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Opthalmic inserts - A Comprehensive Review

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ABSTRACT

Ophthalmic insert is one of the most challenging tasks that pharmaceutical researchers are required to complete. The capacity to maintain a therapeutic level of the drug at the site of action for an extended period of time is one of the primary obstacles in ocular therapy. The ophthalmic formulations are offered as sterile, isotonic, buffered solutions. For the eyes Several different dose forms are created and sold for the delivery of medications. The most common dosage form provided is eye drop solution since drops are simpler to use. Also employed for sustained therapeutic action include ointments, suspensions, and gelled systems. [1] The biggest problem with this approach is that eye drops require frequent dosage. Ocuserts, which are innovative medication delivery methods for this form of distribution, include Gelled systems, ointments, and solutions. The major issue with this strategy is that eye drops need to be used often. [2]

Key Words

Novel Ophthalmic Drug Delivery System, Ocular Inserts, Bio-erodible erodible Implantable Elements, Predetermined Bioavailability. [3]

I. INTRODUCTION

One of the most exciting and difficult issues facing pharmaceutical researchers is the delivery of drugs into the eye. One of the biggest obstacles to using ocular medicine is to each a therapeutic level at the site of action and keep it there for an extended length of time. The eye is extraordinarily impenetrable to foreign chemicals due to its anatomy, physiology, and biochemistry. **[4]** The tricky part for the formulator is getting beyond the eye's defences without inflicting long-term tissue damage. The creation of the most effective and cutting-edge ocular medication delivery systems is urgent due to the advancement of new, more sensitive diagnostic methods and therapies. An ocular drug's therapeutic effectiveness can be significantly increased by extending its contact time with the corneal surface. In order to accomplish this, viscosity-improving To maintain the duration of close drug-eye contact, agents are added to eye drop preparations or the medicine is manufactured in a water-insoluble ointment formulation.

Unfortunately, these dose forms do not produce a constant drug bioavailability and only slightly increase the maximum sustained drug-eye contact compared to eye drop solutions. It is still necessary to take multiple drugs throughout the day. **[5]** These practical concerns have sparked an investigation into other approaches of ocular medication delivery. Ocular implants, which serve as the vehicle for the release of one or more active ingredients. However it is now obvious that creating an ocular implant that consistently combines controlled release with no patient irritability presents a significant technical difficulty. **[6]**

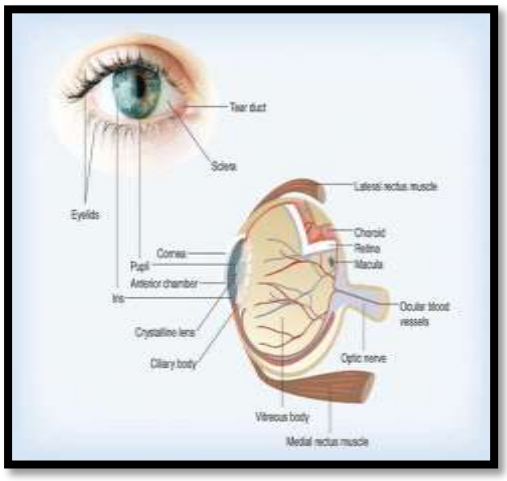

Fig. Structure of Eye

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The traditional drug delivery methods for the eyes include:

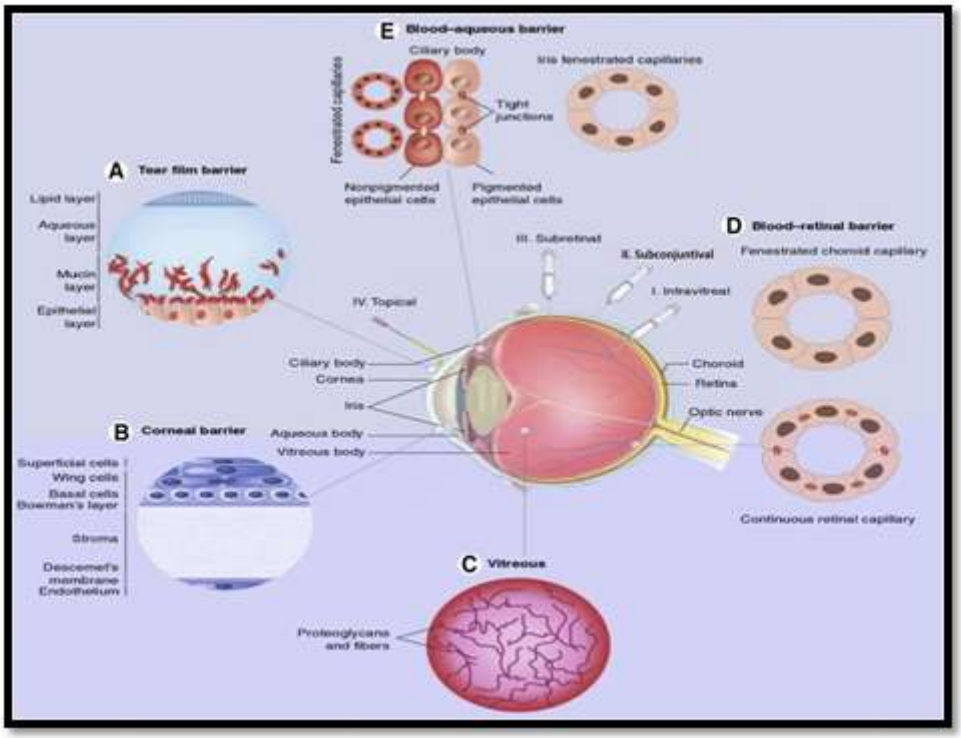
1.Eye drops (solution, suspension)
2.Ophthalmic ointments

The pre-corneal area is where the majority of the injected volume is eliminated from the eye drop dosage form, which has the inherent disadvantage of being difficult to install . resulting in a bioavailability of between 1 and 10% of the total administered dose. **[7]** Due to conjunctival absorption, rapid solution drainage by gravity, induced lachrymation, the blink reflex, low corneal permeability, and normal tear turnover, medications administered as eye drops have a limited bioavailability and quickly pass through the pre-corneal layer of the eye. **[8]** Many ocular drugs are used at high concentrations because of their poor ocular bioavailability. Due to the high peak drug concentrations in the eye and systemic circulation, this can have both ocular and systemic side-effects. To maintain a continuous sustained vision, frequent intermittent instillations of eye drops. **[9]**

This delivers an enormously variable dose of medicine to the eye. IN order to avoid the intolerably high toxicity caused by saturated fat, suspension types of pharmaceutical dosage forms are made using relatively water-insoluble medicines. **[10]** Medication solutions that are water soluble.

Objective

1. The duration of a drug's ongoing contact with corneal tissue simplicity in both
2. The duration of a drug's ongoing contact with corneal tissue simplicity in both installation an d removal.
3. A non-irritating variant
4. Excellent rheological qualities**.[11]**



History

In the 19th century, dry filter paper squares were employed as the first solid medicament (the forerunners of the modern insoluble inserts).impregnated with dry liquids, such as pilocarpine hydrochloride and atropine sulphate. Little pieces were cut and placed beneath the eyelid. **[12]** Lamellae, the forerunners of the modern soluble inserts, were later created. They were made of glycerinated gelatine that included several ophthalmic medications. **[13]** Up to the early part of the 20th century, official compendia contained glycerinated gelatine" lamellae." "Lamellae were used, but their use was discontinued when stricter guidelines for the sterility of ophthalmic preparations were implemented. Ophthalmic inserts are currently generating more interest. **[14]**

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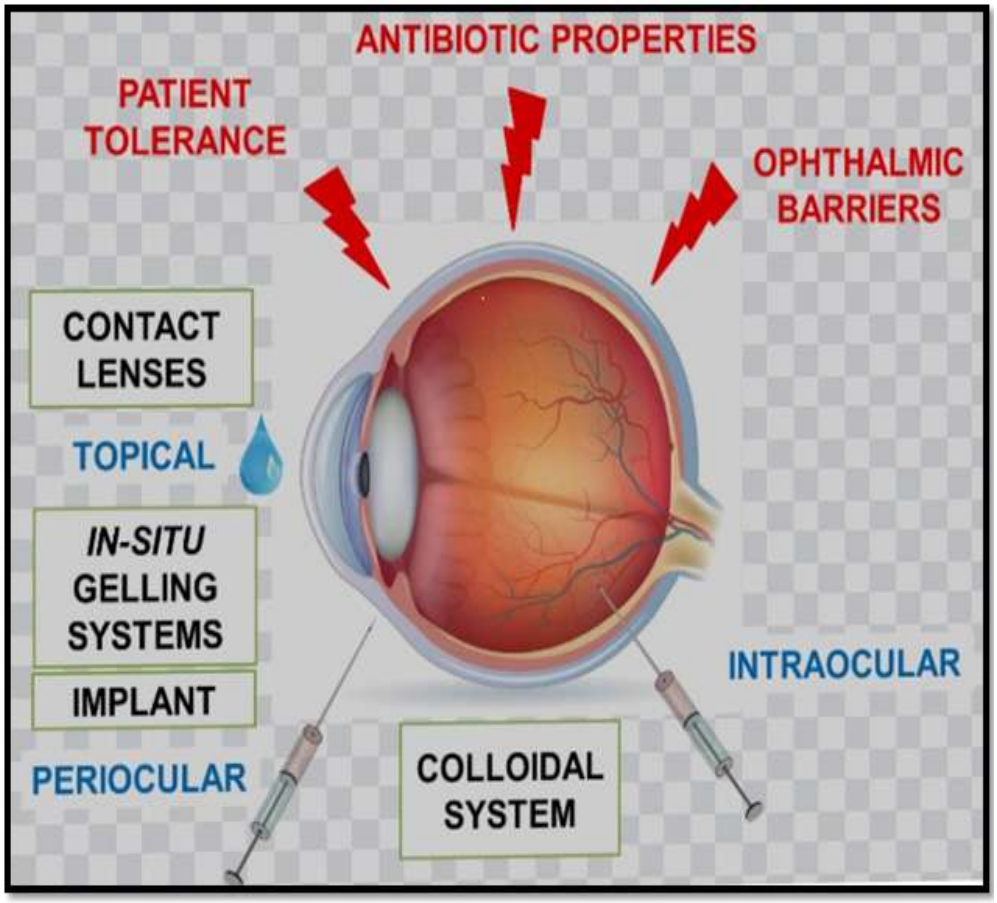

Advantages

- Administration of an accurate dose in the Eye and thus a better therapy.
- Reduction of systemic side effects and

Thus reduced adverse effects.

- Reduction of the number of

Administrations and thus better patient.

- Compliance, Comfort.
- Lack of explosion.
- Easy to handling and insertion.
- Non-interference with vision and oxygen

Permeability

- Sterility
- Stability
- Exclusion of preservatives.
- Increased shelf life with comparison to

Aqueous solutions due to absence of

Water

- Increased dosing accuracy to combat the negati ve effects of pulsed dosing produced by traditi onal systems
- To provide a controlled and sustained drug deli very.
- To extend the duration of corneal contact to bo ost the drug's ocular bioavailability.
- By successfully adhering to the corneal surface , this is possible.
- To offer targeting within the ocular globe to st op the loss to other ocular tissues.
- To get around defences like conjunctive absorp tion, drainageand lacrimation.
- To increase the patient's comfort, compliance, and drug performance during therapy.
- To provide a better location for the delivery sy stem. **[15]**

Disadvantages

- The insert can be quickly lost.
- Occasionally, the insert twists to create a "a" decreasing the delivery rate by using a figure eight.
- There might be a leak.
- Dislocation of the instrument in front of the eye.
- The cornea's limited permeability, which result s in reduced

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ophthalmic medication absorption, is the physi ological
constraint.

- A significant portion of the dose that is admini stered drains
into the lacrimal duct, which may result in unin tended
systemic side effects.
- Because the therapeutic action of the medicine is quickly eliminated by eye blinking and tear production, frequent
dosing is required. **[16]**

Classification of ophthalmic inserts

❖ Insoluble ophthalmic inserts

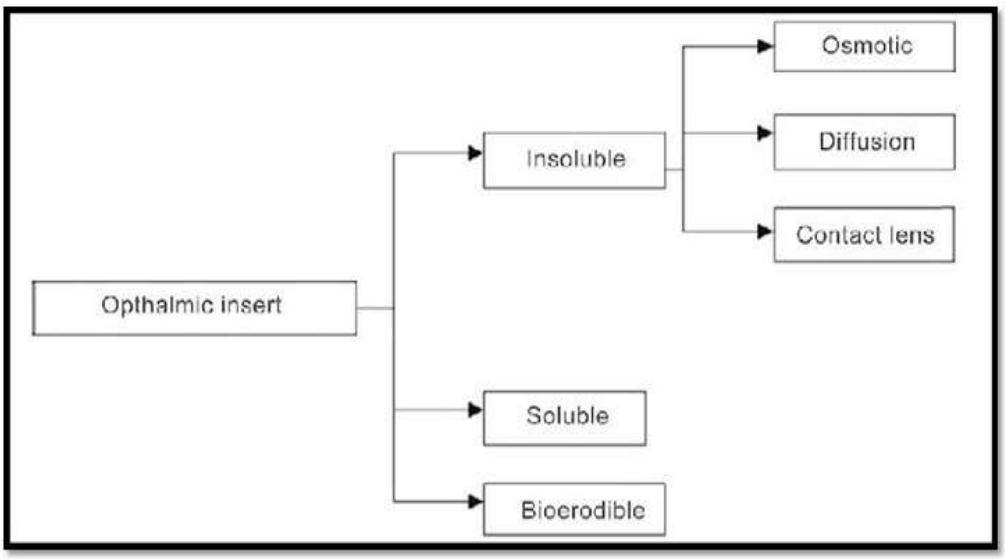
1. Diffusional insert
2. Osmotic Insert
3. Hydrophilic contact
4. Contact lenses

❖ Soluble opthalmic inserts

1. Natural polymers inserts
2. Synthetic inserts

❖ Bio-erodible opthalmic inserts

1. Soluble opthalmic drug inserts
2. Lacrisert
3. Minidisc
4. Collagen shields



Flow Diagram

Insoluble ophthalmic inserts

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1. Diffusion insert

- ❖ semi-permeable or microporous membrane surrounds the central reservoir of the drug to allow for drug diffusion.
- ❖ In order to control diffusion,It is penetrated by lacrimal fluid.
- ❖ It stops the barrier's ongoing decline in release rate.
- ❖ **Release follows:** Zero order kinetics[16]

2. Osmotic Insert

- The two types of osmotic inserts typically cons ist of a centre portion surrounded by a peripher y.

Type 1

- The centre portion is made up of a single drug reservoir enclosed by a polymer as distinct tiny deposits, with or without an extra osmotic solution scattered throughout the polymeric matrix.
- The second peripheral component of these inserts was made up of an insoluble semipermeable polymer film.
- The osmotic pressure against the surface takes the shape of apertures.
- It ruptures due to the polymer matrix.
- In close proximity to the device's surface, the medicine is then released from the deposits through these pores. **[17]**

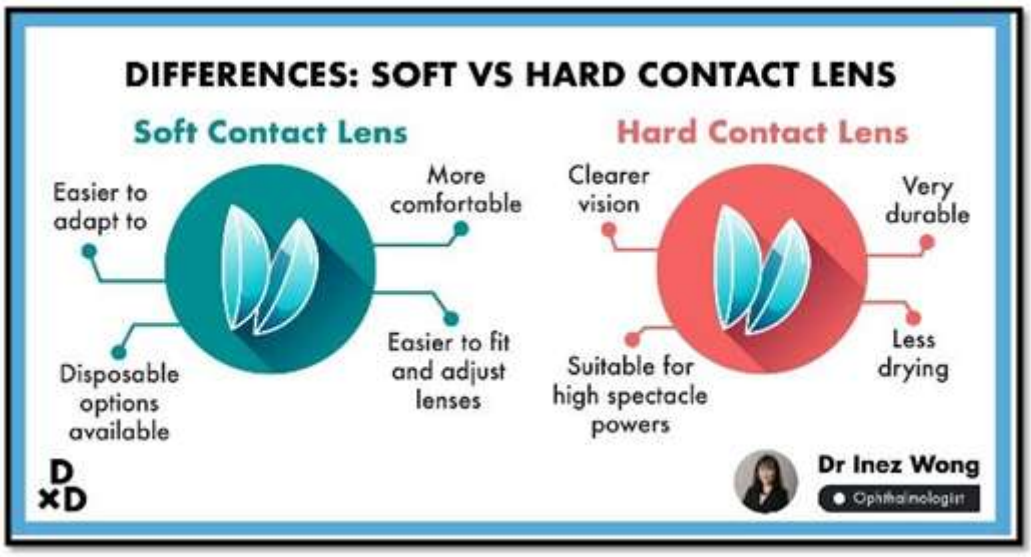
Type 2

- Two distinct sections make up the core portion. The drug and osmotic solutes are placed in two distinct compartments, with the drug reservoir being surrounded by an elastic impermeable membrane and the osmotic solute reservoir being surrounded by a semi-permeable membrane.
- Similar to type 1, the second peripheral component of this type. **[18]**

3. Hydrophilic contact

- Give the eye a prolonged release of the medication.
- These conveniently cross-linked hydrophilic or hydrophobic polymers provide a three-dimensional matrix that may hold water or solid components in aqueous solutions. **[19]**
- **There are two type of contact lenses -**

1-Soft contact leases
2- Hard contact lenses



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4. lens Contact

- Hydrophilic lens that has been pre-soaked.
- **Drug release:** Within the first 30 minutes
- **Alternate approach:** incorporate drug either as solution or suspension of solid monomer mixture
- The maximum release rate is 180 hours. **[20]**

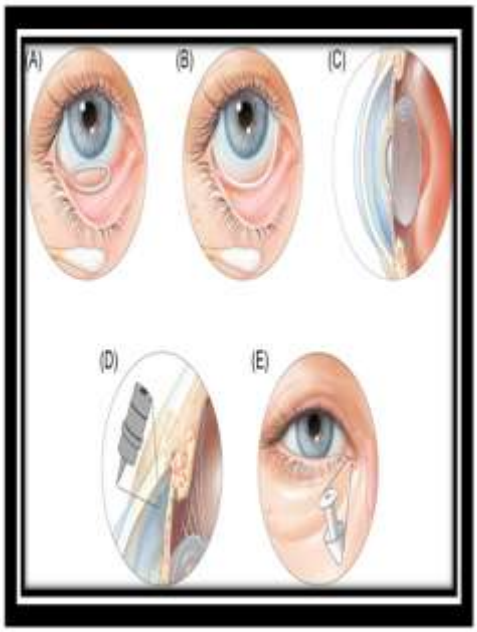
Soluble opthalmic inserts

1. Natural polymers inserts

- Natural polymer, especially collagen, is used to make soluble ophthalmic inserts.
- The insert is soaked in a solution containing the therapeutic agent, dried, and then rehydrated before being applied to the eye in order to absorb the medication.
- Depending on the amount of medication solution added to the composite, how long it is soaked for, and how long it is allowed to soak, The amount of medicine loaded will depend on the presence of the binding agent.
- Drug is progressively released from between collagen molecule spaces when the collagen degrade. **[21]**

2. Synthetic inserts

- This is centred on the usage of polymers, namely synthetic polymers like polyvinyl alcohol and semi-synthetic polymers like cellulose derivatives.
- Eudragit, a polymer frequently utilised for enteric coating or as an insert coating agent, can be employed to reduce release rate. **[22]**



Bio-erodible opthalmic inserts

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A. Soluble opthalmic drug inserts

- Soviet scientists created little water-soluble eye drops specifically for astronauts because they could not be used in weightlessness.
- **Composition:** Acryl amide, Vinyl Pyrolidone, Ethyl acrylate.
- **Weight** 15-16 mg
- Softens in 10–15 seconds; transforms into viscous liquids in 10–15 minutes; takes 30–60 minutes. Turns into a polymeric solution.

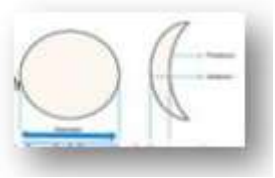
➢ **Advantages of SODI:**

- A single SODI application reduces the need for 4–12 eye drops or 3–6 applications of ointments.
- Daily treatment for glaucoma and trachoma. **[23]**

B. Lacrisert

- Sterile, Rod Shaped device.
- **Composition:** HPC without preservative.
- **Weight:** 5mg
- **Dimension:** Diameter: 12.5mm, Length: 3.5mm
- **Use:**Dry eye treatment, Keratitis Sicca.

C. Minidisc



- It is composed of a counter disc with an eyeball-contactable convex front and concave back surface.

- **Composition:**

1. Silicon based pre polymer.
2. Hydrophilic or Hydrophobic.
3. Drug release for 170 hr.
4. Further increase in gentamycin sulphate to 320 hrs.

- Due to further cross-linking of the polymer matrix, exposure to heat and gamma radiation may slow down release rate **[24]**

D. Collagen shields

- Collagen makes up more than 25% of the protein in animals' bodies overall and is the structural protein of bones, tendons, ligaments, and skin.
- This protein, which is produced from intestinal collagen and used mostly for catgut suture, has a number of biomedical applications.

[25]

Evaluation of opthalmic inserts

1. Thickness of opthalmic inserts
2. Weight variation test
3. Surface pH determination
4. Drug content uniformity
5. Swelling index
6. Folding endurance
7. Tensile Strength
8. Hardness
9. Accelerated Stability study
10. Occular insertion

1. Thickness of ocular insert

- Using a dead weight thickness gauge, the thickness of the inserts is measured.
- With the assistance of the lifting lever fixed to the side of the dial, the foot is raised after initial Adjustments Gauge
- The insert is positioned on the anvil so that the measurement area for thickness is below the foot. **[26]**

2.Weight variation test

- A random sample of inserts is taken from each batch, and each one is weighed on an electronic balance.
- Each formulation's mean insert weight is kept track of.

3.Surface pH Determination

- Inserts are left to swell for 5 h on agar plate prepared by Dissolving 2% (w/v) agar in warm simulated tear fluid (STF; sodium chloride: 0.670 g, sodium bicarbonate: 0.200 g, calcium

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chloride. 2H 2 O: 0.008 g, and purified Water q. s. 100 g) of pH 7.4 under stirring and then Pouring the solution into Petri dish till gelling at room Temperature. After the time of soaking, the pH of the Wet surface is measured by placing the electrode in Contact with the surface of the insert. **[27]**

4.Drug content uniformity

- The individual inserts are each tested to determine the uniformity of the medication content.
- STF is added after each insert is pounded in a glass pestle and mortar Suspension.
- The resulting suspension is filtered, and the filtrate is spectrophotometrically measured. **[28]**

5. Swelling index:

- The polymer will swell depending on the water content, ionic strength, and polymer concentration.
- The prepared food's swelling index can be calculated Ocular inserts (n = 3) are weighed at the beginning and then put on an agar gel plate with 2% agar by weight in STF at a pH of 7.4 while being incubated at 37 1 °C.
- The insert is taken off the plate once every hour for five hours, the surface water is wiped away with filter paper, and the insert is reweighed.
- % swelling index = [wt – wo/wo] X 100
- Where,

- Wt = weight of swollen insert after time t,

Wo= original weight of insert at zero time. **[29]**

6. Folding endurance:

- The film's folding endurance was tested by repeatedly folding the inserts in the same spot until they broke.
- The core of the ocuserts was folded, between finger and thumb, followed by opening.
- The value of folding endurance was determined by how many times the film could be folded in the same location without breaking. **[30]**

7.Tensile strength:

- An ocular insert with good tensile strength would be able to withstand the stress that an eye blinking causes without tearing.
- Strips of the insert were cut out.
- The device is composed of a base plate. With the plate set in place.
- On one end of the base plate, where the insert was clipped, was fastened a single aluminium clip.
- In order to attach the little pan holding the weights to the pulley, a thread was tied to a movable clip and passed over it.
- Up until the insert broke, weights were gradually added to the pan.
- Break force was defined as the amount of weight required to break the insert. **[31]**

8.Hardness :

- The apparatus consists of a wooden platform with a top size of 16 x 16 cm and a height of 11 cm.
- On one end of the 2 mm thick iron rod, which has the other end secured with a tiny pan, to a Sharp ended to a point.
- To support the pan rod, a 0.2 cm diameter hole was drilled through the centre of the hardwood stand's top section.\\
- Through the use of a battery, an electric circuit was created in which the bulb only illuminates when the circuit is complete between the sharp end of the rod and the contact of the metal plate.
- Between the metal plate and the rod's short end, the insert was put.
- After the light bulb began to shine, the weights were gradually added to the pan at intervals of 10 seconds in order to stabilise the force.
- The ultimate tally was regarded as a hardness indicator. **[32]**

9.In vitro drug release:

- Bi-chamber donor-receiver compartment model consisting of a transparent and regenerated cellulose type of semi-crystalline material is used for in vitro release experiments Permeable barrier.
- The donor chamber, which is an open cylinder, has it tied at one end.
- The donor compartment is where the ocular implant is put. **[33]**
- 0.7 m to 1 m of distilled water is placed in a donar compartment and kept at the same level throughout the study to simulate the tear volume.
- Ocular in vivo conditions, such as a corneal epithelial barrier, are created using the semi-permeable membrane. **[34]**

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- The reservoir compartment, which contains 25 ml of pH 7.4 phosphate buffer, is in contact with the membrane's surface.
- A magnetic stirrer is used to continuously stir it. At regular intervals, 1 ml samples are taken out of the receptor compartment and replaced with an equivalent volume of pure water.
- Using a pH 7.4 phosphate buffer as a blank, the extracted sample is examined at 246 nm against the reference standard using a UV/visible spectrophotometer.**[35]**

10. In vivo drug release:

- Before an in-vivo investigation, the inserts are disinfected using UV radiation.
- Inserts are placed in a Petri dish with 100 mg of pure medication that has been thinly layered on top.
- This Forceps, plastic bags, and a petri dish are placed within a UV sterilisation chamber (hood).
- The materials are exposed to UV light for an hour, including the inserts. Using forceps within the sterilisation chamber, inserts are transferred into polyethylene bags after being sterilised.
- After a proper dilution with pH 7.4, the pure pharmaceuticals that are sterilised together with inserts are examined for potency by UV spectrophotometer buffer for phosphate.
- For the experiment, male albino rabbits weighing 2.5 to 3.0 kg are needed.
- The animals are kept in isolated cages under specially designed lab conditions for a single day.
- Get unrestricted use of food and water. **[36]**
- On the day of the experiment, the lower conjunctivas of the subjects' eyes are injected with the drug-containing ocular inserts for an in-vivo investigation de-sac.
- The implants are placed into seven eyes at once, with one eye from each of the seven rabbits acting as the control.
- At 2, 4, 6, 8, 10, 12 and 24 hours, ocular inserts are carefully removed and the drug content is analysed as dilution is mentioned in the drug content uniformity.
- The amount of drug release in the rabbit eye is calculated by subtracting the residual medication from the initial drug content of inserts.
- Throughout the experiment, the inserts are being watched for any potential falls out and being recorded.
- The experiment is repeated twice as previously after a one-week wash interval. **[37]**

11. Accelerated stability study:

- Studies on accelerated stability are c periods of storage under typical shelf conditions.
- The movies of the formulation are placed in a separate Petri dish and kept at three different temperatures—400°C, 500°C, and 600°C—while the time for the ocular inserts' break down or deterioration is monitored. When ocular inserts degrade, the time in days is noted and applied to the drug content uniformity technique to ascertain the drug content of each unique film. **[38]**

12. Ocular irritation test:

- By checking for any redness, inflammation, or increased tear production, the test ocusert's potential for ocular irritation and or harm was assessed.
- Five rabbits were used in the formulation test, and the inserts were put in the left eye's cul-de-sac. **[39]**

II. CONCLUSION:

- For the past 20 years, the design of systems to extend the period that medications given topically remain in the eye have received the majority of attention in the field of ocular drug delivery
- Pharmaceutical researchers are creating a number of innovative techniques, including ocular inserts, collagen shields, in-situ triggered gel creation, non-corneal routes of ocular drug penetration, and nanoparticle-based polymeric solutions and gels.
- Ocular inserts have various benefits for the treatment of eye-related issues, but few of these are accepted by the market.[40]

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