SEMINAR ON OCUSERTS

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INTRODUCTION

Ophthalmic drug delivery system is one of the most important, interesting & challenging endeavors facing by the pharmaceutical scientist.

Anatomy, physiology & biochemistry of eye render this organ highly impervious to foreign substance.

BA following intraocular administration of drops may hardly be 1.2% to the aqueous humor and therefore demands suitable intraocular delivery system to increase the BA to a substantial level.
ANATOMY AND PHYSIOLOGY OF EYE

Structure of eye can be depicted with three layers:
1. Outer layer (Cornea & Sclera)
2. Middle layer (Iris-ciliary body & choroid)
3. Inner layer (Retina)

Eye is filled with two kinds of fluids:
1. Aqueous humor between cornea & iris
2. Vitreous humor between lens & retina
ROUTES OF OCULAR DELIVERY

- Topical
  - Sub-Conjunctival injection
- Intravitreal injection
  - Diabetic Retinopathy (Retina)
  - AMD (Choroid)
- Sub-Tenon injection
  - Glaucoma (Iris-Ciliary Body)
ABSORPTION OF DRUGS IN EYE

Moment drug is placed in the lower cul-de-sac of eye, several factors immediately begin to affect the bioavailability of drug.

**Pre-corneal disposition:**

Pre-corneal constraints include
A. Spillage of drug by over flow
B. Dilution of drug by tear turnover
C. Naso-lacrimai drainage/ systemic drug absorption
D. Conjunctival absorption
E. Enzymatic metabolism

**Trans-corneal penetration:**

Trans-corneal penetration of drug is mainly affected by
A. Physicochemical properties of drug
B. Corneal barriers
C. Active ion transport systems present at cornea
TRANSPORT BARRIERS IN THE EYE

Cornea, conjunctiva and sclera form the most significant barriers for drug penetration into the intra-ocular tissues.
# Conventional Ocular Drug Delivery Systems

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solutions</td>
<td>Convenience</td>
<td>Loss of drug by drainage, No sustained action</td>
</tr>
<tr>
<td>Suspensions</td>
<td>Best for drugs with slow dissolution</td>
<td>Loss of both solution and suspended solid</td>
</tr>
<tr>
<td>Emulsions</td>
<td>Prolonged release of drug from vehicle</td>
<td>Patient non-compliance, Blurred vision</td>
</tr>
<tr>
<td>Ointment</td>
<td>Improved drug stability, Increased tissue</td>
<td>Sticking to eyelids, poor patient compliance, Blurred vision</td>
</tr>
<tr>
<td></td>
<td>contact time, Resistant to nasolacrimal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>drainage</td>
<td></td>
</tr>
<tr>
<td>Gels</td>
<td>Comfortable, less blurred vision than ointment</td>
<td>Matted eyelids after use, No rate control on diffusion</td>
</tr>
<tr>
<td>Erodible inserts</td>
<td>Sophisticated &amp; effective delivery, Flexibility</td>
<td>Patient discomfort, Movement of system around eye can cause</td>
</tr>
<tr>
<td></td>
<td>in drug type, Need only be introduced into eye</td>
<td>abrasion</td>
</tr>
<tr>
<td></td>
<td>and not removed</td>
<td></td>
</tr>
<tr>
<td>Non-erodible inserts</td>
<td>Controlled rate release, Prolonged delivery,</td>
<td>Patient discomfort, Irritation to eye, Patient placement and</td>
</tr>
<tr>
<td></td>
<td>Flexibility for type of drug selected</td>
<td>removal</td>
</tr>
</tbody>
</table>
## CRITERIA FOR SELECTION OF OCULAR DOSAGE FORM

<table>
<thead>
<tr>
<th>Gels</th>
<th>Injectables</th>
<th>Inserts</th>
<th>Ointments</th>
<th>Solutions</th>
<th>Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRUG:</strong> Long duration required</td>
<td>Target site accessibility, onset of response</td>
<td>Long duration required</td>
<td>Long duration required</td>
<td>Soluble or solubilizable Less potent</td>
<td>Insoluble drug potent</td>
</tr>
<tr>
<td>Low bioavailability</td>
<td>----</td>
<td>Low bioavailability</td>
<td>Low bioavailability</td>
<td>Requiring high conc.</td>
<td>-----</td>
</tr>
<tr>
<td>Intermediate cost</td>
<td>Requires physician</td>
<td>High cost per dose</td>
<td>Low cost</td>
<td>Low cost</td>
<td>Low cost</td>
</tr>
<tr>
<td>Some blurring</td>
<td>----</td>
<td>No blurring</td>
<td>Severe blurring</td>
<td>Little blurring</td>
<td>Little blurring</td>
</tr>
<tr>
<td>Simple administration Reduced frequent administration</td>
<td>Last alternative surgical application</td>
<td>Good control of rate of administration</td>
<td>Slight threatening</td>
<td>Convenient Accepted</td>
<td>Convenient Accepted Some extend duration</td>
</tr>
</tbody>
</table>
OCULAR CONTROLLED DRUG DELIVERY DEVICES---OCULAR INSERTS

Definition-

- Sterile preparations, with a solid or semisolid consistency
- Main objective is to increase contact time between conjunctival tissue and preparation
- Inserted into the eye and worn under the upper or lower lid
- Ensures a sustained and controlled release effect

Requirements for success-

- Comfort
- Ease of handling
- Reproducibility of release kinetics
- Sterility & stability
- Ease of MFG
- Non-interference with vision
- Lack of toxicity & expulsion
ADVANTAGES

- Improves BA
- Prolonged drug release & better efficacy
- Overcomes side effects of pulsed dosing
- Accurate dose & better therapy
- Circumvent the protective barriers like drainage etc

LIMITATIONS

- Ophthalmic inserts resides in their solidity
- Patient discomfort
- Movement around eye cause abrasion
- Inadvertent loss during sleep & while rubbing eye
- Difficult placement & removal
- Interference with vision (in elderly)
CLASSIFICATION

The ocular implants are flexible, oval inserts which consist of a medicated core reservoir prepared out of a hydrogel type of materials.

They are classified as follows
1. Insoluble inserts
   - Diffusion controlled ocular inserts
   - Osmotic ocular insets
   - Hydrophilic matrix type ocular inserts (contact lens type)
2. Soluble inserts
3. Bio-erodible inserts
4. Implantable silicone devices
5. Implantable infusion devices
   - OcuFit® & Lacrisert®
   - Minidisk ocular therapeutic system
   - New ophthalmic delivery systems (NODS®)
INSOLUBLE OPHTHALMIC INSERTS

Diffusion controlled ocular inserts
These consists of a medicated core prepared out of a hydrogel polymer like alginites, sandwiched between two sheets of transparent lipophilic, rate controlling polymer.

The drug molecule penetrate through the rate controlling membranes at zero order rate process.

\[
dQ/dt = D_p \ K_m \ (C_r - C_t)/\delta m
\]

\[
dQ/dt = D_p \ K_m \ C_s/\delta m \ (C_r >> C_t \ sink \ condition)
\]

eg ; ocusert pilo-20
**Osmotic inserts**
Generally composed of a central part (drug) surrounded by a peripheral part (osmotic solute).

**Components of osmotic inserts**

<table>
<thead>
<tr>
<th>Water permeable</th>
<th>Ethylene- vinyl esters copolymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi permeable</td>
<td>Cellulose acetate derivatives, others- ethyl vinyl acetate, Polyesters of acrylic and methacrylic Acids (Eudragits)</td>
</tr>
</tbody>
</table>
| Osmotic agents          | **Inorganic-** Mg sulfate, Nacl, Pot. Phosphate dibasic, Sod. Carbonate, Sod. Sulphate  
                          | **Organic-** ca. lactate, mg. succinate, tartaric acid  
                          | **Carbohydrates-** sorbitol, mannitol, glucose, sucrose |

Generic osmotic mini pump (**ALZET**) is useful implantable drug delivery system with a const drug delivery rate with a pumping duration of up to 2 weeks.
Hydrophilic matrix type ocular inserts (contact lens type)

This system is a coherently cross-linked hydrophilic or hydrophobic polymer that forms a 3D-network or matrix, capable of retaining water, Aq. Solution or solid components.

Polymers used are 2-hydroxy ethyl methacrylate, vinyl pyrrolidone acrylic co-polymer etc.

Contact lenses are the only class that have the ability to correct any refractive errors that the patient may have and thereby provide improved visual acuity.

Biomedical application in intra-ocular administration of antibiotics, anti-glaucoma drugs, anti-inflammatory steroids etc.

This type of device substantially prolongs the drug/eye contact time and thus increases bioavailability.
SOLUBLE OCULAR INSERTS

Offer great advantage of being entirely soluble.

Broadly divided into two types based on natural polymers & semi-synthetic polymers.

**Natural polymers**-
- Eg., collagen derivatives
- Chitosan derivatives

1 & 4. Ethylene/ vinyl acetate membrane
2. TiO2 white ring
3. Drug reservoir
Synthetic and semi-synthetic polymers-

Offer additional advantage of simple design & easily processed.

<table>
<thead>
<tr>
<th>Soluble synthetic polymers</th>
<th>Cellulose derivatives - HPC, MC, HEC, HPMC, SOD. CMC others - poly vinyl alcohol, ethylene vinyl acetate co polymer</th>
</tr>
</thead>
</table>
| Additives                 | Plasticizers - poly ethylene glycol, glycerine, propylene glycol complexing agent - PVP  
Bioadhesives - poly acrylic acids, methyl hyroxy ethyl cellulose |

Soluble cellulose derivative inserts are composed of 30% of water. Presence of water is unfavorable from stand point of stability of drug.

Insert can be sterilized by exposure to gamma radiation without the cellulose component being altered.
The first soluble ophthalmic drug insert (SODI) developed was of soluble co-polymer of acrylamide, N-vinyl pyrrolidone & ethyl acetate.

It was in form of sterile thin films or wafers or oval shape, weighing 15 – 16 mg.

A new type of ophthalmic insert incorporating a water-soluble bio-adhesive component in its formulation has been developed to decrease risk of expulsion & ensure prolonged residence in eye, combined with the controlled release.

These inserts, named bio-adhesive ophthalmic drug inserts (BODI)
BIO ERODIBLE INSERTS

Main component of this type of inserts is the bio-erodible polymers.

They undergoes hydrolysis of chemical bonds & hence dissolution.

Bio-erodible matrix controlling the release rate of the drug ensures zero order release rate.

Eg., poly (ortho esters), poly (ortho carbonates)

Great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis.
IMPLANTABLE SILICONE DEVICES

Developed for the local delivery of an anti-neoplastic drug to the intra-ocular site.

Composed of 2 sheets of silicone rubber glued to the edge with adhesive to form a balloon like sac through which a silicone tubing (0.3 mm dia) is inserted.

Such devices have significant potential for local controlled delivery of anti-bacterial, anti-cancer, & anti-viral drugs to anterior chamber of eye.
Implantable Infusion Devices

In this device, the canalicular system is intubsted with fenestrated silastic tubing.

It is subcutaneously tunneled & then attached to a miniaturized & computerized pumping device, which is capable of pumping a predetermined volume of solution continuously.

Intra-ocular drug delivery pumping device is Infusaid®.  

Here the energy for pumping is met by an expanding fluid like a fluorocarbon in gas-liquid equilibrium at body temperature.
OTHER DELIVERY DEVICES

**Ocufit®** is a sustained release rod shape device made up of silicone elastomer.

**Lacrisert®** is another cylindrical device, which is made of HPC and used for treating dry-eye patients.

**Mini disk ocular therapeutic systems (OTS)** - It is a miniature contact lens shaped, made of silicone based pre polymer. It requires less time & less manual dexterity for insertion, when compared with lacrisert®.

**New ophthalmic delivery system (NODS)** - It is a method for delivering precise amounts of drugs to eye within a water soluble, drug-loaded film. When evaluated in humans, the NODS produced an 8 fold increase in BA for pilocarpine with respect to std. eye drop formulations.
PREPARATION OF OCULAR INSERT

Casting method

- Polymer solution of different compositions were prepared in boiling distilled water.
- Kept aside for 20-24 hrs to get a clear solution, then a 10% w/w plasticizer was added and stirred for 3 hrs.
- Weighed amounts of the drug were added and stirred for 4 hrs to get a uniform dispersion.
- Dispersion was degassed and casted onto a glass substrate and dried at 50°C for 18-20 hrs.
- Dried films were carefully removed and inserts of required dimensions were punched out, wrapped individually in Al. foil.
CHARACTERIZATION OF INSERTS

- Uniformities of weight & thickness
- Uniformities of drug content
- Surface pH
- In-vitro release studies (continuous flow through apparatus)
- Ocular irritation test
- In-vitro microbial studies
PACKAGING

Ophthalmic insert 5 mg supplied in packages of 60 sterile unit dosage forms.

Each wrapped in an aluminum blister.

With two reusable applicators.

A plastic storage container to store the applicators for use.
HOW TO USE

• To apply the system, wash hands first.
• Tilt your head back, gaze upward and pull down the lower eyelid to make a pouch.
• Place the system into the pouch.
• Blink a few times and roll your eye to move the insert into place.
• Practice inserting and removing the system in the doctor’s office where you can be shown the proper technique.
• Damaged or deformed systems should not be used or kept in the eye.
• Replace with a new system.
CONCLUSION

Solution or suspension drops and ointments still remain the first line approach to treatment in standard therapies.

However, in circumstances demanding less frequent dosing, or dosing into less accessible compartments of the eye, more unique approaches are indicated.

Small, ocular solid dosage forms, in particular gel-forming erodible inserts, show interesting in vivo performances and allow for therapeutic levels to be obtained over an extended period of time in the tear film and anterior chamber.

Mucoadhesive inserts are promising ocular drug delivery systems to treat external and intraocular eye infections, and diseases that require frequent eye drops instillation in order to maintain therapeutic drug levels.
Successful development of these novel formulations will obviously require assimilation of a great deal of emerging information about the chemical nature and physical structure of new polymeric materials.

However the attempts based on these principles are surely a route to better drug Bioavailability through the stubborn sites (as eye) for drug delivery.
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“Sight is the sense which is more valuable than all the rest”

So Take Care Of Eyes!!!!!!