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Review Article

REVIEW ON OCULAR INSERT DRUG DELIVERY SYSTEM

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ABSTRACT

An ocular insert represents an advanced technology in eye disease therapy. Designing and development of an ocular insert is a challenge ever faced by Pharmaceutical researchers or manufacturer. In the ophthalmology; eye drop have ever found to be an easy remedy from the administration point of view. In case of conventional dosage forms the fast precorneal loss of drug has been a major difficulty. To improve ocular drug bioavailability, there are significant guidelines have been directed towards newer drug delivery systems for ophthalmic administration. By means of ocular insert, the researcher has always taken efforts to release the drug at controlled rate to avoid frequent administration of drug. The ocular insert consist of controlled, delayed or sustained release biodegradable implantable components of different material in multiple layers. The inserts can be classified in various classes like Insoluble, soluble or biodegradable as per its solubility. The release of drug from the insert depends upon the diffusion, osmosis, and bioerosion of the drug.

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1. INTRODUCTION

Delivery of drug to the eye has remained as one of the most challenging task for pharmaceutical scientists. The intraocular bioavailability of the drug through conventional eye drops is very poor due to factors such as naso-lachrymal drainage, lacrimation, and drug dilution with tear fluid, tear turnover and conjunctival absorption.¹ binding of drugs to protein also contributes to loss of drugs through the precorneal parallel elimination loss pathway. Consequently, only a small amount of (1-3%) drug actually penetrates the cornea and reaches the intraocular tissue.^{2,3}

A sincere attempt to prolong the contact of ophthalmic drug with cornea can improve its efficiency. This can be fulfilled by incorporating viscosity enhancing agent in eye drops or by using water insoluble ointment base in ophthalmic formulation which increase the drug content with cornea. Unfortunately these attempts have shown limited improvement in drug cornea contact than

conventional eye drop solution, but consistent drug availability is still a challenging task to be achieved to avoid repeated medication throughout the day. To solve this problem the search for finding the alternative method for ocular drug delivery system has stimulated. Now days much of the work recently devoted to ocular inserts, which serves as the platform for the release of one or more active substances. It has become clear, however that the development of an ocular insert that reliably combines controlled release with absence of any irritation to the patient.⁴ Is an area of thirst Ocular insert are the new drug delivery systems which are prepared in such a way that they release the drug at predetermined and predictable rates which eliminates the problem of the frequent administration of the drug. Ophthalmic inserts are defined as sterile preparations, with a thin, multilayered, drug-impregnated, solid or semisolid consistency devices placed into cul-de-sac or conjunctival sac and whose size and shape are especially fabricated for ophthalmic application. Ophthalmic inserts offer

many advantages over conventional dosage forms such as increased ocular residence, sustained release, accurate dosing, and reduced dose frequency.

History of ocular inserts

The first solid medication (precursors of the present insoluble inserts) was used in the 19th century, which consisted of squares of dry filter paper, previously impregnated with dry solutions (e.g., atropine sulphate, pilocarpine hydrochloride). Small sections were cut and applied under eyelid. Later, lamellae, the precursors of the present soluble inserts, were developed. They consisted of glycerinated gelatin containing different ophthalmic drugs. Glycerinated gelatin 'lamellae' were present in official compendia until the first half of the twentieth century. However, the use of lamellae ended when more stringent requirements for sterility of ophthalmic preparations were enforced. Nowadays, growing interest is being observed for ophthalmic inserts⁵

OCULAR PHARMACOKINETICS

The drug pharmacokinetics from the eye follows the following paths

- Transcorneal permeation from the lacrimal fluid into the anterior chamber.
- Non-corneal drug permeation across the conjunctiva and sclera into the anterior uvea.
- Drug distribution from the blood stream via blood-aqueous barrier into the anterior chamber.
- Elimination of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and sclemm's canal.
- Drug elimination from the aqueous humor into the systemic circulation across the blood-aqueous barrier.
- Drug distribution from the blood into the posterior eye across the blood-retina barrier.
- Intra vitreal drug administration.
- Drug elimination from the vitreous via Eg. Posterior route across the blood-retina barrier.
- Drug elimination from the vitreous via anterior route to the posterior chamber.⁶

Mechanism of ocular drug absorption

Topical delivery into the cul-de-sac is, by far, the most common route of ocular drug delivery. Absorption from this site may,^{7,8}

1. Corneal
2. Non-corneal

Merits of ocular inserts^{9,10}

1. The side effects due to the pulsed dosing of conventional dosage form can be overcome by using ocular insert.
2. Provides sustained and controlled drug delivery.

3. Increases the ocular bioavailability of drug by increasing the corneal contact time
4. Provides targeting within the ocular globe so as to prevent the loss to other ocular tissues.
5. Circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
6. Provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
7. Provide better housing of delivery system.
8. Increased shelf life with respect to aqueous solutions.

Demerits of ocular insert^{11,12,13}

1. A capital demerit of ocular inserts resides in their 'solidity', i.e., it is experienced as a foreign body in the eye by the patient.
2. Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix.
3. The occasional inadvertent loss during sleep or while rubbing the eyes,
4. Their interference with vision, and difficult placement of the ocular inserts (and removal, for insoluble types).

Classification of ocular inserts:

Ocular insert are mainly divided in three classes.

1. Insoluble ocular inserts.
2. Soluble ocular inserts
3. Bioerodible ocular inserts

Insoluble ophthalmic inserts

The insoluble inserts have been classified into three groups:-

- i. Diffusion systems
- ii. Osmotic systems
- iii. Hydrophilic contact lenses.

The first two classes include a reservoir in contact with the inner surface of the rate controller and supplying drug thereto. The reservoir contains a liquid, gel, colloid, semisolid, solid matrix or a carrier-containing drug homogeneously or heterogeneously dispersed or dissolved therein. Carriers can be made of hydrophobic, hydrophilic, organic, inorganic, naturally occurring or synthetic material. The third class includes the contact lenses. The insolubility of these devices is their main disadvantage, since they have to be removed after use.¹⁴

Diffusion inserts

The diffusion systems are comprised of a central reservoir of drug enclosed in semi permeable or micro porous membranes, which allow the drug to diffuse through the reservoir at a precisely determined rate. The drug release from such a system is controlled by the

lachrymal fluid permeating through the membrane until it form an adequate internal pressure to drive the drug out of the reservoir. The drug delivery rate is controlled by diffusion through the membrane, which can be controlled.¹⁵

Osmotic inserts

The osmotic inserts are generally divided into two types, in first type the central part covered by a peripheral part. The first central part can be composed of a single reservoir or of two distinct compartments. In first Type, it is composed of a drug with or without an additional osmotic solute dispersed through a polymeric matrix, so that the drug is covered by the polymer as discrete small deposits. In the second type, the drug and the osmotic

solutes are placed in two separate compartments, the drug reservoir being covered by an elastic impermeable membrane and the osmotic solute reservoir is covered by a semi permeable membrane. The peripheral part of these osmotic inserts comprises in all cases a covering film made of an insoluble semi permeable polymer. The tear fluid diffuses into peripheral deposits through the semi permeable polymeric membrane and wets them to induce their dissolution. The solubilized deposits generate a hydrostatic pressure against the polymer matrix which causes bursting of matrix. the Drug is then released through the matrix. This corresponds to the osmotic part characterized by zero order drug release profile.¹⁶

Table 2: Components of osmotic inserts

Water permeable matrix	Ethylene: vinyl esters copolymers, Divers: plasticized polyvinyl chloride (PVC), polyethylene, cross-linked, Poly vinyl pyrrolidone(PVP)
Semi permeable membrane	Cellulose acetate derivatives, Divers: Ethyl vinyl acetate (EVA), polyesters of acrylic and methacrylic acids (Eudragit ®).
Osmotic agents	Inorganic: magnesium sulfate, sodium chloride, potassium phosphate dibasic sodium carbonate and sodium sulfate. Organic: calcium lactate, magnesium succinate and tartaric acid. Carbohydrates: Sorbitol, mannitol, glucose and sucrose.

Soft contact lenses

These are shaped 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. When a hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic systems. The drug release from such a system is generally very fast at the beginning and then declines exponentially with time. The release rate can be decreased by incorporating the homogenous mixture of drug during the manufacture or by adding a hydrophobic component.¹⁷

Soluble Ophthalmic inserts

Soluble inserts correspond to the oldest class of ophthalmic inserts. They offer the great advantage of being entirely soluble so that they do not need to be removed from their site of application, thus limiting the interventions to insertion only.¹⁸

Types of soluble ophthalmic inserts

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

The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying and rehydrating it before use on the eye. The amount of drug loaded will depend upon the amount of binding agent, and on the concentration of the drug solution into which the composite is soaked, as well as the duration of the soaking.

The soluble ophthalmic inserts containing synthetic/semi synthetic polymer: Offers the additional advantages of being generally of a simple design.

- Based on products well adopted for ophthalmic use.
- Easily processed by conventional methods – slow evaporating extrusion, compression or injection molding.

The release of the drug from such system is by penetration of tears into the insert which induces release of the drug by diffusion and forms a gel layer around the core of the insert, this external gelification induces the further release, but still controlled by diffusion. The release rate, J , is derived from Fick's law yields the following expression.

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

When A - Surface area of the membrane.

K – Diffusion coefficient of the drug

L – Membrane thickness

CS – Drug solubility in water

D – Diffusion coefficient of the ocusert membrane.

Since all the terms on the right hand side of the above equation are constant, so is the release rate of the device. The other factors affecting drug release from these Ocuserts include:

- Penetration of the inclusion.
- Swelling of the matrix.
- Dissolution of the drug and the polymers.
- Relaxation of the polymeric chain.

The soluble insert made of cellulose derivatives can be sterilized by exposure to gamma radiation without the cellulose components being altered. A decreased release rate is obtained by using a component of the matrix a polymer normally used for enteric coatings or by

introducing a suitable amount of hydrophobic polymer capable of diminishing the tear fluid penetration and thus decreasing the release of the drug without modifying the solubility of the insert when added in proper proportion.¹⁹

Table 3: Components Of Soluble Inserts Containing Synthetic Polymers

Soluble synthetic polymers	Cellulose derivatives –Hydroxypropyl cellulose methylcellulose, hydroxyethyl Cellulose and hydroxypropyl cellulose. Divers – Polyvinyl alcohol, ethylene vinyl acetate copolymer.
Additives	Plastisizer – Polyethylene glycol, glycerin, propylene glycol Enteric coated polymer –Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate. Complexing agent – Polyvinyl pyrrolidone. Bioadhesives – Polyacrylic acids.

A. Bio-erodible ocular inserts

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution.^{20,21} The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants. A cross-linked gelatin insert was used by Attia *et al.*²² to increase bioavailability of dexamethasone in the rabbit eye. The dexamethasone levels in the aqueous humor were found to be four-fold greater compared to a dexamethasone suspension. However, erodible systems can have significantly variable erosion rates based on individual patient physiology and lachrimation patterns, while degradation products and residual solvents used during the polymer preparation can cause inflammatory reaction. The solid inserts absorb aqueous tear fluid and gradually erode or disintegrate. Then the drug is slowly leached from hydrophilic matrix. After completion of drug delivery bio-erodible ocular inserts are not needed to be removed. The marketed devices of erodible drug inserts are Lacriserts, SODI, and Minidisc.

1. Lacrisert

Lacriserts are hydroxyl propyl cellulose rod shaped device lack of preservative useful for dry eye syndrome. It weighs 5 mg and measures 12.7 mm in diameter with a length of 3.5 mm. Lacrisert is useful in treatment of keratitis whose symptoms are difficult to treat with artificial tear alone. It is inserted into cul-de-sac cavity where it absorbs water from conjunctiva and cornea, forms a hydrophilic film which stabilizes tear film for hydration and lubrication of cornea. It dissolves in 24 hours.⁶

2. SODI

Soluble Ocular Drug Insert (SODI) is a small oval wafer developed for space pilots who could not use eye drops in weightless conditions. It is sterile thin film of oval shape made from acryl amide, N-vinyl pyrrolidone and ethylacrylate called as ABE. It weighs about 15-16 mg.

It is used in treatment of glaucoma and trachoma. It is inserted into inferior cul-de-sac and gets wets and softens in 10-15 seconds. After 10-15 min film turns into a viscous polymer mass, after 30-60 minutes it turns into polymer solutions and delivers drug for about 24 hours.²³

3. Minidisc

The minidisc consists of a contoured disc with a convex front and concave back surface in contact with eyeball. It is like a miniature contact lens with a diameter of 4-5mm. The minidisc is made up of silicone based pre-polymer- α -bis (4-methacryloxy) butyl polydimethyl siloxane. Minidisc can be hydrophilic or hydrophobic to permit extend release of both water soluble and insoluble drugs.²⁴

4. Collagen shields

Collagen shield basically consist of cross linked collagen, fabricated with foetal calf skin tissue and developed as a corneal bandage to promote wound healing. Tear fluid makes these devices soft and form a thin pliable film which is having dissolution rate up to 10, 24 or 72 hours. Because of its structural stability, good biocompatibility and biological inertness, collagen film proved as a potential carrier for ophthalmic drug delivery system. Collagen ophthalmic inserts are available for delivery of drug to the eye.²⁵

B. Non-Erodible Ocular Insert

The Non-erodible ocular inserts include Ocusert, and Contact lens.

1. Ocusert

The technology used in this is an insoluble delicate sandwich technology. In ocusert drug reservoir is a thin disc of drug complex sandwiched between two transparent discs of micro porous membrane prepared from ethylene-vinyl acetate copolymer. The micro porous membranes permit tear fluid to penetrate into drug reservoir compartment to dissolve drug from complex. The sandwich technology which is used in ocular insert shown in figure 1.^{26, 27}

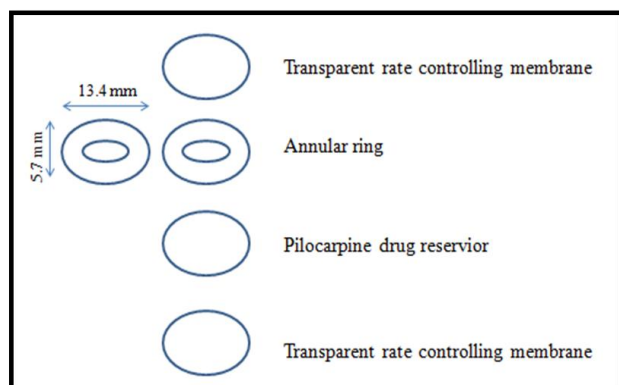


Figure 1: Ocusert

2. Contact lenses

Contact lenses can absorb water soluble drugs when soaked in drug solutions. These drug saturated contact lenses are placed in eye for releasing drug for long period of time. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs.^{20,28,29}

Mechanism of Drug Release from Ocular Inserts

Diffusion

In this mechanism, the drug is released continuously at a controlled rate through the membrane. If the insert is formed of a solid non-erodible body having pores and drug is in a dispersed form, the drug release takes place via diffusion through the pores. Controlled release of the drug can be maintained by a gradual dissolution of the solid dispersed drug in the matrix, as a result of the inward diffusion of aqueous solutions. In a soluble device, true dissolution occurs mainly through polymer swelling. In swelling-controlled devices, the active agent is homogeneously dispersed in a glassy polymer. As glassy polymers are essentially drug-impermeable, no diffusion occurs through the dry matrix. When the insert is placed in the eye, water from the tear fluid begins to penetrate the matrix, swelling occurs, and consequently polymer chain relaxation occurs and drug diffusion takes place. The dissolution of the matrix, followed by the swelling process depends on the polymer structure. A linear amorphous polymer dissolves at a faster rate than a cross-linked or partially crystalline polymer.^{30,31}

Osmosis

In the Osmosis mechanism, the insert is made of a transverse impermeable elastic membrane, which divides the interior of the insert into two compartments, first and second; the first compartment is surrounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is surrounded by an impermeable material and the elastic membrane. There is a drug release orifice in the impermeable membrane of the insert. The first compartment contains a solute that cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for the drug, which is in liquid or gel form. When the insert is placed in the aqueous environment of the eye, water diffuses in the first compartment, which stretches the elastic membrane to expand the first compartment and contract the second

compartment so that the drug is forced to come out through the drug release orifice.³¹

Bioerosion

In the bioerosion mechanism, the insert is comprised of a matrix of bioerodible material in which the drug is dispersed. Contact of the insert with the tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. The drug is dispersed uniformly throughout the matrix, but it is believed that a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible or E-type devices, the drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degrades to smaller, water-soluble molecules. These polymers may undergo bulk or surface hydrolysis, which displays zero order release kinetics; provided the devices maintain a constant surface geometry and the drug is poorly water soluble.

Evaluation test for ocular inserts:

1. Thickness
2. Folding Endurance Test
3. Surface pH
4. Weight uniformity
5. Drug content uniformity
6. Tensile strength
7. In vitro drug release study
8. Ex vivo transcorneal permeability study
9. Drug release kinetics
10. Accelerated stability study.

Thickness of film

Film thickness is measured by using the Dial caliper at different points of the formulation and the mean value is calculated.¹⁰

Folding Endurance

Folding endurance was determined by repeatedly fold the film at the same place till breaking or first sign of breaking. The number of time the film could be folded at the same place without breaking gives the folding endurance value.³²

C. Surface pH

The Dorzolamide inserts were allowed to swell in closed petridish at room temperature for 30 min in 1 ml of distilled water. The swollen device was removed and solution placed under digital pH meter to determine the surface pH.³³

D. Weight Uniformity

From each batch (n = 3), inserts were taken and weighed individually using digital balance. The mean weights of the insert were recorded.³²

E. Drug Content Uniformity

To check the uniformity of drug in insert, each insert was placed in a glass vial containing 10 ml of artificial tear fluid. The insert was dissolved by aid of a magnetic stirrer, solution was then filtered and 1 ml from filtrate was withdrawn and diluted up to 10 ml distilled water

and absorbance was measured by UV-Visible spectrophotometer.³²

F. Tensile strength

Tensile strength of the prepared films was calculated according to the following equation.^{34,35}

$$\text{Tensile strength} = \frac{N}{\text{mm}^2}$$

i. e. Breaking load N

Cross sectional area of the sample mm^2

In vitro drug release study

In vitro drug release from the different ocular inserts was studied by using franz diffusion cell and dialysis membrane. The dialysis membrane mimics corneal epithelium. The receptor compartment was filled with freshly prepared artificial tear fluid. 1.5 cm^2 area of ocular film was placed on the dialysis membrane and opening of the donor compartment was sealed with a glass cover slip, while the receptor fluid was maintained at $37 \pm 0.5^\circ\text{C}$ with constant stirring, using magnetic stirrer. 1 ml sample was withdrawn from receptor compartment at various time intervals up to 6 h and was analyzed spectrophotometrically. Each sample withdrawn was replaced with equal volume of artificial tear fluid.³²

H. Ex vivo transcorneal permeation study

Whole eye ball of goat was transported from local butcher shop to the laboratory in cold (4°C) normal saline within 1 h of slaughtering the animal. The cornea was carefully excised along with 2–4 mm of surrounding scleral tissue and was washed with cold normal saline till the washing was free from proteins. Isolated cornea was mounted by sandwiching surrounding scleral tissue between clamped donor and receptor compartments of an all glass modified Franz diffusion cell in such way that its epithelial surface faced the donor compartment. The receptor compartment was filled with freshly prepared artificial tear fluid. 1.5 cm^2 area of ocular film was placed on the cornea and opening of the donor compartment was sealed with a glass cover slip, while the receptor fluid was maintained at $37 \pm 0.5^\circ\text{C}$ with constant stirring, using magnetic stirrer. 1ml sample was withdrawn from receptor compartment at various time intervals up to 6 h and was analyzed spectrophotometrically. Each sample withdrawn was replaced with equal volume of artificial tear fluid.^{34,35}

I. Drug release kinetics

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. To describe the kinetics of the drug release from optimised Ocular insert, mathematical models such as zero-order, first order,

Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness or fit test.

J. Sterility testing as per I.P. 2014

The test for sterility on the sterilized ocular insert was carried out by direct inoculation method.

Culture media

Alternate thioglycolate medium and soyabean casein digest medium was used as a culture medium for bacteria (*S. aureus*) and fungi (*C. albicans*) respectively. Media were prepared according to I.P.2014 and 20 ml was taken in boiling test tube, properly plugged with cotton and sterilized by autoclaving at 121°C at 15 lb/inch gauge pressure for 20 minutes.

Inoculation and incubation

Formulation was aseptically added in test tube containing respective media and simultaneously positive and negative control was prepared for each media. The inoculated culture media for bacteria and fungi were incubated at $30^\circ\text{C} - 35^\circ\text{C}$ and $20^\circ\text{C} - 25^\circ\text{C}$ respectively in incubator for not less than 14 days.

K. Accelerated stability studies as per ICH Guidelines

The accelerated stability studies are carried out to predict the degradation that occurs over prolonged periods of storage, at normal conditions. The films of the insert are taken in a separate Petri dish and are kept at three different temperatures and humidity condition.

CONCLUSION

Ocular insets have been found advantageous as it eliminates side effect of pulsed dosing of conventional dosage form by providing controlled and sustained drug delivery with increase in bioavailability and corneal contact time, preventing the loss of drug with better patient compliance improving drug efficacy. Various classes of ocular insert have been developed till date like soluble, insoluble, and bio-degradable ocular insert which are further categorized in different types depending upon material used and its behavior in drug delivery like soluble ocular insert based natural, synthetic or semi-synthetic polymer, insoluble ocular inserts including diffusion insert, osmotic insert and soft contact lenses while bio-erodible involve lacrisert, SODI, Minidisc and collagen shield. Non-erodible encompasses ocular insert and contact lenses etc. thus the ocular insert represent a significant advancement in eye ailment.

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