

Ophthalmic Insert: A Controlled Drug Delivery System for Eye Diseases

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ABSTRACT: Ocular inserts play important role in evolution of eye diseases therapy. They are sterile, thin multi-layered, drug containing solid/semi-solid devices placed into a cul-de-sac/conjunctival sac which are designed for ophthalmic application. It also includes polymeric support, which may or may not contains drug in it. They offer several advantages as increasing the contact time and thus improving the drug bioavailability. They are classified on the basis of their solubility (soluble, insoluble, and bio-erodible) inserts. From inserts the release of drug depends on their diffusion, osmosis, and bio-erosion of the drug. In this review, we discussed the introduction, classification, ocular insert devices, mechanism of drug release in the eye, absorption of the drug in the eye, formulation methods of ocular inserts, and evaluation parameter of ophthalmic inserts. This review is written to present a brief information about the ophthalmic insert.

I. INTRODUCTION

Ophthalmic drug delivery is a bigger challenge for the pharmaceutical and medical science field. In recent, these drug delivery system to improve the efficacy of dosage form. These ocular devices are difficult to treat, and ocular forms required to be safe, non-allergic to the patient and it should be disinfected. The nasolacrimal drainage, the corneal epithelium, and the blood ocular barrier are decreasing the bioavailability of drug and residence time in topical application. The drug crosses the corneal barrier only 5-10%. The delivery of the anterior segment region includes such as blepharitis, conjunctivitis, scleritis, Keratitis, and dry eye syndrome are included with topical or periocular administration. The delivery of drugs to the posterior segment of the eye for glaucoma, endophthalmitis, or uveitis. Ocular drug delivery improves bioavailability in the eye [1]. It is a bigger challenge for the formulation to pass through the barriers without any tissue damage. Viscosity enhancers were used while preparation of inserts or water insoluble ointment drug formulations. Insert provides less drug-eye-contact in comparison to eye drops and also does not give constant bioavailability of drug. Eye drops can be easily administered in eye, but due to pre-corneal loss less bioavailability will be there. This occurs low corneal permeability, blinking reflex, conjunctival absorption, and rapid solution drainage by gravity. This causes both systemic and ocular side effects. Ocular inserts devices it is developed polymeric system and collagen shields to achieve the better ocular bioavailability or sustained drug action. Ophthalmic insert drug delivery system which releases the drug predetermined and predictable rate.

Ophthalmic inserts are defined as sterile thin multi-layered drug containing, solid or semi-solid devices. They are installed into a cul-de-sac or conjunctival region of eye for eye treatments. Ocular inserts offer several advantages over conventional dosage forms. These conventional dosage forms increase ocular residence, sustained release, dosing, or reduce the dose frequency [2]. In the case of ophthalmic drug delivery, the conventional ocular dosage form includes suspension, emulsion, and ointments [3].

II. CLASSIFICATION OF OPHTHALMIC INSERTS: [4,5,6]

They are classified on the basis of their solubility profile:

1. Insoluble inserts
2. Soluble inserts
3. Based on synthetic/semisynthetic polymers

These are further classified into different categories as follows:

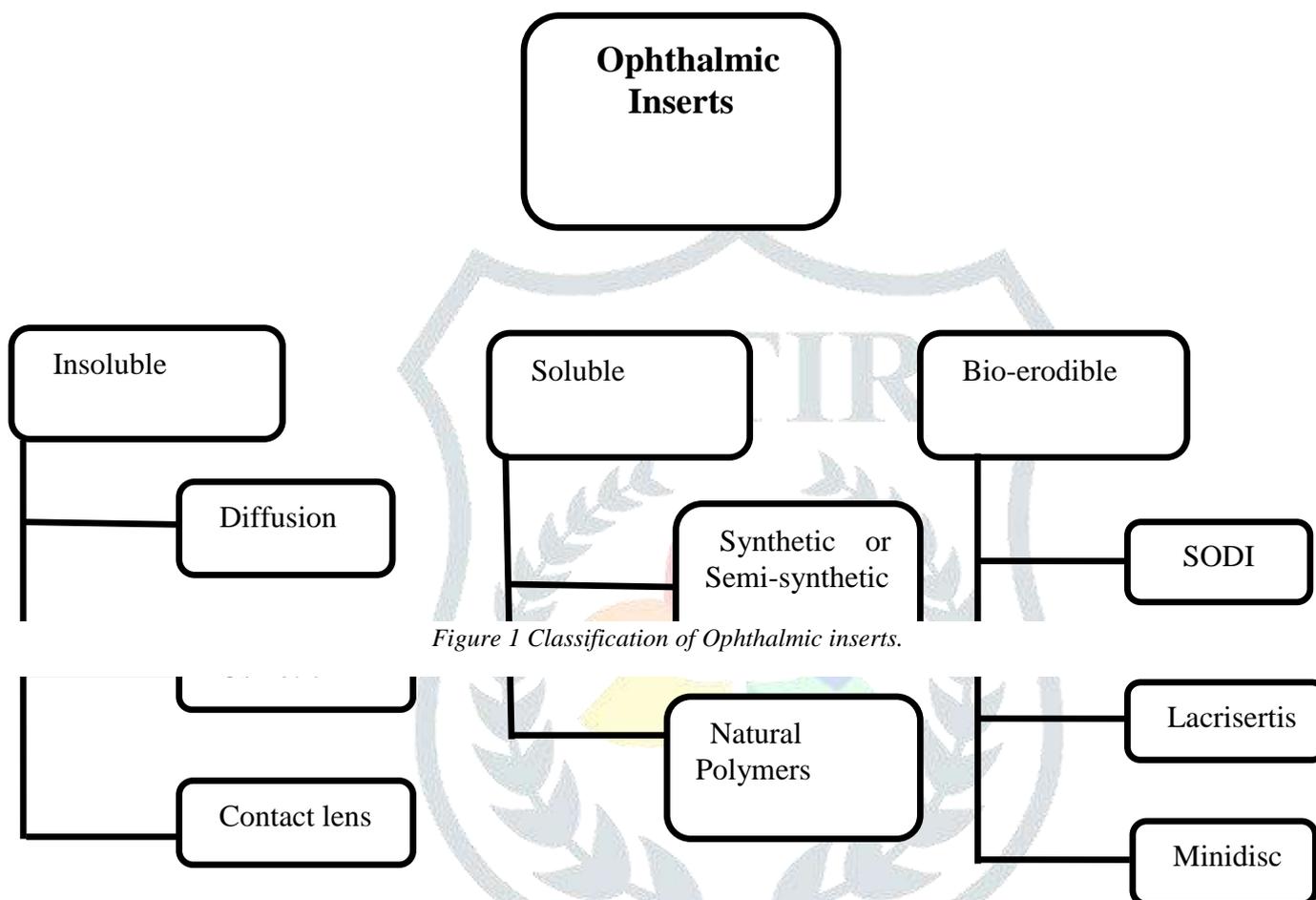


Figure 1 Classification of Ophthalmic inserts.

- Insoluble insert (Diffusion, osmotic, contact lens).
- Soluble inserts (based on natural polymers).
- Based on synthetic/semisynthetic polymers.

1. Insoluble Ocular inserts:

These are made up of insoluble polymer, can be classified into types: reservoir system& matrix system.

A. Reservoir System: In this system drug release by diffusion/osmotic process. It contains liquid, gel, semisolid& solid matrix containing drug. Carriers is made up of hydrophobic/hydrophilic, organic, natural, or synthetic polymers [5,6]

It is further classified into two types:

1. Diffusional inserts/Ocuserts
2. Osmotic inserts

1. Diffusional inserts/Ocuserts:

During the release of drugs in diffusional inserts, it depends upon the diffusion mechanism. The diffusion system comprises a central reservoir for a drug incapsulated in semipermeable/microporous membrane, due

to drug diffusion takes place at controlled rate. The release of drug from such a system was regulate by a lachrymal fluid, when internal pressure was developed, then drug comes out of the reservoir [4,5,6].

Further, it is classified into two types:

- Pilo-20
- Pilo-40

These types of Pilo release drug at a rate of twenty microgram/hour for seven days and after one week at rate of forty microgram/hour for seven days. Pilocarpine alginate is enclosed by a thin EVA (ethylene-vinyl acetate) membrane [5].

2. Osmotic inserts:

It is generally composed of central or peripheral part and it is of two types:

In type one central part is, formed by a single reservoir may or may not including osmotic solute, distributed throughout the matrix, so that drug remain surrounded by polymer. The second peripheral part is enclosed by an insoluble semi-permeable membrane. When an osmotic pressure against the polymer matrix it causes a rupture in the form of apertures. These apertures release the drug and deposits nearly to the surface of device.

Type2: The central part is made up of two different compartments, which isosmotic solutes. The second part is similar totypel.

B. Matrix System:

This system is a type of insoluble ophthalmic devices (contact lenses). They contain cross-linked hydrophilic/hydrophobic polymer which form a 3D-matrix. They are good in retaining water, aqueous drug solution, or solid components. The polymer (hydrophilic/hydrophobic) after absorbing water get swelled. That's welling occurs due to the osmotic pressure of polymeric segments.

• Contact lenses:

Contact lenses are shaped structures it is used for vision correction. The main benefit of these contact lenses is the correcting vision and release the drug simultaneously. According to Refojo there are five types of contact lenses i.e.: (Rigid, Semi-rigid, Elastomeric, Bio-polymeric, &Soft-hydrophilic).

Contact lenses when placed in solution it absorbs water-soluble drugs, provides extended release of drug in the eye. Some disadvantages of a rigid contact lens are composed of poly-methyl methacrylic acid and permeable to moisture and oxygen. In case of prolonged delivery to eye they are very uncomfortable to wear whole day.

2. Soluble ocular inserts:

Soluble ocular is divided into two types:

- A) Based on natural polymer
- B) Based on synthetic and semi-synthetic polymer

A) Based on natural polymer:

The soluble inserts are made up of natural polymer, in this case amount of drug depends on the amount of binding agent used while preparation.

B) Based on Synthetic &Semi-Synthetic polymer:

The soluble insert is formed of synthetic and semi-synthetic polymer for e.g., synthetic polymers such as polyvinyl alcohol or cellulose derivatives. Hydrophobic Ethyl-cellulose polymerized to prevent deformation of ophthalmic inserts and also to prevent blurred vision.

3. Bio-erodible Ocular inserts:

It contains metrical homogeneous dispersion of drugs may or may not contain hydrophobic coating, which is impermeable to the drug. They are mainly made of "cross-linked gelatin derivatives, polyester derivatives" like polymers, upon hydrolysis chemical bond dissociates and dissolution occurs [5,6].

Some important ocular inserts are discussed below:

III. SODI (Soluble Ocular Delivery Inserts):

It comprises acrylamide, vinyl pyrrolidone, ethyl acrylate. Its weight up to 15-16mg. The First 10-15 second softens than other 10-15 second viscous liquid, after 30-60 minutes it becomes a polymeric solution.

Advantages:

- Used for the treatment of Glaucoma and Trachoma.
- It includes some active ingredients such as neomycin, kanamycin, atropine, pilocarpine, and tetracaine.

2. Lacrisertis: Lacrisertis are sterile, pole molded erodible which is produced using hydroxypropyl cellulose. It is used for the treatment of dry eye syndrome without any preservatives. Lacrisert is useful in the treatment of Keratitis. Lacrisert which decrease the corneal sensitivity and corneal erosions.

3. Minidisc: It consists of convex and concave. It is made up of silicone-based pre-polymer. It can be a hydrophilic or hydrophobic release of both water-soluble and insoluble drugs [5].

IV. CURRENTLY AVAILABLE OCULAR INSERTS [8]:

Table 1

Sr. No	Name	Company	Shape	Composition	Weight	Dimension	Uses	Advantages
1	Soluble ocular drug insert	Alza corporation	Oval shape	Acryl amide, Vinyl Pyrrolidone	15-16mg	Diameter-12.5.mm, Length-3.5mm	Glaucoma, Dry eye treatment	Better patient compliance
2	Collagen Shields	Bausch and Lomb pharmaceuticals	Ring-shaped	Glycine, proline, hydroxyproline, and arginine	More than 25% of total body weight	Diameter-14.5mm	Treatment of dry eye	Reduce the corneal inflammation
3	Minidisc	Alza Corporation	Rod-shaped	Silicon-based prepolymer	6.7-7.5gm	Diameter-4-5mm	Dry eye syndrome	Improve patient compliance
4	Lacrisert	Merck and co.INC	Rod-shaped	Ethanol, propylene glycol, dioxane, methanol,	5mg	Diameter-12.7mm, Length-3.5mm	Dry eye syndromes	Increase ocular residence
5	Bio adhesive ophthalmic eye inserts	Sigma Aldrich Corporation	No specific shape	Hydroxypropyl cellulose, polyacrylic acid cellulose-alate	20.5mg	Length-5mm, diameter-2mm,	Treatment of Glaucoma	Reduction of the systemic side effects
6	Ocuserts	Alza Corporation	Oval shaped	Pilocarpine, alginic acid, ethylene-vinyl acetate copolymer	5.86-6.06mg	Length-3.5mm, Diameter-12.5mm	Dry eye treatment	Quick absorption, easily administered by the patient himself

V. MECHANISM OF DRUG RELEASE [7,8,9]:

In case of controlled drug delivery system, the release of drug into the eye based on (Diffusion, Osmosis, Bio-erosion).

1. Diffusion:

In diffusion, drug will release at controlled rate through membrane into lachrymal fluid. Drug release takes place through diffusion into the pores. The controlled release can be regulated by the gradual dissolution of the solid dispersed drug within the matrix, due to which inward diffusion of an aqueous solution occur. When inserts placed in eye lachrymal fluid release, due to which swelling, polymer chain relaxation, and drug diffusion take place.

2. Osmosis:

In osmosis, the insert is composed of transverse elastic impermeable membrane. Interior parts of inserts are divided into 2 compartments. The first compartment contain solute which will not permeate through semi-permeable membrane, while the second compartment acts as reservoir of drug in (liquid/gel form). Insert when placed into eye, water starts diffusing into first compartment because of that contraction happen which results in drug release from second compartment into the aperture of eye.

4. Bio-erosion:

In bio-erosion, the body of insert is made from the matrix of a bio-erodible material in which drug present in dispersed form. The contact of insert with tear fluid results in the controlled release of the drug from matrix, it may or may not be disperse uniformly throughout the matrix, but controlled release property of drug can be achieved. These devices maintain constant surface geometry and that drug is poorly water-soluble.

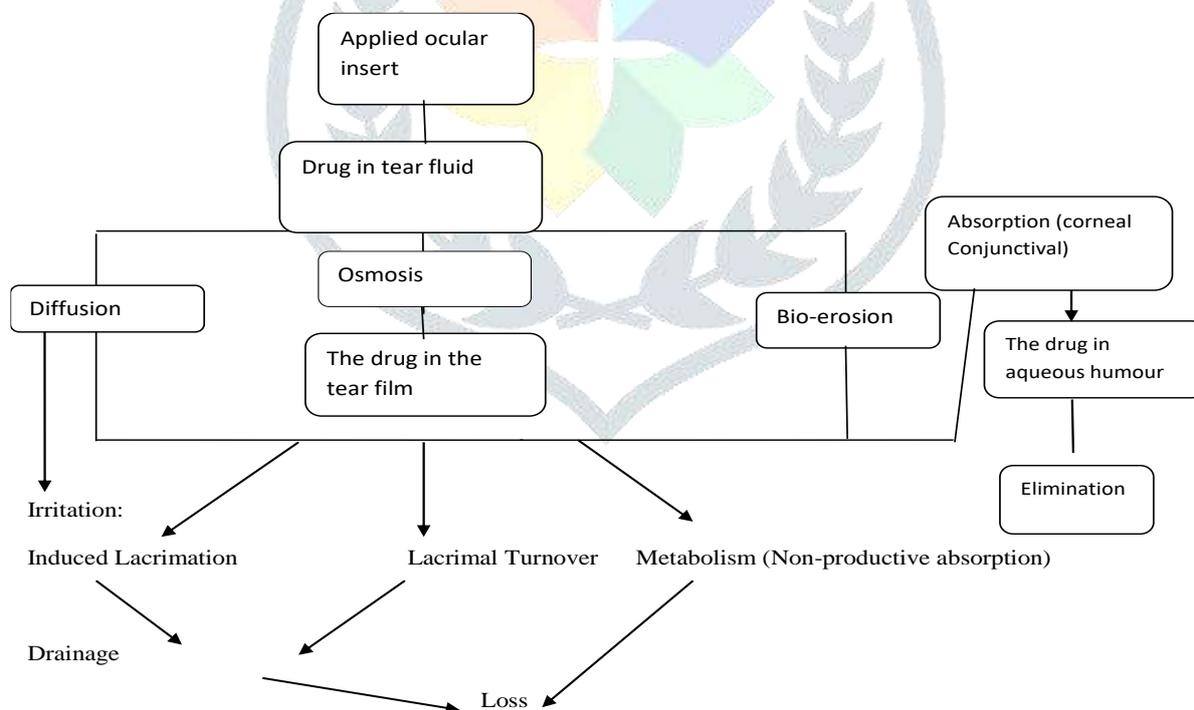


Figure 2 Mechanism of action of drug release from ophthalmic inserts.

Absorption of the drug in the eye:[7]

The absorption route of ocular drug delivery is:

- Corneal
- Noncorneal routes

In the corneal region high absorption occurs due to which concentration of drug increased in aqueous humor. Apart from that absorption of drugs occurs through scleral and conjunctival route, but these route does not provide good bioavailability because of retention in entry of drug into intraocular tissue.

VI. ADVANTAGES AND DISADVANTAGES OF OCULAR INSERTS: [8,10,11]

Advantages	Disadvantages
Increasing contact time and thus improving the bioavailability.	It is difficult for the unwanted migration of the insert to the upper fornix.
Reduction of systemic side effects.	Their interference with the vision.
Reduction of the administrations and improve better patient compliance.	The difficulty for the placement of ocular inserts.
Increase ocular residence and prolong drug activity.	Leakage may occur
Releasing of the drug slow and constant rate.	Dislocation of the device in front of the pupil.
Increase shelf life concerning the aqueous solution.	It's poor bioavailability.

VII. METHOD FOR FORMULATION OF OCULAR INSERTS:[12]

1. Solvent casting method:

Number of batches are prepared of different ratio of drug and polymer. A polymer and plasticizer are added under continuously stirred conditions. The weighted amount of drug was added to previously prepared solution, stirred to get uniform dispersion mixture. The solution is transferred into a petri dish. The dried film was cut into definite size. The ocular inserts are stored in an airtight container.

2. Glass Substrate technique:

Drug reservoir film 1% w/w polymer for e.g., chitosan in 1% v/v acetic acid solution (24 hours) to get transparent solution. The solution was filtered and to remove the undissolved polymer by a muslin cloth. Required quantity of drug-(B) CD complex and vortexed were added for 15 minutes to dissolve the complex in chitosan solution. 1% w/v propylene glycol was added and mixed well. Pouring the solution into the glass tray and stored at room temperature for 24 hrs. After drying, the thin films were cut down into the required shape.

3. Melt extrusion technique:

Acyclovir polymer sieved through size 60 mesh, weighed and mixed geometrically. The plasticizer was added and mixed properly. The extrudate was cut down into desired size, packed in polyethylene lined Aluminum foil, sterilization done in gamma radiation.

VIII. EVALUATION PARAMETERS OF OCULAR INSERTS: [13,14,15]

Ocular inserts are evaluated based on various evaluation parameters like, thickness, weigh, content uniformity, percentage moisture absorption, percentage moisture loss, in vivo drug release, in vitro drug release, surface pH, accelerated stability studies, folding endurance etc.

1. Uniformity of thickness:

Thickness was determined by use of Vernier-caliper/micro-meter gauze. Thickness was measured at five different points of each insert. Reading were determined over a circular film of the area of 38.5mm square area. The mean value was calculated.

2. Uniformity of weight:

Three patches were weighed and cut at three different sites of the same formulation and individual weight of every piece determined by using the digital balance.

3. Drug content uniformity:

Insert films were cut and placed in separate vials containing phosphate buffer, shake properly to extract the drug. Then 1ml of solution withdrawn from the vial and diluted for evaluation of absorbance by spectrophotometer using a pH 7.4 phosphate buffer as blank.

Mg of the drug in one patch = $A_s \times C_r / A_r$

Where, A_s (Absorbance of above solution), A_r (Absorbance of standard solution), C_r (Concentration of drug in standard solution).

4. Percentage moisture absorption:

This test is carried out to check the stability of ocular inserts. They were weighed and place in desiccators containing saturated solution of aluminum chloride and humidity maintained at 79.5%. After three-day time period inserts were taken out and weighed properly. Then percentage moisture absorption was calculated by using the formula:

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

5. Percentage moisture loss:

This checks the adherence of the film in the dry condition. Inserts were weighed and kept in desiccator containing CaCl_2 and after three day they were weighed again. Then by formula moisture loss was calculated: -

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

6. In vivo-drug release:

First, sterilization of ocular inserts was done by gamma radiation, then for drug release study two group of healthy rabbits (6 in each) used. Ocular inserts implanted in the cul- de sac of each rabbit. At regular interval 2, 4, 6, 8, 12 up to 24 hours the inserts taken out. Then calculate the left drug content, and was subtracted from the initial amount, which will tell the exact quantity of drug released inside eyes.

7. In vitro drug release:

This study is done by using bi-chamber donor-receiver compartment model, made by transparent regenerated cellulose cell. Insert tied on open cylinder acts as donor compartment. The semi-permeable membrane like a corneal epithelial barrier that stimulates the tear volume 0.7 ml (distilled water) kept in donor compartment. The reservoir contains phosphate buffer of pH-7.4 stirred by using magnetic stirrer. Specified amount of sample was taken out and analyzed at 246nm wavelength using standard phosphate buffer of same pH as blank by UV-Visible spectrophotometer.

8. Surface pH:

In this phenomenon ocular inserts were taken out and kept in a petri dish to swell freely at 27°C for thirty-minute in zero point one milliliter of double-distilled water. The swollen devices were removed, and surface pH was determined.

9. Accelerated stability studies:

In this study, Inserts are placed in square petri-dish and film of them are taken out, kept at 3 different temperatures (400, 500 and 600) °C and time taken for the degradation checked.

10. Folding endurance:

Folding endurance for ocular insert determined by number of folds to produce the crack was counted. The folding endurance test was repeated using other sets of ocular inserts.

IX. CONCLUSION:

The ocular inserts constitute in evolution of the eye diseases therapy. The purpose of preparing an ocular insert is to increase the bioavailability of the drug. Inserts are available in a different form depending upon their composition and applications. There are various types of ocular inserts which are classified on the basis of their solubility. From the insert drug release depends on diffusion, osmosis, and bio-erosion of drug. The absorption of the drug in the eye is divided into two routes corneal and non-corneal. Ocular inserts have various advantages such as increasing the contact time and increasing its bioavailability. Ocular inserts have various disadvantages such as leakage, solidity, dislocation of the device, etc. There are various methods to prepare the formulation of the ocular insert like - solvent casting and glass substrate technique etc., and for evaluation parameter of ocular insert.

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