

Review Article on Ocuser: A Novel Ophthalmic Drug Delivery System

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INTRODUCTION

Eye is the most fantastic creation of God among all the sense organs in human body as it makes us aware of various objects all around us near and far. The eye is one of the most soft and most valuable of all the sense organs and is a challenging subject for topical administration of drug to the eye.⁽¹⁾ Topical application of drug in the form of eye drops in the eye is the well accepted route of administration for the treatment of various eye disease like conjunctiva, eye flu etc.⁽²⁾ The eye as a portal for drug delivery is generally used for local therapy in order to avoid the risk of eye damage from high blood concentration of the drug which is not intended.⁽³⁾ The field of ocular drug delivery system is one of the most interesting and challenging task usually faced by pharmaceutical scientist/researchers. This field has significantly improved over the past 10-20 years. The eye is very difficult to study from a drug delivery point of view. The anatomy physiology and biochemistry of the eye render this organ impervious to foreign substances. It is a challenge to the formulator to circumvent the protective barriers of the eye so that the drug reaches the bio-phase in sufficient concentration.⁽⁴⁾ Ocular inserts have been developed in which the drug is delivered on the basis of diffusional mechanism. Such a solid dosage form delivers an ophthalmic drug at near constant rate, minimizing side effect by avoiding absorption peaks.⁽⁵⁾ Physiological barriers to diffusion and productive absorption of topically applied drug exist in the pre-corneal and corneal space.⁽⁴⁾ The novel system offers manifold advantages over conventional systems as it increases the efficiency of drug delivery by improving the release profile and also reduces drug toxicity. The rapid progress of the biosciences opens new possibilities to meet the need.⁽⁶⁾ Most ocular treatments are done by topical administration of ophthalmically active drugs to the tissue around the ocular cavity. Several types of conventional dosage are applied as ocular drug delivery systems. Mostly prescribed conventional dosage forms are eye drop solutions, suspensions, and ointments. The conventional dosage forms are easy to administer but have a drawback that the content of medicine is immediately diluted in the tear film as soon as the conventional dosage form is administered into the cul-de-sac and rapidly drained away from the pre-corneal cavity by constant tear flow. Therefore, only a very small amount of the administered dose is absorbed in the target tissue because of reduced contact time of drug with target tissue and thus leads to poor ocular bioavailability.⁽⁷⁾ The efficacy of any ophthalmic drug depends on the rate and extent to which the drug reaches aqueous humor and from there to the interior segment, the target tissue for providing expected therapeutic response. The zero order

kinetics is a characteristic of sustained release type of delivery systems whereby the drug is held in a reservoir and is released in to the target tissue at a constant rate to provide constant concentration more than one doses are placed in such drug delivery systems which provides greatly improved compliance.⁽⁸⁾ In case of ophthalmics the ocuserts are probably a good choice for this purpose since they increase the contact time with the conjunctival tissue.⁽⁹⁾

CONVENTIONAL OPHTHALMIC FORMULATIONS

Eye drop: It is a liquid preparation in which all ingredient are completely dispersed in solution. Limited ocular absorption occurs through corneal epithelium. When eye drops is topically administered then only less than 5% of administered dose is absorbed. The retention time of eye solution in the eye can be influenced by various properties of eye solution like hydrogen ion concentration, viscosity etc.

Eye gel: It is a semi solid preparation made up of either small or larger molecules are interpenetrated by liquid. When this preparation is applied in the eye region, results in increased drug absorption, contact time and provides prolonged duration of action/therapeutic effect and decreased dosage frequency compare to solutions.

Eye ointment: It is a sterile and semisolid anhydrous preparation in which medicament is dispersed in a suitable non-irritant bases like mineral oil and white petroleum. The eye ointment remains popular as a pediatric dosage form. The ointment provides longer contact time and increased drug bioavailability after application in the eye, but its use is limited to bed time instillation because it interferes with vision due to its greasy nature.

Eye suspension: It is defined as the preparation in which the drug substances, insoluble in an aqueous vehicle, are dispersed with the help of a suitable suspending and dispersing agent. The eye suspensions contain small particles which are non-irritating to the eye. These particles are retained in cul-de-sac region and thus increased drug bioavailability results.⁽¹⁰⁾

DRAWBACKS OF CONVENTIONAL OPHTHALMIC FORMULATION

- They have poor bioavailability due to:-
 - Conjunctival absorption
 - Solution drainage by nasolachrimal route
 - Rapid pre-corneal elimination
 - Normal tear turnover
- Viscous vehicles may cause blurred vision.
- Frequent instillation is required/necessary to achieve a therapeutic effect of concentrated medicine.
- Produce undesirable side effects after instillation of ophthalmic formulations due to systemic absorption of drug and nasolachrimal drainage of additives.
- The delivery of drug is generally not correct due to non-uniformity of drop size of ocular medication.⁽¹¹⁾

NOVEL OPHTHALMIC DELIVERY SYSTEMS

To overcome the drawbacks of conventional ophthalmic formulations, various workups have been done to better pre-corneal drug absorption and minimizing pre-corneal drug elimination.

Mucoadhesives: Mucoadhesive is defined as the formulation which is retained in the eye by virtue of non-covalent bonds accomplished with the corneal conjunctival mucin for improving the pre-corneal residence time.

Phase transition systems: The phase transition system is a liquid dosage form which converts into the gel or solid phase when instilled into the cul-de-sac of eye. These converting gel remains in contact with the cornea of the eye for prolonged period of time due to slower drainage from the cornea.

Liposomes: Liposomes are defined as simple microscopic vesicles in which aqueous volume is entirely enclosed by a bilayered phospholipids membrane. The lipophilic drug is entrapped in bilayer of lipids and hydrophilic drug in aqueous phase and thus increased drug residence time in the eye is achieved.

Niosomes: Niosomes are non ionic surfactant small vesicles in which both hydrophilic and lipophilic drugs are enclosed in aqueous or in vesicular membrane, made up of lipid material. It prevents the metabolism of the drug by enzymes, present at the corneal surface of the eye.

Nanoparticles: Nanoparticles are solid particles made up of polymers with particle size ranging from 1-1000 nm in which the drug or active ingredient is entrapped. These entrapped drugs provide a sustained effect.

Contact lenses: The drug saturated contact lenses are placed in the eye which release the drug in the eye for a prolonged period of time. Hydrophilic or water soluble drugs soaked in drug solution can be absorbed through contact lenses and thus hydrophilic contact lenses can be used for improving ocular residence time of drug.

Pharmacosomes: pharmacosomes are vesicles made up of amphiphilic drugs. Any drug having a free carboxylic group or active hydrogen atom can be esterified to the amphiphilic prodrug. These amphiphilic prodrugs are converted to pharmacosomes on dilution with water and thus show greater shelf stability and facilitated transport across the cornea and a controlled release profile.^(10,11)

Ophthalmic inserts: Ocusert system was firstly developed in 1975 by 'Alza Corporation, in the United State of America. It is a flat, flexible, solid and semisolid device which consists of drug reservoir and rate controlling membrane by using various polymers.^(4,12) The prime objective of development of the ocuserts is continuous controlled delivery of ophthalmically active drug to the eye. The ocusert is inserted in the upper or lower cul-de-sac of the eye, which releases the drug at a predetermined rate constant. Thus improved patient compliance by reduced dose frequency, better therapeutic outcomes by reduced over/under dosing, lesser local side effects/toxicity and increased bioavailability by increased drug eye contact time is observed.⁽¹³⁾ Generally, all types of ocusert consist of three components namely, "a central drug reservoir" in which the drug is incorporated

in a polymer; “rate controlling membrane”, which ensures the controlled release of medicament from the drug reservoir; and “an outer annular ring”, meant for easy handling and proper insertion.⁽⁸⁾

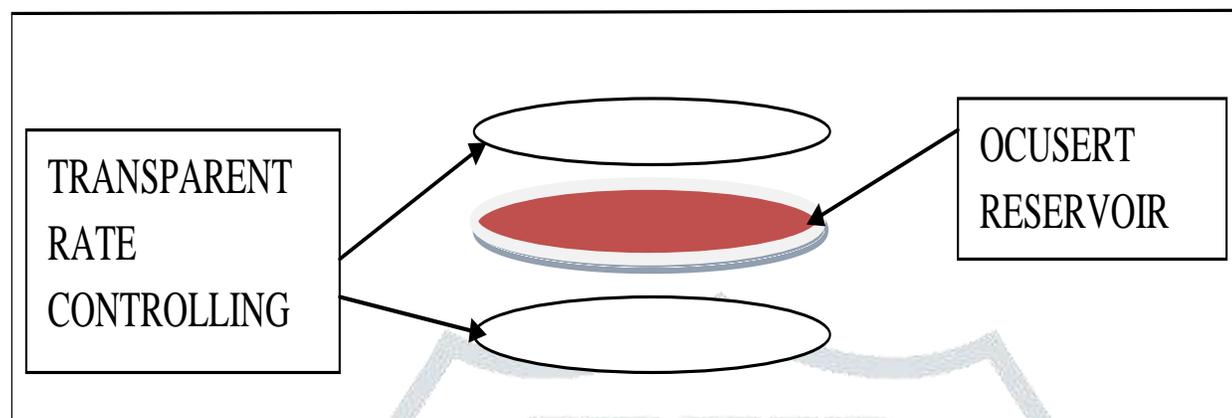


Fig. 1.1: Schematic diagram of ocular insert

Advantages of ocusert:

Ocusert enjoys following advantages over conventional ophthalmic dosage forms:-

- 1) Increased ocular contact time and thus improved drug bioavailability.⁽¹¹⁾
- 2) Increased ocular permeation with respect to standard formulation and thus providing prolong drug activity and hence increased ocular bioavailability of drug.⁽¹³⁾
- 3) Administration of an accurate dose in the eye gives better therapy.⁽¹¹⁾
- 4) Better patient compliance by reduction of the number of administered dose.⁽¹⁰⁾
- 5) Better efficacy by providing a constant drug release.⁽¹¹⁾
- 6) Increased possibility of internal ocular tissue targeting through non-corneal,(conjunctival and sclera) penetration routes.
- 7) Increased shelf life with respect to standard formulation due to the absence of water.⁽¹³⁾
- 8) Reduced systemic absorption and thus lesser adverse effects.

Limitations of ocusert:

- 1) Initially discomfort due to their movement around the eye.⁽¹¹⁾
- 2) Occasional accidental loss during sleep or while rubbing the eye.
- 3) Difficult placement and intervention with vision.⁽¹⁰⁾

MECHANISM OF CONTROL DRUG RELEASE INTO THE EYE

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

- 1) Diffusion
- 2) Osmosis
- 3) Bio-erosion

1. Diffusion: In the diffusion mechanism, the drug is released incessantly at a controlled rate through the membrane into the tear fluid. If the insert is consist of a solid non erodible body with pores and dispersed drug. The release of the drug occurs through the pores via diffusion. Controlled drug release can be further regulated by gradual dissolution of solid dispersed drug and thus this matrix as a result of directed diffusion of aqueous solutions. In a soluble device, true dissolution mainly occurs through polymer swelling. In swelling controlled devices, the active ingredient is homogeneously dispersed in a glassy polymer. These glassy polymers are essentially drug impermeable, no diffusion occurs through the dry matrix. When the ocular insert is inserted in the eye, the water from the tear fluids begins to penetrate the matrix, then swelling and thus polymer chain relaxation and drug diffusion occurs. The dissolution of the matrix follows the swelling process which depends on polymer structure.⁽¹⁴⁾

2. Osmosis: In the osmosis mechanism, the insert consist of a transverse impermeable elastic membrane dividing the interior of the insert in to a first compartment and second compartment, the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by impermeable and elastic membrane. There is a drug release aperture in the impermeable wall of insert. The first compartment contains a solute which cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for the drug which a gain is in liquid or gel form. When the insert is inserted in the aqueous environment of the eye then water diffuse into the first compartment and stretches and contract the second compartment so that the drug is forced through the drug release aperture.⁽¹⁵⁾

3. Bio-erosion: In the Bio-erosion mechanism, the insert is made up from a matrix of bio-erodible material in which the drug is dispersed. When insert contact with tear fluid and gives results in controlled sustained release of the drug by bio-erosion of the matrix. The drug may be homogeneously dispersed throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.⁽¹⁶⁾

CLASSIFICATION OF OPHTHALMIC INSERTS/OCUSERTS

The ophthalmic inserts/ocuserts are classified on the basis of their solubility behavior.

1. Insoluble ophthalmic inserts/ocuserts
2. Soluble ophthalmic inserts/ocuserts
3. Bio-erodible ophthalmic inserts/ocuserts⁽¹⁰⁾

1. Insoluble ophthalmic inserts/ocuserts:

The insoluble inserts are sub-classified into three groups.

- a) Diffusional inserts/ocuserts
- b) Osmotic inserts/ocuserts
- c) Contact lenses⁽¹⁶⁾

a) Diffusional inserts/ocuserts:

Ocuserts system is a novel drug delivery system is based on porous membrane. The release of drug from diffusional inserts/ocuserts is based on a diffusional release mechanism. The diffusional inserts/ocuserts are consist of a central drug reservoir enclosed in specially designed semi permeable/microporous membrane, which allow the diffusion of drug from the reservoir at a precisely determine rate.⁽¹⁴⁾ The lachrymal fluid penetrating through the membrane until the sufficient internal pressure is reached which control the drug release from such a system. The principle for its operation can be operated by the Fick diffusion equation.

$$J = DA \frac{dc}{dx}$$

Where J = solute flux

D = difference co-efficient for the drug within the polymer membrane.

A = area of membrane

$\frac{dc}{dx}$ = drug concentration gradient within the membrane along the direction of drug flow⁽¹⁰⁾

b) Osmotic inserts/ocuserts:

The osmotic inserts/ocusert are generally consist of two distinct contains osmotic solute. The drug and the osmotic solute are placed in to seprate compartment, the drug reservoir being surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi-permeable membrane.⁽¹⁴⁾ The tears diffusion in to the osmotic compartment inducing on osmotic pressure due to drug diffusion.⁽¹⁰⁾

c) Contact lenses:

Contact lenses are covalently cross-linked hydrophilic or hydrophobic polymer that forms a three dimensional network which able of retaining aqueous drug solution or solid components.⁽¹⁰⁾ Contact lenses are structures shaped and initially used for vision correction. Contact lenses are widely used as a potential drug delivery device by presoaking them in drug solutions. The main advantage of this system is increase the possibility of correct vision and drug release at the same time.⁽¹⁴⁾

2. Soluble ophthalmic inserts/ocuserts:

Soluble ophthalmic inserts/ocuserts represent to the oldest class of ophthalmic inserts/ocuserts. These soluble inserts/ocuserts offer the advantage of completely soluble so that they do not need to be removed from their site of application thus, limiting the interference to insertion only. The therapeutic agents are preferably absorbed

by soaking the insert in a solution containing the drug, dry and re-hydrating it before use on the eye. The amount of drug loaded will be depend upon the amount of binding agent, upon the concentration of drug solution in to which the composite is soaked as well as the duration of soaking.⁽¹⁶⁾ The release of drug from this type of inserts/ocuserts due to permeation of tear fluid into the inserts that increase high release rate of drug through diffusion and form a gel layer around the core of the insert.⁽¹⁰⁾

3. Bio-erodible inserts/ocuserts:

The bio-erodible inserts/ocuserts are consist of material homogenous dispersion of drug included or not into a hydrophobic coating which is substantially impermeable.⁽¹⁶⁾ The bio-erodible inserts/ocusert consist of bio-erodible poly (e.g. cross-linked gelatin derivatives, polyester derivative) which undergo hydrolysis of chemical bond and hence dissolution. The main advantage of these bio-erodible polymers is the possibility of modification of their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants.⁽¹⁴⁾ The release of the drug from such a system is the outcomes of the contact of the device with the tear fluid inducing a superficial diversion of the matrix.⁽¹⁰⁾

According to the world health organization, corneal disease is a major cause of loss of vision and blindness. The fungal keratitis is a serious corneal disease. The first line therapy in fungal keratitis are not effective in severe keratomycosis, while imidazole derivatives prepared themselves be the as a better choice in the future.

Table 1.1: List of ocuserts of different ophthalmic drugs (all categories) available in market

S. No.	Drug	Category of drug	Polymer/Bases
1	Ciprofloxacin	Anti-Infective agent	HPMC, MC, EC and PVP
2	Ofloxacin	Antibacterial agent	Poly ethylene oxide and EUD L100
3	Ciprofloxacin	Anti-Infective agent	Eudragit and Polyvinyl acetate
4	Norfloxacin	Antibacterial agent	HPMC, EC and PVP K-30
5	Pefloxacin	Antibiotic agent	EUD RS100, EUD RL100 and PVP K-30
6	Ofloxacin	Antibacterial agent	HPMC, PVP and PVA
7	Acyclovir	Antiviral agent	MC, HPMC, HPC and Starch
8	Acyclovir	Antiviral agent	PVA, MC, EC and Carbapol 934

9	Levofloxacin	Antibacterial agent	EC, PEO and sodium alginate
10	Brimonidine Tartrate	Intraocular pressure lowering agent	PVA, EC and PVP K-30
11	Fluconazole	Antifungal agent	HPMC, PVP and PVA
12	Natamycin	Polyene antibiotic agent	EUD L100, EUD S100, EUD RL100, HPMC and EC
13	Indomethacin	Non-steroidal anti-inflammatory agent	EUD L100, EUD RL100, HPMC and EC
14	Levobunolol	β -blocker agent	MC, PVP and HPMC
15	Levobunolol	β -blocker agent	EC and EUD RL100
16	Timolol Maleate	Anti-glaucoma agent	MC, HPC, EUD RL100, EUD RS100, EC and PVP
17	Aceclofenac	Non-steroidal anti-inflammatory agent	HPMC and EC
18	Moxifloxacin	Antibacterial agent	EUD RL100, EUD RS100 and NaCMC
19	Ketorolac Tromethamine	Non-steroidal anti-inflammatory agent	Gelatin, HPMC and EC
20	Natamycin	Polyene antibiotic agent	MC, Sodium alginate and Gelatin
21	Diclofenac Sodium	Non-steroidal anti-inflammatory agent	HPMC, and EUD L100
22	Moxifloxacin	Antibacterial agent	Chitosan, MC and HPMC K4M

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