UNIT VII

Ocular Drug Delivery System

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Difficulties that arise during study of human eye from **DRUG DELIVERY** point of view

- **ISOLATED ORGAN**
- DIFFICULT TO OBTAIN SPECIMENS OF EYE TISSUE CONTAINING DRUGS FROM HUMANS
- ANIMAL MODELS USED, SO LOWER ACCURACY AND COMPATIBILITY PROBLEMS MAY ARISE
Human eye consist of :-

1. **Sclera** - tough sheath around eyeball
2. **Choroids** - absorbs unused light
   - Outer-Epithelium(lipophilic),
   - Middle-Stroma(hydrophilic),
   - Inner-Endothelium(lipophilic).
3. **Cornea** - refracts light into eye
4. **Ciliary Body** - Secretion of aq. humor,
5. **Lens** - flexible unit
6. **Retina** - screen where image is formed
7. **Conjuctiva** - layer of eye
8. **Vitreous Compartment**,
9. **Pupil** - aperture through which light enters
BARRIERS PROTECTING THE EYE

CORNEA • PROTECTS FRONT OF THE EYE

BLOOD-RETINAL BARRIER • PROTECTS BACK OF THE EYE
PRECORNEAL CONSTRAINTS RESPONSIBLE FOR POOR OCCULAR BIOAVAILABILITY

<table>
<thead>
<tr>
<th>Solution drainage</th>
<th>Drains from pre corneal area</th>
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<tbody>
<tr>
<td>• Naso lacrimal drainage</td>
<td>Absorbed across nasal mucosa in systemic circulation</td>
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<table>
<thead>
<tr>
<th>Conjunctival drainage</th>
<th>Major site for drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tear turnover</td>
<td>Amount of tears circulated</td>
</tr>
<tr>
<td>• Dilution by tears</td>
<td>Decreases absorption</td>
</tr>
<tr>
<td>• Metabolism in pre corneal area</td>
<td></td>
</tr>
<tr>
<td>• Misc: drug entity, pH, tonicity of dosage form etc</td>
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KEY POINTS FOR THE OPTIMIZATION OF OCULAR DRUG DELIVERY

- Improving ocular contact time
- Enhancing corneal permeability
- Enhancing site specificity
**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: rate limiting barrier, with pore size 60Å, Only access to small ionic & lipophilic molecules
- Trans cellular transport: transport between corneal epithelium & stroma.
General Pathway For Ocular Absorption
Factors Affecting Intraocular Bioavailability:

- 1. Inflow & Outflow of Lacrimal fluids.
- 2. Efficient naso-lacrimal drainage.
- 4. Dilution with tears.

Role Of Polymer In ODDS.

- Solution Viscosity : Solution Drainage.
- Polymer Mucoadhesive Vehicle: Retained in the eye due to non-covalent bonding between with conjunctival mucine.
- Mucine is capable of picking of 40-80 times of weight of water.
ROLE OF MUCOADHESIVE IN ODDS

MUCOADHESIVE RETAINED IN EYE BY NON COVALENT BONDING

EXTENDS PRE OCULAR RESIDENCE TIME

BETTER OCULAR ABSORPTION
Classification Of Ophthalmic Dosage Form:

<table>
<thead>
<tr>
<th>A) Based on Route of Administration</th>
<th>B) Based on Physical Form</th>
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</thead>
<tbody>
<tr>
<td>1. <strong>Topical Sol</strong>\textsuperscript{n} \textsuperscript{1}: Multiple Dose container With Preservatives.</td>
<td>1. Aqueous Sol\textsuperscript{n}.</td>
</tr>
<tr>
<td>2. <strong>Intra-ocular Sol</strong>\textsuperscript{n} \textsuperscript{1}: For Surgery, Single dose, Without preservative.</td>
<td>2. Suspension.</td>
</tr>
<tr>
<td>3. <strong>Ophthalmic Sol</strong>\textsuperscript{n} \textsuperscript{1} <strong>Injections</strong>: Intra-ocular injection, given in eye tissues, without preservative.</td>
<td>3. Ointments.</td>
</tr>
<tr>
<td></td>
<td>4. Gels.</td>
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<td></td>
<td>5. Eye Lotions.</td>
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</table>
**Ocular Control Release System: Ophthalmic Inserts**

Definition:- Solid or Semisolid in nature,
- Placed in lower Fornix
- Composed of Polymeric vehicle containing drug.

**Desired Criteria For Control Release Ocular Inserts.**
Advantages

1. Accurate dosing.
2. Absence of preservative.
3. Increase in shelf life due to absence of water.

Limitations

• 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.
Types Of Ocular Control Release System

A) Non-Erodible
1. Ocusert
2. Contact Lenses.
3. Diffusional Inserts

B) Erodible
1. Lacrisert.
2. SODI
3. Minidisc

C) Nanoparticle

D) Liposome
A) Non-Erodible:

1. Ocusert:

- Developed by Alza Corporation,
- Oval flexible ocular insert,
- Release Rate: 20-40 micro.gm/hr for 7 days
- Consist of:

<table>
<thead>
<tr>
<th>Part</th>
<th>Material</th>
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<tbody>
<tr>
<td>Drug Reservoir</td>
<td>Pilocarpine</td>
</tr>
<tr>
<td>Carrier material</td>
<td>Alginic acid</td>
</tr>
<tr>
<td>Rate controller</td>
<td>Ethylene vinyl acetate copolymer</td>
</tr>
<tr>
<td>Energy Source</td>
<td>Conc. Of Pilocarpine</td>
</tr>
<tr>
<td>Delivery Portal</td>
<td>Copolymer membrane</td>
</tr>
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</table>

- Annular ring: Impregnated with TiO$_2$: For Visibility
**Merits of ocuserts**

- Controlled rate of delivery
- Greater drug absorption

**Demerits of ocuserts**

- Patient discomfort
- Placement and removal of insert
2) Contact Lens:
- Presoaked Hydrophilic lens.
- Drug Release: within 1st 30 Min.
- Alternate approach: incorporate drug either as soln or suspension of solid monomer mixture.
- Release rate is up to: 180 hr.

3) Diffusional Inserts:
- Central reservoir of drug enclosed in Semi permeable or micro porous membrane for diffusion of drug.
- Diffusion is controlled by Lacrimal Fluid penetrating through it.
- It prevents continues decrease in release rate due to barrier.
- Release follows: Zero Order Kinetics.
MARKETED PRODUCTS : LENS
B) Erodible Inserts

1. Lacrisert:
   - Sterile, Rod Shaped device.
   - Composition: HPC without preservative.
   - Weight: 5mg,
   - Dimension: Diameter: 12.5mm, Length: 3.5mm
   - Use: Dry eye treatment, Keratitis Sicca.

2. SODI: Soluble Ocular Drug Insert.
   - Small water soluble developed for Cosmonauts by soviet scientists who could not use their eye drop in weightless conditions.
   - Composition: Acryl amide, Vinyl Pyrrolidone, Ethylacrylate.
   - Weight 15-16 mg.
   - In 10-15 sec Softens;
   - In 10-15 min. turns in Viscous Liquids;
   - After 30-60min. Becomes Polymeric Solution.
MARKETED PRODUCTS

: LACRISERTS
Advantages of SODI:

- Single SODI application replaces 4-12 eye drops instillation, or 3-6 application of ointments.
- Once a day treatment of Glaucoma & Trachoma.

3) Minidisc:

- It is made up of counter disc with Convex front & Concave back surface in contact with eye ball.
- 4-5mm in diameter.
- Composition: Silicon based pre polymer.
- Hydrophilic or Hydrophobic.
- Drug release for 170 hr.
- Further increase in gentamycin sulphate to 320 hrs.
- Gamma irradiation and heat exposure may decrease release rate due to additional cross linking of polymer matrix.
C) Nanoparticle:

- For water soluble drugs.
- Size: 10-1000nm
- Drug is Dispersed, Encapsulated, or Absorbed
- Produced by Emulsion Polymerization
- Polymerization is carried out by:
  - Chemical initiation, Gamma irradiation, Visible light.
- Emulsifier stabilizes polymer particle
- Polymer used are Biodegradable.
- E.g.:- Nanoparticle of Pilocarpine enhances Miotic response by 20-23%.
D) Liposome

Biodegradable, Non-toxic in nature.

Vesicle composed of lipid membrane enclosed in an aqueous volume.

Formed when matrix of phospholipids is agitated in aqueous medium to disperse two phase.

Phospholipids used are: Phophotidylcholine, Phophotidic acid, Sphingomyline, Phosphotidyleserine, Cardiolipine
Advances in ocular drug delivery

1. Ophthalmic gel for pilocarpine
   - Poloxamer F127 (low viscosity, optical clarity, mucomimetic property)
   - Solution at room temp but forms gel when instilled into eye thereby enhancing time of contact.

2. Ophthalmic prodrug
   - Dipivalyl epinephrine (Dipivefrin)
   - Lipophilic → increase in corneal absorption
   - Esterase within cornea and aqueous humor

3. Continuous delivery system based upon the osmotic property
   - Thin flat layer, contoured three-dimensional unit.
   - Conform to the space of the upper conjunctival fornix.
   - Delivery of diethyl carbamazine in ocular onchocerciasis.
4. Gel delivery system

• Biodegradable polyisobutyl-cyano acrylate (PIBCA) colloidal particulate system of pilocarpine to incorporate it into a Pluronic F127 (PF 127)-based gel delivery system.

5) Mucoadhesive Polymer.

• mucoadhesive polymer, the tamarind seed polysaccharide, as a delivery system for the ocular administration of hydrophilic and hydrophobic antibiotics.

6) Carboxymethyl cellulose:

• Sodium CMC found to be excellent mucoadhesive polymer. Ophthalmic gel formulated using NaCMC, PVP and corbopol on the in vivo studies on the gel showed diffusion coefficient in corbopol 940 1% > NaCMC 3% > PVP 23%. Recent research suggests that adhesive strength increases as molecular weight increases up to 100000 da.
7) NANOPARTICLES

Study using nanosphere done on system constituted of pilocarpine-loaded nanosphere of polymethyl methacrylate acrylic acid copolymer by Gurny et al. developed pH sensitive latex nanoparticles for pilocarpine and result found to be promising.

In another study binding of pilocarpine to polybutyl cyanoacrylate nanoparticles enhanced the meiotic response by about 22 to 33%.
Reference:

• N.K. Jain, Advances in Controlled & Novel Drug Delivery, CBS Publication, & distributor, New Delhi, pg No.219-223.


Web Sites:

• www.vision-care-guide.com
• www.google/images/eye/anatomy& physiology
• www.pharmainfo.net/reviews/recent-advances-ophthalmic-drug-delivery-system
Creativity is allowing oneself to make mistakes.
Art is knowing which one to keep.