Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-VII

Subject Name: Novel Drug Delivery System
Subject Code: BP704TT

CHAPTER-5- Unit:1- OCULAR DRUG DELIVERY SYSTEM

SYLLABUS:

Ocular drug delivery system:

Introduction, intra ocular barriers and methods to overcome – Preliminary study, ocular formulations and ocuserts

This subject is designed to impart basic knowledge on the area of novel drug delivery systems.

Learning objectives

Upon completion of the course the student shall be able to

1. To understand various approaches for development of novel drug delivery systems.
2. To understand the criteria for selection of drugs and polymers for the development of Novel drug delivery systems, their formulation and evaluation.

Ocular Drug Delivery System

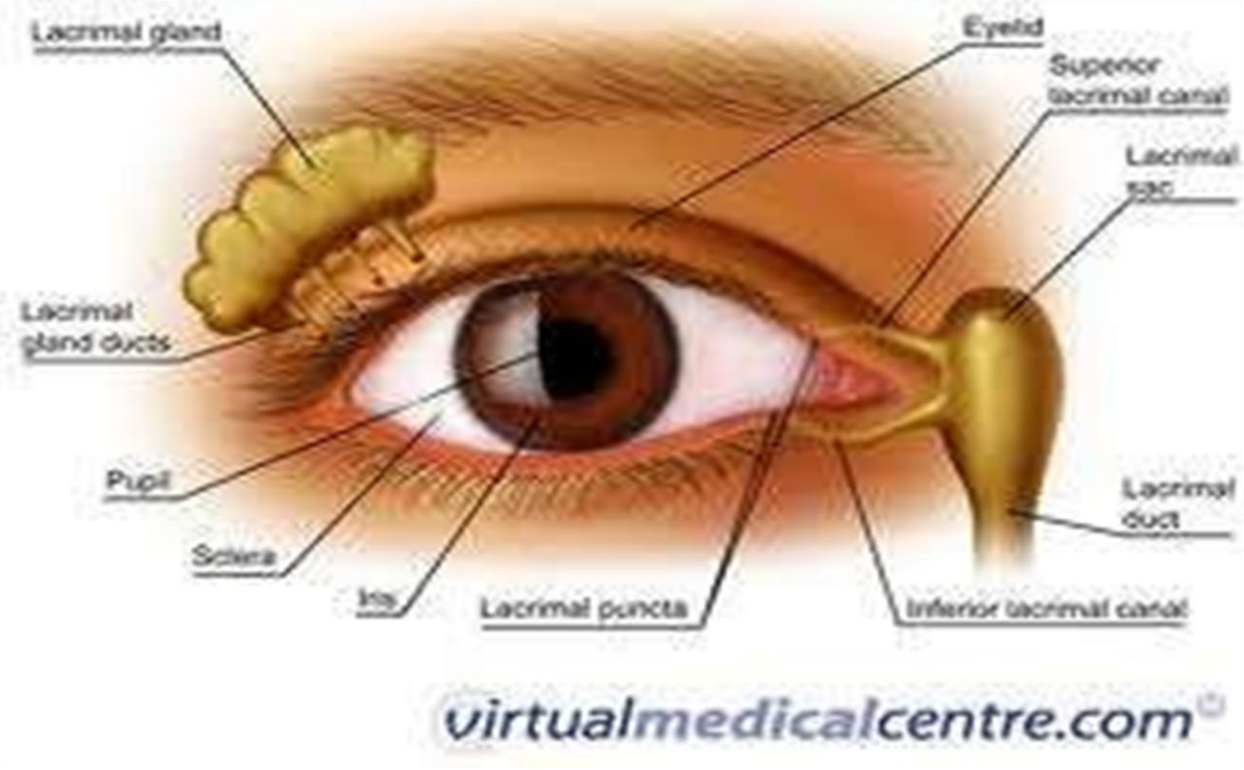
What is Ocular Drug Delivery System (ODDS)

- Ocular administration of drug is primarily associated with the need to treat ophthalmic diseases.
- Eye is the most easily accessible site for topical administration of a medication.
- Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain near front of the eye for prolong period.

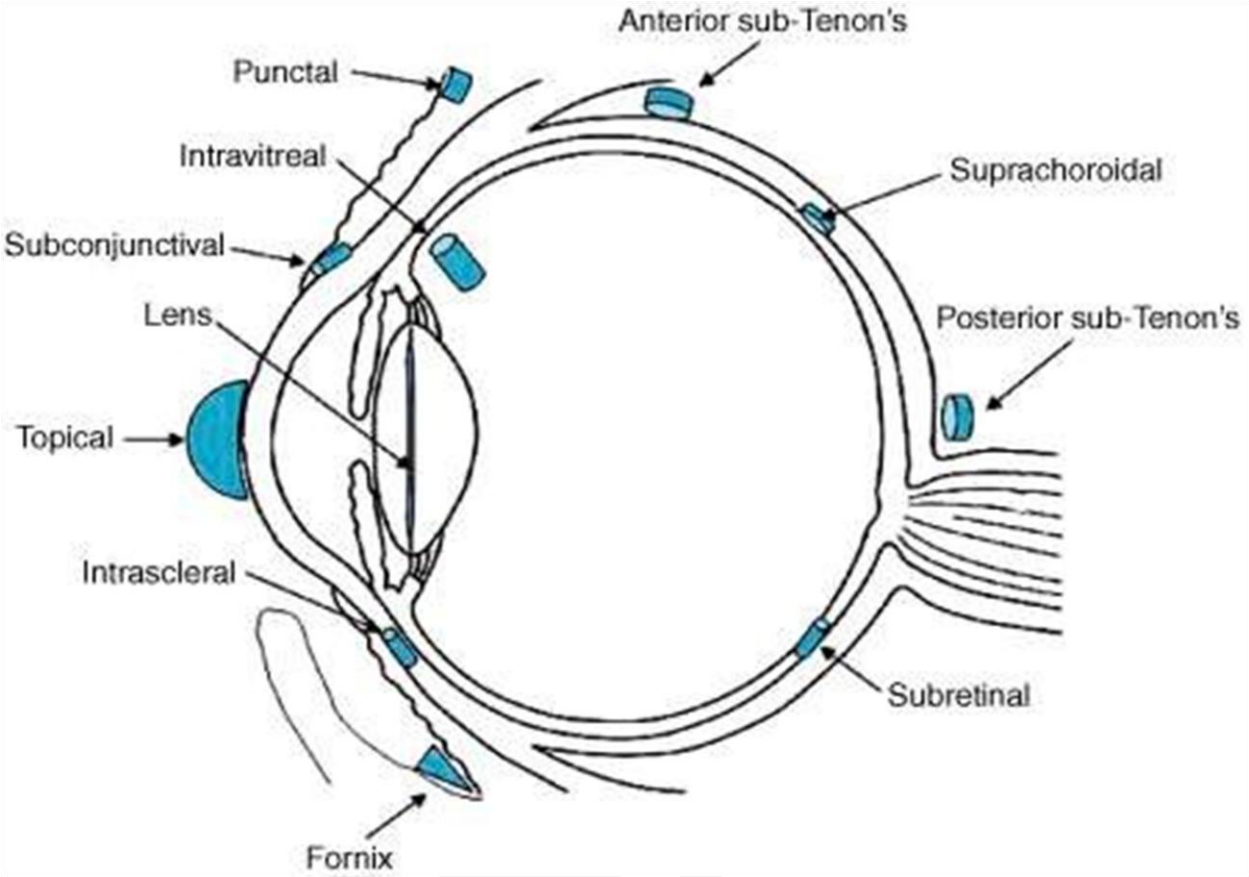
Composition of eye

- Water- 98%, Solid -1.8%, Organic element – Protein - 0.67%, sugar - 0.65%, NaCl - 0.66% Other mineral element sodium, potassium and ammonia- 0.79%.

Eye and Lachrymal Drainage System



Routes Of Delivery Of Drug To Eye



Mechanism of Ocular Absorption

Non- corneal absorption:

- Penetration across sclera & conjunctiva into intra ocular tissues.

Non productive:

- Because penetrated drug is absorbed by general circulation.

Corneal absorption:

Outer epithelium: r

- Rate limiting barrier, with pore size 60 d, only access to small ionic and lipophilic molecules.

Trans cellular transport:

- Transport between corneal epithelium and stroma.

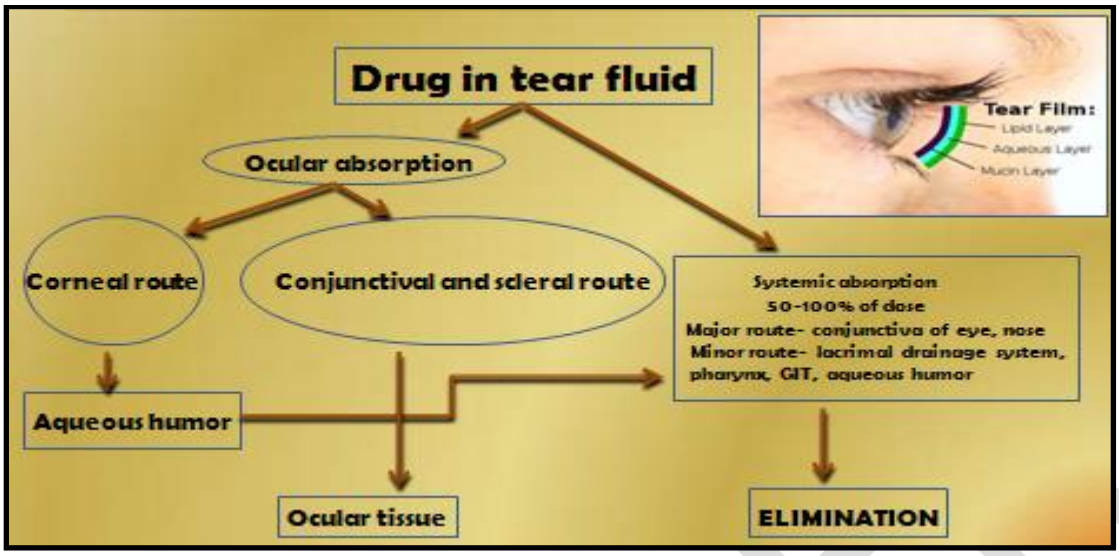
FACTORS AFFECTING INTRAOCULAR BIOAVAILABILITY:

1. Inflow & outflow of lacrimal fluids.
2. Efficient naso-lacrimal drainage.
3. Interaction of drug with proteins of lachrymal fluid.
4. Dilution with tears.
5. Corneal barriers.
6. Active ion transport at cornea.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Ideal ophthalmic drug delivery must be able to ?	sustain the drug release and to remain near front of the eye for prolong period.
2	Water content in Eye?	98%
3	In which absorption, the penetration across sclera & conjunctiva into intra ocular tissues?	Non corneal
4	Rate limiting barrier is?	Pore size
5	In which transport, the drug is travelled between corneal epithelium and stroma	Transcellular transport
6	Protein content in Eye?	0.67%

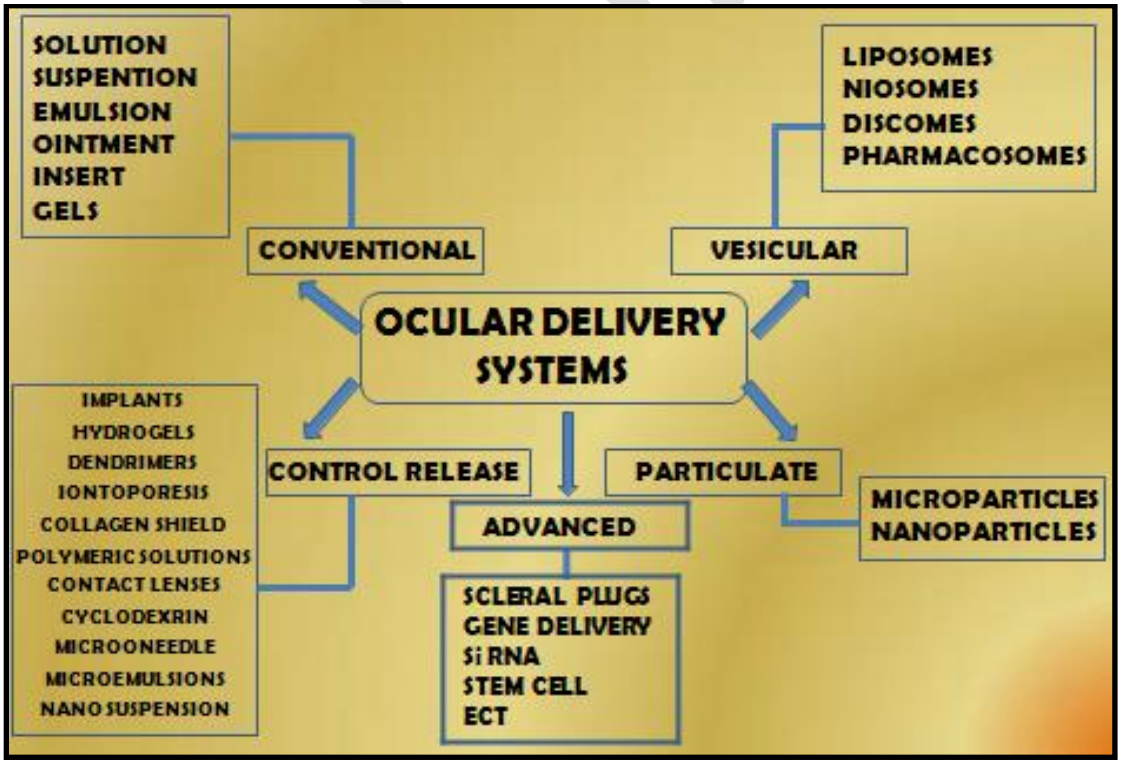
Barriers Avoiding Drug Delivery



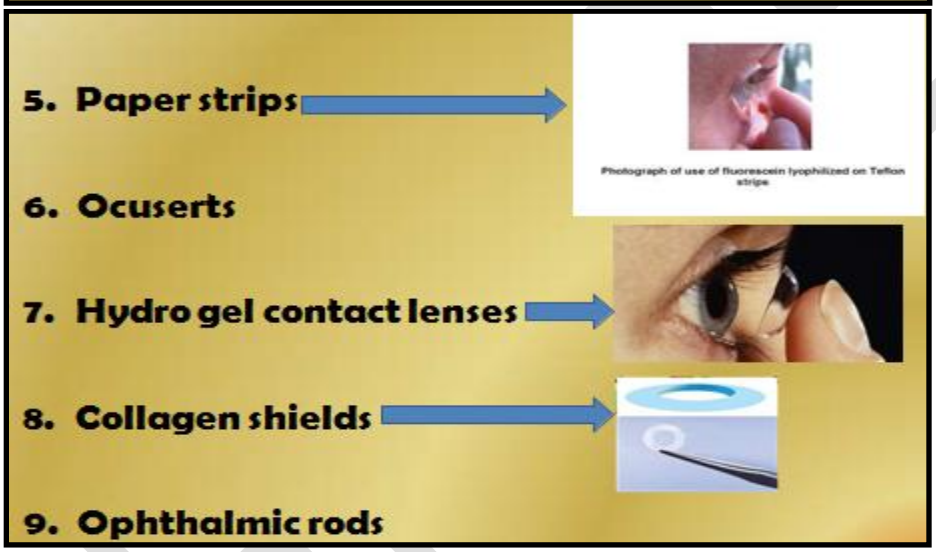
Ophthalmic Dosage Forms

- Ophthalmic preparations are sterile products essentially free from foreign particles, suitably compounded and packaged for instillation in to the eye.
- The following dosage forms have been developed to ophthalmic drugs.
- Some are in common use, some are merely experimental, and others are no longer used.

ODDS



Selected Types of ODDS



Advantages

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

Disadvantages

- 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.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which are sterile products essentially free from foreign particles, suitably compounded and packaged for instillation in to the eye?	Ophthalmic preparations
2	Disadvantages of ODDS	Poor bioavailability
3	Which dosage form has short contact time?	ODDS
4	Vesicular, controlled, particulate type of?	ODDS
5	Better compliance offered by which dosage forms?	ODDS

IDEAL CHARACTERISTICS OF OCDDS:

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

FORMULATION OF OCULAR DRUG DELIVERY SYSTEM:

Dosage Form	Advantages	Disadvantages
solutions	convenience	Rapid precorneal elimination, non sustained action
suspension	Patient compliance, best for drug with slow dissolution	Drug properties decide performance loss of both solutions and suspended particles
emulsion	Prolonged release of drug from vehicle	Blurred vision, patient non compliance
ointment	Flexibility in drug choice, improved drug stability	Sticking of eyes lids, blurred vision, poor patient compliance

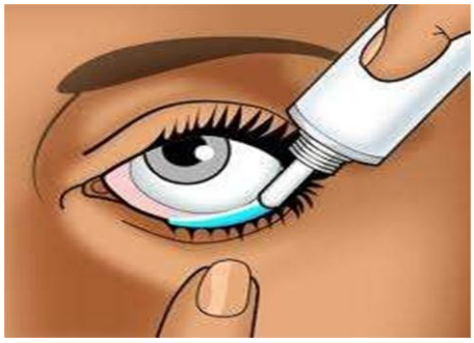
1. CONVENTIONAL DELIVERY SYSTEMS:

Eye Drops:

- Drugs, which are active at eye or eye surface, are widely administered in the form of Solutions, Emulsion and Suspension.
- Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye.
- Less than 5 % of the dose is absorbed after topical administration into the eye.
- The dose is mostly absorbed to the systemic blood circulation via the conjunctival and nasal blood vessels.

Ointments and Gels

- Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but the major drawback of this dosage form like, blurring of vision & matting of eyelids can limit its use.



Occusert and Lacrisert

- Ocular insert (Ocusert) are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage.
- Inserts are available in different varieties depending upon their composition and applications.
- Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca.
- They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film, which lubricates the cornea.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Isotonicity is achieved in ODDS by?	1.9% boric acid, 0.9% NaCl
2	Drugs, which are active at eye or eye surface, are widely administered in the form of Solutions, Emulsion and Suspension is called?	Eye drops
3	How much dose absorbed after topically administration into eye?	Less than 5 % of the dose
4	Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume	Retention time of eye drops
5	Prolongation of drug contact time with the external ocular surface can be achieved by?	Ointments and gel
6	What is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca?	Lacrisert

OPHTHALMIC INSERTS

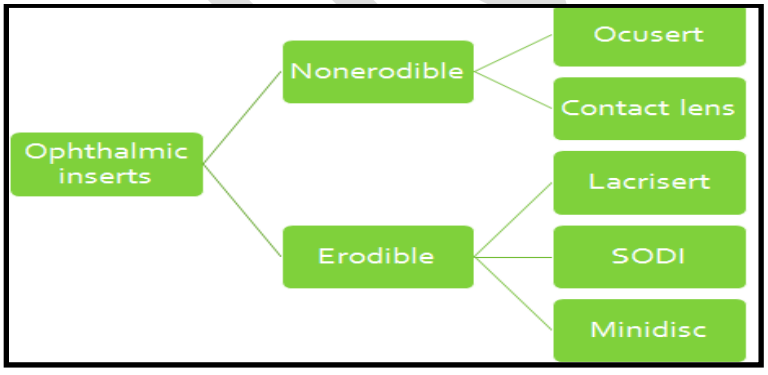
- Ophthalmic inserts are polymer based delivery devices, which are solid or semisolid consistency, the size and shape of which are especially, designed for ophthalmic application.
- It offers the potential advantage of improving patient compliance by reducing the dosing frequency.
- They generally consist of a reservoir of active substance embedded in a matrix or bounded by a rate-controlling membrane.
- The active substance, which is more or less soluble in physiological fluids, is released over a determined period.
- With the advent of ophthalmic inserts, it is now possible to administer drugs in a truly continuous and controlled manner.

Criteria of ophthalmic inserts

- Comfort
- Ease of handling &insertion
- Non interference with vision and oxygen permeability
- Sterility
- Stability
- Ease of manufacture

Advantage

- Allow accurate dosing
- Reduces systemic absorption
- Better patient compliance
- Reduced frequency of administration
- Lower incidence of visual and systemic side effects

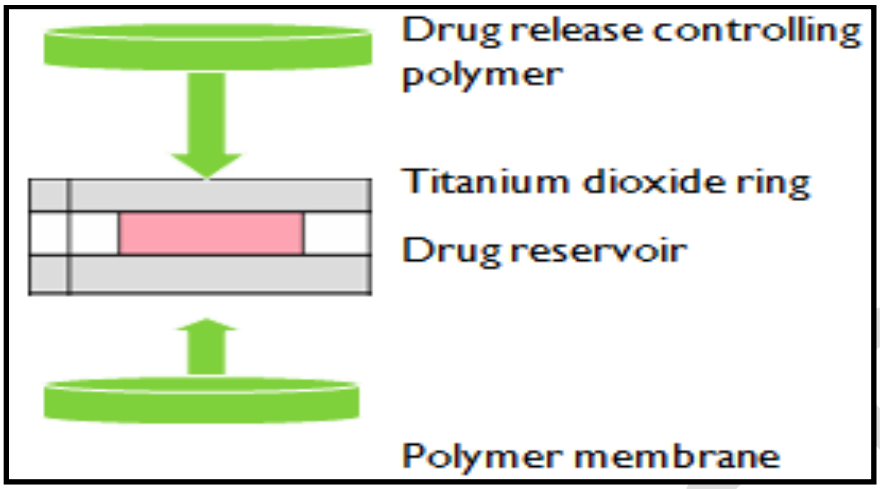


NONERODIBLE INSERTS

Ocusert

- Ocusert is a flat, flexible, elliptical device consisting of three layers.
- Two outer layers of ethylene vinyl acetate [EVA] enclose in the inner core of pilocrpine gelled with alginate.

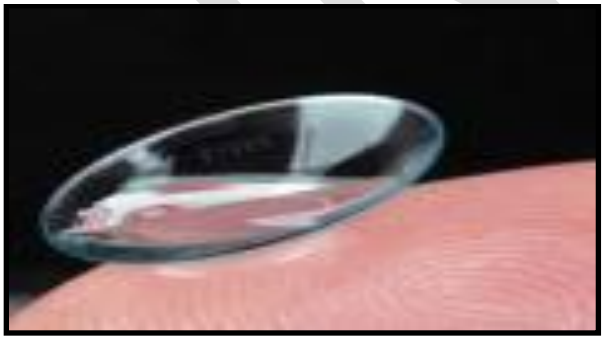
- Two types of ocuserts are available for humans: the pilo-20 & pilo-40.



- It is preprogrammed to release pilocarpine at constant rate of 20 or 40 mcg/hr around the clock for 7 days.
- The higher release rate of Ocusert pilo-40 is achieved by making its rate controlling membrane thinner and by the use of flux enhancer di (2 ethyl-hexyl) phthalate.
- Mainly used in chronic glaucoma.

CONTACT LENS

- It is a type of potential drug delivery device in which they are inserted by presoaking them in drug solution.
- It has been seen that most of the drug from contact lens is released within the first 30 min.
- The use of preservative benzalkonium chloride has come in question due to its toxic effect on the corneal epithelium.



- Therefore, an alternative approach to presoaking soft contact lenses in drug solutions is to incorporate the drug either as a solution or as suspension of solid particles in the monomer mix.
- The polymerization is then carried out to fabricate the contact lenses.
- This technique has demonstrated the promise of longer times of release up to 180h as compared to presoaked contact lenses.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	The devices, which are solid or semisolid consistency, the size and shape of which are especially, designed for ophthalmic application is called?	Ophthalmic inserts
2	Ocusert pilo-40 is used in treatment of?	Glaucoma
3	Which device are inserted by presoaking them in drug solution?	Contact lens
4	Most of the drug from contact lens is released within time?	30 min
5	Most common preservative is found in Contact lens is?	Benzalkonium chloride
6	Release rate of pilocarpine is?	20 or 40 mcg/hr around the clock for 7 days
7	A device have a flat, flexible, elliptical device consisting of three layers is called?	Ocusert

TYPES OF CONTACT LENSES:

1- Hard contact lenses

- Made of rigid plastic resin polymethylmethacrylate
- Impermeable to oxygen and moisture

2- Soft contact lenses

- Made of hydrophilic transparent plastic, hydroxyethylmethacrylate.
- Contain 30 – 80% water so are permeable to oxygen.

3- Rigid gas permeable (RGP)

- Take the advantages of both soft and hard lenses, they are hydrophobic and oxygen permeable.

Advantages

- Prolonged delivery
- Controlled rate of release
- Flexibility for type of drug selected
- Sustained release

Disadvatages

- Patient discomfort
- Irritation to eye
- Patient placement and removal
- Tissue fibrosis

ERODIBLE INSERTS

- These are soluble inserts, which undergo gradual dissolution in the process of drug release and thereby need not to be removed.
- It occurs mainly due to swelling, whereas erosion involves chemical or enzymatic hydrolytic degradation of polymer.
- The erodible system consists of,
- Lacriserts
- Soluble Ophthalmic Drug Inserts (SODI)
- Minidisc Ocular Therapeutic System (MOTS)

LACRISERT

- The LACRISERT is a sterile; water soluble, rod-shaped device made of hydroxypropyl cellulose without any preservative is used for the treatment of dry eye syndromes.
- It weighs 5 mg and measure 12.7mm in diameter with a length of 3.5 mm.

- It is inserted into the inferior fornix where it imbibes water from conjunctiva and cornea, forms a hydrophilic film, which stabilizes the tear, film and hydrates and lubricates the cornea.
- **LACRISERT** is supplied in packages of 60 units, together with illustrated instructions and a special applicator for removing LACRISERT from the unit dose blister and inserting it into the eye.
- A spare applicator is included in each package.

Indications and Uses

- LACRISERT is indicated in patients with moderate to severe dry eye syndromes, including keratoconjunctivitis sicca.
- LACRISERT is also indicated for patients with:
  - Exposure keratitis
  - Decreased corneal sensitivity
  - Recurrent corneal erosions

Contradictions

- LACRISERT is contraindicated in patients who are hypersensitive to hydroxypropyl cellulose.

SODI

- The unit is made from acryl amide, N-vinylpyrrolidone and ethylacrylate designated as ABE.
- It is in the form of sterile thin films of oval shape weighing 15 to 16mg.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	A sterile; water soluble, rod-shaped device made of hydroxypropyl cellulose without any preservative that used for the treatment of dry eye syndromes is called?	LACRISERT
2	Which type of contact lens is made of rigid plastic resin polymethylmethacrylate?	Hard contact lens
3	Which type of contact lens is made of hydrophilic transparent plastic, hydroxyethylmethacrylate	Soft contact lens
4	What are soluble inserts, which undergo gradual dissolution in the process of drug release and thereby need not to be removed?	Erodible insert
5	Lacrisert is inserted into which part of eye?	Inferior fornix
6	Which unit is made from acryl amide, N-vinylpyrrolidone and ethylacrylate designated as ABE.	SODI

- After introduction into inferior cul-de-sac, where wetted by the tear film it softens in 10-15 seconds.
- After 10-15 min., the film turns into a viscous polymer mass; thereafter in 30-60 min, it becomes a polymer solution.
- A single application has been reported to replace 4-12 drops instillations or 3-6 applications of ointment.
- It is used in the treatment of ***glaucoma* and *trachoma***.
- A prolonged pulse release of the drug has been observed from SODI.
- Once a day therapy.

MOTS

- The minidisc consists of a contoured disc with a convex front and a concave back surface in the contact with the eyeball.
- It is having a diameter of 4-5mm.
- The major component of the minidisc is a silicone based prepolymer 4-methecryloxy-butyl polydimethyl siloxane.
- The minidisc can be hydrophilic or hydrophobic to permit extended release of both water soluble and insoluble drugs.
- Ex: A poorly water-soluble drug sulfisoxazole is incorporated in a hydrophilic matrix.
- The *in-vivo* dissolution studies show that the drug was released from minidisc for 170 h.
- However, the hydrophobic minidisc released gentamicin sulphate for longer than 320 h.
- Gamma radiation and heat exposure of the system were found to slow down the drug release rates.

Advantages

- Sophisticated and effective delivery system.
- Flexibility in drug type and dissolution rate.
- Needs only insertion into eye and not to remove.

Disadvantages

- Patient discomfort.
- Requires assistance for insertion.
- Movement of system around the eye can cause abrasion.
- Occasional product loss during sleep or while rubbing eyes.
- Interference with vision and difficulty in placement.

NEW OPHTHALMIC DELIVERY SYSTEM (NODS)

- It is a great method for delivering precise amounts of drugs to eye within a water-soluble, drug loaded film.

- It provides accurate, reproducible dosing in an easily administered preservative free form.
- The device consists of medicated flag, which is attached to paper-covered handle film.
- NODS is 50 mm in length, is 6 mm in width, semicircular in shape and has an area of 22 mm^2 and a thickness of 20 µm and a total weight of 500 µg of which 40% can be drug.
- The components are made of the same grade of water-soluble polyvinyl alcohol (PVA) and the devices are individually packed, sterilized by gamma irradiation.
- The flag is touched onto the surface of the lower conjuctival sac for use followed by dissolution of membrane, which leads to releasing of flag, which swells and dissolves in the lachrymal fluid, delivering the drug.
- Both soluble drugs such as pilocrpine and insoluble drugs such as tropicamide can be formulated into the NODS.
- NODS produced an 8-fold increase in bioavailability for pilocarpine with respect to standard eye drop formulations.
- NODS are well tolerated, easy to use and convenient.

CORNEAL AND COLLAGEN SHIELD

- Collagen is a structural protein, found in bones, tendones, ligaments & skin and applied to body.
- It comprises more than 25% of the total body protein in mammals.
- To prepare collagen shields, collagen is extracted and moulded into a contact lens configuration.
- The shields are 14.5 mm in diameter with 9 mm base curve and thickness of 0.15-0.19 mm.
- The shields are sterilized by gamma radiation then dehydrated and individually packed for storage and shipping.
- Drugs can be incorporated in the collagen matrix during manufacture absorbed into the shields in the eye.
- As the shield dissolves, the drug is released gradually in the tear film, maintaining high concentration in the corneal surface and increasing drug permeation through cornea.
- The simplicity of use and the convenience afforded by shields make them an attractive delivery device.
- The study showed that wafer shaped collagen inserts impregnated with gentamicin produced the highest levels of drug in tear film, and tissue, in the rabbit eye compared to drops, ointments and conjuctival injection.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	SODI is used in the treatment of?	glaucoma and trachoma
2	Which dosage form is showing effect after 10-15 min., the film turns into a viscous polymer mass; thereafter in 30-60 min, it becomes a polymer solution?	SODI
3	What is diameter of MOTs.	4-5 mm
4	The release of drug from minidisc for up to?	170 h
5	A structural protein, found in bones, tendones, ligaments & skin and applied to body is called?	Collagen
6	Which device is consists of medicated flag that is attached to paper-covered handle film. Is calle?	NODS
7	What is diameter of collagen shield?	14.5 mm

Advantage

- Need not to be removed.

Disadvantage

- It may cause inflammatory response in ocular tissues.
- If collagen shields are not used along with antibacterial secondary infection may occur.