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NDDS

Occular delivery system

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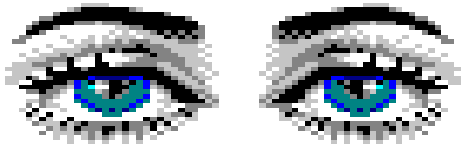

OCULAR DRUG DELIVERY SYSTEM

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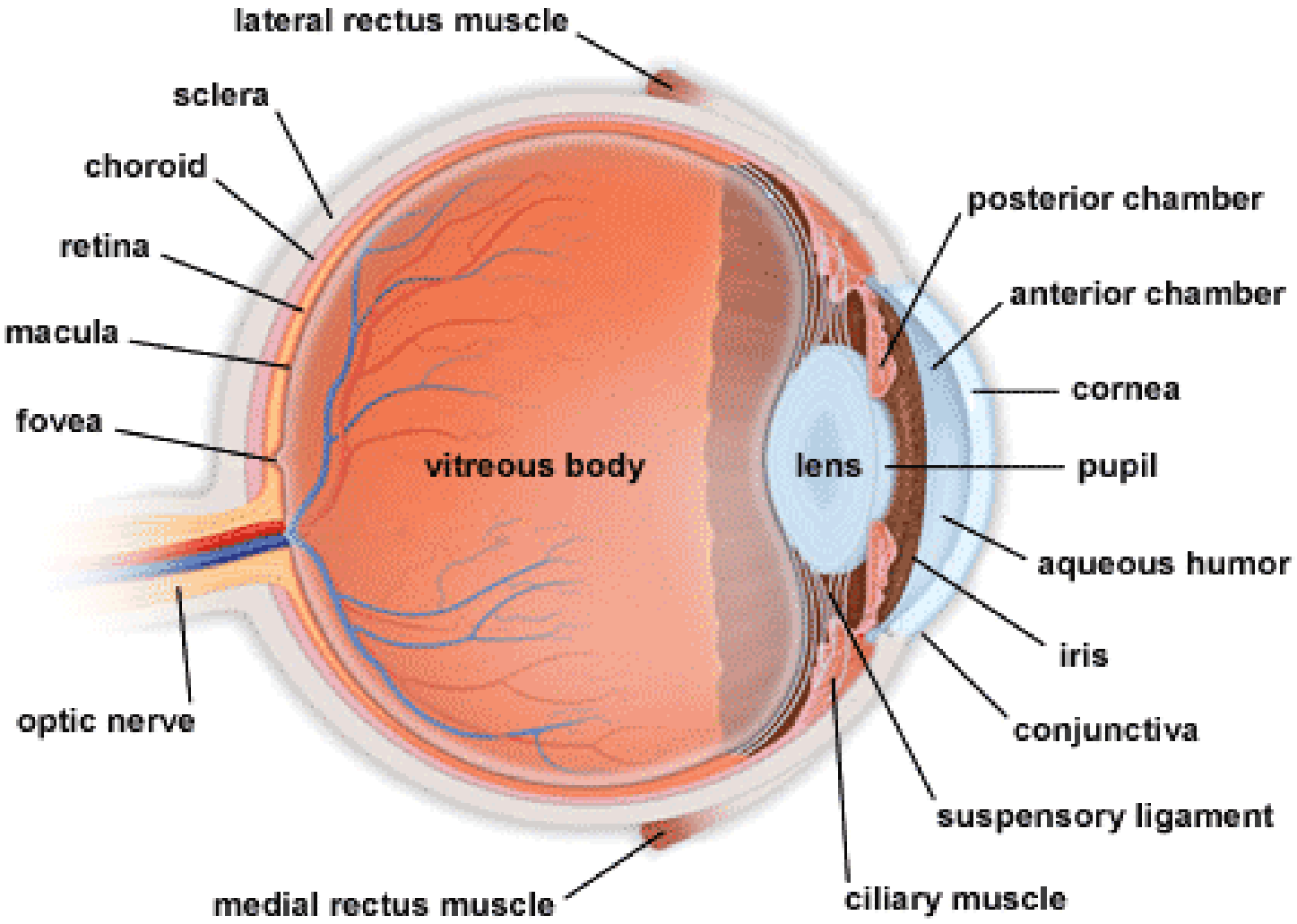
Anatomy of the Eye



INTRODUCTION

- Ophthalmic preparation
  - Applied topically to the cornea, or instilled in the space between the eyeball and lower eyelid
  - Solution
    - Dilutes with tear and wash away through lachrymal apparatus
    - Administer at frequent intervals
  - Suspension
    - Longer contact time
    - Irritation potential due to the particle size of drug
  - Ointment
    - Longer contact time and greater storage stability
    - Producing film over the eye and blurring vision

INTRODUCTION

- Emulsions
  - Prolonged release of drug from vehicle but blurred vision, patient non compliance and oil entrapment are the drawbacks.
- Gels
  - Comfortable, less blurred vision but the drawbacks are matted eyelids and no rate control on diffusion.

INTRODUCTION

- **Controlled delivery system**
  - Release at a constant rate for a long time
  - Enhanced corneal absorption
  - Drug with not serious side effect or tolerate by the patient

ADVANTGES

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

ADVANTGES

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

CLASSIFICATION

- ✓ Mucoadhesive dosage forms
- ✓ Ocular inserts
- ✓ Collagen shield
- ✓ Drug presoaked hydrogel type contact lens
- ✓ Ocular iontophoresis
- ✓ Polymeric solutions

CLASSIFICATION

- ✓ Ocular penetration enhancers
- ✓ Phase transition systems
- ✓ Particulate system like, microspheres and nanoparticles
- ✓ Vesicular systems like liposomes, niosomes, phamacosomes and discomes
- ✓ Chemical delivery system for ocular drug targeting

MUCOADHESIVE DOSAGE FORMS

- The capacity of polymer to adhere to mucin coat forms the basis of mucoadhesion.
- These system significantly prolong the drug residence time since clearance is controlled by rate of mucus turn over.
- Mucoadhesive polymers are usually macromolecular hydrocolloids which establishes electrostatic, hydrophobic interaction & hydrogen bonding with the underlying surface.
- It should exhibit a near zero contact angle to allow maximum contact with the mucin.

Ocular Mucoadhesive polymers

Non-ionics	Hydroxy Propyl Cellulose
Polycationics	Chitosan, Dextran
Polyanionics	Polyacrylic acid derivatives (carbopols, polycarbophils & CMC)

Factors affecting mucoadhesion power

- Chain flexibility
- Molecular weight
- pH
- Ionic strength

OPTHALMIC INSERTS

Introduction

- It is polymeric ocular controlled drug delivery system
- The drug is incorporated as dispersion or a solution in the polymeric support

OPTHALMIC INSERTS

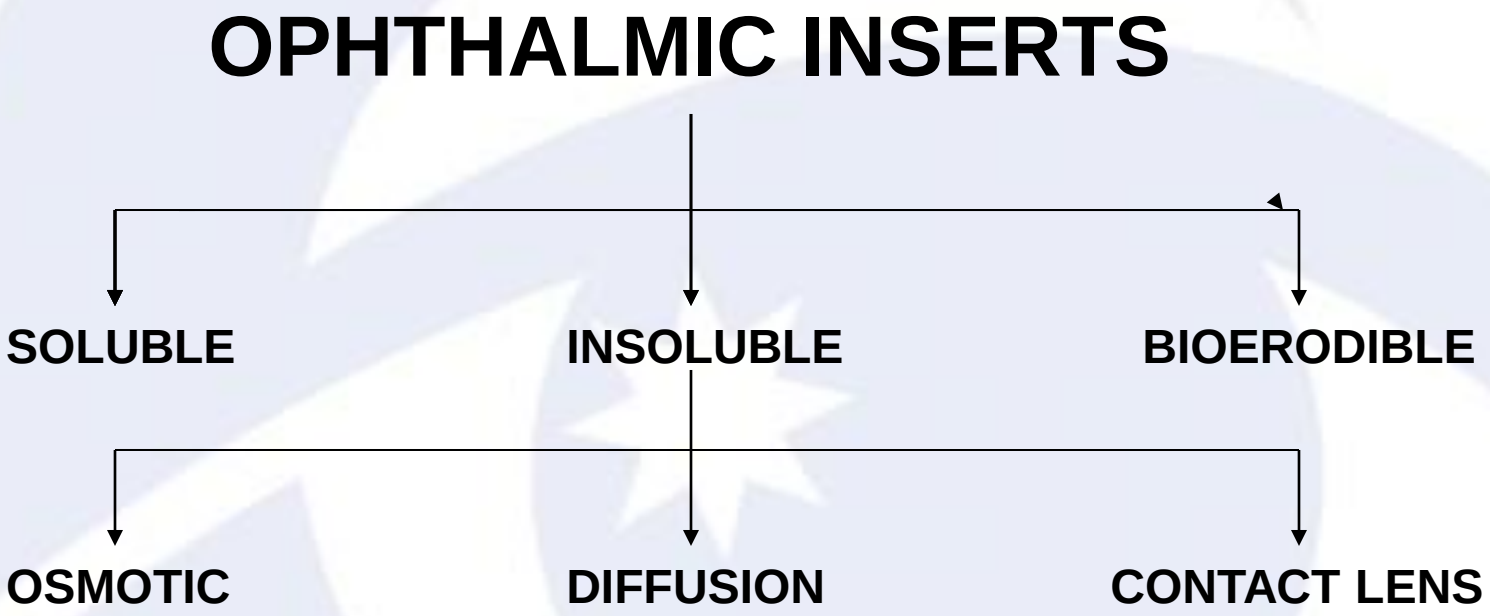
Definition

- Ophthalmic insert is a sterile preparation, with a solid or semisolid consistency and whose size and shape are especially designed for ophthalmic application.

Objective

- To increase the contact time between the preparation the conjuctival tissue to ensure a sustained/controlled release suited to topical or systemic treatment.

Classification of Ophthalmic Inserts



Soluble ophthalmic inserts

- They are the oldest class of the ophthalmic inserts.
- They don’t need to be removed from their site of application.
- Here, the drug is absorbed by soaking the insert in a solution containing the drug, drying and re-hydrating it before use.
- The amount of drug loaded will depend upon the amount of binding agent, concentration of the drug solution and duration of the soaking.

⇨***Types :***

- ✓ Based on natural polymers e.g. collagen.
- ✓ Based on synthetic or semi-synthetic polymers.

⇨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,

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

Other factors affecting on 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.

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.

i. Osmotic inserts

There are two types of osmotic inserts :

- In first type, drug with or without an additional osmotic solute dispersed in a polymeric matrix.
- In second type, the drug and the osmotic solute are placed in two separate compartments, the drug reservoir being surrounded by an elastic impermeable membrane the osmotic solute reservoir by a rigid, semi-permeable membrane.
- The tear fluid diffuse into peripheral deposits through the semipermeable membranes, wets them and thus generates hydrostatic pressure by which the drug is extruded.
- Here, zero order drug release profile is achieved.

Components of osmotic inserts

Water permeable matrix	Ethylene-vinyl ester copolymers, Divers- plasticized PVC, polyethylene, cross-linked PVP.
Semi permeable membrane	Cellulose acetate derivatives, Divers- Ethyl vinyl acetate, polyesters of acrylic and methacrylic acids.
Osmotic agents	Inorganic- $MgSO_4$, NaCl, K_2PO_4, dibasic sodium carbonate and Na_2SO_4. Organic- Calcium lactate, magnesium succinate, tartaric acid. Carbohydrates- Sorbitol, mannitol, glucose and sucrose.

Insoluble ophthalmic inserts

ii. Diffusion inserts

- They are composed of a central reservoir of drug enclosed in specially designed semipermeable or microporous membranes.
- The drug release from such a system is controlled by the lachrymal fluid, permeating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir.
- The drug delivery rate is controlled by diffusion through the membrane, which can be controlled.

Components of diffusional inserts

Central Reservoir	Glycerin, ethylene glycol, propylene glycol, water, methyl cellulose mixed with water, sodium alginate, PVP, poly oxyethylene stearate.
Microporous membrane	Polycarbonates, PVC, polysulfones, cellulose esters, cross-linked poly ethyl oxide, cross-linked PVP, cross-linked polyvinyl alcohol.

iii. Contact lenses

- 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

Drug incorporation and release

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

Biodegradable ophthalmic inserts

- The biodegradable inserts are composed of material, homogeneous dispersion of a drug included into a hydrophobic coating which is impermeable to the drug.
- The release of the drug from such a system is the consequence of the contact of the device with the tear fluid inducing a superficial diversion of the matrix.
- Materials used are the poly (orthoesters) and poly (orthocarbonates).

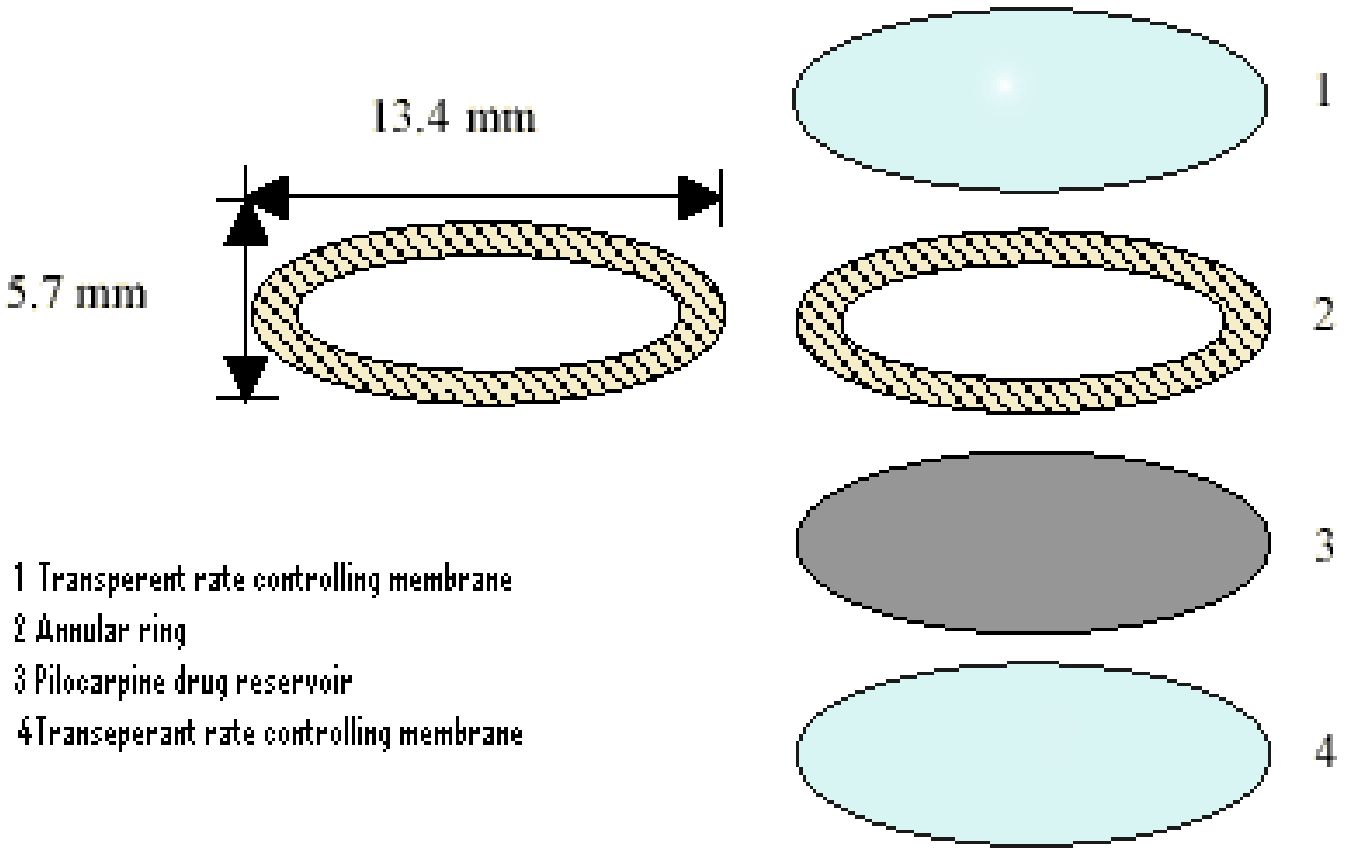
Advantages of Ophthalmic Inserts

- Ease of handling and insertion
- Lack of expulsion during wear
- Reproducibility of release kinetics
- Applicability to variety of drugs
- Non-interference with vision and oxygen permeability
- Sterility
- Stability
- Ease of manufacture

PILOCARPINE OCUSERT

- Pilocarpine, a parasympathomimetic agent for glaucoma
- Act on target organs in the iris, ciliary body and trabecular meshwork
- Ethylene-vinyl acetate copolymer
- Carrier for pilocarpine : alginic acid in the core of Ocusert
- White annular border :EVA membrane with titanium dioxide (pigment) (easy for patient to visualize)

Structure of pilocarpine ocusert



1 Transperent rate controlling membrane
2 Annular ring
3 Pilocarpine drug reservoir
4 Transeperant rate controlling membrane

COLLAGEN SHIELDS

- Belongs to soluble ophthalmic inserts.
- 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.

COLLAGEN SHIELDS

ADVANTAGES :

- Appropriate delivery systems for both hydrophilic and hydrophobic drugs with poor penetration properties.
- Biological inertness, structural stability, good biocompatibility and low cost of production.

COLLAGEN SHIELDS

DISADVANTAGES :

- Insertation is difficult.
- Problem of expulsion.
- Not fully transparent
- Not Individually fit for each patient.

OCCULAR IONTOPHORESIS

- It is the process in which the direct current drives ions into cells or tissues.

- **TYPES**

I. Trans-corneal

II. Trans-scleral

- Antibiotics, antifungals, anesthetics and adrenergics are delivered by this method.

POLYMERIC SOLUTIONS

- Enhances viscosity of the formulation.
- Slows elimination rate from the precorneal area and enhance contact time.

❑ Polymers :

- Poly vinyl alcohol, PVP, methyl cellulose, hydroxy ethyl cellulose, HPMC, hydroxy propyl cellulose.
- A minimum viscosity of 20 cSt is needed for optimum corneal absorption.

OCULAR PENETRATION ENHANCERS

- Substances which increases the permeability characteristics of the cornea by modifying the integrity of corneal epithelium are known as penetration enhancers.

❑ MODES OF ACTIONS

- By increasing the permeability of the cell membrane.
- Acting mainly on tight junctions.

Classification

- Calcium chelators :

  e.g. EDTA

- Surfactants :

  e.g. palmiloyl carnitine, sodium caprate, Sodium dodecyl sulphate

- Bile acids and salts :

  e.g. Sodium deoxycholate, Sodium taurodeoxycholate, Taurocholic acid

Classification

- Preservatives :

  e.g. Benzalkonium chloride

- Glycosides :

  e.g. saponins, Digitonon

- Fatty acids :

  e.g. Caprylic acid

- Miscellaneous :

  e.g. Azone, Cytochalasins

PHASE TRANSITION SYSTEM

- These system when instilled into the cul-de-sec shift from liquid form to gel or solid phase.

PHASE TRANSITION SYSTEM

POLYMERS	MECHANISM
Lutrol FC – 127 and Poloxamer 407	Viscosity increased when their temperature raised to eye temperature.
Cellulose acetate phthalate latex	Coagulates when its native pH 4.5 raised by tear fluid to pH 7.4
Gelrite	Forms clear gel in the presence of cations

MICROSPHERES AND NANOPARTICLES

- The drugs are bound to small particles which are dispensed in aqueous vehicles.
- They are akin to colloidal solutions.
- Nanoparticles of polybutylcyanoacrylate have been used for human being as a drug carrier.

VESICULAR SYSTEMS

The possible vesicular systems are as follows :

i. LIPOSOMES :

- Phospholipid-lipid vesicles.

ii. NIOSOMES :

- Vesicles based on some non-ionic surfactants like dialkyl polyoxyethylene ethers.

iii. PHARMACOSOMES :

- Colloidal dispersions of drugs co-valently bound to liquids.

VESICULAR SYSTEMS

iv. DISCOMES :

- Systems formed by addition of specific amount of surfactant to vesicular dispersions consisting of mixed vesicular and micelle regions.

- **DISADVANTAGES :-**
- Problems of drug leakage,
- Limited drug loading capacities,
- Opacity.

MARKETED OCULAR DRUG DELIVERY PRODUCTS

- Ocusert by Alza
  - ☑ it is a pilocarpine ocular insert.
- Lacrisert by Merck
  - ☑Patients with dry eyes (keratitis sicca)
  - ☑A substitute for artificial tears
  - ☑Placed in the conjunctival sac and softens within 1 h and completely dissolves within 14 to 18 h
  - ☑Stabilize and thicken the precorneal tear film and prolong the tear film break-up time

MARKETED OCULAR DRUG DELIVERY PRODUCTS

- Ophthalmic gel for pilocarpine
  - ☑Poloxamer 407 (low viscosity, optical clarity, mucomimetic property)
- Ophthalmic prodrug
  - ☑Dipivalylepinephrine (Dipivefrin)
  - ☑Lipophilic → increase in corneal absorption
  - ☑Esterase within cornea and aqueous humor

EVALUATION OF OCULAR DRUG DELIVERY SYSTEM

➢ THICKNESS OF THE FILM :

- Measured by dial caliper at different points and the mean value is calculated.

➢ DRUG CONTENT UNIFORMITY :

- The cast film cut at different places and tested for drug as per monograph.

➢ UNIFORMITY OF WEIGHT :

- Here, three patches are weighed.

➢ PERCENTAGE MOISTURE ABSORPTION :

- Here, ocular films are weighed and placed in a dessicator containing 100 ml of saturated solution of aluminiumchloride and 79.5% humidity was maintained.
- After three days the ocular films are reweighed and the percentage moisture absorbed is calculated using the formula –

$$\% \text{ moisture absorbed} = \frac{\text{Final weight} - \text{initial weight}}{\text{Initial weight}} \times 100$$

➢PERCENTAGE MOISTURE LOSS

- Ocular films are weighed and kept in a dessicator containing anhydrous calcium chloride.
- After three days, the films are reweighed and the percentage moisture loss is calculated using formula –

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

IN VITRO EVALUATION METHODS

➢ BOTTLE METHOD

- In this, dosage forms are placed in the bottle containing dissolution medium maintained at specified temperature and pH.
- The bottle is then shaken.
- A sample of medium is taken out at appropriate intervals and analyzed for drug content.

➢DIFFUSION METHOD

- Drug solution is placed in the donor compartment and buffer medium is placed in between donor and receptor compartment.
- Drug diffused in receptor compartment is measured at various time intervals.

➢ MODIFIED ROTATING BASKET METHOD

- Dosage form is placed in a basket assembly connected to a stirrer.
- The assembly is lowered into a jacketed beaker containing buffer medium and temperature 37 °C.
- Samples are taken at appropriate time intervals and analyzed for drug content.

➢MODIFIED ROTATING PADDLE APPRATUS

- Here, dosage form is placed in a diffusion cell which is 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 °C.
- Aliquots of sample are removed at appropriate time intervals and analyzed for drug content.

IN VIVO DRUG RELEASE RATE STUDY

- Here, the dosage form is applied to one eye of animals and the other eye serves as control.
- Then the dosage form is removed carefully at regular time interval and are analyzed for drug content.
- The drug remaining is subtracted from the initial drug content, which will give the amount of drug absorbed in the eye of animal at particular time.
- After one week of washed period, the experiment was repeated for two times as before.

ACCELERATED STBILITY STUDIES

- These are carried out to predict the breakdown that may occur over prolonged periods of storage at normal shelf condition.
- Here, the dosage form is kept at elevated temperature or humidity or intensity of light, or oxygen.
- Then after regular intervals of time sample is taken and analyzed for drug content.
- From these results, graphical data treatment is plotted and shelf life and expiry date are determined.

COMPATIBILITY STUDY

- This is required to confirm that the drug does not react with the polymer and other ingredients of the formulation.

CONCLUSION

- Controlled ocular drug delivery systems increase the efficiency of the drug by reducing its wastage and by enhancing absorption by increasing contact time of drug to the absorbing surface.
- They improve patient compliance by reducing the frequency of dosing.
- They reduces the dose and thereby reduces the adverse effects of the drug.

CONCLUSION

- Although controlled release devices could be more useful in the management of many ophthalmic conditions, they are not very much popular because such devices have to be put in place and taken out from under the eyelid periodically.
- Moreover, the devices can move around in the precorneal space resulting in discomfort and visual disturbances.

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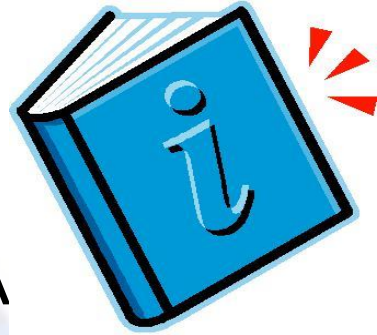

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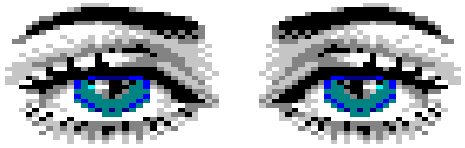

Thank You

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