Ocuserts: A novel ocular-drug delivery method: An update

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Abstract

Ocuserts are sterile ocular preparations that may follow a controlled release technique to extend medication residence duration and reduce nasolacrimal discharge. The goal of the ocuserts is to improve medication contact with conjunctiva tissue to sustain consistent dosage release. Uniform ocular medication levels decrease systemic side effects, minimizes dose, boosting patient compliance. Ocuserts are prepared by solvent casting, glass substrate, and melt extrusion technique. Modified ocuserts may be used to obtain desired medication concentration for a given time at the site of action. Extended corneal contact duration is the major success in ocular medication delivery. Non-conventional approaches like liposome, microsphere, prodrug, etc. may improve ocular drug delivery systems and reduce side effects. Diffusion, osmosis, or bioerosion are the various methods that govern drug release from ocusert.

Keywords: Ocuserts; Eye; Ophthalmic preparation; Conjunctiva; Corneal contact

1. Introduction

The eye poses unique challenges in drug delivery. Ophthalmic medication distribution is the most fascinating and difficult task[1]. Eye is impervious to numerous foreign materials because to its anatomy, physiology, and biochemistry. The key problem for pharmaceutical experts is to penetrate ocular defences without substantial tissue damage[2]. Ophthalmic preparation is employed for local therapy rather than systemic treatment owing to the high concentration of medications in the eye's blood[3]. Formulating novel and enhanced ocular medication delivery systems is important for developing breakthrough diagnostic and treatment procedures[4, 5]. Ocular disease treatment is tough for scientists owing to the kind of disease and obstacles on the ocular surface, notably in the posterior area. In recent years, researchers have tried to improve ocular medication absorption by varying viscosity and adding polymers[6]. Due to limited ocular bioavailability and frequent eye drop instillation, medication persistence is crucial. A large and inconsistent dose of medicine is given, creating local and systemic adverse effects. For current ocular medication delivery methods to be improved, dosage formulations with an extended time period and controlled administration are required[7].

2. Human eye

Human eye is a composite organ that exhibits anatomical wonders. Drug delivery to the eye is tricky owing to tissue structure and corneal penetrability. The administered drug gets rapidly removed from the eye due to the defensive function of the eyelids and lacrimal system[8]. To avoid this, the material should be tiny and compatible with the skin.
The eye is a sphere with a spherical component within another encircled within the little front sphere. Various ocular barriers must be overcome to get a therapeutic medication concentration in the eye through local or systemic pathways. The blood ocular barrier (BOB) controls the influx and outflow of aqueous humour, regulating its composition and eye pressure. Physiological and anatomical barriers hinder ophthalmic drug administration.

- Physiological barriers, which include:
  - Tear turn over
  - Naso lachrymal drainage
  - Blinking action of the eye
- Anatomical barriers, which include static and dynamic barriers, are responsible for restricting drugs into the anterior portion of the eye. Static barriers include:
  - Corneal epithelium
  - Stroma
  - Blood aqueous barrier (BAB)
- Dynamic barriers include:
  - Conjunctival blood
  - Lymph flow
  - Tear drainage

2.1. Absorption of drugs in the eye

Most ocular drugs are topically applied to the fornix. Corneal and non-corneal are the two pathways to absorb medications from cul-de-sac. Most medication absorption occurs via the cornea and aqueous fluid. Non-corneal absorption includes the sclera and conjunctiva, however this pathway limits medication entry into intraocular tissues. Drugs enter the cornea through transcellular and paracellular pathways. Paracellular transit is a pathway for lipophobic drugs across intercellular gaps. The transcellular route includes a channel for lipophilic drugs. Passive diffusion along the concentration gradient permeates both pathways.

2.2. Ophthalmic preparations

Ophthalmic preparations are sterile liquid, semi-solid, or solid treatments for the conjunctiva or eyelids. Ophthalmic medications cure corneal ulcers, conjunctivitis, bacterial keratitis, and other eye diseases. Eyedrops, suspensions, ointments, etc. are common ocular medication delivery systems. These standard dose forms are extensively used but have drawbacks include shorter duration of action, lower corneal contact time, poor absorption, frequent dosing, and patient noncompliance. Ophthalmic medication therapy like gels, gelforming solutions, ocuserts, intravitreal injections, and implants are controlled dosage forms.

Easy-to-administer eye drops are most often given. The primary disadvantage is the rapid and widespread removal of the medication from the eye, requiring more frequent administration. Very little medication penetrates the cornea and reaches ocular tissue.

Modern medication delivery technologies like ocuserts manage drug release to alleviate these drawbacks with better corneal penetration and improved drug contact time. Reservoir-based systems consist of micro-structured and have several benefits. These technologies may be utilized outside or within the body to manage dosage form. It improve dosage form stability and distribution time. It can aid with zero-order medication delivery vs sustained-release. Progress in reservoir medication delivery assisted pinpoint delivery.

3. Ocuserts

Ocuserts are sterile controlled-release formulations that extend medication residence duration and prevent nasolacrimal leakage. They are sterile, solid or semisolid formulations designed for ocular delivery. They're drug-filled polymers. Ocuserts are put in the eye's lower cul-de-sac. Ocuserts enhance medication contact time with conjunctival tissue to sustain continuous dosage release. Ocusert is a drug reservoir sandwiched between two microporous membrane sheets. Lachrymal fluid penetrates the membrane, controlling medication release. Internal pressure is high enough to force medication from the reservoir. Diffusion controls medication delivery rate.
Ocuserts extend medication duration, improve bioavailability, and decrease dosage frequency, improving patient compliance. The regulated release of the medication allows for ocular administration. Ocuserts save time for doctors and patients.\[26\]

### 3.1. Advantages of ocuserts

Various advantages of ocuserts are as follows -

- Increased contact time with the ocular surface can be obtained and hence bioavailability is also increased
- Sustained and controlled drug delivery can be achieved
- Due to extended drug release, better efficacy is obtained
- Accurate dosing can be done
- Less systemic side effects
- Less frequent dosing is required unlike conventional dosage form
- Overcoming the effects of repeated administration of a conventional dosage form is possible
- Increased comfort and patient compliance
- Handling is easy
- Vision and oxygen permeability are not interfered
- Reproducible release kinetics
- Sterile preparation
- A stable drug delivery system and better therapeutic performance of the formulation can be obtained
- Due to the lack of water in the formulation, shelf life is improved when compared to aqueous solutions.
- Barriers like drainage, lacrimation, conjunctival absorption, etc. can be avoided.\[3, 27\]

### 3.2. Disadvantages of ocuserts

Various disadvantages of ocuserts are as follows -

- Accidental loss of ocusert can occur while sleeping or rubbing the eyes
- For a while, the patient feels like there is some foreign body in their eye
- Removal of ocusert can get difficult due to unnecessary relocation of the ocusert to the upper fornix of the eye
- Not as easy to administer the ocuserts in the eye and also difficult removal in case of insoluble ocuserts
- Dislocation of the ocusert in front of the pupil can occur
- Ocusert can twist in the eye which can decrease the rate of drug delivery
- Leakage can happen\[4, 28, 29\]

### 3.3. Classification of ocuserts

According to the solubility, ocuserts can be classified into different types. \[6\]

![Figure 1 Classification of ocuserts](image)
3.3.1. Insoluble ocluserts

This type of delivery system gives drugs at a controlled rate and in different ways, but the delivery system needs to be removed once it's empty.

Insoluble ocluserts are divided into 2 categories:

Reservoir system

In this system, diffusion or osmosis release drugs. It may be colloid, gel, semisolid, liquid, solid matrix, or carrier.

Diffusional inserts - In this form, drug release is diffusional. The ocular insert is a permeable membrane medication delivery method.

Osmotic inserts - These consist of a centre component surrounded by a part and may be classed into two groups:

- Type 1 - The innermost section is a drug reservoir surrounded by polymer, which may contain osmotic solute. Semi-permeable, insoluble polymeric membrane forms the periphery. Due to osmotic pressure, matrix apertures leak drugs.
- Type 2 – This kind has a two-compartment centre. One compartment contains medicine, the other osmotic solute. A semipermeable membrane surrounds the solute compartment. The medication compartment is impermeable.

Matrix systems

This system includes contacts and insoluble ophthalmic equipment. A 3-D matrix holds water, aqueous preparations, or solids. This system contains hydrophilic or hydrophobic cross-linked polymers e.g. vision correction contact lenses. This mechanism corrects eyesight while releasing medicines.\(^3\)

3.3.2. Soluble ocluserts

Soluble inserts are homogenous polymeric ocluserts that gradually dissolve and release the medicine in the eye. Hydrolysis of enzymes or chemicals causes dissolution and erosion. Owing to tear fluid penetration, oclusert's drug content is released due to swelling and chain relaxation, resulting in drug diffusion. It's not necessary to remove it after administration.\(^4, 30\)

According to the type of polymer source, they can be further divided into two groups:

Natural polymers

Collagen is utilised to manufacture soluble ophthalmic inserts. Ocusert is soaked, dried, then rehydrated before application. The amount of medicine in oclusert depends on the preparation's concentration, soaking time, and binding agent concentration. The medication is released when the collagen dissolves.\(^6\)

Synthetic and semi-synthetic polymers

Ophthalmic inserts are made from synthetic and semisynthetic materials. Cellulose derivatives and synthetic polymers like polyvinyl alcohol may be used to make it. Coating the oclusert with eudragit might slow release.\(^6\)

3.3.3. Bio-erodible ocluserts

Bio-erodible ocluserts employ cross-linked gelatin and polyester derivatives. These polymers’ key benefit is that their final structure may be changed during manufacture or by adding anionic or cationic surfactants to limit erosion.\(^30\) They include:

Soluble ophthalmic drug insert (SODI)

SODI is a small oval wafer, which is made to use in weightless conditions as eye drops cannot be used in these conditions.\(^31\)
Collagen shields

Collagen is found bone, tendons, ligaments, and skin. It makes about 25% of mammalian body proteins. This intestine collagen protein has several biological uses, including catgut suturing. This insertion must be applied with anaesthetized cornea and blunt forceps.\(^{[32]}\)

### 4. Mechanism of drug release

Drug from the ocuserts can be released by one of the following methods depending upon the type of ocusert:

- Diffusion\(^{[33]}\)
- Osmosis\(^{[34]}\)
- Bioerosion\(^{[33]}\)

### 5. Formulation methods of ocuserts

#### 5.1. Solvent casting method

Due of its cost-effectiveness and simplicity, solvent casting is utilised to make ocuserts. In this procedure, rheological properties of polymer are examined since they impact ocusert thickness, drying rate, homogeneity, etc. De-aeration is needed because polymer mixing might create air bubbles. Polymers are casted onto the correct substrate after adequate mixing. After the mixture dries, the solvent evaporates, leaving the ocusert film. Then, ocusert films are trimmed to size.\(^{[35]}\)

#### 5.2. Glass substrate technique

Glass substrate technology is utilised to produce thin films. A transparent polymer solution is utilised to form a drug reservoir film. The polymer solution is vortexed to mix in the medication. Drug dissolution is followed by plasticizer addition. To make films, solution is added to a glass mould and dried. Drying at room temperature takes 24 hours. Dried films are then trimmed to size and then stored.\(^{[34]}\)

#### 5.3. Melt extrusion technique

Melt extrusion is an alternative for solvent casting. It’s utilised for non-organic solvents. In this process, polymers and other components are melted and then passed through a die to prepare films. The films are then trimmed. This approach isn’t for thermolabile substances.\(^{[35]}\)

### 6. Evaluation parameters for ocuserts

#### 6.1. Organoleptic characteristics

Ocuserts are evaluated for the organoleptic characterization i.e. color, appearance, texture, and odor.

#### 6.2. Uniformity of thickness

The ocusert’s uniform thickness facilitates the even dispersion of components. A micrometre screw gauge is utilised to determine uniform thickness.\(^{[35][36]}\)

#### 6.3. Uniformity of weight

The ocusert’s weight homogeneity shows how constant its constituents are. Three ocuserts are weighed from each batch. Mean weights are recorded.\(^{[37]}\)

#### 6.4. Drug content

Drug content measures active substances in each formulation. Ocusert is dissolved in 10 ml STF. UV visible spectrophotometer is used to estimate absorbance value after proper dilutions.\(^{[37]}\)
6.5. Swelling index
Swelling index measures a formulation's swelling or water-absorption characteristics. Ocusert is weighed and added to 4 ml of STF. After 5 minutes, the ocusert is removed and excess simulated tear fluid is weighed.\[30\] The % swelling index can be calculated by the formula given below –

\[
\% \text{Swelling index} = \frac{\text{Weight of swollen ocusert after time } t - \text{ initial weight of ocusert}}{\text{initial weight of ocusert}} \times 100
\]

6.6. % Moisture absorption
Moisture absorption test measures ocusert's physical stability in wet environments. After weighing each batch, 3 ocuserts are inserted in aluminium chloride desiccators. After 3 days, the ocuserts are weighed again.\[39\] The % moisture absorption is determined by the formula given below -

\[
\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

6.7. Folding endurance
This test measures the ocusert's folding resistance. For this, the film is folded repeatedly until it breaks. Folding endurance is the number of times a film can be folded without breaking.\[40\]

6.8. Surface pH
Ocusert is allowed to swell at room temperature for 30 minutes in 1ml of distilled water in a closed petri plate. A digital pH metre measures the surface pH.\[39\]

6.9. In-vitro drug release study
Diffusion cell method was utilised to conduct this study. An open cylinder used as a donor compartment is lined with pre-hydrated cellophane membrane. Simulated tear fluid touches the membrane's ocusert. Using a magnetic stirrer, the simulated tear fluid is mixed and kept at 37 ± 0.5 °C. After certain times, 1 ml of receptor compartment is spectrophotometrically analysed. For each sample, artificial tear fluid is added.\[41\]

6.10. Ex-vivo permeation studies
This study utilizes diffusion cells. Goat cornea is taken from the eye and put on a diffusion cell so the corneum side remains in touch with the donor ocusert. A magnetic stirrer is used to mix artificial tear fluid at 37 ± 0.5 °C. 1 ml of receptor compartment is spectrophotometrically analysed after particular times. Each sample is replaced with artificial tear fluid\[42\].

6.11. Sterility test
This test uses Indian Pharmacopoeia. 2 ml of ocusert solution is aseptically transferred to fluid thioglycolate and soyabean-casein digest media. During 14 days, fluid thioglycolate media must be kept at 30 °C to 35 °C, and soyabean-casein digest medium at 20 °C to 25 °C.\[43\]

6.12. Stability study
Stability study is done following ICH guidelines. Increasing a product's temperature speeds up its breakdown, determining its shelf life, variation in medication concentration, colour, folding endurance, etc. may be tracked during stability experiments\[44\].

7. Conclusion
Ocuserts are sterile ophthalmic preparations that may follow a controlled release strategy to lengthen the drug's residence time and minimise nasolacrimal discharge. This is performed by regulating medication release into the eye. These are available in a number of forms, each characterised by the application to which it is put. The ocuserts extend the duration of drug contact with the conjunctiva to keep the dose constant. Because of the stable drug level in the eye, it has fewer detrimental effects on the body. It reduces dosage frequency, which increases patient compliance. Ocuserts are manufactured via solvent casting, the glass substrate method, or melt extrusion. After being put through their paces, optimised ocuserts may be used to achieve an effective medicine concentration at the suitable rate for a given duration.
This technique of delivering medicine maintains therapeutically-relevant drug concentrations at the target site of action for a particular duration. The most crucial step in success of ocular medicine delivery has been enhancing corneal contact duration. Therefore, it makes sense to examine non-conventional techniques such as liposomes, microspheres, prodrugs, and the like for efficient release, as well as to enhance ocular drug delivery systems and lessen after effects.

**Compliance with ethical standards**

*Disclosure of conflict of interest*

No conflict of interest.

**References**


