JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue

JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)

An International Scholarly Open Access, Peer-reviewed, Refereed Journal

# Novel Controlled Drug Delivery System: A Review of Ocular Insert

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## ABSTRACT:

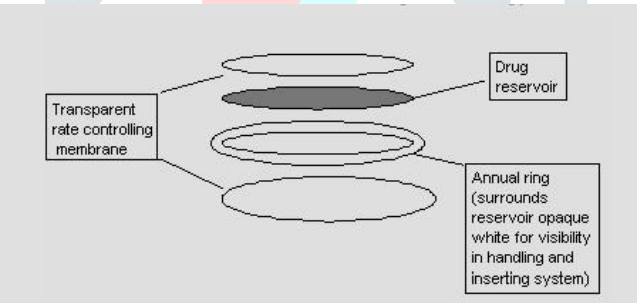
In the field of eye therapy, ocular Inserts are a cutting-edge innovation. It has always been difficult for pharmaceutical researchers to design and produce an ocular insert. The brand-new medication delivery method, ocuserts is created in a way that prevents repeated drug administration by releasing the medicine at predetermined and predictable rates. 90% of the currently available optical formulations are available in conventional dosage forms. With traditional dosing formulations, a significant challenge has been the quick pre-corneal loss of medication. Significant recommendations have been made in favor of more modern drug delivery methods for ophthalmic administration to increase ocular medication bioavailability. The capacity to sustain a therapeutic level of the drug at the site of action for an extended duration of time is one of the primary obstacles in ocular therapy. Ocular Inserts are described as sterile, thin, solid, or semi-solid constancy devices that are sized and shaped specifically for ophthalmic delivery and are put into a cul-de-sac or conjunctiva sac. The advantages of ocular Inserts over traditional dose forms are highlighted in the review study.

**Keywords**: Ocuserts, Ophthalmic delivery, Bioerodible, Polymers, Lens

## INTRODUCTION:

One of the most interesting as well as difficult issues pharmaceutical researchers are faced with is ocular medication delivery. Achieving and keeping a therapeutic level at the site of action for an extended period is one of the fundamental challenges for ocular medication. Getting through the eye's protective defenses without

enduring long-term tissue damage is difficult for the formulator. The creation of more effective and sophisticated ocular medication delivery systems is urgently needed in light of the advancement of newer, more sensitive diagnostic and treatment procedures [1]. By extending its contact with the corneal surface, an ocular drug's therapeutic efficacy can be significantly increased. The preparations for eye drops often contain viscosity-enhancing chemicals to attain this goal. It has become obvious, therefore, that creating an ocular insert that consistently combines regulated release with the patient-pleasant absence of any irritation presents a substantial technical hurdle [2]. i. Eye drops (solution, suspension) ii. Ocular Ointments The eye drop dosage form is simple to use but has the intrinsic disadvantage that the majority of the volume implanted is removed from the pre-corneal area [3], resulting in a bioavailability of 1 to 10% of the whole administered dose [4]. Many ocular medicines are administered at high doses due to their poor ocular bioavailability. As a result of the high peak medication concentrations in the eye and systemic circulation, this has negative effects [5] that affect the eyes as well as the whole body. To keep the therapeutic drug level continuous and sustained, ocular drops must be infused frequently and periodically. This administers an enormous and erratic dosage of medicine to the eye [6]. To prevent the intolerably high toxicity produced by saturated solutions of water-soluble medications, suspension types of pharmaceutical dosage forms are devised using comparatively water-insoluble substances. The rate at which the drug particles In the suspension dissolve, however, determines how quickly the drug is released from the suspension. The medium's composition changes constantly due to the ongoing influx and outflow of lachrymal fluid [7]. Because of these delivery limitations imposed by the ocular route of administration, an integrated understanding of the drug entity is necessary for the design of a drug delivery system. To achieve a continuous release suitable for topical or systemic treatment, the primary goal of the ophthalmic inserts is to lengthen the preparation's contact time with the conjunctival tissue [8].




## HISTORY OF OCULAR INSERT:

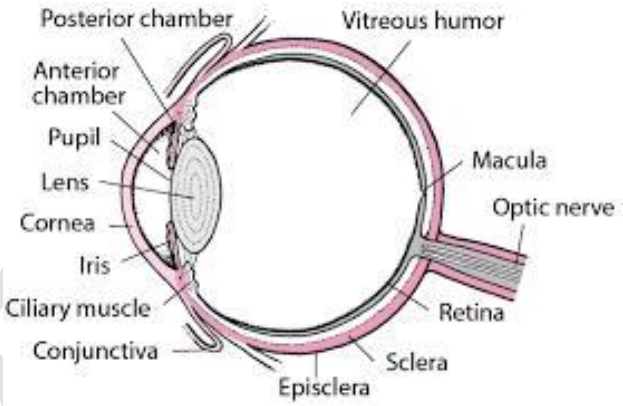
In the 19th century, dry filter paper squares were employed as the first solid medicament (the forerunners of the modern insoluble inserts). Impregnated with dry liquids, such as pilocarpine hydrochloride and atropine sulfate. Small pieces were cut and placed beneath the eyelid. Lamellae, the forerunners of the current soluble inserts, were later created. They were made of glycerinated gelatin that included several ophthalmic medications. Up to the early part of the 20th century, official compendia contained 'lamellae' of glycerinated gelatin. Lamellae were used, but their use was discontinued when stricter guidelines for the sterility of ophthalmic preparations were implemented. Ophthalmic inserts are currently seeing an increase in attention [9].

## OCULAR ANATOMY AND PHYSIOLOGY:

According to some descriptions, the eye is a sophisticated structure that is extremely resistant to outside influences, including medications. There exist several parts that resemble the human eye as a "camera". The two main portions of the eye with distinct anatomical and physiological functions are the anterior and posterior segments. Since traditional topical formulations are given mostly to the anterior area of the eye and the majority of the dose is lost as a result of the eye's defense mechanism, the application of ocular preparation also differs. To improve the therapeutic impact and reduce systemic/local effects, it is necessary to make conscientious efforts to direct the formulation and lengthen the retention duration on the ocular surface. [10]

## STRUCTURE OF EYE:

Sclera, or the white of the eye, is the outer protective layer of white. The clear, curving structure called the cornea has a low medication penetration rate. The colored iris is a component of the eye. The black area of the eye in the center of the iris is the pupil. The clear disc lenses are located behind the iris and pupil. The clear liquid that flows in front of the lenses and behind the cornea is called aqueous humor. Between the lens and the retina, the eyeball is filled with vitreous, a substance that resembles transparent jelly. Millions of nerve cells that line the back of the eyeball form the light-sensitive layer known as the retina. The choroid is a huge network of blood vessels that transport O2 and other nutrients to the retinal pigment cells. [11]




Systemic administration or intravitreal injection and implant are preferred via retina, vitreous humor, and choroid. The choroid and conjunctival tissues are susceptible to penetration enhancers, which maximize therapeutic benefits but pose a high degree of danger. Additionally, there is a constraint because the therapy requires a higher dose due to the robust blood-ocular tissue barrier. Thus, a regulated drug delivery method is required to provide both a therapeutic impact and a longer pre-corneal resistance duration. There are many diseases where it is necessary to take medication 4-5 times a day, which is a laborious process. Consequently, fabrication of such drug delivery systems that accept sustained drug release for up to 8–12 hours a day. As a result, drug use is decreased.

## MERITS OF OCULAR INSERTS: [12-13]

1. The use of an ocular insert can reduce the negative effects brought on by the pulsed dosing of traditional dosage forms.
2. Offers regulated and sustained medication delivery.
3. It lengthens the time the medicine is in contact with the cornea, enhancing the drug's ocular bioavailability.
4. Offers targeting inside the eye's globe to stop damage to other ocular structures.
6. To enhance patient comfort, patient consent, and drug remedial performance
7. Make the delivery system's housing good.
8. Longer storage life in contrast to aqueous solutions

## DEMERITS OF OCULAR INSERTS: [14-16]

1. The "solidity" of ocular inserts, or how the patient feels as though an unknown substance is in his or her eye, is a major flaw.
2. In rare cases, the insert's unintended migration to the upper fornix makes the simple removal of their movement about the eye more challenging.
3. The unintended loss that occurs now and then when sleeping or scratching one's eyes,
4. Their obstruction of vision, difficult ocular insert installation (and removal for insoluble forms), and their impact on vision.

## CLASSIFICATION OF OCULAR INSERTS:

There are three main classes of ocular inserts.

1. Insoluble eye implants
2. Dissolvable eye implants
3. Bio-erodible eye implants

**1)Insoluble Eye inserts:**

Three categories have been used to categorize the insoluble inserts:

a) Diffusion methods

b) Osmotic methods

c) Hydrophilic Disposable lens

In the first and second classes, a reservoir that supplies medicines to the rate controller's inner surface is in touch with it. The container includes a medicine carrier, liquid, gel, colloidal, semi-solid, or solid form that is disseminated or dissolved therein in a homogeneous or heterogeneous manner. Carriers can be constructed of synthetic, natural, organic, inorganic, hydrophobic, or hydrophilic materials. Disposable lenses are added in the third class. The fundamental drawback of these devices is that they are insoluble, necessitating removal after usage. [17]

a) Diffusion Methods

The drug diffuses through the central reservoir of the diffusion systems at a precisely calibrated rate recognition to selectively permeable or microporous membranes that surround it. In such a device, the lachrymal fluid pervades the membrane to control the release of the medicine by building up enough internal pressure to push the drug out of the container. Diffusion through the membrane, which is controllable, regulates the rate at which medicines are delivered. [18]

b) Osmotic methods

Osmotic inserts are often separated into two categories; the first type has a center portion that is surrounded by a periphery. A single reservoir or two separate sections can make up the first central component. The first kind consists of a medicine disseminated across a polymeric matrix with or without an extra osmotic solute so that the medicine is coated by the polymer as distinct tiny deposits. The second form uses separate sections for the drug and osmotic solutes, with the drug container being balanced by a flexible impermeable membrane and the osmotic solute container being balanced by a selectively permeable membrane. A covering film consisting of an insoluble selectively permeable polymer always makes up the peripheral portion of these osmotic inserts. Through the selectively permeable polymeric membrane, the tear fluid disperses into peripheral covering and moistens them to promote their breakdown. The hydrostatic pressure that the solubilized deposits create against the polymer matrix causes the matrix to explode. After that, the matrix releases the drug. This is in line with the osmotic portion, which is an order medicine release analyzed. [19]

c) Hydrophilic Disposable lens

These are structured structures made of a covalently bonded hydrophilic or hydrophobic polymer that creates a three-dimensional complex or system capable of holding onto water, aqueous solution, or solid units. A hydrophilic disposable lens will absorb a drug solution, but it won't administer the medication with the same level of precision as other non-soluble ophthalmic methods. Drug release from such a device often starts quickly and then decreases rapidly over time. Incorporating a homogeneous drug combination during production or adding a hydrophobic unit can both reduce the release rate. [20]

**2) Dissolve eye implants**

The soluble class of eye implants is the most traditional. The fact that they are entirely soluble is a huge advantage, eliminating the need to remove them from the application site and limiting treatments to mere implantation. [21]

Types of soluble ocular implants include:

i) Natural polymers e.g., collagen

ii) Artificial or semi-artificial polymers.

Preferably, the implant is immersed in a drug-containing solution, dehydrated off, and then absorbed before being applied to the ocular to absorb the therapeutic medium. The quantity of binding medium, the application of the drug solution the composite is immersed in, the length of time it is soaked in, and other components will all affect the quantity of drug-loaded.

The artificial/semi-artificial polymer-containing soluble ophthalmic inserts: have the added benefit of having a normally straightforward design.

a. Based on widely used products for ophthalmic usage.
b. Easily processed using standard techniques such as compression, injection molding, or slow-evaporating extrusion.

The medication is released from such a system by tearing through the insert, which causes the drug to disperse out and form a gel layer around the implant's core. This external gelification causes the drug to diffuse out even more but is still controlled by diffusion. The following expression is obtained by deriving the release rate, J, from Fick's law.

$$J=AdkCS/L$$

When

A – The membrane's surface area

K – The drug's Diffusivity

L – wideness of the membrane

CS – Drug solvability in water

d – Ocusert membrane diffusion coefficient.

The release rate of the device is constant since all the terms on the right side of the aforementioned equation are. These are some of the other elements influencing drug release from these Ocuserts.

- Penetration of the inclusion
- The matrix expanding.
- The medication and the polymers dissolve.
- The polymeric chain relaxing.

Gamma radiation can be used to sterilize the soluble insert composed of cellulose derivatives without affecting the cellulose itself. Using a matrix polymer typically used for enteric coatings or adding a suitable amount of a hydrophobic polymer capable of reducing tear fluid penetration and subsequently decreasing the release of the drug while maintaining the insert's solubility are two methods for reducing release rates. [22]

**3) Bio-erodible eye implants:**

These implants are constructed of bio-erodible polymers, such as hybrid-related gelatin derivatives and polyester derivatives, which dissolve chemical bonds through hydrolysis, and as a result, dissolution. [23-24] The key benefit of these bio-erodible polymers is the ability to control how quickly they erode by altering their final structure during compound and adding cationic or anionic surfactants. To improve dexamethasone's absorption in the rabbit ocular. The levels of dexamethasone in the liquefied humor were discovered to be four times higher than those in a dexamethasone solution. Still, erodible systems can have drastically different erosion rates depending on the physiology and lachrymation patterns of individual patients, and degradation byproducts and leftover solvents from the polymer synthesis process can result in an inflammatory response. The solid implants slowly erode or disintegrate after absorbing aqueous tear liquid. The medication is then moderately leached from the hydrophilic form. It is not necessary to remove bio-erodible eye inserts when medicine administration is finished. The marketed erodible medication insert devices are Lacriserts, SODI, Collagen Shields, and Minidisc.

a) Lacriserts

Lacriserts are rod-shaped, preservative-free tools constructed of hydroxypropyl cellulose that are helpful for dry ocular disorder. It has a length of 3.5 mm, a width of 12.7 mm, and a weight of 5 mg. When artificial tears are ineffective in treating the symptoms of keratitis, a sacrist is helpful. It is introduced into the cul-de-sac cavity, where it draws moisture from the conjunctiva and cornea to create a hydrophilic coating that balances the tear film for moisturizing and lubrication of the corneal. It dissipates in one day. [25]

b) SODI

The Soluble Ocular Drug Insert is a tiny oval wafer that was created for astronauts who couldn't use eye drops in zero gravity. It is an oval-shaped, aseptic thin film formed of acrylic amide, N-vinylpyrrolidone, and ethyl acrylate named ABE. It measures 15–16 milligrams in weight. It is applied to the management of trachoma and glaucoma. It is pushed into the lower cul-de-sac, where it soaks up water and softens within 10 to 15 seconds. The film releases medication for roughly 24 hours before transforming into an adhesive synthetic mass after 10-15 minutes and synthetic solutions after 30–60 minutes. [26]

c) Minidisc

The minidisc is made out of a curved disc with an eyeball-contact-pointed convex front and concave back. With a 4- to 5-mm diameter, it resembles a small contact lens. The minidisc is constructed from the silicone-formed pre-polymer bis 4-methacryloxyethyl polydimethylsiloxane. To allow for the increased release of both water-dissoluble and unsoluble Medicines, minidiscs can be either hydrophilic or hydrophobic. [27]

d) Collagen shield

A collagen shield is a corneal bandage designed to accelerate wound healing that is primarily made of cross-linked collagen and manufactured with fetus calf skin tissue. These devices become malleable and mushy due to the tear fluid, and they dissolve throughout 10, 24, or 72 hours. Collagen film has demonstrated promise as a transporter for the Ophthalmic drug delivery system because of its systemic balance, high biocompatibility, and biological inactivity. For the delivery of medication to the eye, collagen eye implants are available. [28]

**Non-erodible eye implants:**

The non-erodible ocular implants category includes accusers and Disposable lenses.

1. Ocusert

This sandwich was constructed with a delicate irresolvable method. In the accuser's drug container, a thin disc of the drug complex is positioned between two transparent discs of a microporous membrane constructed of an ethylene-vinyl acetate copolymer. The microporous membranes allow tear fluid to enter the drug container unit, dissolving the medication from the complex. [29,30]

2. Disposable lenses

Disposable lenses can absorb water-dissoluble drugs when submerged in pharmaceutical solutions. To gradually release the medication over time, these contact lenses with medication are placed in the eye. The use of hydrophilic disposable lenses can prolong the drug's time in the eyes. [23,31,32]

# OCULAR INSERT DRUG RELEASE MECHANISM

**DIFFUSION**:

Through the membrane, the medicine is repeatedly released at a controlled rate. When a medication is in a dispersed form and the insert is developed as a solid non erodible body containing pores the medicine is allowed to leave by diffusion through the pores. Regulated release may also be accomplished through optimal aqueous solution diffusion-induced dissolution of the drug's solid dispersed form within the matrix. True dissolution in soluble systems mostly happens as a result of polymer swelling. The active substance is uniformly disseminated in a glassy polymer in devices that control swelling. Diffusion via the dry matrix doesn't happen because glassy polymers are essentially resistant to drugs. As drugs cannot pass through glassy polymers. When the device is placed into the eye, tear fluid starts to seep into the matrix, causing swelling. This swelling causes the matrix to enlarge, which causes the polymer chains to relax and the medicine to diffuse. Following the process of swelling, the matrix dissolves. This process is dependent on the polymer's structure, such as its linear or amorphous form. In comparison to cross-linked or partly crystalline polymers, a linear amorphous polymer degrades more quickly. [33,34]

**OSMOSIS**:

The Osmosis procedure is divided into two compartments by a transverse impenetrable flexible membrane that lines the interior of the insert. The first compartment is surrounded by an elastic membrane and a semi-permeable membrane, while an impenetrable substance and a membrane with elastic enclose the second compartment. The impermeable membrane of the insert has a medication release hole. The second compartment serves as a storage container for the medicine, which is present in liquid or gel form, while the first compartment stores a solute that is unable to flow through the semi-permeable barrier. When the insert is placed inside the watery atmosphere of the optic, the elastic membrane is stretched. Water diffusion into it, enlarging the first compartment and constricting the second compartment so that the medication can escape via the drug release valve.[34]

**BIOEROSION**:

In the bioerosion process, the insert is made of a matrix of bioerodible material in which the medicine is disseminated. By causing the matrix to bioerode, exposure of the insert with tear fluid causes a controlled, prolonged release of the medication. Although the medication is evenly distributed throughout the matrix, it is thought that a better-controlled release is obtained if the medication is just applied superficially. A chemical substance or enzyme-mediated hydrolytic reaction that dissolves the polymer or splits it down into smaller, water-soluble molecules controls the drug administration in completely erodible or E-type devices. These polymers can hydrolyze in bulk or on the surface, leading to zero order release kinetics, if the devices maintain a stable surface shape and the drug is not extremely water soluble.

# EVALUATION PARAMETERS FOR OCULAR INSERT:

1. **Uniformity of Weight:**

Using an electronic balance, each developed film is individually weighed, and the amount of weight of every film is recorded. The average film weight is then determined. The mean value is used to compute the deviation from the mean.[35]

2. **Percentage moisture absorption:**

The ocular inserts are checked for weight and placed in desiccators with 100 ml of saturated aluminum chloride solution to calculate what percentage of moisture is retained in the inserts. After three days, ocular implants are reweighed. Determining the percentage of absorption of moisture is as follows:

Percentage moisture absorption = Final weight – Initial weight/ Initial weight × 100[36]

3. **Thickness**:

At various stages of the formulation, the film thickness can be determined with a dial caliper, and the mean value is calculated.[37]

**4. Swelling Index:**

A small quantity of film is first cut and measured, after which it is soaked for an hour in pH 7.4 tear fluid. The film is weighed again after an hour. [38-39]

The following formula is used to compute the swelling index.

Swelling index = initial weight/ final weight *100

## 5. Drug content uniformity:

Each insert was put in a vial made of glass holding 10 ml of synthetic tear fluid to test the homogeneity of the medication therein. The insert was broken down with the help of a magnetic stirrer, the mixture was filtered, 1 ml of the filtrate was taken out, diluted with up to 10 ml of distilled water, and the absorbance was assessed using a UV-visible spectrophotometer.[40]

**6. Surface pH:**

Insert is submerged in distilled water for 30 minutes on a closed Petri plate. After that, the insert began to enlarge. After that, a swollen insert is put into an electronic pH meter to calculate the surface pH [38-39]

**7. Folding endurance:**

The process of folding a film involves starting from one side and folding it repeatedly until it is torn. The quantity of folds a film experiences determines how long it can be folded before breaking. All of the film's folding resistance is evaluated. [39,41]

**8. In vitro diffusion studies**

Utilizing a Franz diffusion cell, an in vitro diffusion investigation of accusers is conducted. It is a tool used to investigate the drug's permeability. It has two compartments: a compartment for donors where dosage form, such as user, is added, and a receptor section where 7.4 tear fluid is injected to mimic the tear fluid in an eye. A partially permeable membrane for dialysis or an egg membrane may be used to divide the two compartments. RPM and temperature are set when the instrument is turned on. Ocusert is put in the donor compartment, while the receptor compartment is filled with tear fluid. After a predetermined amount of time, a 1 ml sample is taken, diluted appropriately, and then analyzed in a UV spectrophotometer. The sample is removed once a steady absorbance has not been attained. Drug release is estimated. [41-42]

## CONCLUSION:

An important development in the treatment of eye diseases is the ocular implant. Ocular implants are described as solid or semisolid, sterile, multi-layered, thin, medicine-impregnated, devices put into the conjunctiva sac or cul-de-sac, whose size and shape are specifically suited for ocular application. They contain a polymeric support that might or might not include a medication. Advantages of using concerts include exact dosing ability to give at a steady rate and delay drug release, enhancing efficacy. Enhancing the duration of contact will enhance bioavailability. Possibly less systemic absorption, which would mean fewer negative systemic effects. Decreased administration frequency, leads to better patient compliance and a decreased risk of side effects on the eyes. Administration of a precise in the eye, leading to better treatment of internal eye tissues may be targeted by non-corneal conjunctival–scleral perforation routes and the absence of water expands the shelf life of eye drops. Using inserts as a dosage form has benefits simplicity in handling and insertion absence of expulsion when wearing Release kinetics reproducibility relevance to a multitude of medicines O2 permeability, sterility, stability, and facility of production, as well as no interference with vision.

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