Ophthalmic Preparations
Ophthalmic preparations:

- **Definition:** 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. But these preparations when instilled into the eye are rapidly drained away from the ocular cavity due to tear flow and lacrimal nasal drainage.

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

- Miotics e.g. pilocarpine HCl
- Mydriatics e.g. atropine
- Cycloplegics e.g. atropine
- Anti-inflammatory e.g. corticosteroids
- Anti-infectives (antibiotics, antivirals and antibacterials)
- Anti-glucoma drugs e.g. pilocarpine HCl
- Surgical adjuncts e.g. irrigating solutions
- Diagnostic drugs e.g. sodiumfluorescein
- Anesthetics e.g. tetracaine
Anatomy and Physiology of the Eye:
Anatomy and Physiology of the Eye (Cont.):

- **The sclera**: The protective outer layer of the eye, referred to as the “white of the eye” and it maintains the shape of the eye.

- **The cornea**: The front portion of the sclera, is transparent and allows light to enter the eye. The cornea is a powerful refracting surface, providing much of the eye's focusing power.

- **The choroid** is the second layer of the eye and lies between the sclera and the retina. It contains the blood vessels that provide nourishment to the outer layers of the retina.

- **The iris** is the part of the eye that gives it color. It consists of muscular tissue that responds to surrounding light, making the **pupil**, or circular opening in the center of the iris, larger or smaller depending on the brightness of the light.
Anatomy and Physiology of the Eye (Cont.):

- **The lens** is a transparent, biconvex structure, encased in a thin transparent covering. The function of the lens is to refract and focus incoming light onto the retina.

- **The retina** is the innermost layer in the eye. It converts images into electrical impulses that are sent along the optic nerve to the brain where the images are interpreted.

- **The macula** is located in the back of the eye, in the center of the retina. This area produces the sharpest vision.
Anatomy and Physiology of the Eye (Cont.):

- The inside of the eyeball is divided by the lens into two fluid-filled sections.

- The larger section at the back of the eye is filled with a colorless gelatinous mass called the vitreous humor.

- The smaller section in the front contains a clear, water-like material called aqueous humor.

- The conjunctiva is a mucous membrane that begins at the edge of the cornea and lines the inside surface of the eyelids and sclera, which serves to lubricate the eye.
Absorption of drugs in the eye:

**Factors affecting drug availability:**

1. Rapid solution drainage by gravity, induced lachrymation, blinking reflex, and normal tear turnover:

   - The normal volume of tears = 7 ul, the blinking eye can accommodate a volume of up to 30 ul without spillage, the drop volume = 50 ul
lacrimal nasal drainage:
Absorption of drugs in the eye:

2- Superficial absorption of drug into the conjunctiva and sclera and rapid removal by the peripheral blood flow:

3- Low corneal permeability (act as lipid barrier)

In general:
- Transport of hydrophilic and macromolecular drugs occurs through scleral route
- Lipophilic agents of low molecular weight follow transcorneal transport by passive diffusion and obey

*Ficks‘s first law of diffusion:*

\[ J = - D \cdot \frac{d C_m}{dx} \]
Corneal absorption:

\[ J = \text{The flux rate across the membrane} \]
\[ D = \text{diffusion coefficient} \]

- The diffusion coefficient \( \uparrow \) as the molecular size of the drug \( \downarrow \)

\[ C_m = \text{concentration gradient} \]

- As the drug solubility \( \uparrow \), the gradient \( \uparrow \), the driving force for drug entry into the aqueous humor \( \uparrow \)

**N.B.** the drug should have dual solubility (oil and water soluble) to traverse the corneal epithelium (lipid barrier) then the aqueous humour.
Corneal absorption:

- Poor Bioavailability
- Protective Mechanisms
  - (Short residence time)
  - * Blinking
  - * Reflex Lacrimation
  - * Nasolacrimal Drainage
- Anatomy of the eye
  - * Barrier properties of the cornea

Drug delivery in ocular therapeutics is a challenging problem.
A. Sterility:

- Ideally, all ophthalmic products would be terminally sterilized in the final packaging.

- Only a few ophthalmic drugs formulated in simple aqueous vehicles are stable to normal autoclaving temperatures and times (121°C for 20-30 min).

*Such heat-resistant drugs may be packaged in glass or other heat-deformation-resistant packaging and thus can be sterilized in this manner.

- Most ophthalmic products, however cannot be heat sterilized due to the active principle or polymers used to increase viscosity are not stable to heat.
A. Sterility (cont.):

* Most ophthalmic products are aseptically manufactured and filled into previously sterilized containers in aseptic environments using aseptic filling-and-capping techniques.
A. Sterility (cont.):

1. Sterile membrane filtration under aseptic conditions
   - But
   - Not suitable for susp.

2. Sterilization by autoclaving in the final container
   - But
   - Not suitable for heat labile drugs & plastic containers

3. Gas, as ethylene oxide
   - Or
   - Ionizing Radiations, as gamma rays
B. Ocular toxicity and irritation:

- Albino rabbits are used to test the ocular toxicity and irritation of ophthalmic formulations.
- The procedure based on the examination of the conjunctiva, the cornea or the iris.
- **E.g. USP procedure for plastic containers:**
  1. Containers are cleaned and sterilized as in the final packaged product.
  2. Extracted by submersion in saline and cottonseed oil.
  3. Topical ocular instillation of the extracts and blanks in rabbits is completed and ocular changes examined.
C. Preservation and 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. **So these products should be packaged in sterile, unit-of-use containers.**

- The most common organism is *Pseudomonas aeruginosa* that grow in the cornea and cause loss of vision.
C. Preservation and preservatives:

**Ophthalmic products may be packaged in multiple-dose containers when intended for the individual use of one patient**

1st Dose

Sterile

Contamination occur

Other doses may cause infection to eye

We add preservative to prevent the growth or to destroy, microorganisms accidentally introduced when the container is opened during use.
C. Preservation and preservatives:

Examples of preservatives:

1- Cationic wetting agents:
   • Benzalkonium chloride (0.01%)
   • It is generally used in combination with 0.01-0.1% disodium edetate (EDTA). The chelating, EDTA has the ability to render the resistant strains of PS aeruginosa more sensitive to benzalkonium chloride.

2- Organic mercurials:
   • Phenylmercuric nitrate 0.002-0.004% phenylmercuric acetate 0.005-0.02%.
C. Preservation and preservatives:

3- Esters of p-hydroxybenzoic acid:
  • Mixture of 0.1% of both methyl and propyl hydroxybenzoate (2:1)

4- Alcohol Substitutes:
  • Chlorobutanol (0.5%). Effective only at pH 5-6.
  • Phenylethanol (0.5%)
Manufacturing considerations:

A. Manufacturing Environment:
The environment should be sterile and particle-free through:

- Laminar-flow should be used throughout the manufacturing area.
- Total particles per cubic foot of space should be minimum.
- Relative humidity controlled to between 40 and 60%.
- Walls, ceilings and floors should be constructed of materials that are hard, non-flaking, smooth and non-affected by surface cleaners or disinfectants.
A. Manufacturing Environment:
A. Manufacturing Environment:

- **Ultraviolet lamps** provided in flush-mounted fixtures to maintain surface disinfection

- **Separate entrance** for personnel and equipment should be provided through specially designed air locks that are maintained at negative pressure relative to the aseptic manufacturing area and at a positive pressure relative to the noncontrolled area
A. Manufacturing Environment:
B. Manufacturing Techniques:

- **Aqueous ophthalmic solutions:**

Manufactured by **dissolution of the active ingredient** and all or a portion of the excipients into all or a portion of the water.

The sterilization of this solution **by heat or by sterilizing filtration** through sterile depth or membrane filter media into a sterile receptacle.

If incomplete at this point, this sterile solution is then mixed with the **additional required sterile components**, such as previously sterilized solutions of viscosity-imparting agents, preservatives, and so on, and the bath is brought to **final volume with additional sterile water**.
B. Manufacturing Techniques:

- **Aqueous suspensions:**

  Are prepared in much the same manner, except that before bringing to final volume with additional sterile water, the solid that is to be suspended is previously rendered Sterile by: *heat*, by *exposure to ethylene oxide* or *ionizing radiation (gamma or electrons)*, or by dissolution in an appropriate solvent, sterile filtration, and *aseptic crystallization*.

* Particle size should be monitored
B. Manufacturing Techniques:

- **Ophthalmic ointment:**

  * The ointment base is sterilized by heat and appropriately filtered while molten to remove foreign particulate matter. It is then placed into a sterile steam-jacketed kettle to maintain the ointment in a molten state under aseptic conditions, and the previously sterilized active ingredient(s) and excipients are added aseptically.

  * The entire ointment may be passed through a previously sterilized colloid mill for adequate dispersion of the insoluble components.

  * After the product is compounded in an aseptic manner, it is filled into previously sterilized container.

- Commonly employed methods of sterilization of packaging components include: Exposure to heat, ethylene oxide gas, and (gamma) irradiation.
B. Manufacturing Techniques:

- **Unpreserved formulations of active drug(s):**

  **The blow/fill/seal method**

  It is used for manufacture of **unpreserved ophthalmic products**, especially for artificial tear products.

  In this process, the first step is: to **extrude polyethylene resin at high temperature and pressure** and to **form the container by blowing the resin into a mold** with compressed air. The **product is filled as air is vented out**, and finally the container is **sealed on the top**.
The blow /fill/seal method:
C. Equipment:

* All tanks, valves, pumps and piping must be of the best available grade of corrosion-resistant stainless steel.
* All product-contact surfaces should be polished either mechanically or be electropolishing to provide a surface as free as possible from scratches or defects.
* Care should be taken in the design of such equipment to provide adequate means of cleaning and sanitization.
* For filling and capping machines, care should be taken in their design to yield equipment as free as possible from particles-generating mechanisms.
Ideal ophthalmic delivery system:

Following characteristics are required to optimize ocular drug delivery system:

- Good corneal penetration.
- Prolong contact time with corneal tissue.
- Simplicity of instillation for the patient.
- Non irritative and comfortable form
- Appropriate rheological properties
CLASSIFICATION OF OCULAR DRUG DELIVERY SYSTEMS:

Topical eye drops:
- Solutions
- Suspensions
- Powders for reconstitution
- Sol to gel systems

- Ointments
- Gels
- Ocular inserts

Intraocular Dosage Forms
* Injections
* Irrigating solutions
* Implants
A. Topical Eye drops:

- **Administration:**
  - Pull down the eyelid
  - Tilting the head backwards
  - Look at the ceiling after the tip is pointed close to the lower cul-de-sac
  - Apply a slight pressure to the rubber bulb or plastic bottle to allow a drop to fall into the eye.
  - Do not squeeze lids

*To prevent contamination:*
- Clean hands
- Do not touch the dropper tip to the eye and surrounding tissue
A. Topical Eye drops:

1- Solutions:
- Ophthalmic solutions are sterile solutions, essentially free from foreign particles, suitably compounded and packaged for instillation into the eye.
1- Solutions:

*Nearly all the major ophthalmic therapeutic agents are water-soluble salts.*

- The selection of the appropriate salt form depends on:
  - solubility
  - Ocular toxicity
  - The effect of pH, tonicity, and buffer capacity
  - Compatibility with the total formulation
  - The intensity of any possible burning sensations

- The most common salt forms used are: the hydrochloride, sulfate, nitrate, and phosphate.

- Salicylate, hydrobromide, and bitartrate salts may be used.

- For drugs that are acidic, such as the sulfonamides, sodium salts is used.
1- Solutions:

**Effects of salt Form on Product Properties**

<table>
<thead>
<tr>
<th>Salt form</th>
<th>Discomfort reaction</th>
<th>pH range</th>
<th>Buffer capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine hydrochloride</td>
<td>Mild to moderate stinging</td>
<td>2.5-4.5</td>
<td>Medium</td>
</tr>
<tr>
<td>Epinephrine bitartarate</td>
<td>Moderate to severe stinging</td>
<td>3.4</td>
<td>High</td>
</tr>
<tr>
<td>Epinephrine borate</td>
<td>Only occasional mild stinging</td>
<td>5.5-7.5</td>
<td>Low</td>
</tr>
</tbody>
</table>

*The bitartarate form is a 1:1 salt, and the free carboxyl group acts as a strong buffer, resisting neutralization by the tears, and may cause considerable stinging.*

- **The borate** solution with lower buffer capacity, a more nearly physiological pH, and better patient tolerance; however, it is less stable than the other two salts.

- **The hydrochloride salt** combines better stability than the borate with acceptable patient tolerance.
Disadvantages of eye solutions:

1- The very short time the solution stays at the eye surface.

The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration and the instilled volume.

2- its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage)

3- the instability of the dissolved drug

4- the necessity of using preservatives.
2- 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, or efficacy.

• The major topical ophthalmic suspensions are the steroid anti-inflammatory agents prednisolone acetate, dexamethasone, fluorometholone, and rimexolone.

• Water-soluble salts of prednisolone phosphate and dexamethasone phosphate are available; however, they have a lower steroid potency and are poorly absorbed.

• An ophthalmic suspension should use the drug in a microfine form; usually 95% or more of the particles have a diameter of 10 μm or less.

to prevent irritation or scratching of the Cornea.
2- Suspensions:

*In some cases it may be advantageous to convert a water-soluble active ingredient to an insoluble form for development as an ophthalmic suspension dosage form.

1- to extend the practical shelf life of the water-soluble form,

2- to improve the compatibility with other necessary compositional ingredients,

3- to improve its ocular tolerability.

Such an example is the β-blocker betaxolol HCL, which is an effective IOP-lowering agent. The ophthalmic solution cause discomfort and transient burning upon instillation.

It was discovered that an insoluble form suspension of betaxolol (Betoptic ® S) increased the ocular bioavailability of betaxolol and the ocular tolerance.
3- Powders for Reconstitution:

Drugs that have only limited stability in liquid form are prepared as sterile powders for reconstitution by the pharmacist prior to dispensing to the patient. These drugs include \textit{\textbf{\textit{\textalpha}-chymotrypsin}}, \textit{\textbf{\textit{\textalpha}-acetylcholine}}.

The sterile powder is usually manufactured by \textit{\textbf{\textit{\textit{\textalpha}-lyophilization in individual glass vials}}.}

\textbf{Mannitol is usually used as a bulking agent and lyophilization aid} and is dissolved in the solution with the drug prior to drying.

It was found that \textit{potassium acetate} used in place of mannitol as a \textit{drying aid} produced a more stable product and allows freeze-drying to lower residual moisture content.
Solutions that are liquid in the container and thus can be instilled as eye drops but gel on contact with the tear fluid and provide increased contact time with the possibility of improved drug absorption and increased duration of therapeutic effect

* Liquid-gel phase transition-dependent delivery systems vary according to the particular polymer(s) employed and their mechanism(s) for triggering the transition to a gel phase in the eye take advantage of changes in temperature, pH, ion sensitivity, or lysozymes upon contact with tear fluid
4- Gel-Forming Solutions

In Situ Forming Gels

Temperature
Poloxamer
Xyloglucan

Ion (Ca)
Alginic acid
Na alginate
Gellan gum

pH
Cellulose acetate phthalate

Lysozyme protein in the tear fluid
Xanthan gum

Mucoadhesive thermosensitive in situ forming gels
Different mucoadhesive polymers were added to poloxamer
1- Carbopol 940
2- Hydroxypropylmethyl cellulose (HPMC)
3- Hydroxyethyl cellulose (HEC)
Example of Gel-forming ophthalmic solutions in the market is;

*Timolol maleate*, which is used to reduce elevated intraocular pressure (IOP) in the management of glaucoma. With the gel-forming solutions, IOP-lowering efficacy was extended from 12 to 24 hours and thus required only once-a-day dosing.
Inactive Ingredients in Topical Drops:

The inactive ingredients in ophthalmic solution and suspension dosage forms are necessary to perform one or more of the following functions:

Adjust concentration and tonicity,
Buffer and adjust pH,
Stabilize the active ingredients against decomposition,
Increase solubility,
Impart viscosity,
and act as solvent or increase solubility.

The use of ingredients to impart a color, odor, or flavor is prohibited.
1- Tonicity and Tonicity-Adjusting Agents:

* The pharmacist should adjust the tonicity of an ophthalmic solution correctly (i.e., exert an osmotic pressure equal to that of tear fluids, generally agreed to be equal to 0.9\% NaCl).

* A range of 0.5-2.0\% NaCl equivalency does not cause a marked pain response and a range of about 0.7-1.5\% should be acceptable to most persons.

* The eye seems to tolerate hypertonic solutions better than hypotonic ones.

*Common tonicity adjusting ingredients include: NaCl, KCl, buffer salts, dextrose, glycerin, propylene glycol, and mannitol.
Isotonicity

Lacrimal fluid is isotonic with blood having an isotonicity value corresponding to that of 0.9% NaCl solution.

Ideally, an ophthalmic solution should have this isotonicity value.

But

The eye can tolerate isotonicity from 0.6% to 2% NaCl without marked discomfort.

Some ophthalmic solutions are necessarily hypertonic in order to enhance absorption and provide a concentration of the active ingredient strong enough to exert an effective action.
2- pH Adjustment and Buffers:

- pH adjustment is very important as pH affects:
  1- to render the formulation more stable
  2- The comfort, safety and activity of the product.
  
  Eye irritation  →  increase in tear fluid secretion  →  Rapid loss of medication.
  3- to enhance aqueous solubility of the drug.
  4- to enhance the drug bioavailability
  5- to maximize preservative efficacy
2- pH Adjustment and Buffers:

Ideally, every product would be buffered to a pH of 7.4 (the normal physiological pH of tear fluid).

The pH values of ophthalmic solutions are adjusted within a range to provide an acceptable shelf life.

When necessary, they are buffered adequately to maintain stability within this range for at least 2 years.

If buffers are required, their capacity is controlled to be as low as possible (Low buffer capacity) thus enabling the tears to bring the pH of the eye back to the physiological range.
Normal tears have a pH of about 7.4 and possess some buffer capacity.

So

Any formulation having different pH than 7.4 will be neutralized by normal buffer of tears.

But

Most alkaloidal salts precipitate as the free alkaloid at this pH. And many drugs are chemically unstable at pH levels approaching 7.4.

So

For this reason, the buffer system should be selected that is nearest to the physiological pH of 7.4 & does not cause precipitation of the drug or its rapid deterioration.
**Conclusion:**
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.

1- to enable the tears to bring the pH of the eye back to the physiological range.
2- to avoid effect of buffers on tonicity.

**Examples of buffer vehicles used:**
- Boric acid vehicle: pH of slightly below 5
- Isotonic phosphate vehicle: pH ranges from 5.9 - 8
3- Stabilizers & Antioxidants:

* Stabilizers are ingredients added to a formula to decrease the rate of decomposition of the active ingredients.

* Antioxidants are the principal stabilizers added to some ophthalmic solutions, primarily those containing epinephrine and other oxidizable drugs.

Sodium bisulfite or metabisulfite are used in concentration up to 0.3% in epinephrine hydrochloride and bitartrate solutions.

Several antioxidant systems have been developed. These consist of ascorbic acid and acetylcysteine, and Sodium thiosulfate.
4- Surfactants:

*The order of surfactant toxicity is: anionic > cationic >> nonionic.*

- Several nonionic surfactants are used in relatively low concentrations to aid in dispersing steroids in suspensions and to achieve or to improve solution clarity.

*Those principally used are the Sorbitan ether esters of oleic acid (Polysorbate or Tween 20 and 80),*
5- Viscosity-Imparting Agents:

Polyvinyl alcohol, methylcellulose, hydroxypropyl methylcellulose, hydroxyethylcellulose, and Carbomers, are commonly used to increase the viscosity of ophthalmic solutions and suspensions. (to retard the rate of setting of particles)

• They *increase the ocular contact time*, thereby *decreasing the drainage rate*, *increase the mucosdhesiveness* and increasing drug bioavailability.

* A secondary benefit of the polymer solutions is a *lubricating effect*. The major commercial viscous vehicles are *hydroxypropyl methylcellulose (Isopto ®)* and *polyvinyl alcohol (Liquifilm ®)*.

Disadvantages: 1- produce blurring vision as when dry form a dry film on the eye lids 2- make filtration more difficult
6- Vehicles:

Ophthalmic drops: (using purified water USP) as the solvent.
Purified water meeting USP standards may be obtained by: distillation, deionization, or reverse osmosis.

• Oils have been used as vehicles for several topical eye drop products that are extremely sensitive to moisture.

• When oils are used as vehicles in ophthalmic fluids, they must be of the highest purity. Vegetable oils such as olive oil, castor oil, and sesame oil have been used for extemporaneous compounding. These oils are subject to rancidity and, therefore, must be used carefully.
Packaging:

- Eyedrops have been packaged almost entirely in plastic dropper bottles (*the Drop-Tainer® plastic dispenser*).
- **The main advantage of the Drop-Tainer are:**
  - convenience of use by the patient
  - decreased contamination potential
  - lower weight
  - lower cost
- The plastic bottle and dispensing tip is made of *low-density polyethylene (LDPE) resin*, which provides the necessary flexibility and inertness.
- The cap is made of harder resin than the bottle.
** Advantage of LDPE resin:
- Compatible with a very wide range of drugs and formulation components

** Disadvantage of LDPE resin:
- Sorption and permeability characteristics e.g. volatile preservatives such as chlorobutanol
- Weight loss by water vapor transmission
- LDPE resin is translucent, if the drug is light sensitive, additional package protection is required (using opacifying agent such as titanium dioxide)

-- LDPE resin sterilized by gamma irradiation or ethylene oxide
Packaging:

- A special plastic ophthalmic package made of polypropylene is introduced. The bottle is filled then sterilized by steam under pressure at 121°C.

A few products still remain in glass dropper bottles because of special stability considerations (drugs that are sensitive to oxygen or contain permeable components that are not sufficiently stable in plastic).

Powders for reconstitution also use glass containers, owing to their heat-transfer characteristics, which are necessary during the freeze-drying processes. A sterile dropper assembly is usually supplied separately.
Packaging:

- The glass bottle is made sterile by dry-heat or steam autoclave sterilization.
- Amber glass is used for light-resistance.
B. Semisolid Dosage Forms: Ophthalmic Ointments and Gels:

- **Formulation:**

  The ointment vehicle used in ophthalmology is usually a mixture of mineral oil and petrolatum base. The mineral oil is added to reduce the melting point and modify the consistency.

  *The chief disadvantages of the use of ophthalmic ointments are their greasy nature, the blurring of vision produced, imprecise dosing, and difficult self administration.*

  They are most often used as *adjunctive night time therapy*, while eyedrops administered during the day.

- Ointments are used as vehicles for antibiotics, sulfonamides, antifungals and anti-inflammatories.
- Petrolatum vehicle used as an ocular lubricant to treat dry eye syndromes.
  **It is suitable for moisture sensitive drugs and has longer contact time than drops.**
B. Semisolid Dosage Forms: Ophthalmmic Ointments and Gels:

*The anhydrous petrolatum base may be made more miscible with water through the use of an anhydrous liquid lanolin derivative.*

*The carbomer polymeric gel base itself has been used successfully to treat moderate to severe cases of dry eye.*

*Gels have increased residence time and enhanced bioavailability than eye drops.*

N.B. Emulsion bases should not be used in the eye owing to ocular irritation produced by the soaps and surfactants used to form the Emulsion.

*Ophthalmmic ointment must be free from large particles and must meet the requirements for "leakage" and for "metal particles"
Chlorobutanol and methyl- and propylparaben are the most commonly used preservatives in ophthalmic ointments.
Ophthalmic ointments are packaged in:

1. **Small collapsible tin tube**, usually holding 3.5 g of product. The pure tin tube is compatible with a wide range of drugs in petrolatum-based ointments.
2. **Aluminum tubes** have been used because of their lower cost and as an alternative should the supply of tin be interrupted.
3. **Plastic tubes made from flexible LDPE resins** have also been considered as an alternative material. • Filled tubes may be tested for leakers.
• The screw cap is made of polyethylene or polypropylene.
* The tube can be a source of metal particles and must be cleaned carefully before sterilization.

(By autoclaving or by ethylene oxide)
How to Use Eye Ointments and Gels Properly?
C. Solid Dosage Forms
Ocular Inserts

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

![Diagram of ophthalmic insert](image)
**C. Solid Dosage Forms**

**Ocular Inserts**

- **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.
C. Ocular Inserts

I. Insoluble inserts:

- **Insoluble insert** is a multilayered structure consisting of a drug containing core surrounded on each side by a layer of copolymer membranes through which the drug diffuses at a constant rate.
- The rate of drug diffusion is controlled by:
  - The polymer composition
  - The membrane thickness
  - The solubility of the drug

**e.g. The Ocusert® Pilo-20 and Pilo-40 Ocular system**
- Designed to be placed in the inferior cul-de-sac between the sclera and the eyelid and to release pilocarpine continuously at a steady rate for 7 days for treatment of glaucoma.

- consists of (a) a drug reservoir, pilocarpine (free base), and a carrier material, alginic acid: (b) a rate controller ethylene vinyl acetate (EVA) copolymer membrane.
C. Ocular Inserts
I. Insoluble inserts:

Photograph of patient with Ocusert (pilocarpine) in place in lower cul-de-sac of right eye
II. Soluble Ocular inserts:

- Soluble inserts consists of all monolytic polymeric devices that at the end of their release, the device dissolve or erode.

**Types**

a) **Based on natural polymers** e.g. collagen.

b) **Based on synthetic or semi synthetic polymers** e.g. Cellulose derivatives – Hydroxypropyl cellulose, methylcellulose or Polyvinyl alcohol, ethylene vinyl acetate copolymer.

- The system soften in 10-15 sec after introduction into the upper conjunctivall sac, gradually dissolves within 1 h, while releasing the drug.

- **Advantage:** being entirely soluble so that they do not need to be removed from their site of application.
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 artificial tear solutions.

The insert is composed of 5 mg of hydroxypropylcellulose in a rod-shaped form about 1.27mm diameter by about 3.5 mm long. No preservative is used, since it is essentially anhydrous.
D. Intraocular Dosage Forms

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

- **Requirements for formulation:**
  1. sterile and pyrogen-free
  2. strict control of particulate matter
  3. compatible with sensitive internal tissues
  4. packaged as preservative-free single dosage
D. Intraocular Dosage Forms: 1- Irrigating Solutions

- It is a balanced salt solution was developed for hydration and clarity of the cornea during surgery.

* It contains the five essential ions: sodium, potassium, calcium, magnesium, and chloride. It also contains citrate, acetate ions, and a potential source of bicarbonate.

* It is formulated to be iso osmotic with aqueous humor and has a neutral to slightly alkaline physiological pH.

* They are required to be preservative-free to prevent toxicity. They must be non-pyrogenic, therefore requiring sterile water for injection (WFI) as the vehicle.

These irrigating solutions have been developed to be used without the addition of any drugs or. Some drugs such as epinephrine are added to the irrigating solution prior to surgery and used by cataract surgeons.
D. Intraocular Dosage Forms
2- Intraocular Injections

The ophthalmologist use available parenteral 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 injections include miotics, viscoelastics and an antiviral agent for intravitreal injection.
of their *lubricant and viscoelastic properties*. They are injected into the anterior segment of the eye during surgery for removal of *cataracts and corneal transplantation*.

*Chondroitin sulfate* is also used in combination with sodium hyaluronate as a viscoelastic surgical aid to provide higher viscosities, which may provide additional tissue protection.

*Sterile hydroxypropyl methylcellulose* are also used as ocular surgical aids similar to the viscoelastics in *cataract surgery (OcuCoat®)*.
• **Intravitreal Implant**

An intravitreal sterile implant containing ganciclovir or antineoplastic agents is a **tablet** of ganciclovir with **magnesium stearate** and is coated to retard drug release with **polyvinyl alcohol** and **ethylene vinyl acetate polymers** such that the device when surgically implanted in the vitreous cavity releases drug over a 5- to 8-month period.
E. Miscellaneous

1- 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.
Iontophoresis
E. Miscellaneous

2- The vesicular delivery system

The Vesicular Delivery System

Liposomes which are phospholipid based vesicles

Niosomes which are non-ionic surfactant based vesicles

Microspheres and nanoparticles
Liposomes are microscopic and submicroscopic vesicles consisting of one or more concentric spheres 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 aqueous media resulting in closed bilayer structures.
Advantages of Niosomes and liposomes

1- Sustained release of active compounds.
2- Protect drugs from degradation.
3- Biocompatible, biodegradable and non-immunogenic.
4- Can entrap both hydrophilic and lipophilic drugs.
5- The bilayer can efficiently penetrate the cornea of the eyes.
6- They have low toxicity because of their non-ionic nature.
Types of contact lenses:

1- **Hard contact lenses**
   - Made of rigid plastic resin *polymethylmethacrylate*
   - Impermeable to oxygen and moisture

2- **Soft contact lenses**
   - Made of hydrophilic transparent plastic, *hydroxyethylmethacrylate*
   - Contain 30 – 80% water so are permeable to oxygen
   - Have two types: daily wear and extended wear
Contact Lenses & Care Solutions:

3- Rigid gas permeable (RGP)
   - Take the advantages of both soft and hard lenses, they are hydrophobic and oxygen permeable.

Advantages of hard contact lenses and RGP lenses:
1- strength durability
2- resistant to absorption of medications and environmental contaminants
3- visual acuity

Disadvantages:
1- require adjustment period of the wearer
2- more easily dislodged from the eye
Contact Lenses & Care Solutions:

Advantages of soft contact lenses:
1- worn for longer periods
2- do not dislodge easily

Disadvantages:
1- have a shorter life span and the wearer must ensure that the lenses do not dry out

"soft" lens | "hard" lens
Care of contact lenses:

- **Products for soft contact lenses:**
  
  **Cleaners**
  
  - To remove lipid and protein debris
  - **formulation:**
    1. viscolizing surface-active agent: to enable gentle friction with fingertips
    2. antibacterial-fast acting: benzalkonium chloride
Products for soft contact lenses:

- **Rinsing and storage solutions**
  - Remove the cleaning solution, facilitate lens hydration, inactivation of microbial contamination and prevent the lens from drying out
  - **Formulation:**
    - 0.9% NaCl (isotonic)
    - Antibacterial- 3% hydrogen peroxide for 30 min followed by inactivation with sodium pyruvate
Enzyme protein digest

- For occasional cleaning followed by washing before wearing

Formulation:

- Proteolytic enzyme: papain solution tablet to produce a solution when dissolved in water
Products for hard contact lenses:

- **Rinsing and storage solutions**
  - For cleaning, microbial inactivation and hydration

  **Formulation:**
  - surface-active agent
  - Antimicrobial:
    (0.01% benzalkonium chloride + 0.1% sodium edetate)

- **Wetting solutions**
  - To achieve rapid wetting by the lachrymal fluid and promote comfort
  - Facilitate insertion of the lens
  - Provide lubrication

**Consist of:** viscosity-increasing agent (hydroxy ethyl cellulose + wetting agent (polyvinyl alcohol) + preservatives (benzalkonium chloride or sodium edetate) + buffers and salts to adjust pH and tonicity.