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Ophthalmic Inserts: A Review on A Novel Approach to Ocular Drug Delivery

Rimpy, vishal , nandini, Dr surrender verma, Dr ajay kumar

1. **Rimpy –institute of pharmaceutical sciences , kurukshetra university , kurukshetra**
2. **Vishal Pandey, Advance Institute of Biotech & Paramedical Sciences, Kanpur,**
3. **Nandini-department of biotechnology , kurukshetra university , kurukshetra**
4. **Dr. ajay kumar, institute of pharmaceutical sciences , kurukshetra university ,**
5. **, institute of pharmaceutical sciences , kurukshetra university , kurukshetra**

Abstract: The five sense organs are the tongue, skin, ears, nose, and eyes. The maintenance and appropriate operation of the human body depend heavily on them. However, a wide range of circumstances can influence how these organs function. The eye has the most intricate anatomy of all these organs. Due of the eye's intricate structure, traditional drug delivery methods have an extremely difficult time delivering drugs to it. Novel approaches to drug administration are being developed to deliver drugs to the eyes. Among these cutting-edge methods are ophthalmic inserts. Sterile preparations having a solid or semi-solid consistency that can be used for ophthalmic applications are called ophthalmic inserts. Their primary goal is to deliver drugs to the eye in the best possible way for an extended amount of time. The significance of this innovative method in ocular medication delivery systems is highlighted in this review paper.

Keywords: Bio-erodible, Microporous, Ocular, Polycarbonate, Sterile

1. Introduction

Among pharmaceutical chemists, one of the most fascinating and thought-provoking topics is ocular medication delivery. The organ eye's intricate structure and multiple protective barriers make it difficult to administer drugs to this location.[1]

Pharmaceutical experts find it difficult to deliver drugs to the eye because of the eye's protective barriers, which impair the drug's ocular route bioavailability and result in subpar drug delivery. The following variables impact how drugs are delivered to the eye:

1. Diluting the medication with tear fluid
2. Drainage of the nasal cavity
3. Protein-drug interaction
4. Tear turnover [2]

There are two primary categories into which ocular medication delivery system can be divided:

A. Typical ocular drug delivery methods

B. Innovative ocular drug delivery methods

A. Conventional Ocular Drug Delivery Systems

Although the above factors may affect eye health, the symptoms caused by these factors are treatable and can be treated using conventional ophthalmic drug delivery systems such as eye drops, eye lotions, ophthalmic ointments, and eye drop suspensions and emulsions [10]

Although these conventional ophthalmic drug delivery systems are easy to instill in the eyes, but they also have some disadvantages, such as conjunctival absorption, blink reflex, reduced corneal permeability, excretion of the drug due to severity and the possibility of contamination by environmental pollutants [3].

To ensure that the eye receives adequate therapeutic levels of drug and overcomes the eye's protective barriers for optimal long-term drug delivery, ophthalmic drug delivery systems must possess the following relevant characteristics:

a. Better absorption by the cornea
b. Easy insertion and removal
c. Prolonged contact with the corneal tissue of the eye
d. No irritation
e. Excellent rheological properties [4]

Considering that one of the previous disadvantages of the conventional ophthalmic drug administration system which has low corneal permeability, it may be defeated by a new ophthalmic drug administration system. One of these new distribution systems includes ‘’OPTHALMIC INSERTS’’.

B. Novel Ocular Drug Delivery System

The new system for the delivery of ophthalmic drugs is a new approach that combines innovative development and compounds, optimizes the delivery of drugs to the eyes. These systems use it to increase the time between devices and contact sites. Novel ocular drug delivery systems could include nanoparticles, liposomes, niosomes, and ophthalmic inserts.

1.1 Ophthalmic Inserts: Introduction

Ophthalmic inserts are also known as "ocuserts", "ocular inserts" or "ocular implants". These are sterile, drug-impregnated, multi-layered, formulations designed specifically for ophthalmic use and have a solid or semi-solid consistency. Ophthalmic inserts are said to be inserted into the upper or lower pouch of the eye, but can also be inserted into the corneal surface of the eye, allowing for a controlled and continuous release of medication into the eye over an extended period of time.[6]

1.1.1 History

The first solid therapeutic agents were introduced in the 19th century and were considered the precursors of insoluble inserts, which were squares of filter paper presoaked or impregnated with drugs and placed under the eyelid to deliver drugs to the eye.[7]Later, around the first half of the 21st century, lamellae were introduced and described in official collections at the time. Lamellae were considered precursors to soluble inserts and were made of glycerinated gelatin pre-impregnated with various ophthalmic drugs, but their use was subsequently discontinued due to stricter sterility requirements in the manufacture of ophthalmic preparations.[8]**To get the better understanding of the ocular drug delivery, the understanding of the structure of the eye is important.**

1.1.2 Eye: the complexity of nature

The eyeball is made up of a transparent shell which consist of three layers:

1. **The outer coat:** Sclera, a highly resistant tissue on the front of the eye, along with cornea.
2. **The uveal/the tunica media:** It is formed of cribriform tissue and is a highly vascular, pigmented area consisting of the iris, choroid, and ciliary body**.**
3. **The intima:** The inner lining of the eyeball, which consists mainly of the retina.

Basically, the structure of the eye or the eyeball can be studied by dividing the structure of the eye in two parts: the "Anterior Segment" and "Posterior Segment" [9]

Anterior Segment: It is made up of the cornea, a transparent layer on the outer surface of the eye that ensures its protection, as well as the iris and pupil, the colored parts of the eyeball that help regulate the amount of light entering the eye.

Other anterior structures:

1. **Lens,** a Crystals and flexible structure in the suspension using a ciliary body.
2. **Ciliary body,** circular muscle, which changes the shape of the lens by contracting and relaxing

Nutritional supplement to the lens and the cornea is provided by **aqueous humour,** present in the anterior chamber.[10]

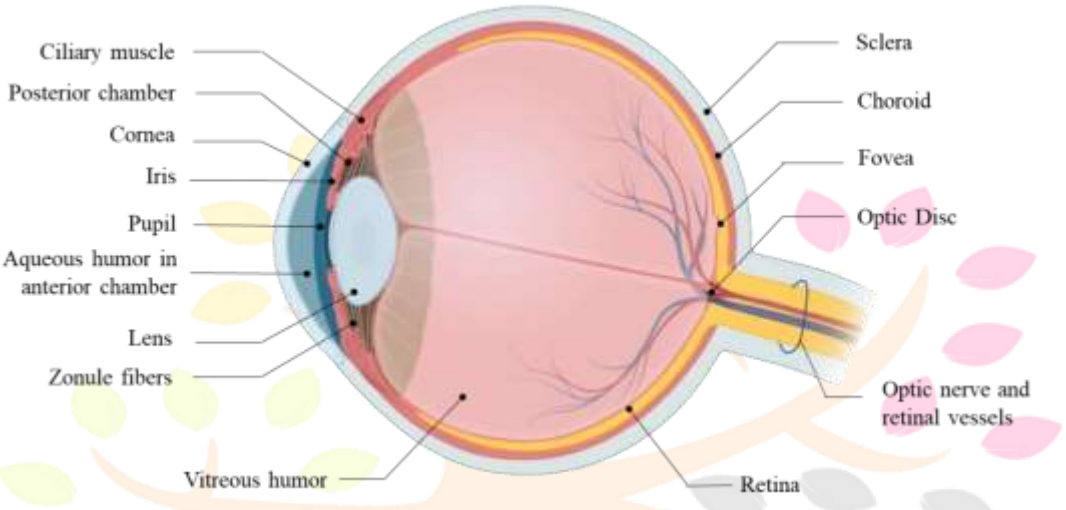

Figure 1: Human Eye (Outer & Inner)

Posterior Segment: This segment consist of: **SCLEROTUS**, a hard white shell, which is a hard fiber membrane, is useful for maintaining the shape of the eye. It also contains visual nerve and helps send signals to the brain[11] The retinal nerve cloth sends a signal to the brain through the visual nerve. It is part of the back of the retina (retina, macula choroid, optic disc).[12]

1.1.3 Routes of Drug Absorption in the Eye

Medication for the treatment of eye diseases is mainly administered as eye drops, and therefore, absorption of drugs by the eye occurs mainly through two routes:

A. Corneal absorption
B. Non-corneal absorption

A. Corneal Absorption: The corneal tissue of the eye mainly consists of three layers which are:

a) Epithelium
b) Stroma
c) Endothelium

Medicines are absorbed by the cornea by the dissemination of the drug through these membranes. The effectiveness of the process depends on the speed and the degree of absorption[13]

B. Non-corneal Absorption: This absorption pathway consists of two main sites: **sclera and conjunctiva**. Although these routes are not as productive as the corneal route, studies have been conducted to administer drugs such as timolol via this route, suggesting that these routes bypass the anterior chamber and provide good site-specific delivery. [14]

The way the eye functions, its structure, and its biochemistry make it vulnerable to a variety of factors. For example, environmental factors like toxic pollutants, UV radiation from the sun, temperature changes, and other factors, can affect the eye [15]. Chemical factors like formaldehyde and ammonia fumes can cause irritation and redness in the eyes, which can interfere with the proper functioning of the eye.[16]

1.1.4 Mechanism of Controlled Drug Delivery System

Controlled drug delivery systems include a number of systems and devices that provide a controlled, sustained release of drugs over an extended period of time, such as transdermal skin patches, liposomes, niosomes, etc. Ophthalmic inserts are one of these new drug delivery systems that are eye drop formulations that release drugs in a sustained and controlled manner and therefore can be considered as a controlled drug delivery system. Mechanism of controlled drug delivery systems mainly follows **three** processes:

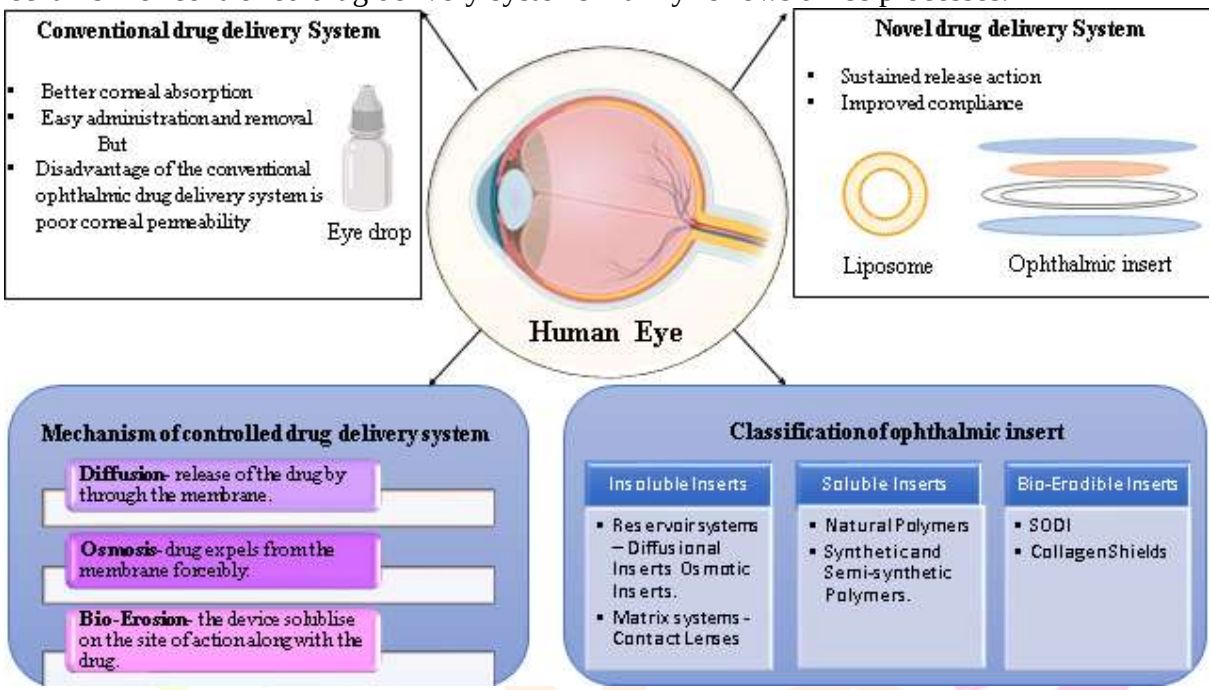

Figure 2: Mechanism of Controlled Drug Delivery Systems [17]

1. **Diffusion:** The mechanism works by releasing the drug across the membrane via the tear fluid in a sustained and controlled manner: when the insert is applied to the eye, the tear fluid penetrates the matrix of the insert. The tear fluid swells the polymer, releasing the drug by diffusion..[18]
2. **Osmosis:** These inserts consist of a transverse impermeable elastic membrane that divides the interior of the insert into two compartments, compartment I and compartment II. Upon administration, tear water diffuses into compartment I (semi-permeable membrane), expanding the elastic membrane in contact with compartment II (drug reservoir), and the drug is expelled from the drug release opening.[19]
3. **Bio-Erosion:** The body of the insert is made of a biodegradable material, a matrix in which the drug is dispersed. When the tear fluid comes into contact with the insert, the drug is released from the matrix in a controlled and protracted manner. Drug release is believed to occur when the drug is present on the surface and concentrated in the matrix. [20]

1.2 Ophthalmic Inserts: Classification

They are classified based on their extent of soubility:

A. Insoluble Inserts
   1. **Reservoir systems –** Diffusional inserts and Osmotic inserts.
   2. **Matrix systems –** Contact Lenses.

B. Soluble Inserts
   1. Based on **Natural Polymers**
   2. Based on **Synthetic** and **Semi-synthetic Polymers**.

C. Erodible or Bio-Erodible Inserts
   1. SODI
   2. Collagen shields [21]

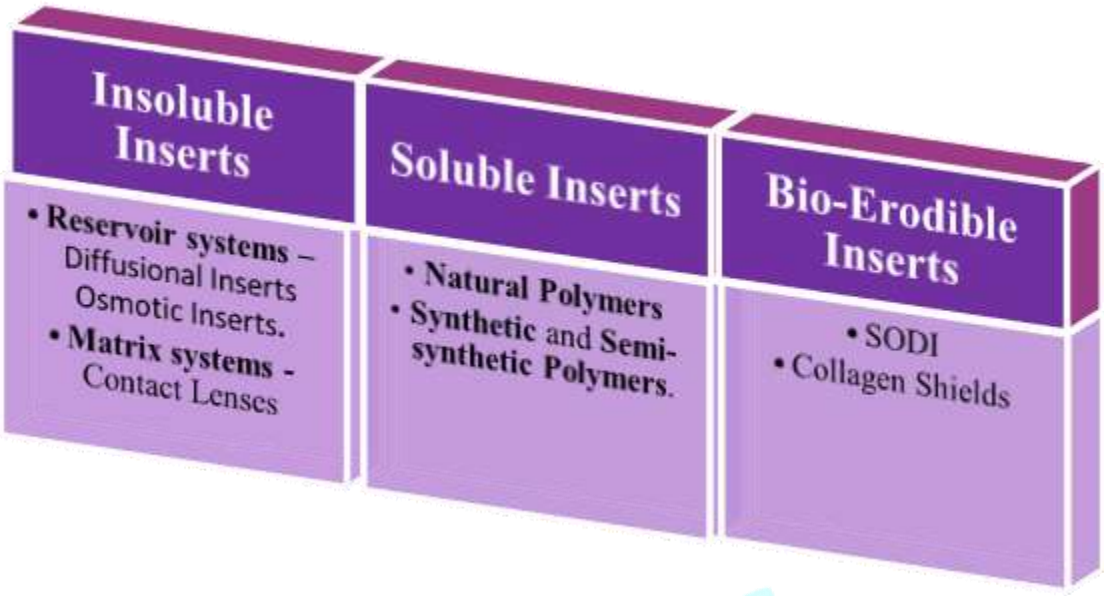

Figure 3: Classification of Ophthalmic Inserts [21]

A. Insoluble Ophthalmic Inserts

Insoluble ophthalmic inserts are classified into three types of systems: diffusion systems, osmotic systems, and contact lenses.

- **Reservoir systems:** Diffusion and osmotic systems follow a reservoir system containing a liquid, gel, semi-solid, solid matrix or carrier containing the drug dispersed or dissolved homogeneously or heterogeneously in the matrix. The reservoir delivers the drug to the membrane controlling the flow rate[22]

a. Diffusional Systems

Delivery systems consist of a central reservoir of drug surrounded by a specially designed semi-permeable membrane.The membrane allows the drug to flow out of the reservoir at a precisely defined rate. The infusion of the lacrimal fluid through the membrane inside the reservoir happens which generates appropriate pressure for the drug to come out from the device.[23]

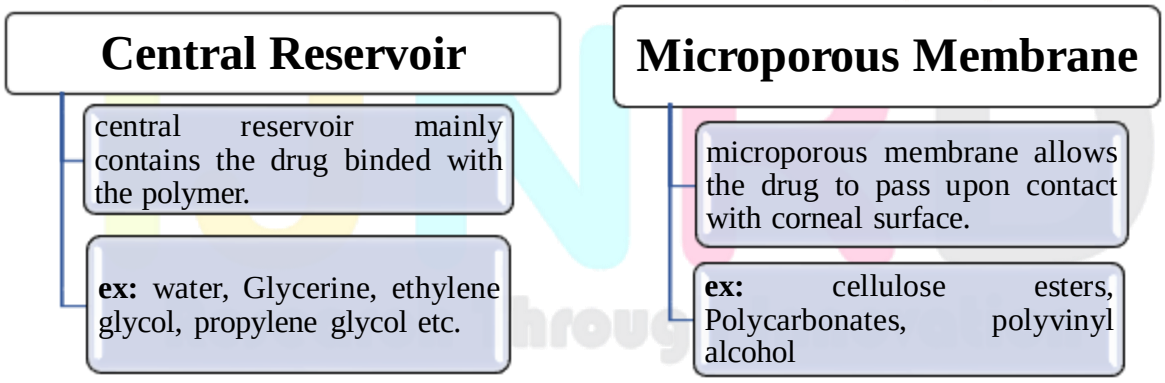

Figure 4: Materials used in Diffusional Insoluble Ophthalmic Inserts [24]

b. Osmotic Inserts They have the center of the area trapped in the periphery. In the center, there are two different sections . In one compartment (case 1), the drug is dispersed throughout the polymer matrix with or without the permeating solute, whereas in the second case, the drug and the permeating solute are located in two different compartments. The drug is surrounded by an elastic, impermeable membrane, and the solute reservoir is surrounded by a semipermeable membrane. Drug is released when the elastic membrane expands due to diffusion of tear fluid into the osmotic compartment. [25]

Water permeable matrix	This matrix contains the drug and the polymers which are water permeable.

- **ex:** polyethylene, Ethylene-vinyl ester copolymers, cross-linked PVP (polyvinyl pyrrolidone)

Semi permeable membrane	These membranes encloses the matrix within them.

- **ex:** Cellulose acetate derivatives, ethyl vinyl acetate, polyesters of acrylic and methacrylic acids.

Osmotic agents	helps in building up the pressure inside the inserts upon infusion of tear fluid.

- **ex:** glucose, sorbitol, calcium lactate, Sodium chloride, sodium carbonate, sodium sulphate, tartaric acid, mannitol and sucrose.

Figure 5: Materials in used in Osmotic Inserts [26]

b. Matrix system: Contact Lenses

Contact lenses are originally trained for visual acuity correction, and their use has been extended as potential drug administration devices. These lenses can be sub classed by five different types: Bio- Polymeric lenses, Soft hydrophilic lenses, Hard lenses, semi -dimensional lenses & elastomeric lenses. Among these, hydrophilic soft lenses are preferable to Rigid lenses because their hardness makes it difficult to wear them for long periods of time and they do not allow moisture or oxygen to pass through. [27]

Uses of Contact Lenses:

1. Making changes to the patient visualization.
2. Later on, they were employed as a method of delivering drugs to the eyes.
3. They are soaked in the drug solution beforehand, allowing them to absorb the water-soluble medications, serving as the drug delivery system. [28]
4. They were inserted into the eyes once they had saturated.
5. To ensure that the medication remains in the eye for as long as possible, hydrophilic or pre-soaked contact lenses are utilized.
6. Aids in the medication's steady and regulated release into the eyes.[29]

B. Soluble Ophthalmic Inserts

These are mainly Based on the type of polymer used to manufacture them, mainly dividing into two types:

1. Based on **Natural Polymers**
2. Based on **Synthetic** and **Semi-synthetic Polymers**

When applied to the site of action, it dissolves completely at the site of action and is absorbed into the eye without the need for removal after use[30]

1. Natural polymer based soluble ophthalmic inserts

The most widely used natural polymer in soluble ophthalmic inserts is Collagen. It shows several uses in the drug delivery to the ophthalmic region such as:

1. Collagen discs and shields were developed from porcine scleral tissue and were used as corneal bandage lens.
2. Collagen is absorbed within 84 days due to higher biocompatibility and biodegradability.
3. The shields of collagen can be used to administer heparin to avoid the postoperative development of fibrin in the eye after glaucoma surgery.

Collagen can be used to administer diverse drugs as well due to its capability to solubilize well at the site of action.[31]

2. Synthetic and Semi-Synthetic polymer based soluble ophthalmic inserts

These inserts are composed of synthetic polymer and dissolve on the surface of the cornea in contact with the lachrymal fluid .Polymer used:

a) The synthetic polymer used in the manufacturing mostly is PVA (polyvinyl alcohol).
b) The semi-synthetic polymer used are usually cellulose based polymers.

Products made from these polymers are suitable for ophthalmic applications and can be easily manufactured by conventional methods such as compression and compression molding. Polymers such as carbomer are used to prevent extrusion of the insert as they are durable even at low concentrations and are bioadhesive polymers.[32]

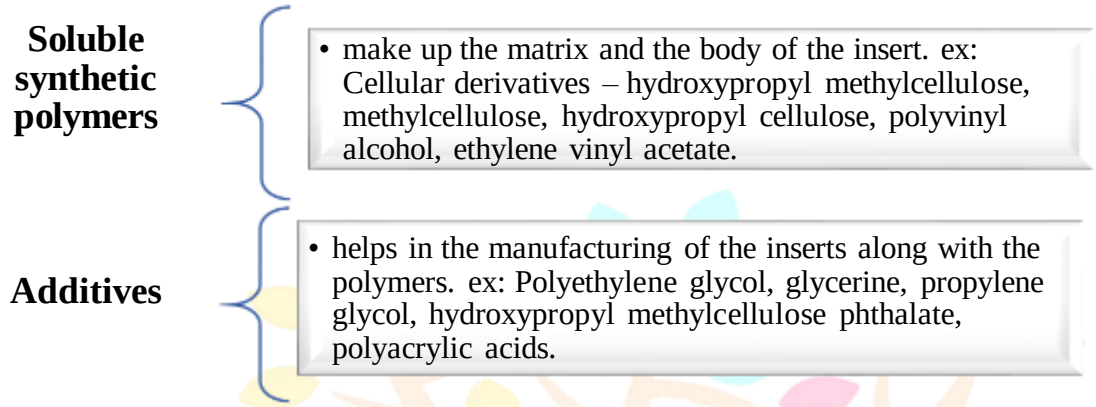

Figure 6: Materials used for Synthetic and Semi-Synthetic Ophthalmic Inserts [33]

C. Bio-Erodible Ophthalmic Inserts

They are composed of biodegradable materials, such as biodegradable polymers, and the mechanism of action depends on the erosion rate of the polymers that compose them.Polymers, such as CMC (carboxymethyl cellulose), polytiviny alcohol and collagen, are generally used in the manufacture of this type of inserts. As a rule, they are different types:

1. SODI (soluble ophthalmic drug inserts)
2. Collagen Shields
3. Other types: Lacrisert, minidisk **[34]**

1. SODI (Soluble Ophthalmic Drug Insert)

SODIs can be made from polymers such as polyacrylamide, ethyl acrylate, vinylpyrrolidone, etc. They are prepared in the form of thin, oval, elastic plates of various sizes, weighing approximately 15-16 mg, placed in the lower fornix and moistened with tear fluid[35]. After the application of the SODI in the eye, in 30-60 minutes it turns into the polymer solution. After it turns into the polymer solution it delivers the drug for about 24 hours**[36]**

2. Collagen shields

They are prepared by a collagen taken by the porcine scleral tissue, which have the same composition as the human cornea. These shields are impregnated in a solution of the drug, so that the drug can be absorbed by a shield of the solution[37] Hydrophilic drugs are loaded in this system of administration of medication at the collagen matrix by saturating it with a drug solution.The hydrophobic formulation is added directly to the shield during the manufacturing process.The collagen shield model was developed by Bloomfield and collegue.[38]

3. Lacrisert

This is a commercially a rod shaped, sterile, preservative-free hydroxypropylcellulose granules weighing approximately 5 mg, measuring approximately 12.7 mm in diameter and 3.5 mm in length, which is implanted inside the lower fornix. Recommended for use by patients suffering from mild to moderate dry eye syndrome.[39]

4. Minidisk

The minidisc, or minidisc, consists of a disc with a convex side and a concave back.The concave back of the device remains in contact with the surface of the eye.The diameter is about 4-5mm.The minidisc is mainly made of a silicon-based material (4-methylacryloxy) butylpolydimethylsiloxane..[40]

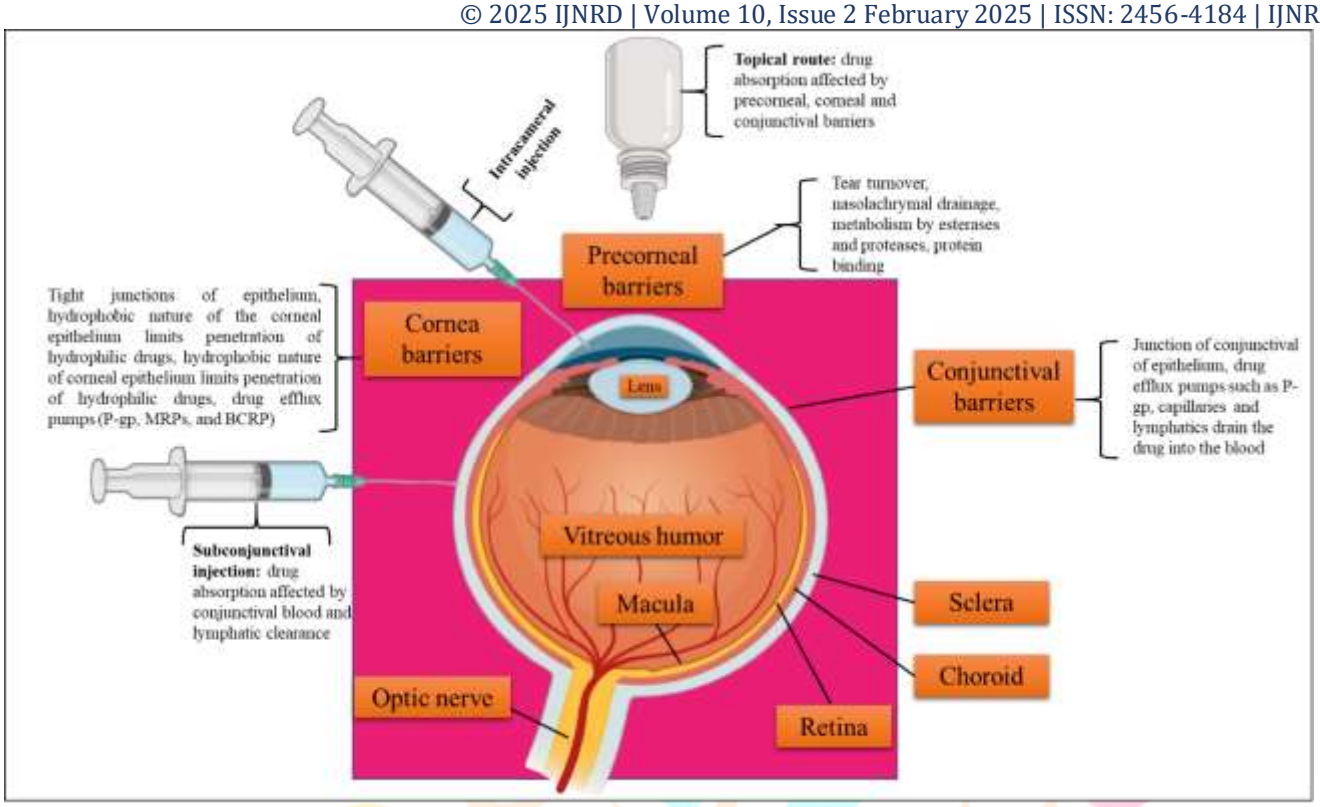

Figure 7: Various Barriers [41]

1.3 Ophthalmic Inserts: Advantages

Ophthalmology inserts, one of the new systems for delivering eye drugs, have some advantages in securing the following optimal amount of ophthalmic drugs: In addition, the use of these devices provides the accurate administration of drugs and the enhancement of the drug's anophyme -blasting ability from the insertion of the cornea on the surface of the cornea. Ophthalmic inserts also overcome protective barriers of the eye such as tear drainage, lacrimation or dilution, conjunctival absorption.[42] Reduces the dosing regimen to improve patient compliance. This reduces the preservative load as the dose per day decreases [43] In ophthalmic inserts such as osmotic inserts, the drug begins to be released as soon as the system meets the dissolution medium and the release is measured so that drug delivery is adequate.

Inserts such as easy inserts in Bioero are easily dissolved on the action site, so it is not necessary to delete them after applying.[44]

1.4 Ophthalmic Inserts: Disadvantages

In addition to the advantages, specific drawbacks related to the use of ophthalmic inserts can affect the effective use of these devices. This is immediately excluded from the device during sleep or after waking up. It can also cause anxiety and stimulation when using a device.[45] They can cause the sense of burning conjunctiva. Patients may complain of the presence of a foreign body in the eye or pain. When the drug is first released, patients may sometimes experience blurred vision. [46]

1.5 Ophthalmic Inserts: Evaluation/Assessment Parameters

1. **Tensile Strength:** Tensile strength states the force required to tear off the insert into two parts. This can be determined using Santam Instrument.
2. **Folding Endurance:** this test may be conducted by repetitively folding the film at the same place till its breakdown.
3. **Thickness and Weight:** A specific number of inserts were weighed independently and then the average of those inserts was calculated. Thickness can be measured using the Digimatic Micrometre.**[47]**

1.6 Use of Ophthalmic Inserts in Eye Disorders

1. **Herpes Simplex Eye Disease**: An infection that impacts the cornea can pose a threat to eyesight. This infection, also known as Cold sore or Fever Blister, can be caused by different strains of the Herpes Simplex

Virus. Acyclovir, a drug effective against HSV, is available commercially as an ointment but is present in low concentration, so it needs to be applied frequently. [48]

- **Ophthalmic insert used:** "The combination of polyvinyl alcohol and methyl cellulose was dissolved in cold water with stirring to create the "Acyclovir ophthalmic insert," which was then refrigerated overnight. Glycerol was added to the measured amount of drug and stirred. The resulting formulation contained acyclovir within the polymer matrix, suitable for treating HSV eye disease..[49]

2. **Glaucoma:** An increase in the pressure inside the eye, known as intraocular pressure, is a characteristic of glaucoma, exceeding the normal level of 15-20 mmHg. Without timely treatment, this condition can lead to the deterioration of the retinal capillaries and the optic nerve, ultimately causing blurred vision or vision loss.[50]

- **Pilocarpine Ophthalmic Inserts:** Pilocarpine has been utilized for an extended period to lower intraocular pressure in glaucoma. While conventional pilocarpine drops are readily available, they may lead to side effects like myopia and miosis due to the higher concentration of the drug in the eye.[51]Two pilocarpine ocusert systems, P-20 and P-40, were examined for their effectiveness. The study's data showed that the intraocular pressure dropped below 22 mmHg in 13 patients..[52]
- **Bromiodine Tartrate Insert:** Bromiodine tartrate has been deemed safe in clinical trials for the long-term treatment of glaucoma. It reduces intraocular pressure through two mechanisms:
  1) It assists in reducing the production of aqueous humor.
  2) It aids in the outflow of aqueous humor from the eye.

The film casting method and bio adhesive polymers were utilized to prepare the inserts, which had an approximate 8-hour shelf life for the ocular drug delivery of bromiodine tartrate. [53]

3. **Dry Eye Syndrome:** The condition known as dry eye syndrome affects the tear film and is brought on by excessive tear evaporation and scarcity, both of which can harm the surface of the eye. The patient might become more vulnerable to infections of the eyes that can cause blindness, like bacterial keratitis. Inflammatory diseases, environmental factors, hormone imbalances, systemic illnesses like rheumatoid arthritis and diabetes mellitus, etc. can all be the cause of it [54]

Ophthalmic insert used:

- **Hydroxypropyl Cellulose Ophthalmic Insert**: The mild to moderate cases of dry eye syndrome are typically treated with hydroxypropyl cellulose ophthalmic inserts. 2-hydroxypropyl ether is the chemical name for hydroxypropyl cellulose. One insert is inserted into the inferior cul-de-sac of the eye to administer this medication. It works by lubricating and protecting the eye, thickening the tear film, and lengthening the time it breaks. [55]

4. **Ocular Inflammation:**
   1. **Ofloxacin and Dexamethasone Ocular Insert**
   2. **Aceclofenac Ophthalmic Insert.**

Ofloxacin and Dexamethasone Ophthalmic Inserts

- **Ofloxacin** –A synthetic fluoroquinolone agent called ofloxacin is used to treat a variety of eye conditions, including conjunctivitis and ocular gingitis, by relieving pain and inflammation. It is an antibacterial agent with a broad spectrum.
- **Dexamethasone** –applied topically to the eyes as an anti-inflammatory and anti-allergic corticosteroid. Solvent casting was used to create the inserts for Dexamethasone and Ofloxacin. In the inserts, the medication is stable and undamaged[56]
- **Ethyl cellulose and hydroxypropyl methyl cellulose (HPMC).** made using the solvent casting technique. For an extended period of time, these inserts' controlled drug release offers the best possible drug delivery to the eye.[57]

1.7 Ophthalmic Inserts: Further Development

Drug delivery through the eyes is now a major focus of research. Research on ocular drug delivery systems should lead to the development of new therapeutic modalities and instruments for the treatment of eye disorders. Prolonged action is promised by implantable and controlled drug delivery systems, which also verify that patients are adhering to their prescribed regimen and therapy. [58]

Whatever the medication or its mode of action, the optimal ocular drug delivery system should be able to reduce systemic exposure, deliver the drug in effective concentrations at the intended site, and promote good patient acceptance, tolerance, and compliance. Creating a preparation that offers high drug bioavailability in the eye despite the presence of the eye's protective barriers, has no unfavorable side effects, and is safe and simple to use should be the primary goal of developing an effective drug delivery system.[59]

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