●OCULAR DRUG DELIVERY SYSTEMS

-**Except for skin, the eye is the most easily accessible site for topical administration of a medication**.

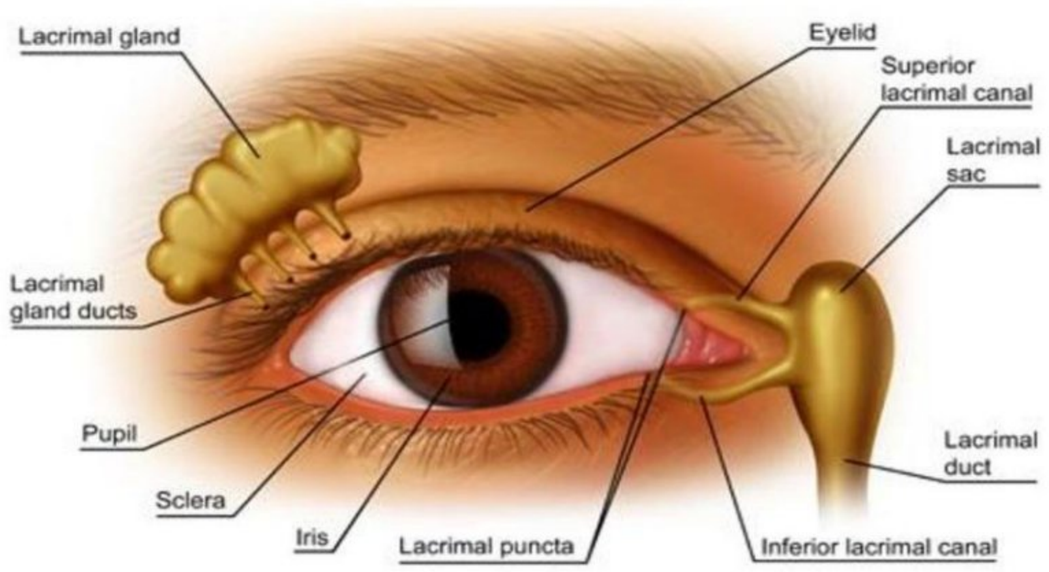
-Drugs are commonly applied to the eye for a localized action, on the surface, or in the interior of the eye.

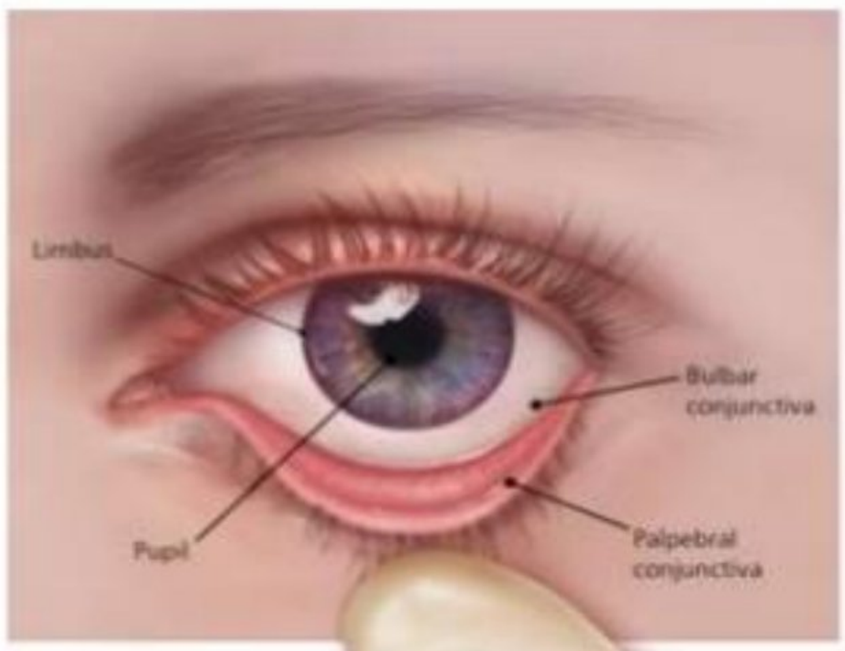
- A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action.

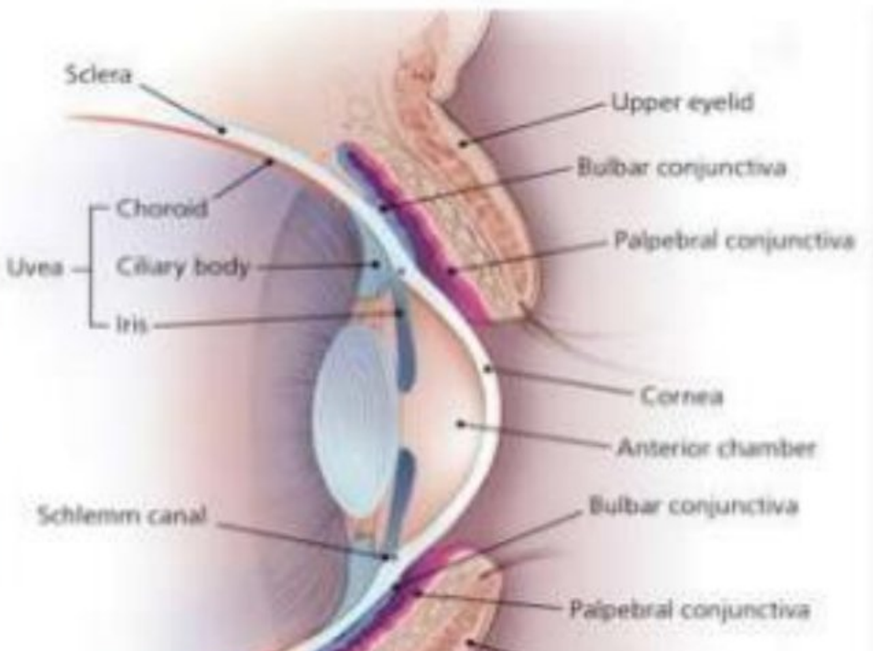
-Poor bioavailability of drugs from ocular dosage forms is mainly due to the pre corneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac (a region near to palpebral conjunctiva) , and the relative impermeability of the corneal epithelial membrane.

-Due to these physiological and anatomical constraints only a small fraction of the drug, effectively 1% or even less of the instilled dose, is ocularly absorbed.

Anatomy of Human eye







The Future Pharmacist

Free Pharmacy related notes,Books,PDFs,Questions papers,and GPAT related Study material

Visit our website:-

www.thefuturepharmacist.com

For more information follow us on

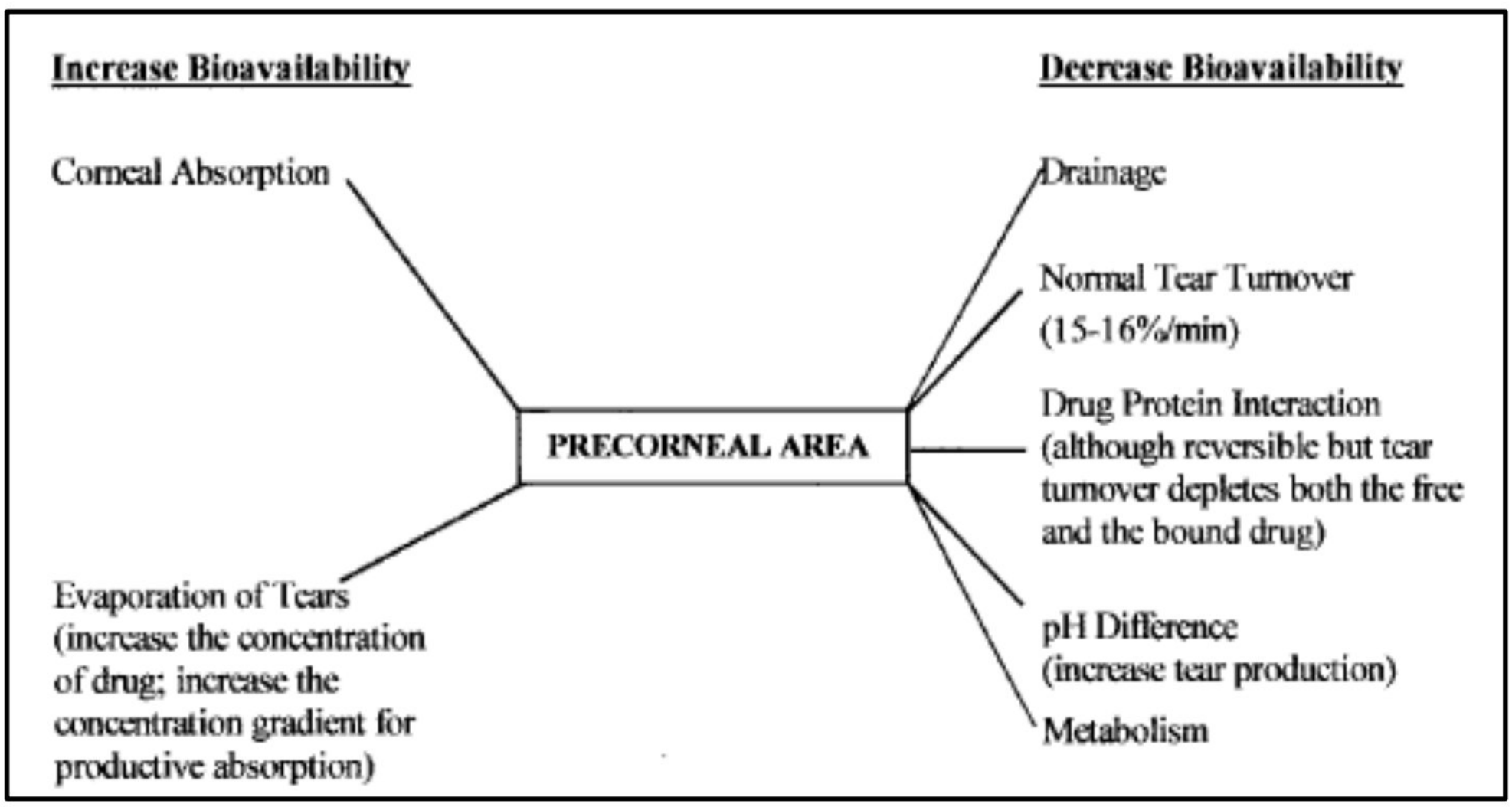
Instagram, YouTube, Telegram and Twitter

➢ Topical Ocular drug delivery and the challenges to ocular therapy-

-It is common knowledge that the ocular bioavailability of drugs applied topically as eye-drops is very poor. The absorption of drugs in the eye is severely limited by some protective mechanisms that ensure the proper functioning of the eye, and by other concomitant factors.

for example:

- drainage of the instilled solutions;
- lacrimation and tear turnover;
- metabolism;
- tear evaporation;
- non-productive absorption/adsorption;
- limited corneal area and poor corneal permeability; and
- binding by the lacrimal proteins.



-It is now definitively established that the rate at which instilled solutions are removed from the eye varies linearly with instilled volume. In other words, the larger the instilled volume, the more rapidly the instilled solution is drained from the precorneal area.

In sort , we can divide various factors in to two classes :

1. which increases the bioavailability.
2. which decreases the bioavailability.

-So looking to the constraints for ocular drug delivery , we should concentrate on two things:
1) To prolong the contact time of drug with corneal surface.
2) To enhance corneal permeability, either by mild or transient structural alteration of corneal epithelium or by modification of chemical structure of the drug molecules.

➢ Classification of Ocular Drug Delievry System-

→ A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:-
1)**LIQUIDS:** Solutions, Suspensions, Sol to gel systems, Sprays
2) **SOLIDS:** Ocular inserts, Contact lenses, Corneal shield, Artificial tear inserts, Filter paper strips
3) **SEMI-SOLIDS:** Ointments, Gels
4) **MISCELLANEOUS:** Ocular iontophoresis, Vesicular systems, Mucoadhesive dosage forms, Particulates, Ocular penetration enhancers:-
Use of Hyaluronic acid, Use of Hydroxy Beta Cyclodextrin.

❖ OCULAR INSERTS (Solids):-

"Ocular inserts are defined as sterile preparations, with a thin, multi-layered, solid or semi-solid consistency devices placed into cul-de-sac or sac of conjunctiva and whose size and shape are especially designed for ophthalmic application."

-They are made-up of polymeric vehicle containing drug and are mainly used for topical therapy.

Advantages:-

Provide controlled, sustained and continuous drug delivery.
Avoid the side effects of pulsed drug delivery.

-Maintain an effective drug concentration in the target tissues &minimize the number of applications.

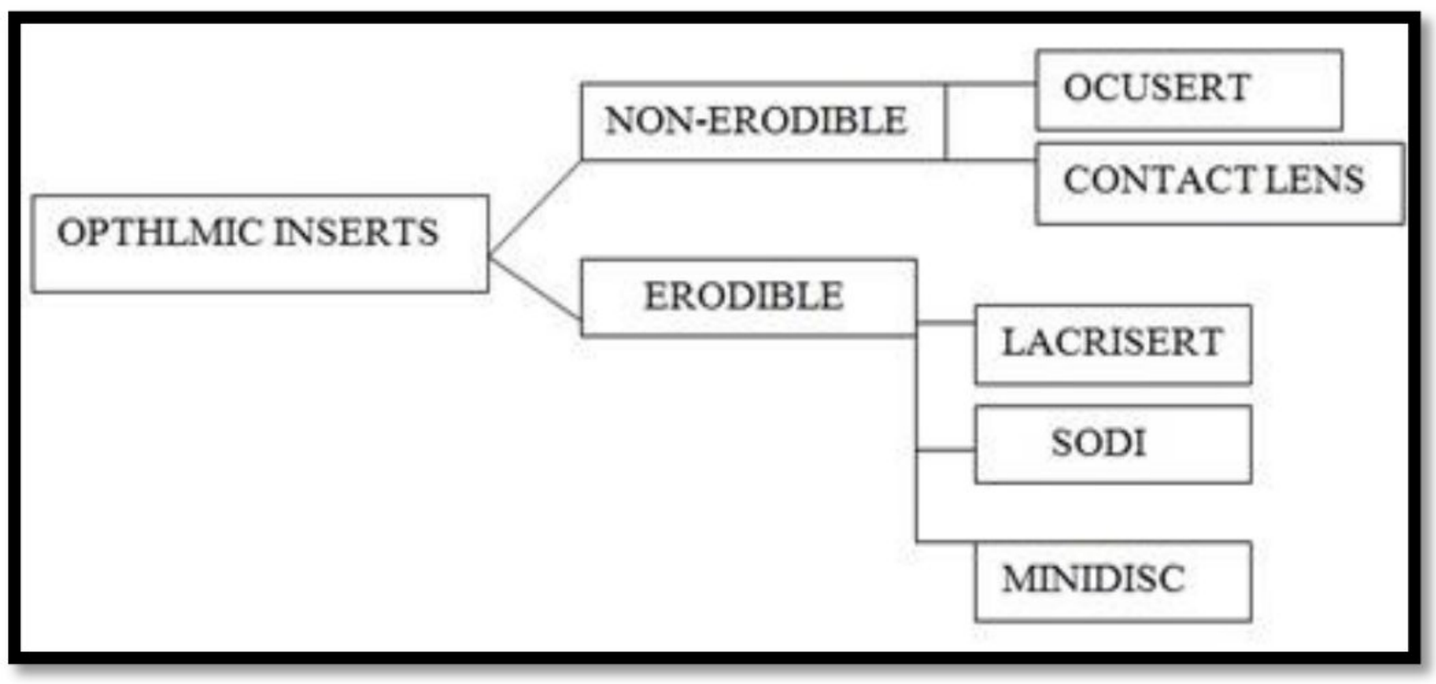
-But they are having limited popularity due to unnoticed expulsion from the eye, membrane rupture etc.

→ Characteristics of Ocular Inserts-

1) Biostable and biocompatible with tissue of eye.
2) Non-toxic and no-carcinogenic.
3) Retrievable and release at a constant rate.
4) Non-immunogenic and non-mutagenic
5) Good mechanical strength.
6) Free from drug leakage.
7) Easily sterilizable.
8) Non-interference with vision and oxygen permeability.

An Ocular Insert

➢ Classification of Ocular Inserts-



1) Non-Erodible-

(i) Contact lens:-

-Currently, approximately 100 million people are estimated to be wearing contact lenses, and the number is increasing exponentially.

-Ocular drug administration is particularly challenging and recent research has been directed towards the design of novel drug delivery systems capable of prolonging the permanence of the drug in the precorneal area and, thus, potentially increasing bioavailability and minimizing adverse effects.

-Conventional hydrogel soft contact lenses have the ability to absorb some drugs and release them into the post-lens lacrimal fluid, minimizing clearance and sorption through the conjunctiva.

-Their ability to be a drug reservoir strongly depends on the water content and thickness of the lens, the molecular weight of the drug, the concentration of the drug loading solution and the time the lens remains in it.

-However, the ability of contact lenses to load drugs and to control their release is in general inadequate and the following approaches,

i) covalent binding of the drug to the lens network via labile bonds
ii) inclusion of the drug in colloidal structures that are dispersed in the lens and are responsible for controlling drug release
iii) functionalization of the network with chemical groups that work as ion-exchange resins

Example:-**Bionite lens** (which was made from hydrophilic polymer:2-hydroxy ethyl methacrylate).

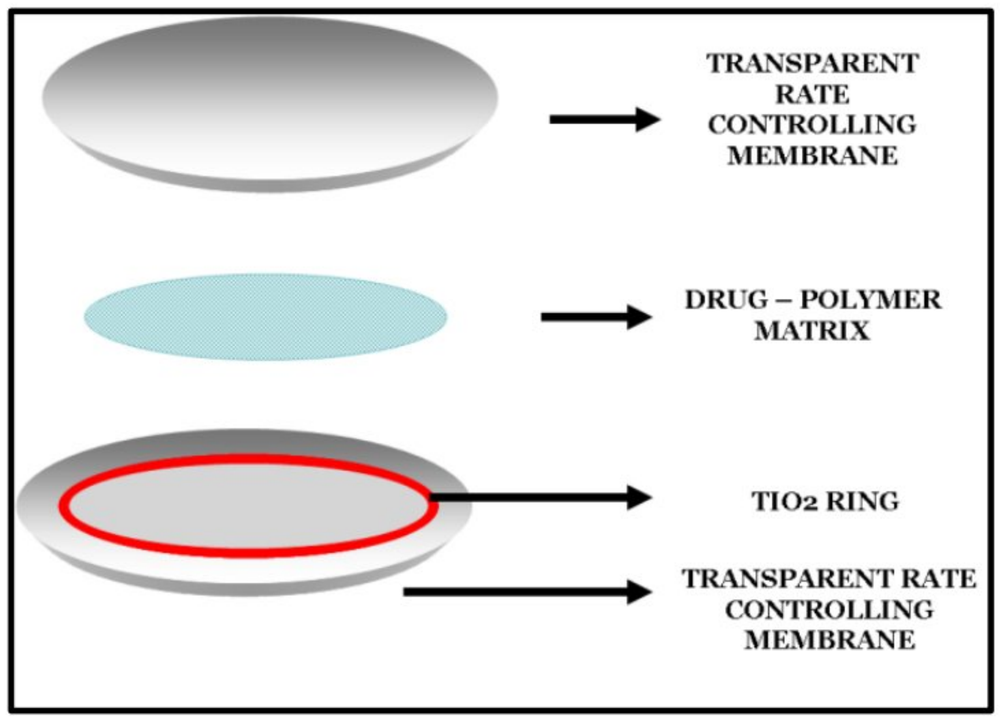
Contact Lens Insertion

(ii) Ocusert® (Osmotic Ocular Insert):-

-A truly continuous controlled release and Zero order kinetic fashion was achieved using ocusert.For hydrophilic Drugs.

-**Pilocarpine ocuserts** (by Alza corporation of California.)

-The system consists of a **Pilocarpine – alginate core (drug) and one osmotic agent in gel form sandwiched between two transparent, rate controlling ethylene-vinyl-acetate copolymer** membranes. Titanium dioxide encloses the drug reservoir circumferentially.



Parts of Ocusert

-The microporous membrane permit the tear fluid to penetrate into the drug reservoir (via osmosis) to dissolve drug from the complex.

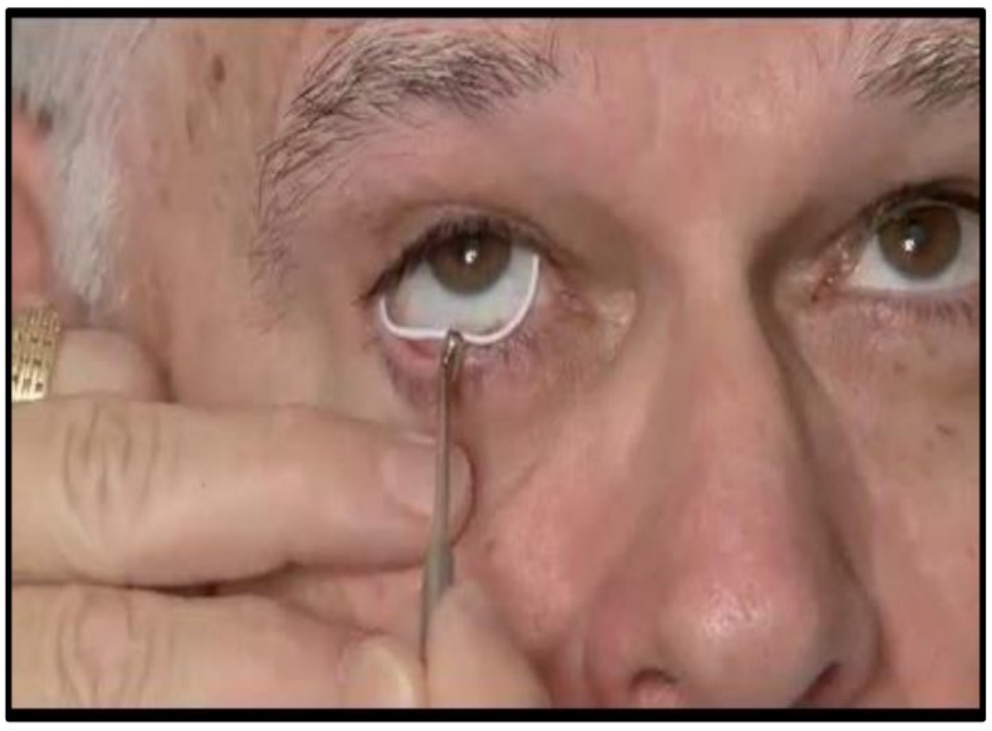
-When this is placed under the upper or lower eyelid, the pilocarpine molecules dissolved in the lacrimal fluid are released through the rate-controlling membranes at predefined rates for a week.

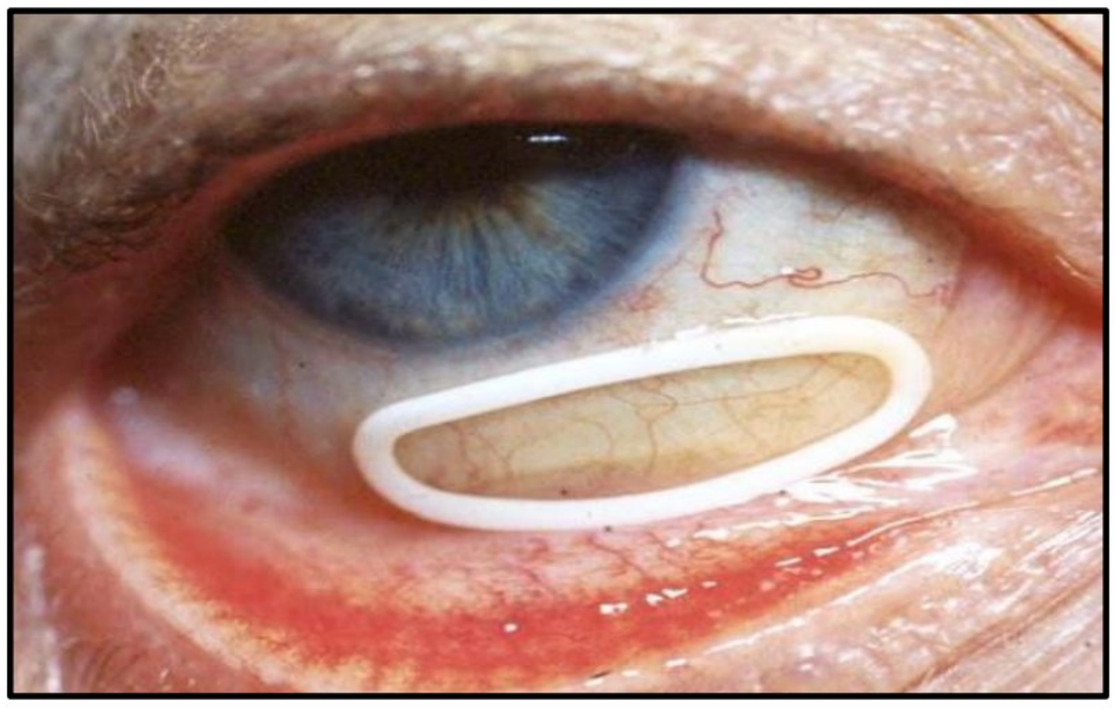
→ Two types of Ocuserts® are available:
1) Ocusert® pilo- 20
2) Ocusert® pilo- 40

This device is more popular among younger patients as compared to elder population who have difficulties in insertion, do not retain device well and often do not notice if it falls out.

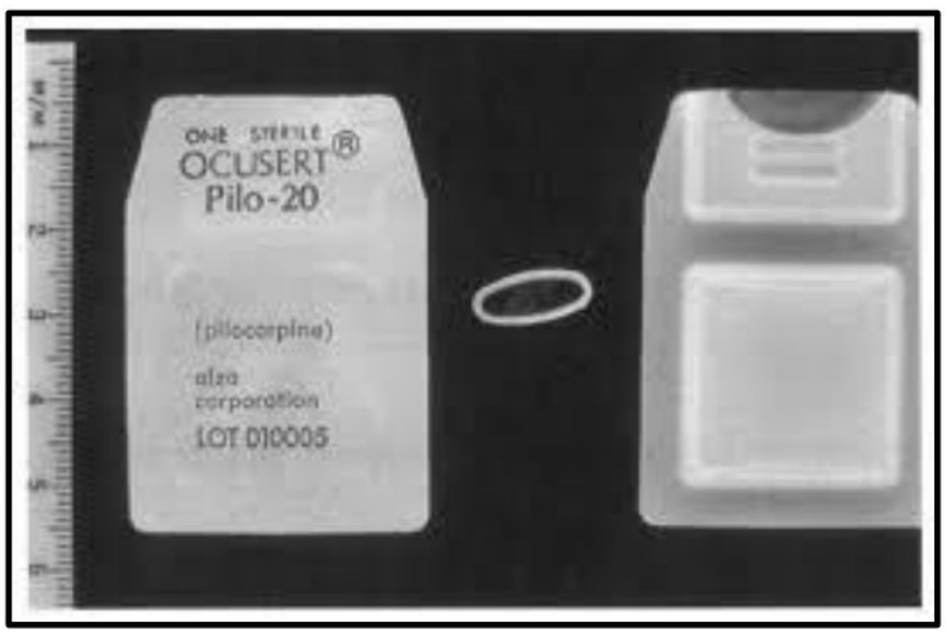
Clinical studies with the pilocarpine Ocusert® demonstrated that slow release of the drug can effectively control the increased intraocular pressure in glaucoma, with a minor incidence of side-effects, such as miosis, myopia, browache, etc.

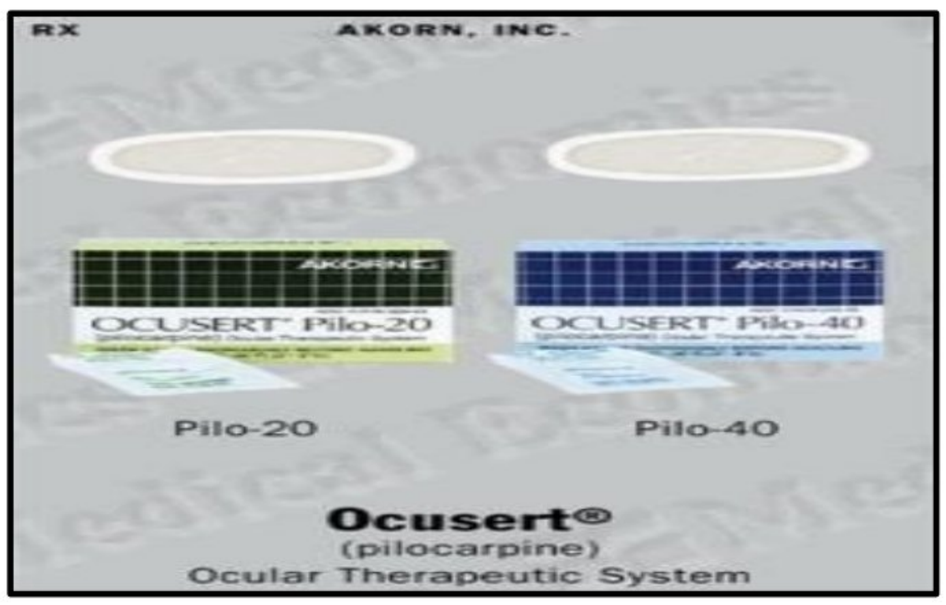
The major drawback for using this therapy is high cost of the device and as this system is not biodegradable, required to be removed and replaced with a fresh one adds to the cost of already expensive therapy.





Pictures showing insertion of Ocusert





Marketed Products of Ocuserts

2) Erodible-

(i) Lacrisert®

-It is **sterile rod shaped device made up of hydroxyl propyl cellulose without any preservative, i.e., used for the treatment of dry eye syndrome**.
-It weighs 5mg and measures 1.27 mm in diameter with a length of 3.5 mm.
-It is inserted into the inferior fornix where it imbibes water from conjunctive and forms a hydrophilic film which stabilizes the tear film and hydrates and lubricates the cornea.
-Daylong relief from dry eye syndrome has been reported from a single insert placed in the eye early in the morning. Learning

Advantages- Replacement of 4 times an hour regimen by once or twice daily regimen is the benefit achieved by this dosage forms.

Pictures showing Insertion of Lacrisert

Marketed Products of Lacriserts

(ii) Soluble Ophthalmic Drug Inserts (SODI):-

-A SODI is a soluble copolymer of acrylamide, N-vinyl pyrrolidone, and ethyl acrylate.
-It is in the form of sterile thin films or wafers of oval shape, weighing 15 to 16 mg.
-After introduction into the upper conjunctival sac, the SODI softens in 10 to 15 sec, conforming to the shape of the eyeball; in the next 10 to 15 min the film turns into a polymeric clot, which gradually dissolves within 1 hr, while releasing the drug.

--The major advantage of these dosage forms is the reduced role of the clinician, since the form is dissolved by total or partial solubilization and there is no need to surgically remove the insert once the drug has been released.

-But they have the drawback that they blur vision while the polymer is dissolving.

-Release of the drug from the SODI is proposed to occur in two stages:
1) hydration of the matrix by penetration of dissolution medium; and
2) diffusion of the medium deep into the matrix and back-diffusion of the dissolved active principle.

(iii) Ocular Therapeutic System (Minidisc):-

-It consists of countered disc with a convex front and concave back surface in contact with eyeball.
-It is like a miniature contact lens with diameter of 4 to 5 mm.
-The major component of it is Silicon based prepolymer.
-The OTS can be hydrophilic or hydrophobic to permit extended release of both water soluble and insoluble drugs.

→ SOME OTHER OCULAR INSERTS:-

VITRASERT®:-

-An ocular implant (Vitrasert) for delivering Ganciclovir (Anti-viral) for the treatment of cytomegalovirus (CMV) has also been developed.

-This implant delivers the drug directly to the retina for over 5 months.

-It is useful for patients with AIDS-associated cytomegalovirus retinitis.

-The pellet was then coated with ethylene vinyl acetate except on its top surface, and again coated with PVA.

The device lasted 4–5 months and all the treated eyes showed resolution of the CMV retinitis.

PROSERT®:-

-PROSERT® is an ophthalmic placebo insert which is insoluble, sterile and biocompatible. This system can contain one or several active components and allow its releasing in a programmed or controlled way.

-PROSERT® is constituted of a matrix able to contain one or several active components, surrounded by a **dyalisantic membrane** of a changeable thickness which allows the releasing controlled by the tears.

-The entirety has the shape of a **small oblong cylinder (reservoir) with rounded forms**.

-When PROSERT® is inserted in the conjonctival cul de sac, the tears enter into the device and saturate the mesh net intended to contain the active component.

-When the osmotic equilibrium is achieved, the active component is released through the dyalisantic membrane and then is spread in the conjonctival bag.

MYDRIASERT®:-

-Mydriasert® is an insoluble ophthalmic insert, gradually releasing two well-known active ingredients: phenylephrine and tropicamide.

- It is indicated in presurgical mydriasis.

-Mydriasert®, a new insoluble ocular insert, ensures a regular and slow *in vivo* release of the drug.

-This release allows the mydriasis to be obtained quickly and to be maintained during surgery.

➢ Evaluation of Ocular Inserts-

1) Uniformity of Thickness-

-Insert thickness should be measured at three different points using Micrometer screw gauge and mean film thickness should be noted.

2) Uniformity of Weight

3) Drug Content Uniformity

4) Percentage Moisture Absorption-

-Individual inserts were weighed and placed in a desiccator maintained at high relative humidity using an excess amount of salt in solution. After three days the inserts were taken out and reweighed. The percentage moisture absorption was calculated using the formula,

$$\% \text{ Moisture Absorption} = \frac{\text{Final Wt. - Initial Wt}}{\text{Initial Wt}} \times 100$$

5) Percentage Moisture Loss-

-Percentage moisture loss is carried out to check the integrity of the film at dry conditions.

-Inserts are weighed individually and kept in a desiccator containing anhydrous calcium chloride.

-After three days, inserts are taken out and reweighed.

-Percentage moisture loss is calculated using the formula,

$$\% \text{ Moisture Loss} = \frac{\text{Initial Wt- Final Wt.}}{\text{Initial Wt}} \times 100$$

6) In vitro Drug Release Study

7) Draize Eye Irritancy Test

-The Draize eye irritancy test is currently the most valuable and reliable method for evaluating hazard or safety of a substance introduced into or around the eye.

-Eye irritancy potential of a substance is determined on the basis of its ability to cause injury to the cornea, iris, and conjunctiva when a substance is applied to the eye.

-Testing is carried out on adult albino rabbits of either sex.

-All rabbits are maintained under 12 h light and dark cycles and are fed with green vegetables throughout the course of study. Food and water is allowed.

-A series of six rabbits are used for testing the eye irritation potential of the polymer. One placebo insert is made up of gelatin sandwiched using films of ethyl cellulose devoid of the drug placed into the cul-de-sac of the rabbit while other eye serve as a control.

Advantages of Ocular Inserts-

-Increasing contact time and thus improving bioavailability.
-Possibility of providing a prolong drug release and thus a better efficacy.
-Reduction of systemic side effects and thus reduced adverse effects.
-Reduction of the number of administrations and thus better patient compliance.
-Reduction in systemic absorption.
-Possibility of targeting inner ocular tissues through non-corneal routes.
-Possibility of incorporation of various novel chemicals and technological approaches of prodrug, mucoadhesives, permeation enhancers, microparticulate, salts acting as buffers.

Disadvantages of Ocular Inserts-

-A Capital disadvantage of ocular inserts recides in their 'solidity' , i.e., in the fact that they are felt by the patients (often oversensitive) as an external body in the eye.
-Their movement around the eyes, in rare instances, the simple removal is made more difficult by unwanted migration of the inserts to upper fornix.
-The occasional inadvertent loss during sleep or while rubbing the eyes.
-The interference with vision.
-Difficult placement of the ocular insert and removal.

The Future

Pharmacist