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REVIEW ARTICLE

Ocusert as A Novel Drug Delivery System

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ABSTRACT

Ophthalmic insert is defined as sterile preparation with solid or semisolid consisting and whose size and shape are especially designed for ophthalmic application. They offer several advantages as increase ocular residence, possibility of releasing drug at a slow constant rate, accurate dosing and increased shelf life with respect to aqueous solutions. Ocusert®, pilocarpine ocular therapeutic system is the first product marketed by Alza Corporation. Glaucoma is a group of disease of the eye characterized by damage to the ganglion cells and the optic nerve. If left untreated, these effects may lead to various degrees of loss of vision and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma. The ocusert is prepared by solvent casting method. The mechanism of controlled drug release into the eye is Diffusion, Osmosis and Bio-erosion. 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.

Key words: Ophthalmic insert, sterile preparations, Ocusert®, Glaucoma, Controlled ocular drug delivery systems.

1. INTRODUCTION

Topical application of drugs to the eye is the well-established route of administration for the treatment of various eye diseases like dryness, conjunctiva, eye flu etc. The protective mechanisms of the eye such as blinking, baseline and reflex lachrymation, and drainage decrease the bioavailability of drug and also help to remove rapidly foreign substances like the dust particles bacteria, including drugs, from the surface of the eye. There are many eye diseases which can be affected to the eye and also eye vision. Therefore marketed ophthalmic dosage formulations are classified as conventional and non-conventional (newer) drug delivery systems. There are most commonly available ophthalmic preparations such as drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into eye they are rapidly drained away from the ocular surface due to blinking tear flow and lacrimal nasal drainage of the eye. Only a small amount of drug is available for its therapeutic effect resulting in frequent dosing application to the eye. So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner [1].

Major approaches are being undertaken to improve topical delivery of drugs [2]:

- Improving ocular contact time
- Enhancing corneal permeability
- Enhancing site specificity

GLAUCOMA [3]

Glaucoma is a group of disease of the eye characterized by damage to the ganglion cells and the optic nerve. If left untreated, these effects may lead to various degrees of loss of vision and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma.

Types of Glaucoma:

Glaucoma is usually described as either angle closure or open angle glaucoma.

Open-Angle Glaucoma:

In open-angle glaucoma, a physical blockage occurs within the trabecular meshwork that retards

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elimination of aqueous humor. The obstruction is presumed to be between the trabecular sheet and the episcleral veins, into which the aqueous humor ultimately flows. The impairment of aqueous drainage elevates the intraocular pressure to between 25 and 35 mm Hg (normal intraocular pressure is 10 to 20 mm Hg), indicating that the obstruction is usually partial. This increase in intraocular pressure is sufficient to cause progressive cupping of the optic disk and eventually visual field defects.

Angle-Closure Glaucoma:

In angle-closure glaucoma, increased intraocular pressure is caused by pupillary blockage of aqueous humor outflow and is more severe. The basic requirements leading to an acute attack of angle closure are a pupillary block, a narrowed anterior chamber angle and a convex iris. When a patient has a narrow anterior chamber or a pupil that dilates to a degree where the iris comes in greater contact with the lens, there is interference with the flow of aqueous humor from the posterior to the anterior chamber. Because aqueous humor is continually secreted, pressure within the posterior chamber forces the iris to bulge forward. This may progress to complete blockage.

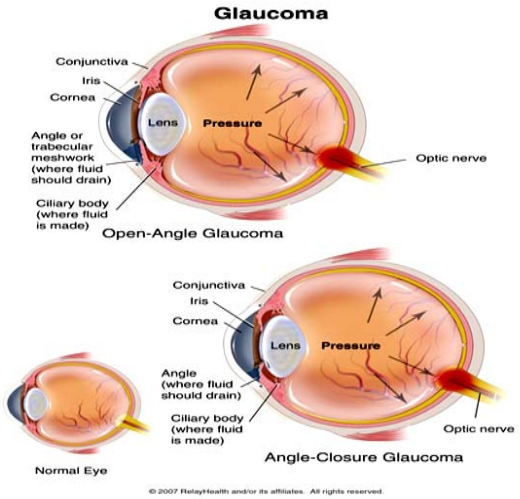

Fig1: Types of Glaucoma

Anatomy and Function of the Eye -

The eye is a spherical structure with a wall made up of three layers; the outer part sclera, the middle parts choroid layer, ciliary body and iris and the inner section nervous tissue layer retina.[1]

Aqueous Humour: The aqueous humour is a jelly-like substance located in the anterior chamber of the eye [4].

Choroid:

The choroid layer is located behind the retina and absorbs unused radiation [4].

Ciliary Muscle:

The ciliary muscle is a ring-shaped muscle attached to the iris. It is important because contraction and relaxation of the ciliary muscle controls the shape of the lens [4].

Optic Nerve:

The optic nerve is the second cranial nerve and is responsible for vision. Each nerve contains approx. one million fibres transmitting information from the rod and cone cells of the retina [4].

Pupil:

The pupil is the aperture through which light - and hence the images we "see" and "perceive" - enters the eye. This is formed by the iris. As the size of the iris increases (or decreases) the size of the pupil decreases (or increases) correspondingly [4].

Retina:

The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, and then the hyaloid and finally the vitreous humour before reaching the retina. The retina contains photosensitive elements (called rods and cones) that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve [4].

Sclera:

The sclera is a tough white sheath around the outside of the eye-ball. This is the part of the eye that is referred to by the colloquial terms "white of the eye" [4].

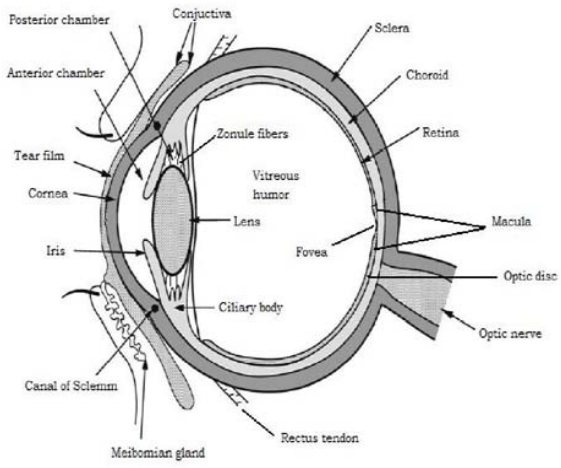

Fig 2: Structure of the eye [1]

MECHANISM OF DRUG RELEASE [5]

The mechanism of controlled drug release into the eye is as follows:

A. Diffusion

B. Osmosis

C. Bio-erosion

A. Diffusion:

In the Diffusion mechanism, the drug is released continuously at a controlled rate through the membrane into the tear fluid. If the insert is formed of a solid non-erodible body with pores and dispersed drug. The release of drug can take place via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

B. Osmosis:

In the Osmosis mechanism, the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable membrane and the second compartment provides a reservoir for the drug which again is in liquid or gel form. When the insert is placed in the aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

C. Bio-erosion:

In the Bio-erosion mechanism, the configuration of the body of the insert is constituted from a matrix of bio-erodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bio-erosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.

CLASSIFICATIONS OF OCULAR DRUG DELIVERY SYSTEMS [6]

1. Liquids: Solutions, Suspensions, Sol to gel systems, Sprays

2. Solids: Ocular inserts, Contact lenses, corneal shield, Artificial tear inserts, Filter paper strips.

3. Semi-solids: Ointments, Gels

4. Miscellaneous: Ocular iontophoresis, Vesicular systems, Mucoadhesive dosage forms, Particulates, Ocular penetration.

CONTROLLED OCULAR DRUG DELIVERY SYSTEMS [7]

High numbers of ocular conditions are aggravated by over treatment with topical drugs. Frequent local instillation of anti-glaucoma agents, antibiotics, antiviral and sulphonamides provides an unusual high drug and preservative concentration at epithelial surface. The need to reduce the local and systemic side-effects and improvements in ocular bioavailability necessarily obviates the use of controlled ocular delivery.

Requisites of Controlled Drug Delivery-

- ✓ To provide sustained and controlled drug delivery.
- ✓ To improve bioavailability by increasing corneal contact time of the drug.
- ✓ To minimize the side effects produced by conventional systems.
- ✓ To give targeting within the ocular globes so as to put off the loss of drugs.
- ✓ To provide better accommodation of the delivery system in the eye so that the loss to other tissues besides cornea is disallowed.
- ✓ To provide comfort and compliance to the patient and improve the therapeutic performance of the drug over conventional systems.
- ✓ To circumvent the protective barriers like drainage, lacrimation and diversion of exogenous chemicals into the systemic circulation by the conjunctiva.

INCLUSIONS OF CURRENTLY EXPLORED FORMULATION TRENDS [7]

1. Polymeric solutions
2. Phase transitions systems
3. Muco-adhesive/bio-adhesive systems
4. Pseudo lattices
5. Collagen shields
6. Ocular penetration enhancers
7. Ocular Iontophoresis
8. Ocular drug delivery devices
9. Particulate systems for ocular drug delivery
10. Vesicular systems for ocular drug delivery

OCULAR INSERTS [4]:

Ophthalmic insert defined as sterile preparation with solid or semisolid consisting and whose size and sharp are especially designed for ophthalmic application. They offer several advantages as increase ocular residence, possibility of releasing drug at a slow constant rate, accurate dosing and increased shelf life with respect to aqueous solutions. Ocusert®, pilocarpine ocular therapeutic system is the first product marketed by Alza incorporation USA from this category.

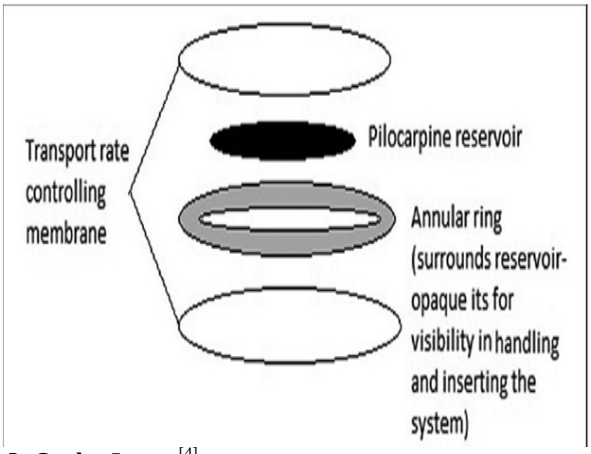

Fig 3: Ocular Insert [4]

ADVANTAGES OF OCULAR INSERTS [9]:

- Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles;
- Possibility of releasing drugs at a slow, constant rate;
- Accurate dosing (contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained at the administration site);
- Reduction of systemic absorption (which occurs freely with eye drops via the naso-lacrimal duct and nasal mucosa);
- Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects;
- Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes;
- Increased shelf life with respect to aqueous solutions;
- Exclusion of preservatives, thus reducing the risk of sensitivity reactions;
- Possibility of incorporating various novel chemical/technological approaches.

DISADVANTAGES OF OCULAR INSERTS [9]:

- A capital disadvantage of ocular inserts reside in their 'solidity', i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye.
- Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the inserts to upper fornix.
- The occasional inadvertent loss during sleep or while rubbing the eyes.
- Their interference with vision.
- Difficult placement of the ocular inserts (and removal, for insoluble types).

FORMULATION METHODS OF OCUSERT [8]:

1. Solvent Casting Method:

In this method using different ratios of drug and polymer a no. of batches are prepared. The polymer is dissolved in distilled water. A plasticizer is added to this solution under stirring conditions. The weighed amount of drug was added to above solution and stirred to get a uniform dispersion. After proper mixing the casting solution was poured in clean glass petridish and covered with an inverted funnel to allow slow and uniform evaporation at room temperature for 48 h.

The dried films thus obtained were cut by cork borer into circular pieces of definite size containing drug. The ocular inserts were then stored in an airtight container (desiccator) under ambient condition.

2. Glass substrate technique:

Drug reservoir film: 1% w/w polymer for example chitosan was soaked in 1%v/v Acetic acid solution for 24hrs, to get a clear solution of chitosan in acetic acid solution. The solution was filtered through a muslin cloth to remove undissolved portion of the polymer (chitin). Required quantity of drug-β CD complex was added and vortexed for 15minutes to dissolve the complex in chitosan solution. 1%w/v propylene glycol (plasticizer) was added to it and mixed well with stirrer. The viscous solution was kept aside for 30 minutes for complete expulsion of air bubbles. The rate controlling films were prepared. The films were casted by pouring solution into the centre of levelled glass mould and allowing it to dry at room temperature for 24hrs. After drying, films were cut into ocuserts of desired size so that each contains equal quantity of the drug. Then, the matrix was sandwiched between the rate controlling membranes using non-toxic, non-irritating, water insoluble gum. They were wrapped in aluminium foil separately and stored in a desiccator.

3. Melt extrusion technique:

Drug for ex. acyclovir and the polymer were sieved through 60#, weighed and blended geometrically. The plasticizer was added and blended. The blend was then charged to the barrel of Melt Flow Rate apparatus and extruded. The

extrudate was cut into appropriate size and packed in polyethylene lined Al foil, heat sealed and sterilized by gamma radiation.

EVALUATION OF FORMULATIONS:

a) Thickness Uniformity
b) Weight Variation
c) Drug Content Uniformity
d) Percentage Moisture Absorption
e) Percentage Moisture Loss
f) Surface pH Determination
g) Swelling Index
h) Folding Endurance
i) In-Vitro Drug Release
j) In-Vivo Study
k) Stability Study
l) Sterility Testing

Table 1: Research Works on Ocular Insert [11]

Drug	Dosage form	Category of drug	Polymers / Bases
Dexamethasone	Ocular Insert	Anti-Inflammatory	Cellulose Acetate Phthalate, Eudragit RS. 100 And RL 100
Pilocarpine Nitrate	Ocular Insert	Miotic Agent	Collagen
Pilocarpine Nitrate	Ocular Insert	Miotic Agent	Mixtures Of Sodium Salts Of Hyaluronic Acid
Tropicamide	Ocular Insert	Mydriatic Agent	Mixtures Of Sodium Salts Of Hyaluronic Acid
Timolol Maleate	Ocular Insert	Anti-Glaucoma Agent	Alkyl Monoesters Of Poly Vinyl Methyl Ether-Maleic Anhydride (PVM - MA)
Ciprofloxacin Hydrochloride	Ocular Insert	Anti-Infective Agent	HPMC, Methyl Cellulose, Ethyl Cellulose And PVP
Ketorolac Tromethamine	Ocular Inserts	Anti-Inflammatory	Hydroxy Propyl Methyl Cellulose, Polyvinyl Pyrrolidone, Methyl Cellulose And Ethyl Cellulose
Natamycin	Ocular Inserts	A Polyene Antibiotic is highly useful for the treatment of conjunctivitis and keratitis	Eudragit L-100, Eudragit S-100, Eudragit RL-100, Hydroxy Propyl Methyl Cellulose Phthalate And

Table 2: Marketed Products of Ocular Drug Delivery System [1,10]

Brand Name	Dosage Form	Uses
Acuvail	4.5mg/ml Ketorolac tromethamine solution (0.45%) in a single-use vial.	Cataract surgery
Alocril	2% is a clear, yellow, sterile solution.	Allergic conjunctivitis
Elestat	0.05% epinastine HCl ophthalmic solution.	Allergic conjunctivitis
Ozurdex	0.7 mg Dexamethasone intravitreal ocular implant.	Retinal vein occlusion
Pred Forte	1% Prednisolone acetate ophthalmic suspension, USP.	Bulbar conjunctiva
Trivaris	80mg/ml Triamicinoloneacetonide injectable suspension.	Sympathetic ophthalmia
Zymar	0.3% Gatifloxacin ophthalmic solution.	Bacterial conjunctivitis

CONCLUSION

The main efforts in ocular drug delivery during the past two decades has been on the design of systems to prolong the residence time of topically applied drugs in conjunctival sac. 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 reduce the dose and thereby reduce the adverse effects of the drug. Ocular delivery systems like inserts, biodegradable polymeric systems, and collagenshields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs.

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