OPHTHALMIC PRODUCTS
(Formulation and Evaluation)

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SIPS

- **Definition:**

- Ophthalmic preparations (eye preparations) are sterile, liquid, semi-solid, or solid preparations that may contain one or more active pharmaceutical ingredient intended for application to the conjunctiva, the conjunctival sac or the eyelids.

- They are specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside (intraocular) or adjacent (periocular) to the eye or used in conjunction with an ophthalmic device.

- The most commonly employed ophthalmic dosage forms are solutions, suspensions, and ointments.

- The newest dosage forms for ophthalmic drug delivery are: gels, gel-forming solutions, ocular inserts , intravitreal injections and implants.

ADVANTAGE:

- They are easily administered by the nurse
- They are easily administered by the patient himself.
- They have the quick absorption and effect.
- less visual and systemic side effects.
- increased shelf life.
- better patient compliance.

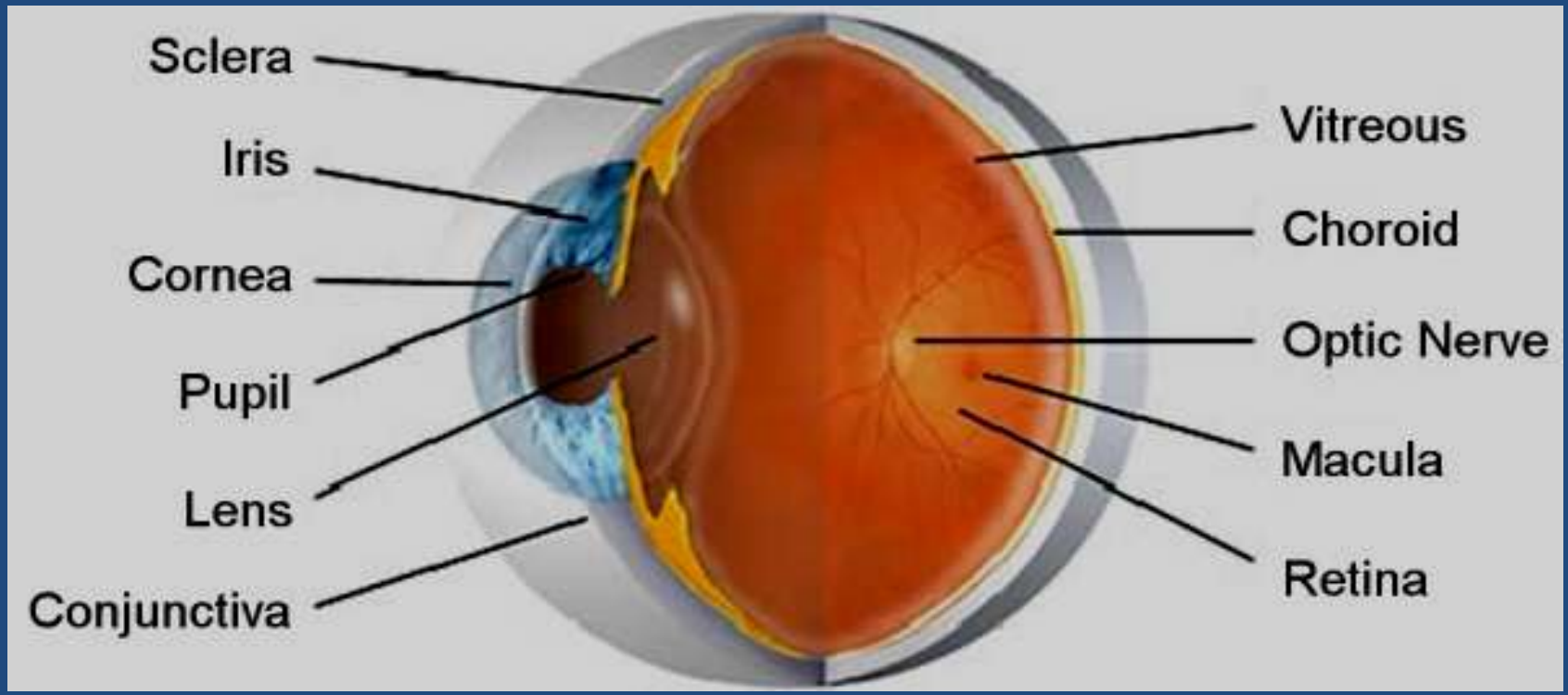
DISADVANTAGES:

- The very short time the solution stays at the eye surface.
- Its poor bioavailability.
- The instability of the dissolved drug.
- The necessity of using preservative.

Drugs used in the eye:-

- Miotics e.g. pilocarpine Hcl
- Mydriatics e.g. Atropine
- Cycloplegics e.g. Atropine
- Anti-inflammatories e.g. corticosteroids
- Anti-infectives (antibiotics, antivirals and antibacterials)
- Anti-glucoma drugs e.g. pilocarpine Hcl
- Adjuncts e.g. Irrigating solutions
- Diagnostic drugs e.g. sodiumfluorescein
- Anesthetics e.g. Tetracaine

Anatomy and Physiology of the Eye:



Formulation:

- 1)Drug
- 2)Preservative
- 3)Sterilization
- 4)Isotonicity
- 5)Buffer
- 6)Viscosity
- 7)Container
- 8)Label

- **1) Drugs-** These contains drugs of various categories including antiseptic, anti-inflammatory agent, mydriatic or miotic properties
- **2) Preservative-** Eye drop should be sterile and should contain preservatives to avoid microbial contamination when container is open. The preservative for ophthalmic use includes benzalkonium chloride, chlorbutanol, phenylmercuric acetate, phenylmercuric nitrate etc.,

- **3)Sterilization-** Eye drops are sterilized by autoclaving at 121°C for 15 minutes or by bacteria filter to avoid thermal degradation for example- preservative chlorbutanol hydrolyzes at high temperature
- **4)Isotonicity-** All the solutes including drug contribute to the osmotic pressure of the eye drip, therefore isotonicity of the formula should be calculated and it is adjusted with sodium chloride, for example sodium chloride 0.9% and boric acid 1.9& are iso-osmotic

- **5)Buffer-** the buffer should be added to maintain balance between comfort, solubility, stability and activity of drug. For example the hydrolysed chlorbutanol forms hydrochloride acid making the drop acidic. Whereas certain drug like pilocarpine hydrochloride are acidic
- **6)Viscosity-** the size of the drop and its residence in eye depends on viscosity of eye drops. Methyl cellulose, hydroxypropyl methycellulose and polyvenyl alcohol are common viscosity inhancer

- **7) Container-** the commonly used container for ophthalmic solutions or suspension is multi-dose container(5ml, 10ml). Glass container is supplied with sterile plastic dropper. Plastic bottles are with built up nozzle.
- **8)Label-** Not for injection. For external use only. Shake well before use (if it is suspension)

DOSAGE FORMS APPLIED TO THE EYE

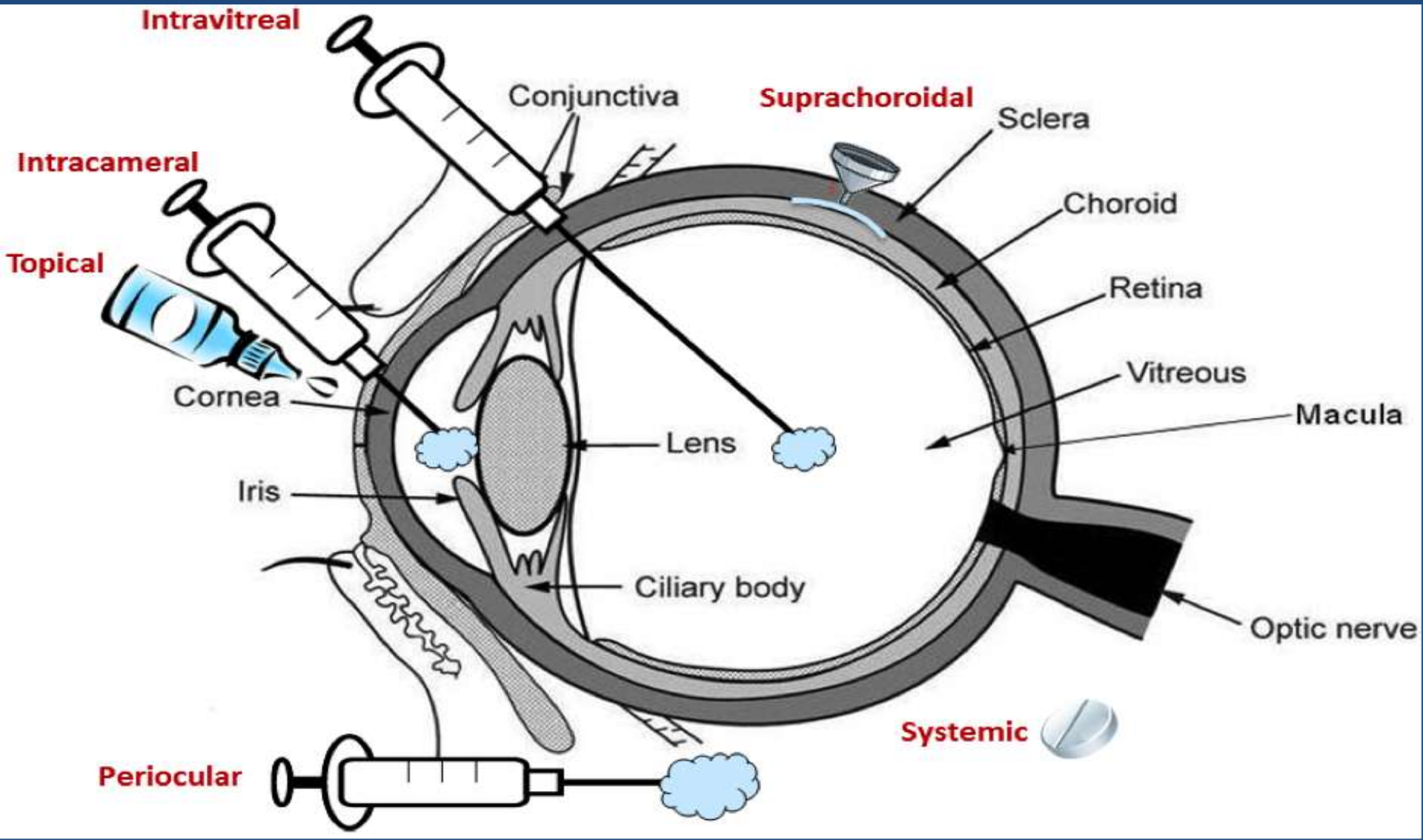
Topical Administration

- **Solutions**
- Suspension
- Emulsion
- Ointment
- Gel
- Perfusion
- Spray
- Inserts

Intraocular drug delivery

- Intraocular injection
- Implant
- Iontophoresis
- Liposome
- Niosome

Drug delivery routes



- Solutions

- Ophthalmic solutions are sterile solutions intended for instillation in the eye. Included in this dosage form category are solid preparations that, when reconstituted according to the label instructions, result in a solution
- Solutions are Manufactured by dissolution of the active ingredients and a portion of the excipients into all portion of water.
- The sterilization of this solution done by heat or by sterilizing Filtration through sterile depth or membrane filter media Into a sterile receptacle.
- This sterile solution is then mixed with the additional required Sterile components such as viscosity –imparting agents, Preservatives and so and the solution is brought to final Volume with additional sterile water

Disadvantages of eye solutions:

- The very short time the solution stays at the eye surface.The retention of a solution in the eye is influenced by viscosity.
- Its poor bioavailability (a major portion i.e. 75% is lost via naso lacrimal drainage).

Examples of topical eye solutions:

- Atropine sulphate eye drops.
- Pilocarpine eye drops .
- Silver nitrate eye drops.
- Zinc sulphate eye drops.

suspensions

- If the drug is not sufficiently soluble, it can be formulated as a suspension.
- A suspension may also be desired to improve stability, Bioavailability ,and efficacy.
- The major topical ophthalmic suspensions are the steroid anti-inflammatory agents.
- An ophthalmic suspension should use the drug in a microfine form; usually 95% or more of the particles have a Diameter of 10µm or less.

Examples of eye suspension

- Prednisolone acetate suspension.
- Besifloxacin suspension.
- Blephamide suspension.
- Fluorometholone suspension

- **Emulsions**

- Topical ophthalmic emulsions generally are prepared by dissolving or dispersing the active ingredient(s) into an oil phase, adding suitable emulsifying and suspending agents and mixing with water vigorously to form a uniform oil-in-water emulsion. Each phase is typically sterilized prior to or during charging into the mixing vessel.

Ointments

- Ophthalmic ointments must be sterile
- The ointment base selected for an ophthalmic ointment must be nonirritating to the eye and must permit the diffusion of the active ingredient throughout the secretions bathing the eye.
- Ophthalmic ointments have a longer ocular contact time when compared to many ophthalmic solutions
- One disadvantage to ophthalmic ointments is the blurred vision that occurs as the ointment base melts and is spread across the lens.

Example of ophthalmic ointment

- Chloramphenicol ointment.
- Tetracycline ointment.
- Hydrocortisone ointment.

Gels

- Ophthalmic gels are composed of mucoadhesive polymers that provide localized delivery of an active ingredient to the eye.
- Such polymers have a property known as bioadhesion meaning attachment of a drug carrier to a specific biological tissue.
- These polymers are able to extend the contact time of the drug with the biological tissues and thereby improve ocular bioavailability

Perfusion

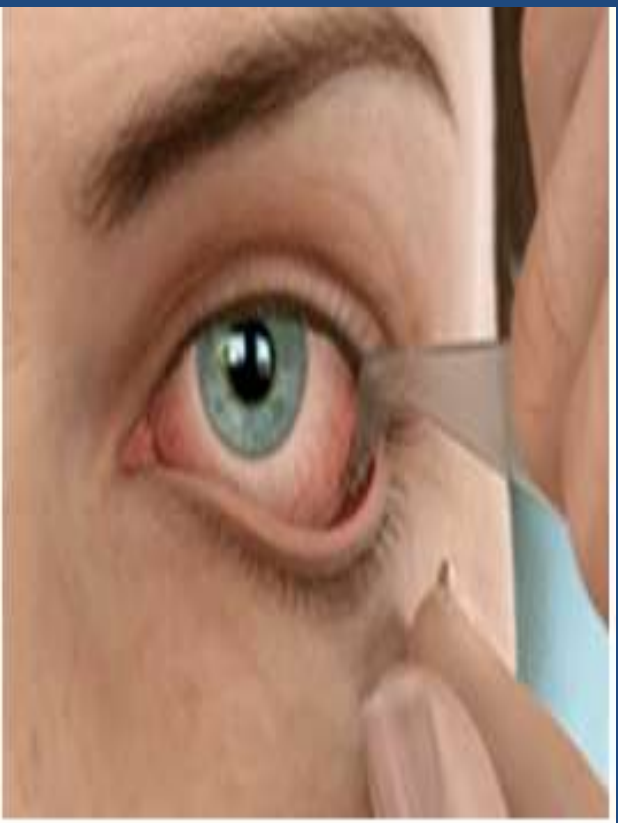
- Continuous and constant perfusion of the eye with drug solutions can be achieved by the use of ambulatory motor driven syringes that deliver drug solutions through fine polyethylene tubing positioned in the conjunctival sac
- This system allows the use of a lower drug concentration than used in conventional eye-drops, yet will produce the same potency. Side effects are reduced and constant therapeutic action is maintained

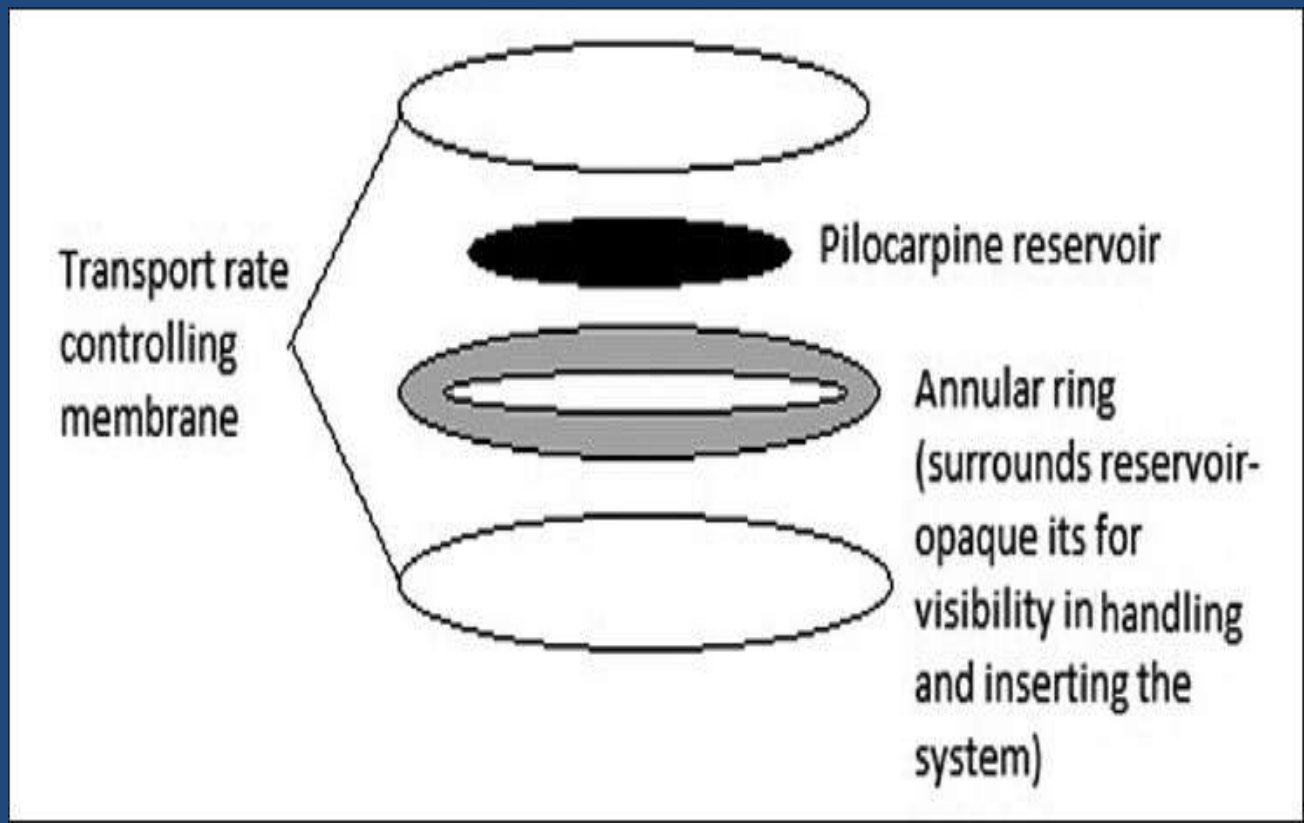
Sprays

- Spray systems produce similar results to eye-drops in terms of duration of drug action and side effects. Sprays have several advantages over eye-drops:
  1. a more uniform spread of drug can be achieved
  2. precise instillation requiring less manual dexterity than for eye-drop administration and is particularly useful for treating patients with unsteady hand movements
  3. contamination and eye injury due to eye-drop application are avoided
  4. spray delivery causes less reflex lacrimation.
  5. Can be used by patients who have difficulty bending their neck back to administer drops.

Ophthalmic inserts

are defined as sterile solid or semisolid preparations, with a thin, flexible and multilayered structure, for insertion in the conjunctival sac.





Advantages:

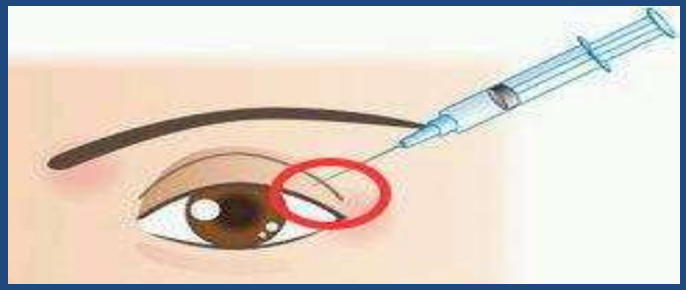
- Increasing contact time and improving bioavailability.
- Providing a prolong drug release and thus a better efficacy.
- Reduction of adverse effects.
- Reduction of the number administrations and thus better patient compliance.

- **FOR EXAMPLE**
- Lacrisert is a sterile ophthalmic insert use in the treatment of dry Eye syndrome and is usually recommended for patients unable to obtain symptomatic relief with artifical tear solutions.

- The insert is composed of 5 mg of Hydroxypropyl cellulose in a rod-shaped form about 1.27 mm diameter by about 3.5 mm long.

Intraocular Dosage Forms

- They are Ophthalmic products that introduced into the interior structures of the eye primarily during ocular surgery.



Intraocular Injections

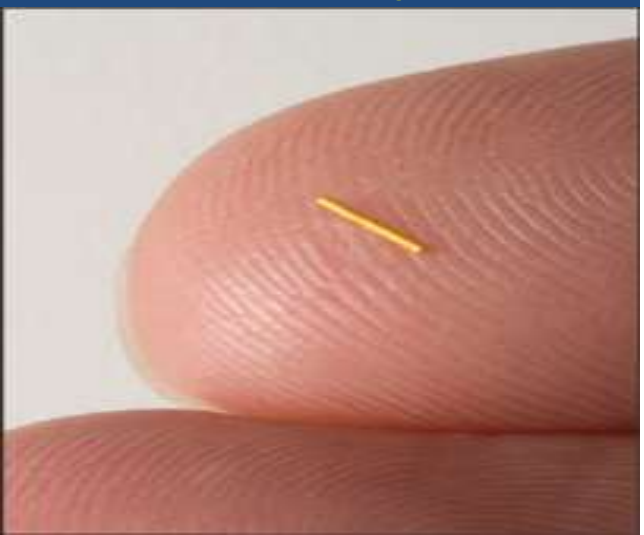
- The ophthalmologist use available parental dosage forms to deliver Anti-infective, corticosteroids, and anesthetic products to achieve higher therapeutic concentrations intraocularly than can ordinarily Be achieved by topical or systemic administration.

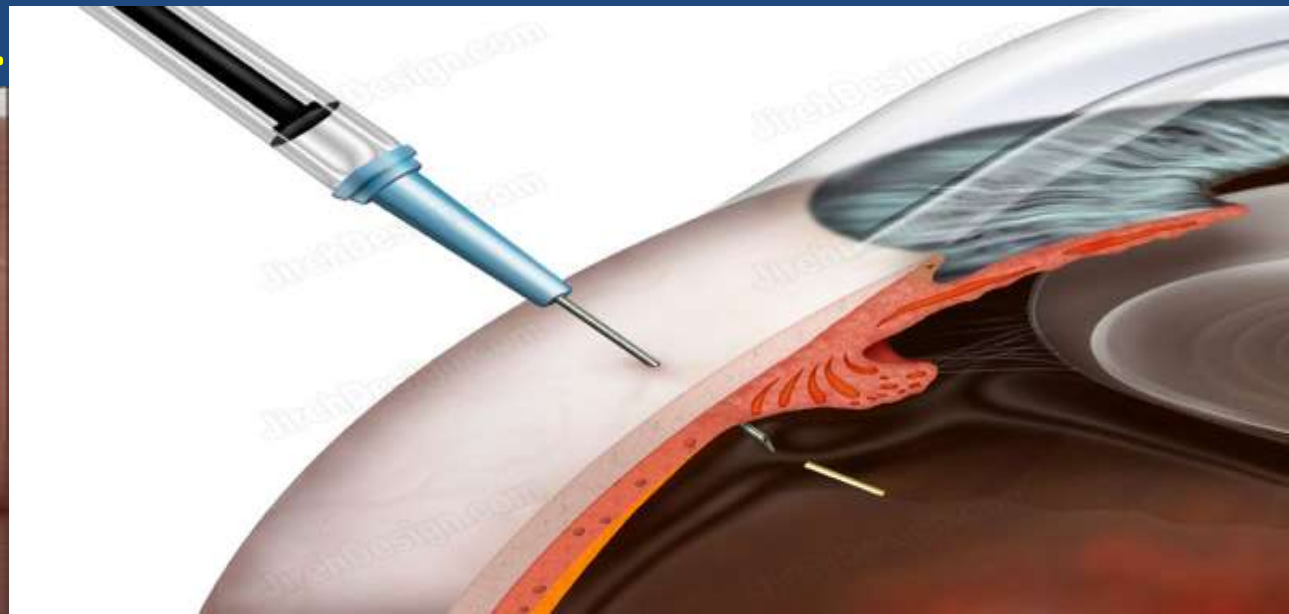
- FDA approved intraocular injection include miotics, viscoelastics and an antiviral agent for intravitreal injection.

Intravitreal implant

- An intravitreal sterile implant containing ganciclovir or antineoplastic agents is a tablet of ganciclovir with Magnesium stearate and is coated to retard release with Polyvinyl alcohol and ethylene vinyl acetate polymers.

  Such that the device when surgically implanted in the Vitreous cavity release drug over a 5 to8 month period .





Ocular iontophoresis:

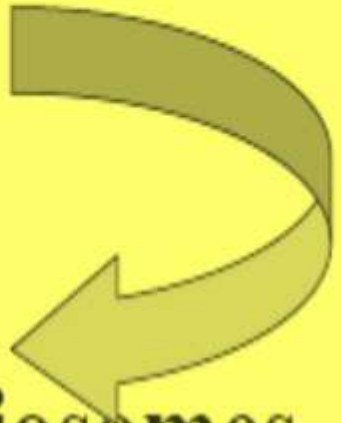
- Iontophoresis is the process in which direct current drives ions into cells or tissues.
- If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode.

- Ocular iontophoresis offers a drug delivery system that is **fast, painless, safe,** and results in the delivery of a high concentration of the drug to a specific site.

- Iontophoresis is useful for the treatment of bacterial keratitis, Iontophoretic application of antibiotics may enhance their bactericidal activity and reduce the severity of disease

The Vesicular Delivery System

Liposomes which are phospholipid based vesicles

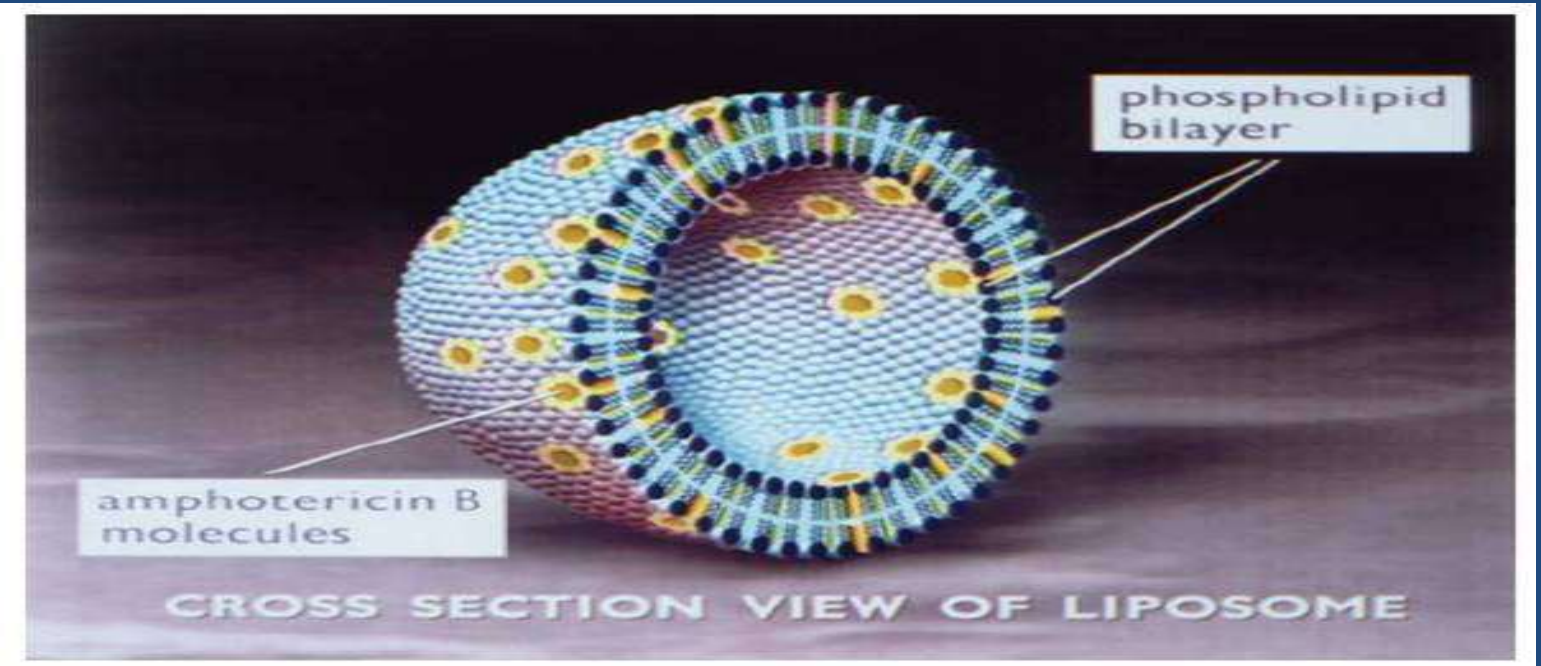


Niosomes which are non-ionic surfactant based vesicles

Microspheres and nanoparticles

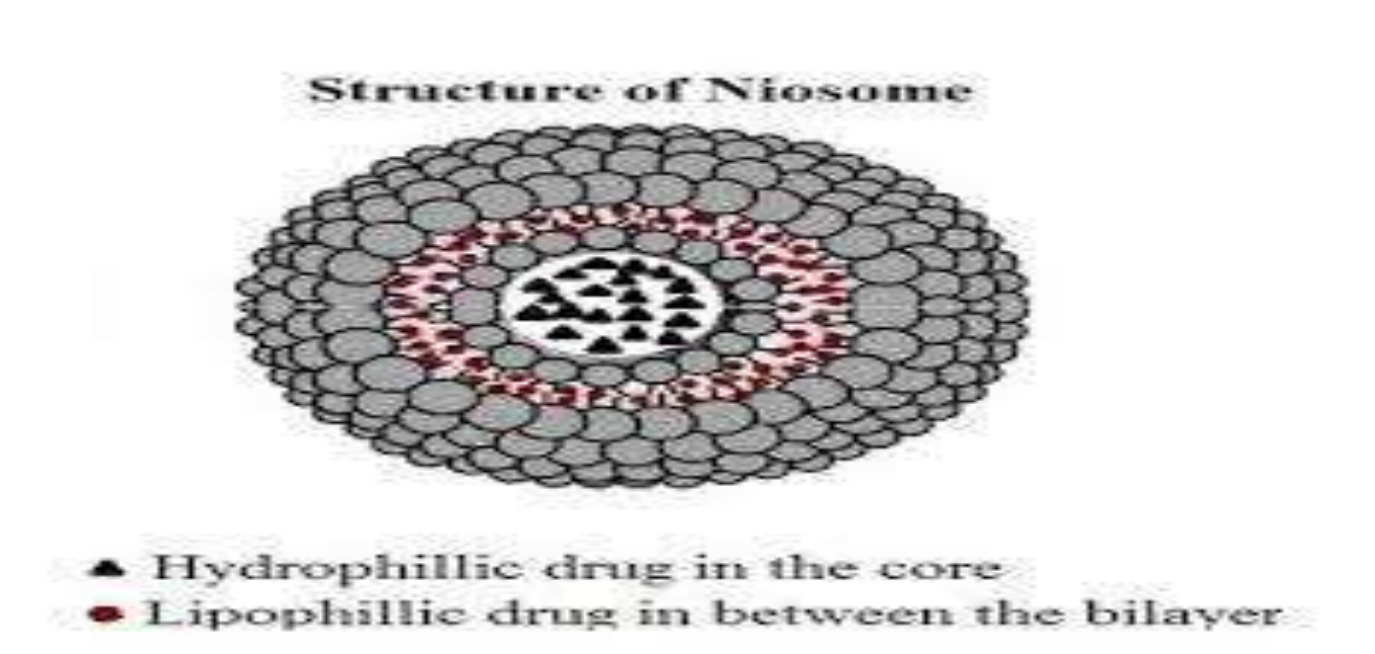
Liposomes

- Liposome's are microscopic and submicroscopic vesicles consists of one or more concentric sphere of Lipid bilayers separated by Water or aqueous buffer compartments



Niosomes

- They are non-ionic surfactant based vesicles , formed from the self assembly of non-ionic amphiphiles in in aqueous media resulting in closed bilayer structures



EVALUATION OF OPTHALMIC PREPARATION

Evaluation is test of finish Parenteral product are free from of micro-organism or not.

Evaluation of the opthalmic product is done by following tests:

1. Sterility Test

2. Clarity Test

3. Leaker Test

4. Metal particles in opthalmic ointment

1. STERILITY TEST :

Two basic methods for sterility testing:

I) Direct Inoculation Method:

It involves the direct introduction of product test samples into the culture media.

II) Membrane filtration Method:

It involves filtering test sample through membrane filter, washing the filter with fluid to remove inhibitory property and transferring the membrane aseptically to appropriate culture media.

Detection of contamination used to two culture media:-

A) Soybean-casein digest medium:- Incubated at 20to 25^{0}C

B) fluid thioglycollate medium:- Incubated at 30 to 35^{0}C on 7 Days

2. CLARITY TEST :

Opthalmic Solution by definition contain no undissolved ingredients and are essentially free from foreign particles .

- **Visual Inspection:**

  Under a good light, baffled against reflection into the eye and viewed against a black and white background with contect set in motion with swilling action.

- **Instrumental method:** It is utilizing the principle of light scattering, light absorption and electrical resistance to obtain particle count and size distribution – destruction of product units-only for quality control testing.

Instrumental method utilizing video image projection detects moving particles without destruction of product units-used for inline detection.

3. LEAKER TEST :

- Select 10 tubes of the ointment with seals applied when specified.
- Thoroughly clean and dry the exterior surfaces of each tube with an absorbent cloth.
- Place the tubes in horizontal position on a sheet of absorbent blotting paper in an oven maintained at temperature of 60 ± 3 for 8 hours.
- No significant leakage occurs during or at the completion of the test.
- If leakage is observed from one, but more than one of the tubes repeat the test with 20 additional tubes of the ointment.
- The requirement is met if no leakage is observed from the first 10 tubes tested or if leakage is observed from not more than one of 30 tubes tested

4. METAL PARTICLES IN OPTHALMIC OINTMENT:

- Extrude as completely as practicable the content of 10 tubes individually into separate, clear, flat-bottom, 60-mm petridishes that are free from scratches.

- Cover the dishes and heat at 85^0C 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 petridish 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.

- Examine the entire bottom of the petridish for metal particles.

- Count the number of metal particles that are 50μm 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.

The requirements are met if the total number of metal particles that are 50μm 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.

THANK YOU FOR WATCHING MY PRESENTATION!!