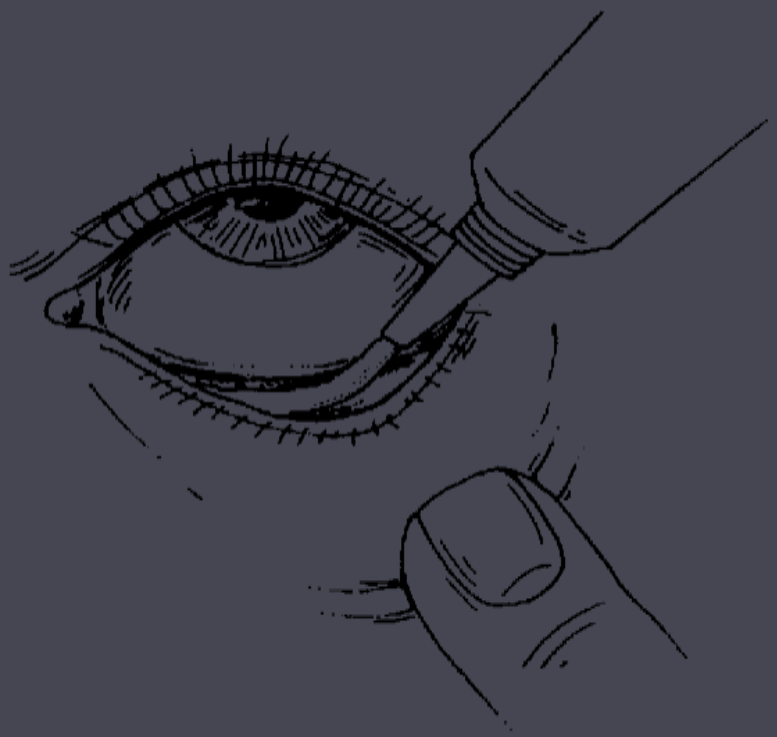

DRUG DELIVERY TO EYE

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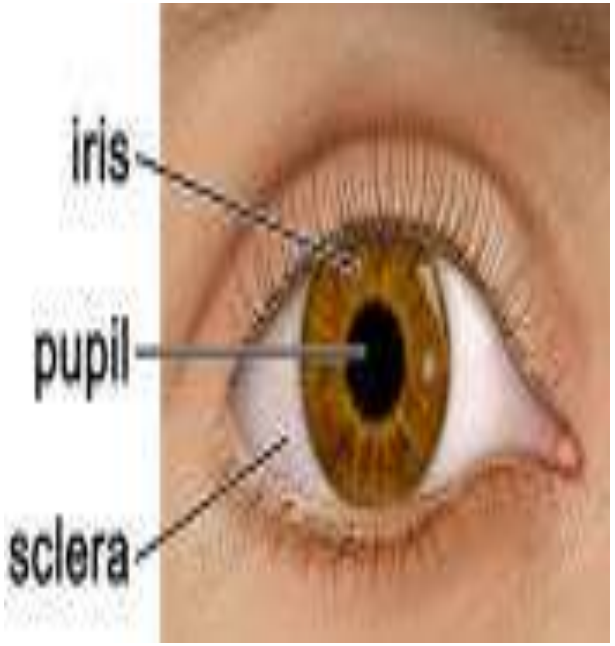
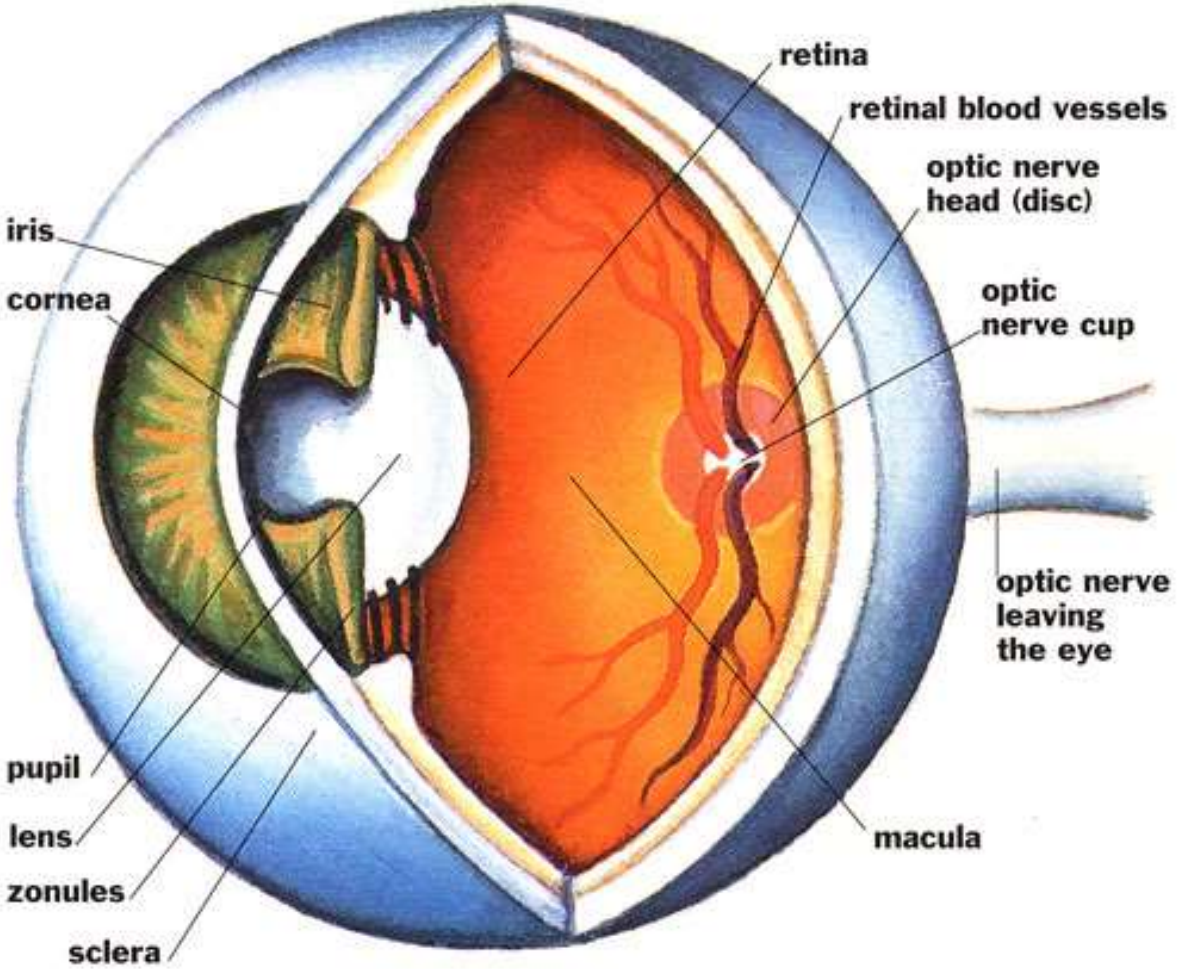
Hyderabad

CONTENTS

THE EYE

- SCLERA
- CHOROID
- RETINA

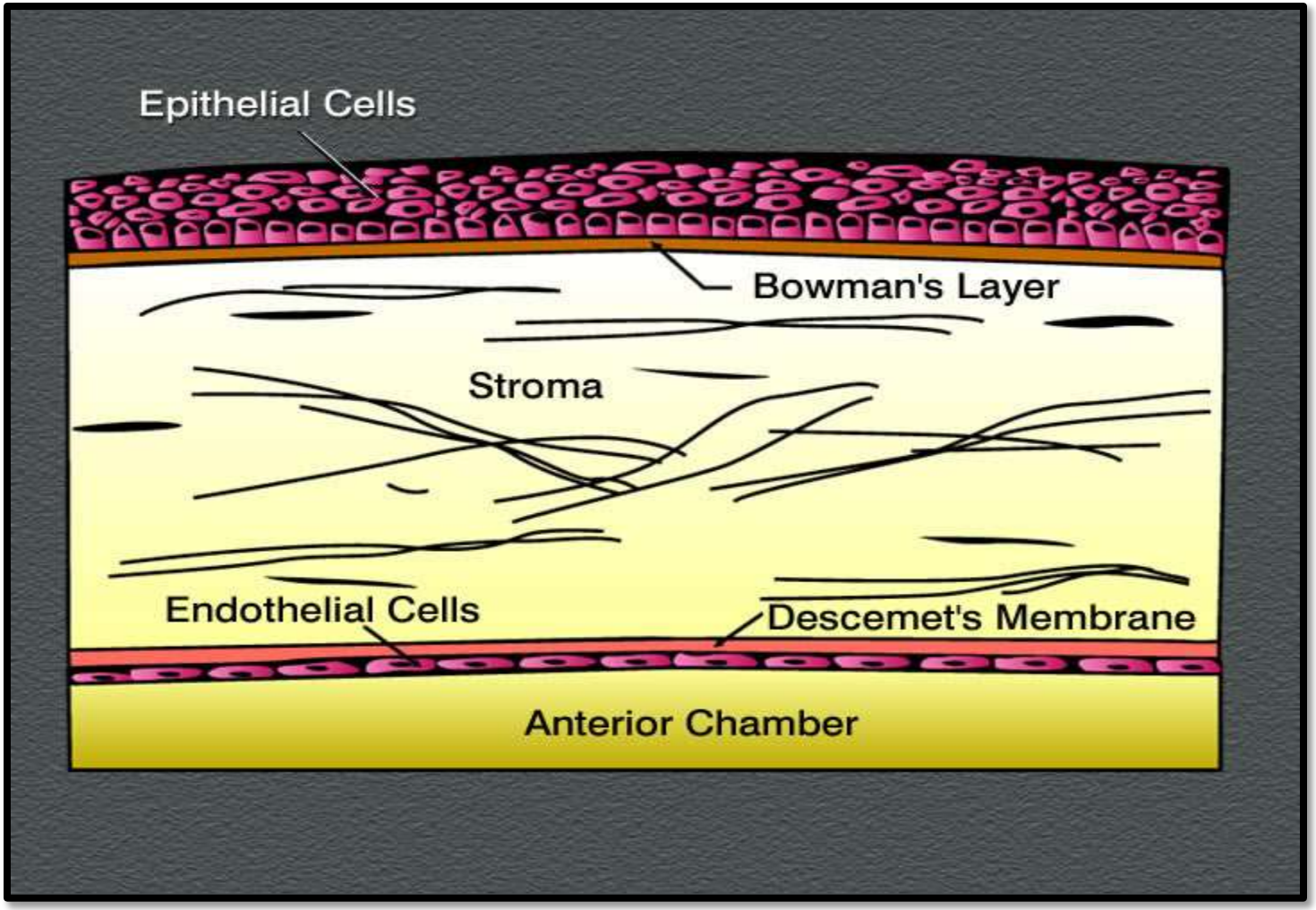




STRUCTURE OF CORNEA

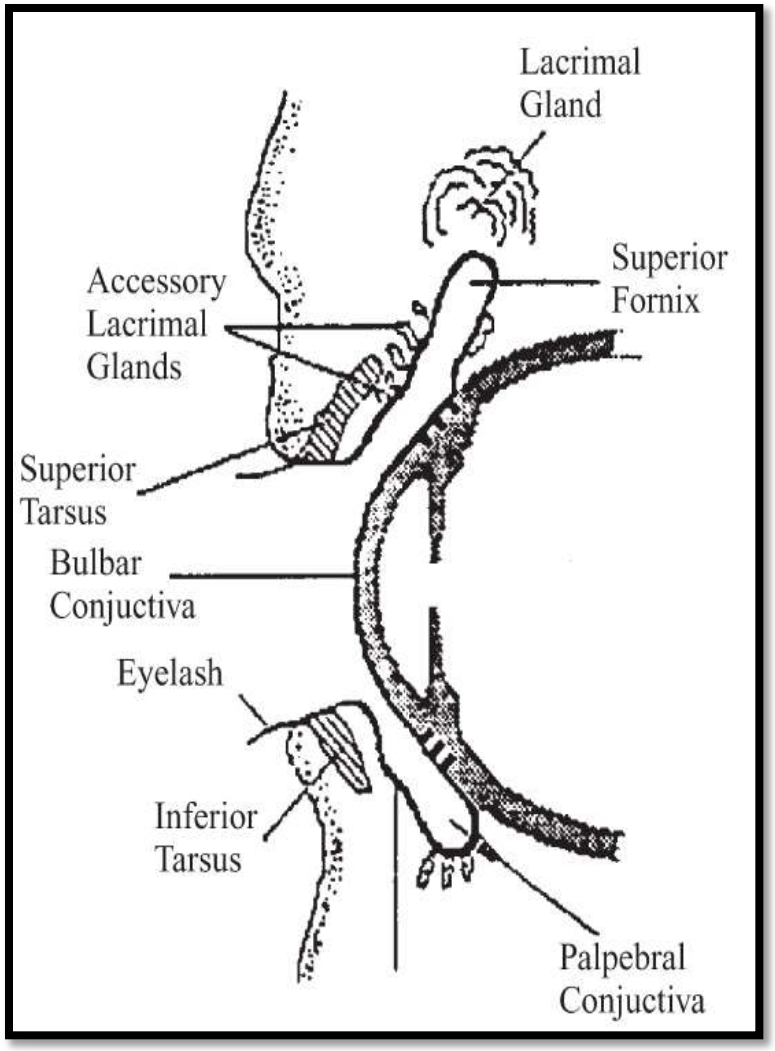
- An avascular tissue
- 0.5 mm thick
- Main pathway for drug Permeation
- Covers $1/6^{th}$ of total Surface area of eye ball

FIVE LAYERS OF CORNEA



THE CONJUCTIVA

- Protects eye
- Thin vascularised mucous membrane
- Posses mucous secreting goblet cells
- 2 to 30 times more permeable to drugs



NASO LACHRYMAL DRAINAGE SYSTEM

SECRETORY SYSTEM

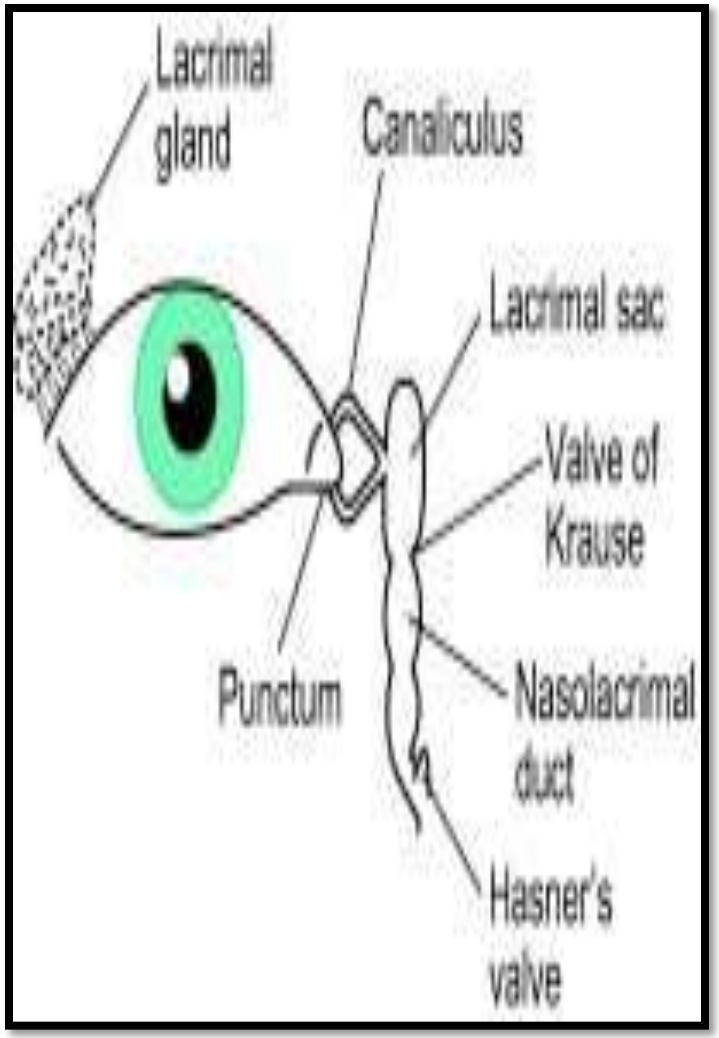
- Consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation

DISTRIBUTIVE SYSTEM

- Consists of eye lids and tear meniscus which spreads tears and prevents dryness in eyes

EXCRETORY SYSTEM

- Consists lachrymal puncta, common canaliculi, lachrymal sac, nasolachrymal duct



TRANS CORNEAL PENETRATION

- **CORNEAL ROUTE**
- Absorption through cornea leads the drug into aqueous humour

- **NON-CORNEAL ROUTE**
- absorption across sclera and conjunctiva into the intraocular tissues

- Corneal epithelium consists of
  - **Basal layer of coloumnar cells**
  - **Three layers of wing cells**
  - **Two layers of superficial cells**

NON-CORNEAL ABSORPTION

- This route involves drug penetration across bulbar conjuctiva and underlying sclera
- This route is important for hydrophilic and large molecules
-
- The limiting molecular size for conjuctival penetration is 20000-40000
- Ocular applied drugs penetrate across the sclera through perivascular spaces

PHARMACOKINETICS

- Rate at which drug disappeared from precorneal compartment is expressed as

$$dCr/dt = -qrCr - (KpSc/Hc)(Ct - CAH)/vde - Kmt + v$$

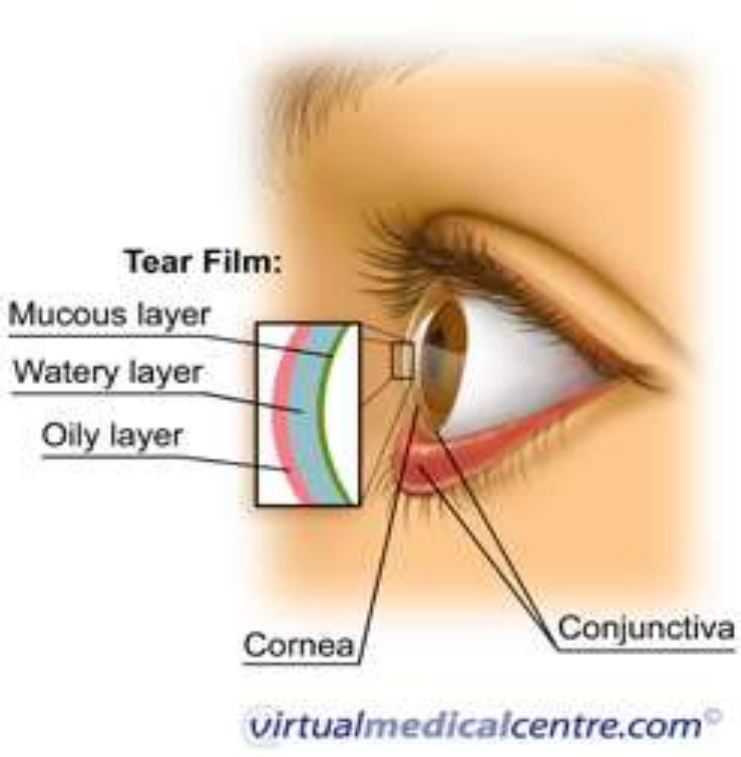
- Rate at which drug appeared in aqueous humour compartment is expressed as

$$Dcah/dt = KPSC/VAHHC(CT - CAH) - KeAH\ CAH/VAH$$

- CT-drug concentration in tear fluid
- Kp-transcorneal permeability rate
- Sc- surface area of cornea
- Hc- thickness of cornea
- CAH- drug concentration in aqueous humour
- Vd- drop size of drug solution
- V0- normal resident tear volume
- VAH- volume of aqueous humour
- Vde- volume of drug pool in precorneal area

OPTHALMIC DISORDERS

- GLAUCOMA
- CONJUCTIVITIS
- DRY EYE SYNDROMI
- KERATITIS
- IRITIS



CLASSIFICATION OF DRUGDELIVERY SYSTEMS TO EYE

- LIQUIDS: Solutions, Suspensions, Sprays
- SOLIDS: Ocular inserts, Contact lenses, Corneal shield, Artificial tear inserts, Filter paper strips
- SEMI SOLIDS: Ointments, Gels
- MISCELLANEOUS: Vesicular systems, Particulates

LIQUIDS~ SOLUTIONS AND SUSPENSIONS

- Solutions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. The drug in the solution is in the solved state and may be immediately active.

- This form also have disadvantages; the very short time the solution stays at the eye surface, its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage), the instability of the dissolved drug, and the necessity of using preservatives.

- A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. This rapid elimination is due to solution state of the preparation and may be influenced by the composition of the solution.

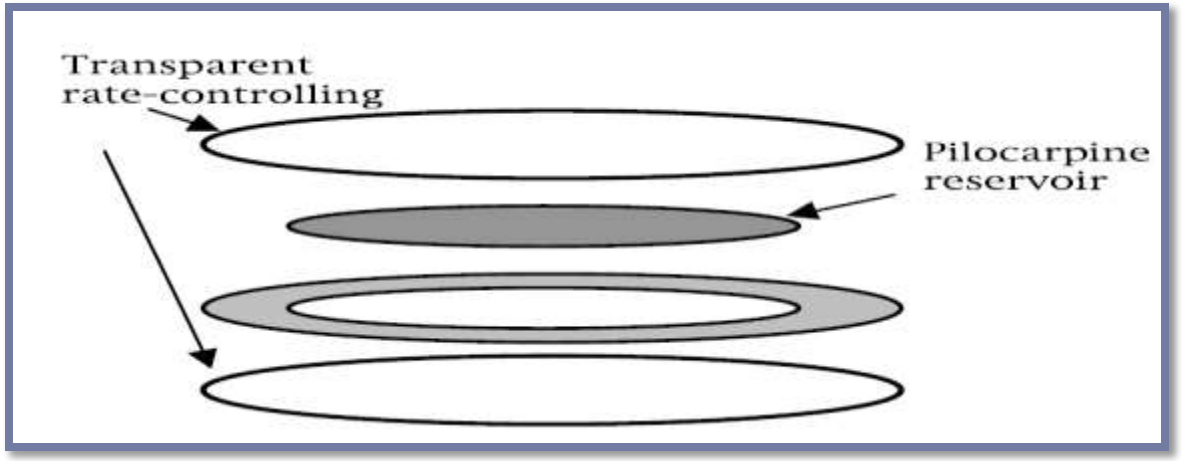
- The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume.

SPRAYS

- Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for cycloplegic examination

OCULAR INSERTS

- Ocular inserts are solid dosage form and can overcome the disadvantage of ophthalmic systems like aqueous solutions, suspensions and ointments.
- The eye drops provided pulse entry pattern of drug administration in the eye which is characterized by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of underdosing.



OCUSERT

- The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications.
- Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane rupture etc.).
- A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible, and hydrogel inserts

CONTACT LENS

- Contact lenses can absorb water soluble drugs when soaked in drug solutions.
- These drug saturated contact lenses are placed in the eye for releasing the drug for long period of time.
- The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs.

CORNEAL SHEILD

- A non cross-linked homogenized, porcine scleral collagen slice is developed by a company (Bausch and Lomb).
- Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers.
- These devices, once softened by the tear fluid, form a thin pliable film that confirms exactly to the corneal surface, and undergoes dissolution up to 10, 24 or 72 hours

ARTIFICIAL TEAR INSERTS

- A rod shaped pellet of hydroxypropyl cellulose without preservative is commercially available (Lacrisert).

- This device is designed as a sustained release artificial tear for the treatment of dry eye disorders. It was developed by Merck, Sharp and Dohme in 1981

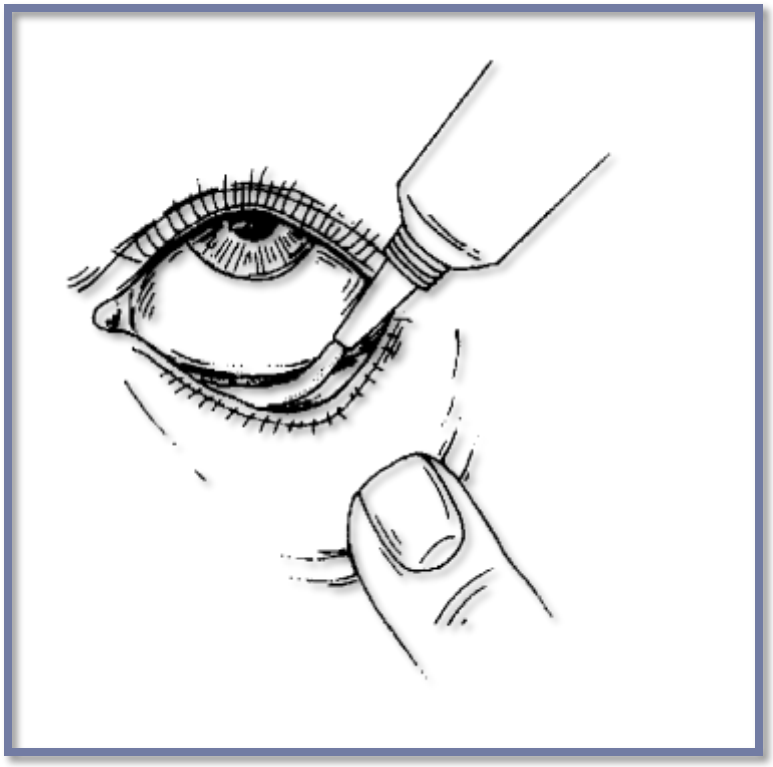
FILTER PAPER STRIPS

- Sodium fluorescein and rose Bengal dyes are commercially available as drug impregnated filter paper strips.

- These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex, and dry eye disorders.

OINTMENTS

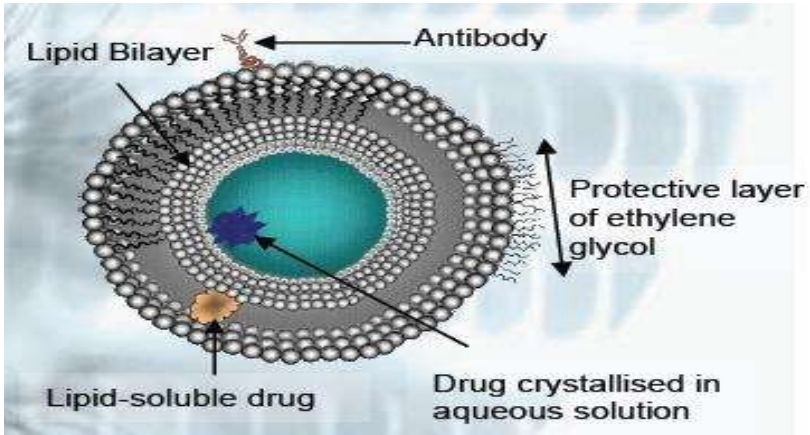
- Ointments provide an increase in the duration of action due to reduction in dilution by tears, reduction in drainage by way of a sustained release effect, and prolonged corneal contact time.
- The primary purpose of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface. But they present a disadvantage of causing blurring of vision and matting of eyelids



VESICULAR SYSTEMS

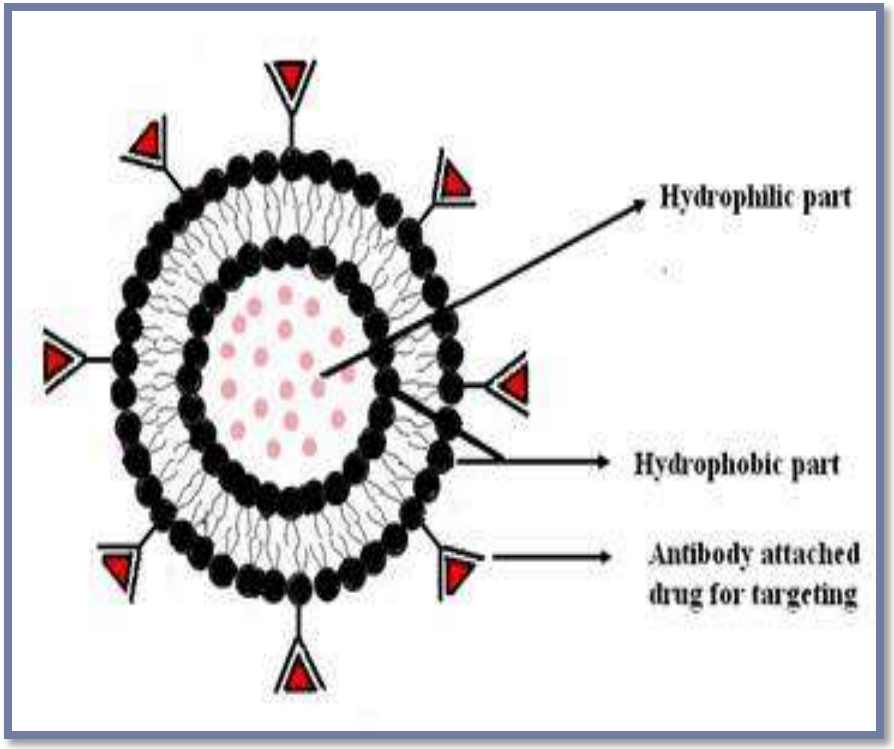
LIPOSOMES: Liposomes are phospholipid-lipid vesicles for targeting the drugs to the specific sites in the body. Because of their structural versatility they can incorporate any kind of drug substance regardless of its solubility.

- They provide the controlled and selective drug delivery and improved bioavailability and their potential in ocular drug delivery appears greater for lipophilic than hydrophilic compounds.
- Liposomes are vesicles composed of a lipid membrane enclosing an aqueous volume.
- Liposomes offer the advantage of being completely biodegradable and relatively nontoxic but are less stable than particulate polymeric drug delivery systems.
- Liposomes were found to be potential delivery system for administration of a number of drugs to the eye



NIOSOMES

- Niosomes are developed as they are chemically stable as compared to liposomes and can entrap both hydrophilic and hydrophobic drugs. They are non toxic and do not require special handling techniques



PARTICULATES

- Particulate polymeric drug delivery systems include micro- and nanoparticles.
- Particles in the micrometer size range > 1mm are called micro particles or microspheres, whereas those in the nanometer size range < 1mm (1000 nm) are called nanoparticles.
- Micro particles with a capsule wall enclosing a liquid or solid core are called microcapsules.
- The upper size limit for micro particles for ophthalmic administration is about 5-10 mm. Above this size, a scratching feeling in the eye can result after ocular application.
- Microspheres and nonoparticles represent promising drug carriers for ophthalmic application .

EVALUATION OF DRUG DELIVERY SYSTEM TO EYE

- These systems are evaluated by various methods. The ocular in-vitro studies include design of specialized apparatus. The ocular in-vivo studies were done in rabbits and include tear pH measurements, pharmacodynamic studies

- ✓ *IN-VITRO* EVALUATION METHODS

- ✓ *IN-VIVO* EVALUATION METHODS

IN-VITRO METHODS

- ***Bottle method***
  In this method, dosage forms are placed in the culture bottles containing phosphate buffer at pH 7.4. The culture bottles are shaken in a thermostatic water bath at 37°C. A sample of medium is taken out at appropriate intervals and analyzed for drug contents.

- ***Diffusion method***
  An appropriate simulator apparatus is used in this method. Drug solution is placed in the donor compartment and buffer medium is placed in the receptor compartment. An artificial membrane or goat cornea is placed in between donor and receptor compartment. Drug diffused in receptor compartment is measured at various time intervals.

- ***Modified rotating basket method***
  In this method, dosage form is placed in a basket assembly connected to a stirrer. The assembly is lowered into a jacketed beaker containing buffer medium. The temperature of system is maintained at 37°C. A sample of medium is taken out at appropriate time intervals and analyzed for drug content.

- *Modified rotating paddle apparatus*

  In this method, diffusion cells (those that are used for analysis of semi-solid formulations) are placed in the flask of rotating paddle apparatus. The buffer medium is placed in the flask and paddle is rotated at 50 rpm. The entire unit is maintained at 37±0.5° C. Aliquots of samples are removed at appropriate time intervals and analyzed for drug content.

IN-VIVO METHODS

- The drug delivery systems can be evaluated for its pharmacokinetic and pharmacodynamic profiles.
- The main objective of the pharmacokinetic studies is to determine the drug release from the dosage form to the eye.
- Rabbit is used as an experimental animal because of a number of anatomical and physiological ocular similarities and also due to larger size of the eye.
- Pharmacokinetic studies are performed by measuring drug concentration in various eye tissues eg. lens, cornea, iris, ciliary body, retina sclera, aqueous and vitreous humour in rabbits.
- The intraocular pressure of the eye is measured with a tonometer

- Ocular pharmacokinetic studies can also be carried out by tear fluid sampling, which is a non-invasive technique.
- Usually, disposible glass capillaries of 1ml capacity are used for sampling. The samples are collected from the marginal tear strip of the rabbits.
- Extreme care must be taken to avoid any corneal contact and possible induced lacrimation.
- To withdraw aqueous humour, rabbits are anaesthetized with ketamine and aqueous humour about 200ml is withdrawn from the anterior chamber using 1ml syringe with 26 guage needle.
- Vitreous samples are also obtained with 20 gauge needle. The entire cornea, lens, and iris-ciliary body are also removed and analyzed for the drug content