Ocular inserts

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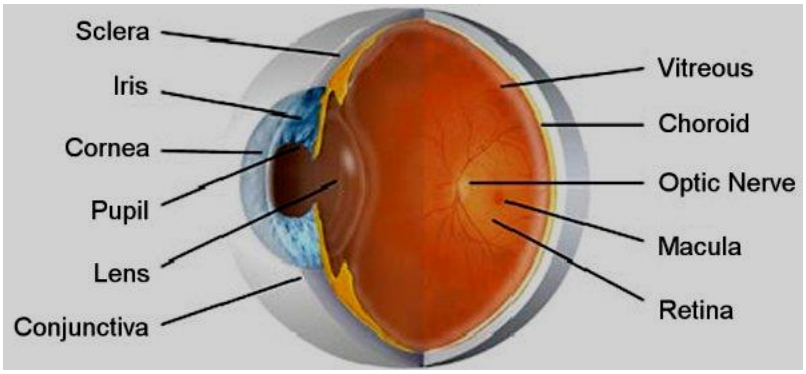
Anatomy and Physiology of Eye



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Human eye

- Diameter of 23 mm
- Structure comprises of three layers
- Outermost coat : The clear, transparent cornea and the white, opaque sclera
- Middle layer : The iris anteriorly, the choroid posteriorly, and the ciliary body at the intermediate part
- Inner layer : Retina (extension of CNS)

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- 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.

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- The **Uvea** is the second layer of the eye and lies between the sclera and the retina.
- The middle coat of the eye is called the uvea (from the Latin for "grape") because the eye looks like a reddish-blue grape when the outer coat has been dissected away.

- 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 opening in the center of the iris, larger or smaller depending on the brightness of the light.
- The centre of this ring is called the pupil. It appears dark because the light passing into the eye is not reflected back to any great extent

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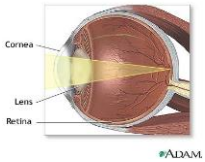

- The **lens** is a transparent, biconvex structure, encased in a thin transparent covering. The function of the lens is to refract and focus incoming light onto the retina.

- 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.

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- 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.

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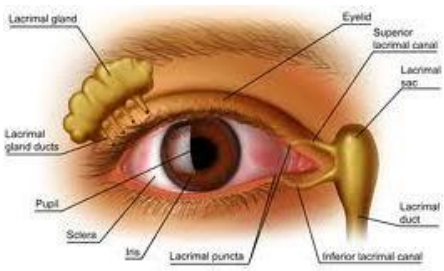
Fluid systems in the eye

- Aqueous humour:
- Secreted from blood through epithelium of the ciliary body.
- Secreted in posterior chamber and transported to anterior chamber.
- Vitreous humour:
- Secreted from blood through epithelium of the ciliary body.
- Diffuse through the vitreous body.
- Lacrimal glands:
- Secrete tears & wash foreign bodies.
- Moistens the cornea from drying out.



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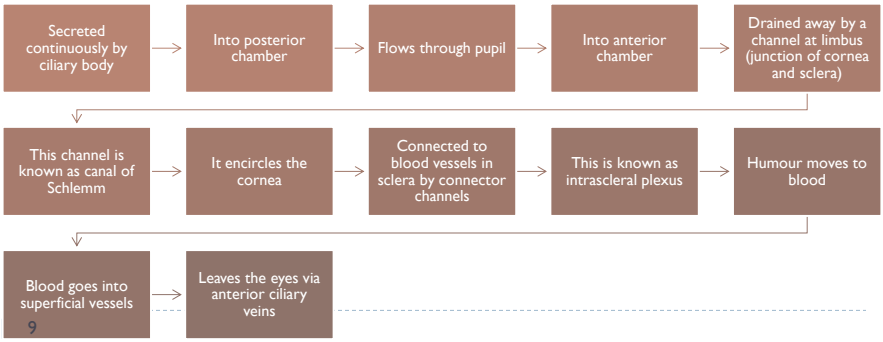
Aqueous humour

- The aqueous humour is a clear colourless fluid with a chemical composition rather similar to that of blood plasma (the blood exclusive of its cells) but lacking the high protein content of the latter.



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- The wall of the canal that faces the aqueous humour is very delicate and allows the fluid to percolate through by virtue of the relatively high pressure of the fluid within the eye.
- Obstruction of this exit causes a sharp rise in the pressure within the eye, a condition that is known as glaucoma.
- Ultimately the abnormal pressure damages the retina and causes a variable degree of blindness.
- The normal intraocular pressure is about 15 mm (0.6 inch) of mercury above atmospheric pressure, so that if the anterior chamber is punctured by a hypodermic needle the aqueous humour flows out readily.
- Its functions:
  - Maintaining the eye reasonably hard
  - Provide nutrition for the crystalline lens and also for the cornea, both of which are devoid of blood vessels; the steady renewal and drainage serve to bring into the eye various nutrient substances, including glucose and amino acids, and to remove waste products of metabolism.

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Vitreous body

- It is a semisolid gel structure that is remarkable for the small amount of solid matter that it contains.
- The solid material is made up of a form of collagen, vitrosin, and hyaluronic acid (a mucopolysaccharide).
- Thus, its composition is rather similar to that of the cornea, but the proportion of water is much greater, about 98 percent or more, compared with about 75 percent for the cornea.
- The jelly is probably secreted by certain cells of the retina.
- It is devoid of cells
- Embedded in the surface of the vitreous body, however, there is a population of specialized cells, the hyalocytes of Balazs, which may contribute to the breakdown and renewal of the hyaluronic acid.
- The vitreous body serves to keep the underlying retina pressed against the choroid.

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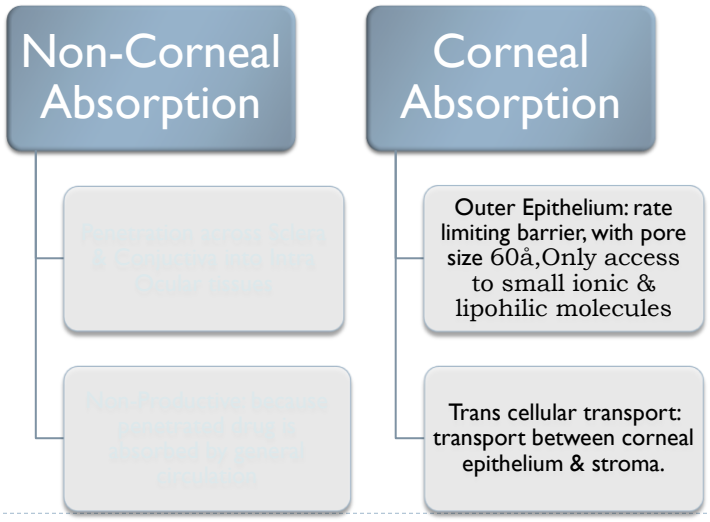
Mechanism of ocular absorption



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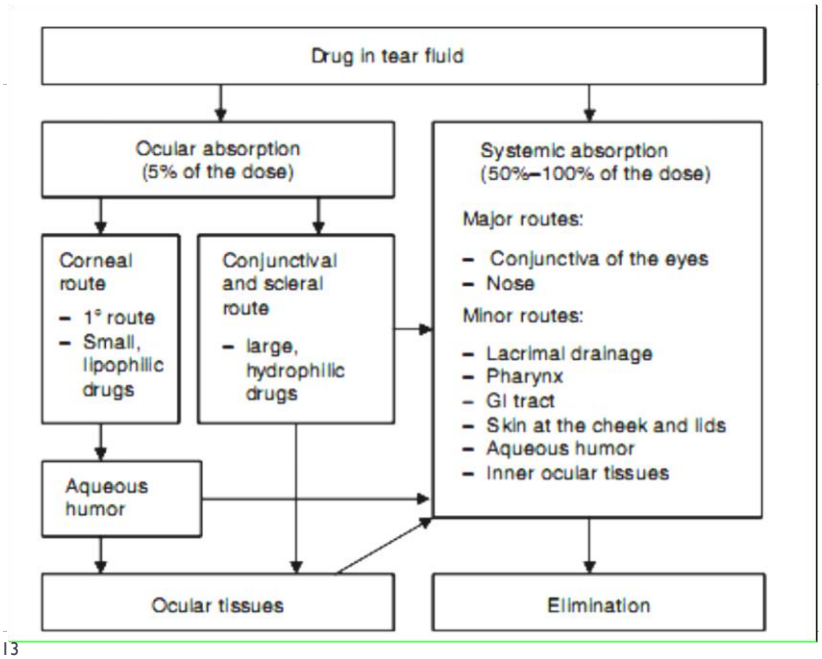

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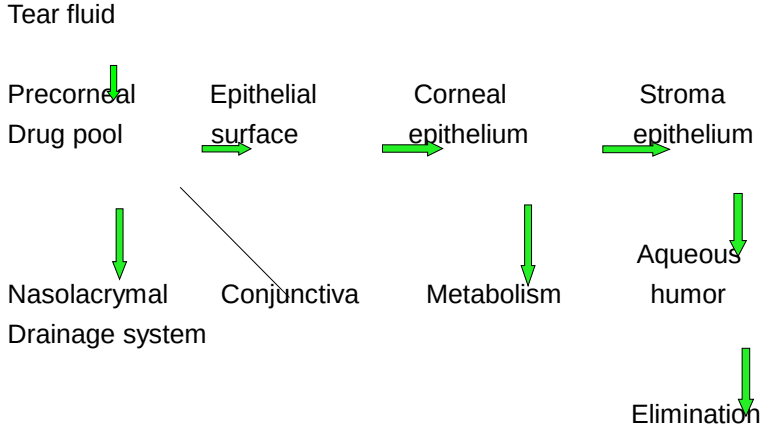
Pharmacokinetics of ocular drug administration



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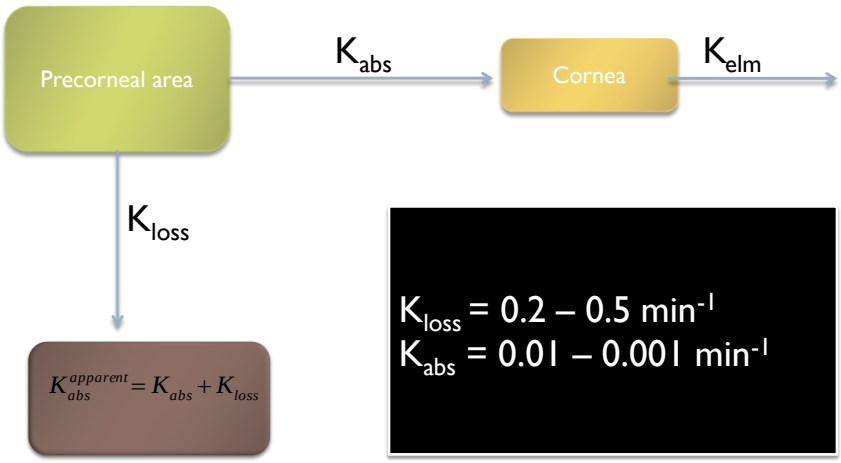

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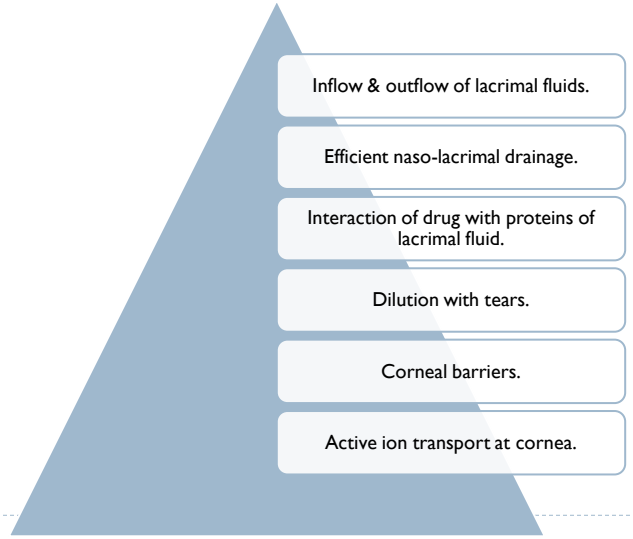
Factors affecting intraocular BA



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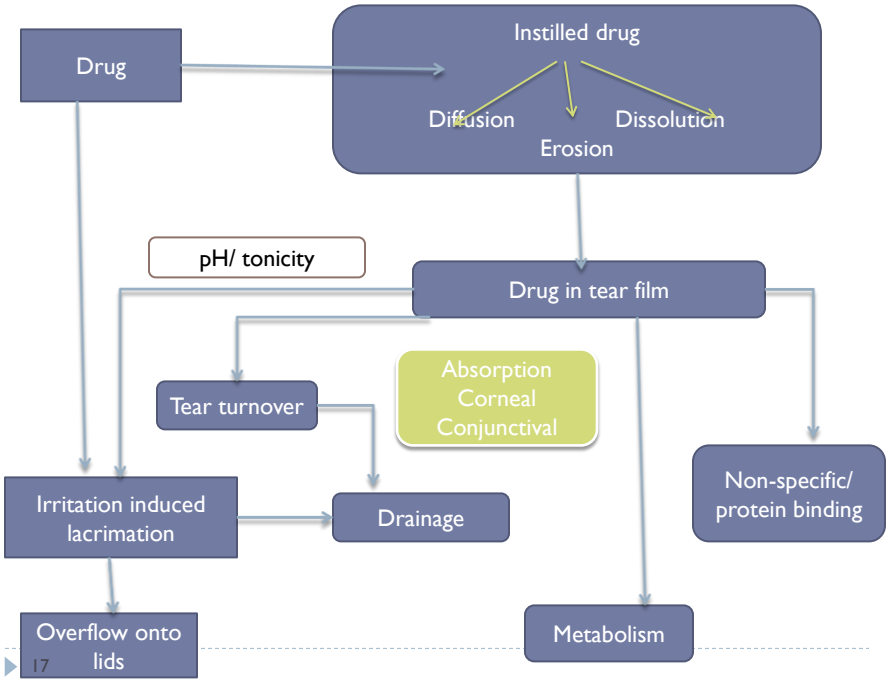

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- Rapid solution drainage by gravity, induced lachrymation, blinking reflex, and normal tear turnover:
- The normal volume of tears = 7 µl, the non-blinking eye can accommodate a volume of up to 30 µl without spillage, the drop volume = 50 µl

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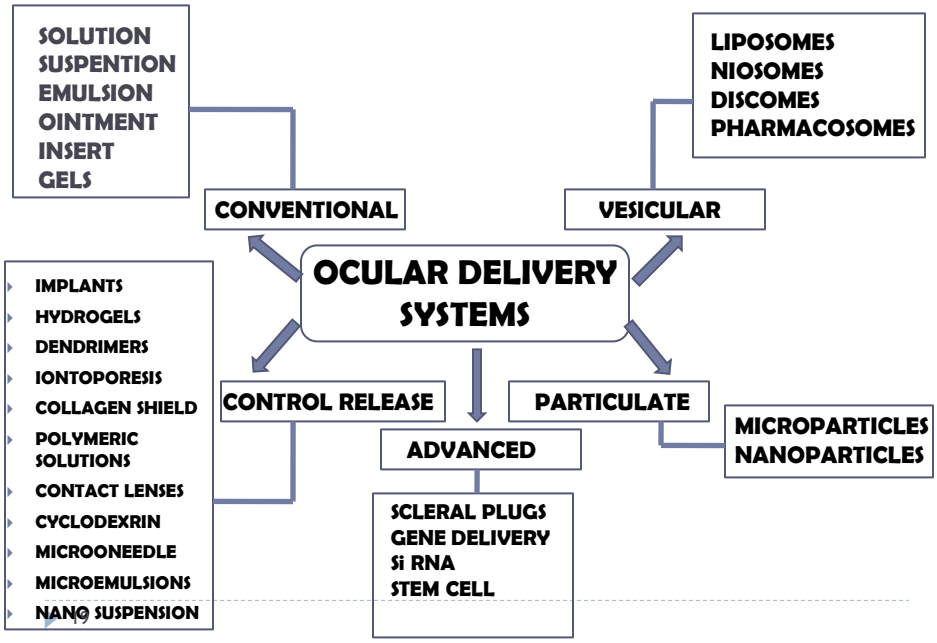

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Advantages of conventional systems

- They are easily administered by the nurse
- They are easily administered by the patient himself.
- They have quick absorption and effect.
- Less visual and systemic side effects.
- Increased shelf life.
- Better patient compliance.

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Disadvantages of conventional systems

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

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Ideal characteristics of OCDDS

- Sterile
- Isotonic - e.g.: 1.9% boric acid, 0.9% NaCl
- Buffer/pH adjustment
- Less drainage tendency
- Minimum protein binding

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Ocular controlled release systems

- Solid or semisolid in nature
- Placed in lower fornix
- Composed of polymeric vehicle containing drug

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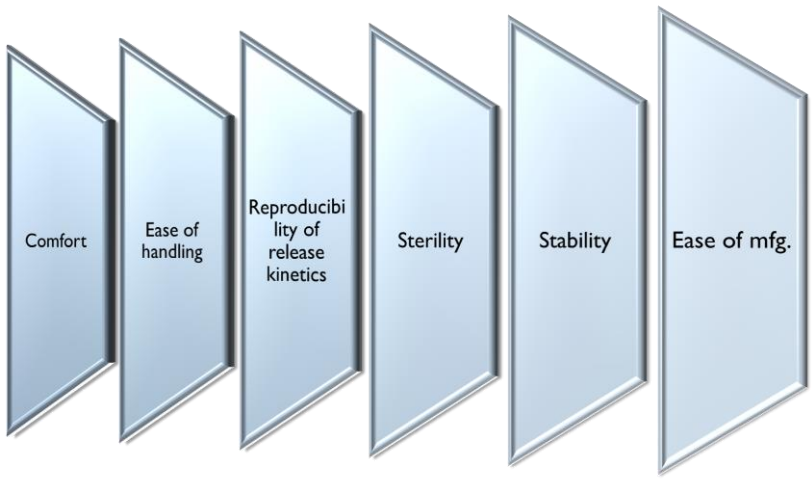
Requisites For Control Release Ocular delivery systems



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Advantages

1. Increase ocular residence, hence, improving bioavailability.
2. Possibility of providing a prolonged drug release and thus a better efficacy.
3. Lower incidence of visual and systemic side effects.
4. Increased shelf life with respect to aqueous solutions.
5. Exclusion of preservatives, thus reducing the risk of sensitivity reactions

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6. Possibility of targeting internal ocular tissue through non-corneal routes
7. Reduction of systemic side effects and thus reduced adverse effects.
8. Reduction of the number of administration and thus better patient compliance.
9. Administration of an accurate dose in the eye, which is fully retained at the administration site, thus a better therapy.

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Disadvantages

1. Perceived by patient as foreign body.
2. Movement around the eye.
3. Occasional loss during sleep or while rubbing eyes.
4. Interference with vision.
5. Difficulty in placement & removal.

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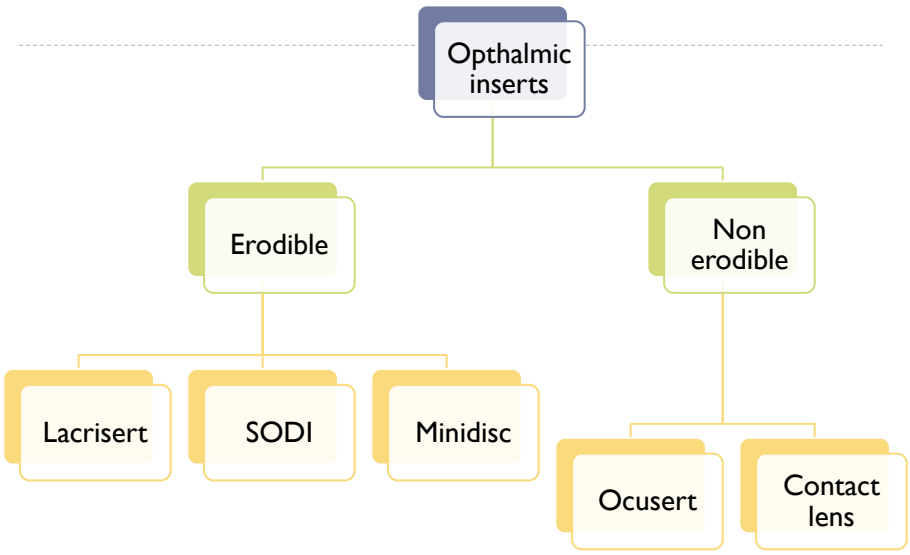

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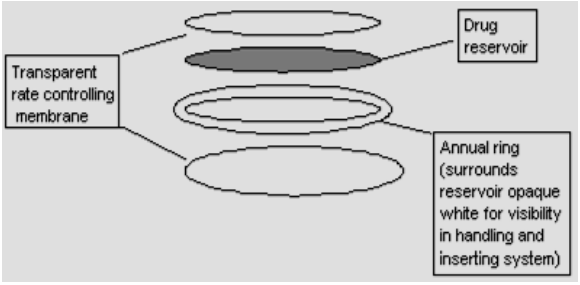
Ocusert

- Developed by Alza Corporation
- It is a flat, flexible elliptical device
- Consists of 3 layers




Ocusert® Anti-glaucoma eye insert containing pilocarpine (RCM = EVA) (Alza Corp.)

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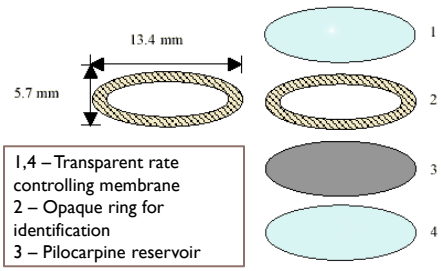
Eg. Pilo 20/ 40 – pilocarpine ocusert



- Two outer layers – made up of copolymer ethylene vinyl acetate (EVA)
- Inner core of pilocarpine in alginate
- Retaining ring of EVA impregnated with TiO_2 for visibility

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- Preprogrammed to release the drug at constant rates for 7 days
- Release rates: 20 – 40 mcg/hr
- Higher release rates of Pilo 40 is achieved by:
  - Making the rate controlling membrane thinner
  - Adding flux enhancer di-(2-ethylhexyl) phthalate

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Advantages

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

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Disadvantages

1. Patient discomfort
2. Placement and removal of insert is difficult
3. Removal of insert leading to loss of the system from eye

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Contact lens

- These are structure made up of a covalently cross-linked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix capable of retaining water, aqueous solution or solid components
- Classification –
  1. Rigid
  2. Semi-rigid
  3. Elastomeric
  4. Soft hydrophilic
  5. Bio-polymeric

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Drug incorporation

- When a hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but dose not give a delivery as precise.
- The drug release from such a system is very rapid at the beginning and then declines exponentially with time.
- Most of the drug from contact lenses is released in the first 30 mins

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The release rate can be decreased by incorporating the drug homogeneously during the manufacture or by adding a hydrophobic component

Drug is incorporated as either a solution or suspension of solid particles in monomer mix.

Polymerization is then carried out

Longer times of release ≈ 180 h

No preservative needed

The problem of discomfort and difficulty in handling and insertion in case of presoaked lenses can be avoided

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Erodible inserts (Soluble inserts)

- They are the oldest class of the ophthalmic inserts.
- They don't need to be removed from their site of application
- Pilocarpine containing CMC wafers
- PVA discs or rods
- Gentamicin sulphate as collagen wafers
- Have been developed
- But only marketed erodible inserts are:
  - Lacrisert
  - SODI
  - Minidisc

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Types

- Based on natural polymers e.g. collagen.

- Based on synthetic or semi-synthetic polymers

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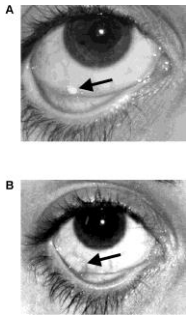
Release

- The release of the drug from such system is by penetration of tears into the inserts, which induces release of the drug by diffusion and forms a gel layer around the core of the insert, this gellification induces the further release, but still controlled by diffusion.
- The release rate, J, is derived from Fick's law,

$$J = \frac{ADKC_s}{L}$$



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Other factors affecting drug release

- Penetration of the fluid.
- Swelling of the matrix.
- Dissolution of the drug and the polymers.
- Relaxation of the polymeric chain.
- A decreased release rate is obtained by introducing a suitable amount of hydrophobic polymer capable of diminishing the fluid penetration and thus of decreasing the release of the drug without modifying the solubility of the insert when added in proper proportion.

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Components of soluble inserts

Soluble synthetic polymers	Cellulose derivatives – Hydroxypropyl methylcellulose, methylcellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Divers – Polyvinyl alcohol, ethylene vinylacetate co-polymer
Additives	Plasticizer – PEG, glycerin, propylene glycol. Enteric coated polymer – CAP, hydroxypropyl methylcellulose phthalate. Complexing agent – PVP. Bioadhesives – polyacrylic acids.

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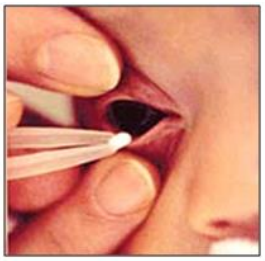
Lacrisert

- Sterile rod-shaped device
- Made of HPMC for dry eyes syndrome
- Free of preservatives
- Introduced by Merck, Sharp & Dohme in 1981
- Weight – 5 mg
- Diameter – 12.7 mm
- Length – 3.5 mm
- Dose: 1-2 times a day



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Proper insertion of lacrisert

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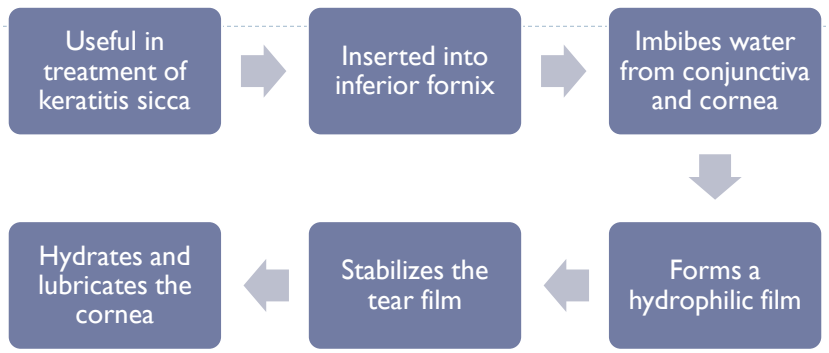

Liquid artificial tears dose: 4 times an hr
Lacrisert dose: 1-2 times a day

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Soluble Ocular Drug Insert (SODI)

- Developed by Soviet scientists for cosmonauts who could not use eye drops in weightless conditions
- Sterile thin oval wafers
- Made up of acrylamide, N-vinylpyrrolidone and ethylacrylate (ratio 0.25: 0.25: 0.5)
- Weight 15-16 mg
- A single dose of SODI replaces 4-12 drops or 3-6 applications of ointment

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Location	• Inferior cul-de-sac
10-15 secs	• Wetted by tear film • Softens and assumes the curved configuration
10-15 mins	• Film turns into a viscous polymer mass
30-60 mins	• Becomes a polymer solution

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Ocular therapeutic system or Minidisc

- Contoured disc with a convex front and concave back surface in contact with the eyeball.
- Like a miniature contact lens
- Size: 4-5 mm
- The symmetric circular design as opposed to the rod shape eliminates the need to align to a particular geometric axis of the device with the eyelid margin

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Made up of silicone prepolymer – α-ω-bis(4-methylacryloxy)-butyl polydimethyl siloxane (M_2D_x)

- M = methylacryloxybutyl
- D = dimethyl siloxane

It can be hydrophilic or hydrophobic and can incorporate both types of drugs

Sulfisoxazole (hydrophobic) + hydrophilic matrix = release within 170 hrs

Gentamicin sulphate (hydrophilic) + hydrophobic matrix = release within 320 hrs

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New Ophthalmic Delivery System (NODS)

- Originally patented by Smith and Nephew Pharmaceuticals Ltd in 1985
- Water-soluble, drug-loaded film approximately 50 mm in length, 6 mm in width
- The device consists of a medicated semicircular flag (4 mm x 6 mm, thickness 20 μm, weight 0.5 g, area 20 m^2) which is attached to a paper-covered handle by means of a short (0.7 mm) and thin (3-4 μm) membrane
- All components (flag, membrane, and handle) are made of the same grade of water-soluble polyvinyl alcohol (PVA)
- The devices are individually packaged and sterilized by gamma irradiation.

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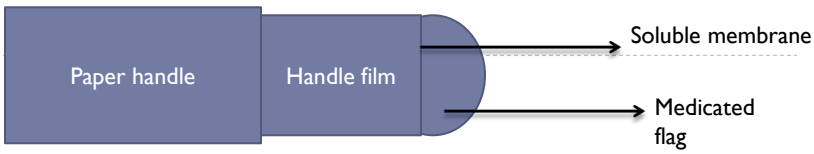

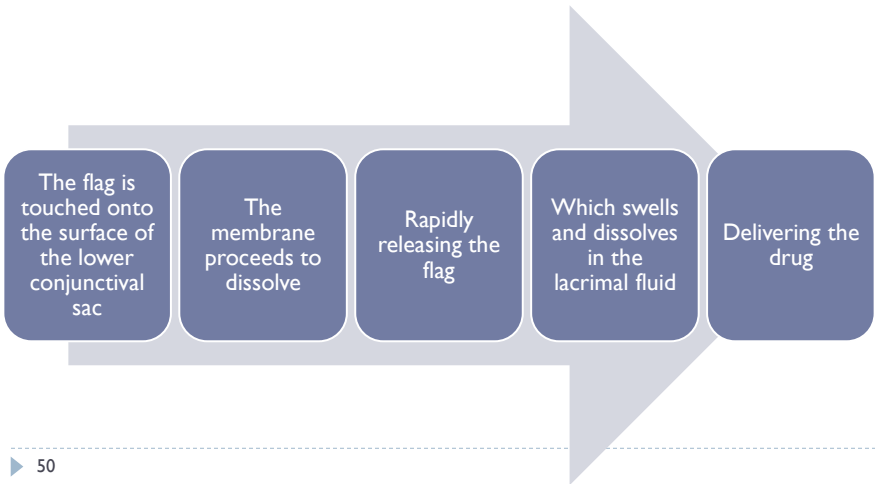

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- Both soluble (pilocarpine) and insoluble drugs (tropicamide) can be incorporated
- Both classes of drugs show increase in bioavailability
- Pilocarpine NODS showed 8-fold increase in the BA as compared to conventional eye drops

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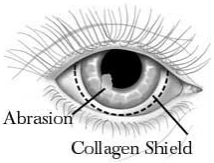
Corneal collagen shields

- Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals
- Bloomfield *et al* . are credited for first suggesting, in 1977 and 1978, the use of collagen inserts as tear substitutes and as delivery systems for gentamicin.
- These shields produced highest levels of drug when compared to drops, ointments and conjunctival injections



- Derived from bovine collagen
- Diameter: 14.5 mm
- Base curve: 9 mm
- Thickness: 0.15-0.19 mm
- Sterilized by gamma radiations
- Then dehydrated and individually packed
- The shield dissolves releasing the drug in tear film maintaining high concentrations on corneal surface and increasing drug permeation through the cornea into the aqueous humor

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- The drug is loaded by soaking the shield in the drug solution.
- The shields are hydrated by tear fluids & then soften and form a clear, pliable thin film.
- These are designed to slowly dissolve within 12, 24 & 72 hr.
- They promote wound healing and used to deliver a variety of drugs like antibiotics, antifungals, steroids & immunosupressives

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Advantages

- Easy to use in ophthalmologist's office
- Prompt drug release
- Maintains high concentration of drug in tear film
- No frequent administration
- Simple and convenient

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Disadvantages

- Insertion technique is difficult
- Expulsion of shield may occur
- Not fully transparent and thus reduce visual acuity

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Bioadhesive Ophthalmic Drug Inserts (BODI)

- The main problem encountered with conventional ophthalmic inserts is their site of application and the risk of expulsion from the site.
- To overcome this drawback, a new type of ophthalmic insert incorporating a water-soluble bioadhesive component in its formulation has been developed to decrease the risk of expulsion and ensure prolonged residence in the eye, combined with controlled drug release
- These inserts, named BODI, are totally eliminated so that they do not need to be removed, thus limiting manipulations to insertion only

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Name	Description
Soluble ocular drug Insert	Small oval wafer, composed of soluble copolymers consisting of actylamide, N-venyl pyrrolidone and ethyl acetate, soften on insertion
New ophthalmic drug delivery system	Medicated solid polyvinyl alcohol flag that is attached to a paper- covered with handle. On application, the flag detaches and gradually dissolves, releasing the drugs
Collagen shields	Erodible disc consist of cross-link porcine scleral collagen
Ocusert	Flat, flexible elliptical insoluble device consisting of two layers, enclosing a areservior, use commercially to deliver Pilocarpine for 7 days
Minidisc or ocular therapeutic	system 4-5 mm diameter contoured either hydrophilic or hydrophobic disc
Lacrisert	Rose-shape device made from Hydroxy propyl cellulose use for the eye syndrome as an alternative to tears
Bioadhesive ophthalmic eye insets	Adhesive rods based on a mixture of Hydroxy propyl cellulose, ethyl cellulose, Poly acrylic acid cellulosephthalate
Dry drops	A preservative free of hydrophilic polymer solution that is freeze dried on the tip of a soft hydrophobic carrier strip, immediately hydrate in tear strip
Gelfoam	Slabs of Gelfoam impregnated with a mixture of drug and cetyl ester wax in chloroform

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