymers have been established as packaging materials for sterile preparations such as large-volume parenterals, ophthalmic solutions and increasingly, small-volume parenterals.

Ampoules

- • A parenteral product container made entirely of glass and intended for single use.
- Vials A glass orplastic container closed with a rubber stopper and sealed with an aluminum crimp

LABEL SHOULD CONTAIN THEFOLLOWING

- 1. The name of the pharmaceutical product.
- 2. The name(s) of the active ingredient(s).
- 3. The concentration of the active ingredients and the amount or the volume of preparation in the container.
- 4. The batch 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.