WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review Article of Ocuserts

Prothibha Das, Dr. L.V. Vigneshwaran, Fathimai Thaisena

Department of Pharmaceutics, Malik Deenar College of Pharmacy, Seethangoli, Kasaragod, Kerala, India

ABSTRACT

The term "ocular inserts" refers to sterile, thin, multilayered, solid or semisolid consistency devices that are specifically sized and shaped for use in ophthalmic applications and are inserted into the cul-de-sac or conjunctival sac. The medication is released at a preset pace constant by inserting the ocusert into either the upper or lower cul-de-sac of the eye. Therefore, it is seen that there is an improvement in bioavailability due to prolonged drug eye contact time, a decrease in local side effects or toxicity, better therapeutic outcomes due to less over- or under-dosing, and greater patient compliance due to reduced dose frequency.

KEY WORDS: OCUSERTS

INTRODUCTION TO OCUSERTS

The Ocusert system was initially created in the United States of America in 1975 by Alza Corporation. A major development in the treatment of eye diseases is the use of ocular implants. The term "ocular inserts" refers to sterile, thin, multilayered, solid or semisolid consistency devices that are specifically sized and shaped for use in ophthalmic applications and are inserted into the cul-de-sac or conjunctival sac. They consist of a polymeric support that might or might not include a medication. Afterwards, the medication may be added to the polymeric support as a solution or dispersion. The continuous administration of an ophthalmically active medicine to the eye is the main goal of the ocusert development process. When the ocusert is placed in the eye's upper or lower cul-de-sac, this has a set rate constant for the drug's release. Therefore, it is seen that there is an improvement in bioavailability due to prolonged drug eye contact time, a decrease in local side effects or toxicity, better therapeutic outcomes due to less over- or under-dosing, and greater patient compliance due to reduced dose frequency.

From the perspective of drug delivery, studying the eye is particularly challenging. The eye's physiology, anatomy, and biochemistry make it immune to outside substances, so it presents a challenge for a formulator to get past the eye's defense mechanisms without permanently damaging any tissue. Drug-delivering ocular inserts that rely on the diffusion mechanism have been created. An ophthalmic medication is delivered in this solid dose form at a very consistent rate., minimizing side effect by avoiding absorption peaks.

Increasing the duration of an eye drug's interaction with the corneal surface can enhance its therapeutic efficacy. In order to prolong the length of drug-eye contact, preparations are made more viscous or the medicine is produced as an ointment that is insoluble in water. Unfortunately, these dose forms do not produce consistent drug bioavailability and only provide a somewhat maintained drug-eye contact compared to eye drop solutions. Throughout the course of the therapy, repeated medication is still necessary. The conventional ocular dosage forms for the delivery of drugs are:

- Eye drops (solution, suspension)
- Ophthalmic Ointments

The eye drop dosage form is simple to use, but it has an intrinsic disadvantage in that only 1–10% of the entire dose is bioavailable because the majority of the instilled volume is removed from the precorneal area. Conjunctival absorption, quick solution drainage caused by gravity, induced lachrymation, blinking reflex, limited corneal permeability, and regular tear turnover are the main causes of this. High dosages of certain eye medications are used to combat this. There are systemic and ocular side effects from this.

Components of ocuserts

Generally, all types of ocusert consist of three components namely:

1. “A central drug reservoir” in which the drug is incorporated in a polymer.
2. “Rate controlling membrane”,which ensures the controlled release of a medicament from the drug reservoir.
3. “An outer annular ring”, meant for easy handling and proper insertion.

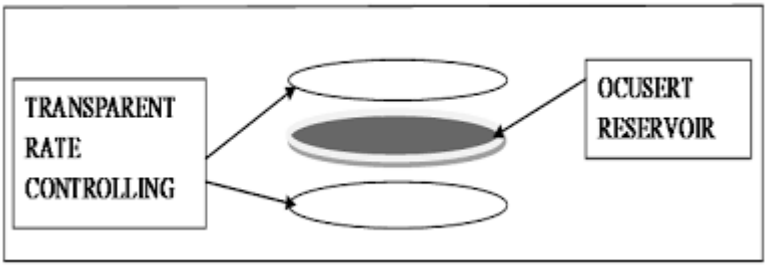


Fig-1: Schematic diagram of ocular insert

Fig-2: Picture of ocusert placed in lower cul de sac of the eye

ADVANTAGES

- Increased ocular contact time and thus improved drug bioavailability.
- Administration of an accurate dose in the eye gives better therapy.
- Better patient compliance by reduction of the number of administered dose.
- Better efficacy by providing a constant drug release.
- Increased shelf life with respect to standard formulation due to the absence of water.
- Reduced systemic absorption and thus lesser adverse effects.

DISADVANTAGES

- Initially discomfort due to their movement around the eye.
- Occasional accidental loss during sleep or while rubbing the eye.
- Difficult placement and intervention with vision.

1) **PREFORMULATION STUDIES**

A study on various physico-chemical properties of procured drug was done along with

chemical authentication by physical appearance, melting point determination, solubility study, FTIR spectroscopy and determination of λmax.

A) **IDENTIFICATION AND CHARACTERIZATION METHODS**

➢ **Determination of organoleptic properties**

The physical appearance of drug was observed and compared with the pharmacopoeial specifications.

➢ **Determination of melting point**

By filling three different capillaries with the drug sample, the melting point equipment was used to estimate the drug sample's melting point using the capillary tube method. For the most accurate findings, the samples were heated gradually and were constantly monitored. The melting range, which starts when the sample starts to melt and stops when it melts entirely, was noted.

➢ **FT- IR spectroscopy**

The drug, HPMC E50LV, polaxomer 407, and carbopol 940 standard functional group frequencies were compared with the resulting drug and polymer sample's FT-IR spectra.

- **Solubility Study**

The drug's solubility was examined in a range of solvents, including ethanol, methylene chloride, ether, and distilled water. The drug's solubility study takes into account the common ion action, temperature effect, and solubilization.

- **Determination of λmax**

Procedure:

1. To set the instrument reference level, set the spectrophotometer's wavelength to 200 nm and use a cuvette filled with pure water.

2. Insert the prepared dilution-containing cuvette into the sample chamber. Note the absorption.

3.Repeat steps 2 with 200 nm to 400 nm wavelength increments, recording absorbance at each wavelength setting.

4. Plot the absorbance vs wavelength to get the findings.

5. Take note of the wavelength at which this solution absorbs light the most from the graph.

B) **DRUG-EXCIPIENT COMPATIBILITY STUDIES**

For four weeks, the medication and excipient mixture was stored at 50°C. The mixture was distinguished by UV spectrophotometric, FTIR, and DSC techniques. In a 10 ml glass vial, the medicines and polymers were weighed individually according to their formulation ratio and combined for two minutes using a vortex mixer. Next, 10% of the water was added to each vial, and the drug-excipient mixture was thoroughly mixed. Vials were kept at 50°C for four weeks after being sealed with a screw cover protected with Teflon. Periodically, the samples were checked for any odd color changes.

- **Characterization by UV spectrophotometer**

The use of UV spectrophotometric test technology has grown significantly in the validation of pharmaceutical formulations and medications for the purpose of quality control. After four weeks, the samples were removed from storage and subjected to UV spectrophotometer analysis. Both the original and preserved samples' drug contents were measured. Using a UV spectrophotometer set to 285.5 nm for gatifloxacin and 247.5 nm for prednisolone against blank, the appropriate dilutions were prepared and examined.

- **FTIR measurement**

FTIR spectroscopy was used to evaluate the compatibility of drugs with each other and with excipients. The sample film was prepared using the Nujol mulling procedure, and finely powdered, dried samples were examined in the 4000–400 cm–1 frequency range. Using a hydraulic press to apply pressure of 1000 kN/m2, a homogenous, clear film was created by combining dried and finely powdered KBr (1%) with ground drug and excipients. The reference spectra and the resultant spectrums were compared.

- **DSC analysis**

The pharmaceutical industry frequently uses DSC, a very sensitive technology, to ascertain the temperature transitions of excipients and APIs. The DSC curve of heat flux versus temperature or versus time at a rate of 50°C min-1 from 50 to 200°C temperature range under nitrogen flow of 25 ml min-1 was used to determine the melting temperature of the drugs-excipient compatibility study on the stored mixture (kept at 50°C for 4weeks).

C. CRITERIA FOR EXCIPIENT SELECTION

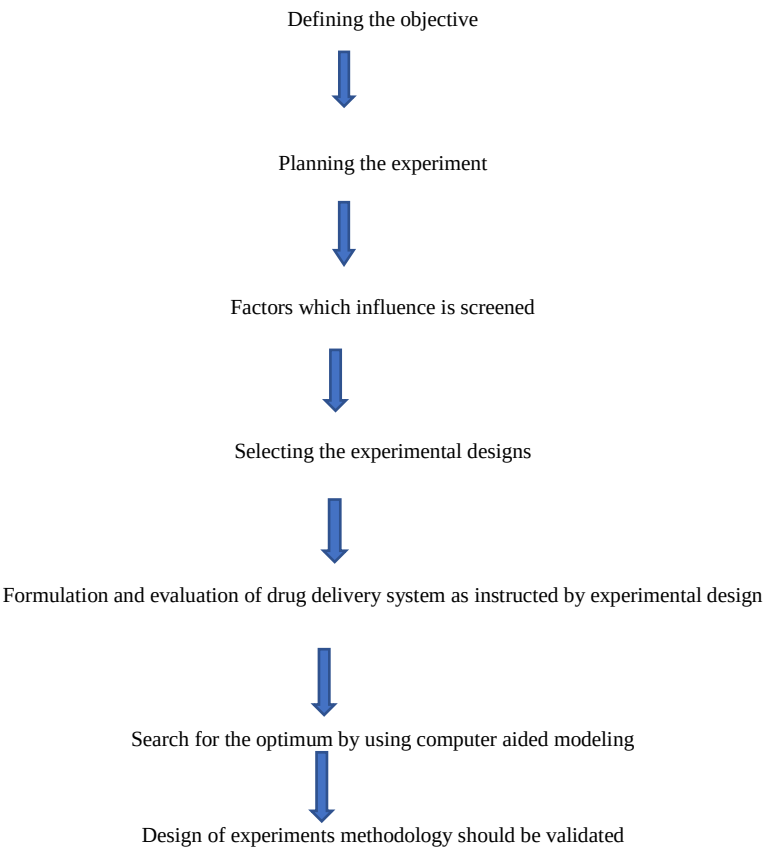
The goal of formulating a medication is to make it as stable, safe, effective, and convenient as possible. The quality of the drug product may be impacted, as well as the safety and efficacy of the medication, if the dose form is chosen incorrectly and the prescription and process designs are unrealistic. As such, formulation research plays a critical role in the creation of new drugs. Excipients, which are a crucial component of pharmaceutical preparations, are the general word for all other ingredients in a preparation other than the primary medication.

Physical and chemical properties and dosage of excipients

The quality of the preparation will be influenced by the physical and chemical characteristics of the excipients, which include the molecular weight and distribution, degree of substitution, viscosity, properties, particle size and changes in distribution, fluidity, moisture content, pH value, etc. of an active pharmaceutical ingredient.

D. FORMULATION OPTIMIZATION TECHNIQUES

Optimization is the process of choosing the best component from the options available in any resource while taking into account every aspect of the experiment. Systematic planning and conducting investigations that alter the experimental variables to determine their impact on a certain response constitute equipment design. During the research, optimization techniques are employed to explore numerous difficulties that arise in design. We must design the experimental procedure such that pertinent data is gathered because if the production's experiments are conducted at random, the results will also be random. The pharmaceutical business uses optimization approaches to build drug delivery systems that are appropriate for their needs. These techniques include,



FORMULATION OF OCUSERTS

Formulation of rate controlling membrane

INGREDIENTS	EXAMPLES
Polymer	HPMC, EC
Plasticizer	Dibutyl phthalate
Solvent	Ethanol

Formulation of ocusert reservoir

INGREDIENTS	EXAMPLES
Polymer	Na CMC
Plasticizer	PEG-400
Solvent	Water+ethanol

Formulation methods of ocuserts

- **Solvent casting method**

Solvent casting is used in the production of ocuserts since it is a simple and affordable process. This process focuses at the rheological characteristics of the polymer since it affects factors like homogeneity, drying rate, and ocusert thickness. Air bubbles could be produced during polymer mixing, hence de-aeration is necessary. After sufficiently mixing, polymers are casted onto the appropriate substrate. The solvent evaporates from the mixture as it dries, leaving behind the occusert layer. After that, ocusert films are cut into sizes that fit.

◆ **Glass substrate technique**

The technique of glass substrate is used to create thin films. A film that serves as a drug reservoir is created using a transparent polymer solution. The drug is mixed into the polymer solution by vortexing it. After the drug dissolves, plasticizer is added. A glass mold is filled with solution, which is then dried to create films. It takes a whole day for room temperature drying. After drying, the films are trimmed to size and stored.

◆ **Melt extrusion technique**

An alternative to solvent casting is melt extrusion. It is applied to solvents that are not organic. In order to create films, polymers and other ingredients are melted and then run through a die. After then, the films are edited. This method is not appropriate for thermolabile materials.

EVALUATION OF OCUSERTS

a) Physical Characterization

The ocuserts' physical characteristics, including shape, color, texture, and appearance, were evaluated.

b) Thickness of Film

A vernier caliper was used to assess the thickness of the films. The mean thickness was computed by averaging five readings taken at various locations on the film. The thickness standard deviations (SDs) were calculated using the mean value.

c) Uniformity in Drug Content

To ensure homogeneous drug content, the ocuserts were immersed in 5 ml of pH 7.4 phosphate buffer saline and shaken at 50 rpm in an orbital shaker incubator to extract the drug. Following a 24-hour incubation period, the mixture was filtered using a 0.45 μm filter, and the resulting filtrate was appropriately diluted using buffer solution. At 254 nm, the absorbance of the resultant solution was measured.

d) Uniformity of Weight

Three patches from each formulation were weighed as part of the weight variation test, which was conducted using an electronic balance. After calculating the mean value, the weight variation standard deviations were obtained.

e) Folding Endurance

A little ocusert strip was cut uniformly, then folded in half at the same spot until it broke. The folding durability of the ocusert was determined by how many times it could be folded in the same direction without breaking.

f) Percentage Moisture Absorption

The purpose of the % moisture absorption test was to evaluate the ocular films' physical stability and integrity. Ocular films were weighed and put in a desiccator with 100 milliliters of an aluminum chloride saturated solution, with a humidity level of 79.5%. The ocular films were removed and reweighed after three days. The following formula was used to determine the percentage of moisture absorption:

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

g) Percentage Moisture Loss

The film's integrity was examined at dry conditions using the percentage moisture loss. Weighed ocular films were stored in a desiccator with anhydrous calcium chloride. The ocuserts were removed and reweighed after three days, and the following formula was used to determine the percentage moisture loss:

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

h) In Vitro Drug Release Studies

The ocuserts were removed and put into 15 ml vials with 10 ml of phosphate buffered saline at pH 7.4. The vials were submerged in a water bath that oscillated at a temperature of 32 ± 1°C and 25 oscillations per minute. At different intervals of 1, 2, 4, 8, 12, 16, and 20 hours, 1 milliliter of the drug-releasing medium was removed and replaced with the same volume of phosphate buffer saline pH 7.4. The 0.45 μm membrane filter was used to filter these samples. The buffer was used to appropriately dilute the filtrate. Each batch's drug content was determined using a twin beam UV-visible spectrophotometer. Mathematical kinetic modeling was applied to the acquired data.

i) **In Vivo Drug Release Study**

Prior to the in vivo investigation, the ocuserts were sterilized using UV light. For one hour, the ocusert and additional components were subjected to UV radiation. Using forceps inside the sterilization chamber, ocuserts were moved from the sterilization chamber into a plastic bag. Following an appropriate dilution with pH 7.4 phosphate buffer, the efficacy of the pure medication that was sterilized along with the ocuserts was assessed using a UV spectrophotometer.For the experiment, albino rabbits of either sex (New Zealand strain) weighing 2.5–3.0 kg were utilized. For a single day, the animals were kept in separate cages with laboratory settings (free access to food and water).

The drug-containing occuserts were removed for the in vivo investigation; they were inserted into the lower conjunctival cul-de-sac after being previously sterilized on the day of the experiment. Each of the seven rabbits received an ocusert, while the other seven rabbits' eyes functioned as a control at the same moment.

After carefully removing the occuserts at 1, 2, 4, 8, 12, 16, and 20 hours, the drug content was determined using the dilution method described in the drug content uniformity. To determine the amount of drug released in the rabbit eye, the leftover drug was deducted from the initial drug content of the ocuserts. Throughout the experiment, records of any falls out of the ocuserts were also kept. Following a week of washing, the experiment was repeated for two times as before.

j) Ocular Irritation

Observing any redness, inflammation, or increased tear production in the test subjects' eyes allowed to assess the possible ocular irritation and/or harmful consequences of the ocusert. Five rabbits were used to test the formulation by inserting the inserts into the left eye's cul-de-sac. Before receiving treatment, the test rabbits' two eyes were checked for any indications of discomfort, and they were monitored for up to twelve hours.

j) Test for sterility

It is carried out to find out if the preparation contains any living microorganisms. Cross-contamination should not exist, and the working conditions should be routinely checked by collecting samples of the air and the surface of the workspace. The test's foundation is the idea that microorganisms would grow in nutritional media given to them and maintained at a temperature that is advantageous to them; the turbidity of the medium indicates the existence of the microorganisms.

STABILITY STUDIES

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture.

STABILITY TESTING METHODS

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development. Depending upon the aim, steps followed, the stability testing procedures have been categorized into four types and they are:

1. Real-time stability testing

2. Accelerated stability testing

3. Retained sample stability testing

4. Cyclic temperature stress testing.

Real-time stability testing

Real-time stability testing is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product which clearly tells that the product is not degraded or decomposed for a long time.

Accelerated stability testing

This type of stability testing is done at higher temperatures and that decomposition the product is determined. The information is used to predict the shelf life or used to compare the relative stability of alternative formulations. The accelerated stability studies are easily predicted by the Arrhenius equation,

$K=Ae^{-Ea/RT}$

Where, K= Specific rate constant

A= Frequency factor or Arrhenius factor

Ea= Energy of activation

R= Real gas constant 4.184 j/mol. k

T= Absolute temperature

In this method the drugs are stored at different temperatures such as 40°C, 60°C, 70°C, 80°C, 100°C etc.

Retained sample stability testing

These studies are to be done at room temperature and at refrigerator temperatures. In this type of testing, the stability is done by selecting one batch for a year. If the number of samples exceeds more than 50 then they are divided into two batches. The samples stability studies help to predict the shelf life. The maximum shelf life of every product predicted could be 5 years which is conventional to the test samples at 3, 6. 9, 12, 18, 24, 36, 48 and 60 months. This method of testing is also known as constant interval method.

Cyclic temperature stress testing

This method is not so much used to the sampling of the products. In this method, cyclic temperature stress tests are designed knowledge of the product so as to mimic likely conditions in the market place storage. In this testing the sampling is considered to be conducted by a cycle of 24 hours which is known as the rhythm of the earth is 24 hours.

PACKAGING AND LABELLING OF OCUSERTS

PACKAGE

- Ophthalmic inserts 5 mg supplied in packages of 60 sterile unit dosage forms.
- Each wrapped in a aluminium blister.
- With two reusable applicators.
- A plastic storage container to store the applicator for use.

Fig-5: Packaging of ocuserts

LABEL

Labeling of ocuserts is crucial for proper identification, usage, and regulatory compliance. It typically includes:

1. Product Information: Name of the ocusert, active ingredients, strength, dosage, and formulation.
2. Manufacturer Information: Name, address, and contact details of the company producing the ocusert.
3. Batch or Lot Number: Unique identification for traceability and quality control.
4. Expiration Date: Indicates the end of the product's shelf life.
5. Usage Instructions: How to apply the ocusert, frequency, and any specific instructions for use.
6. Storage Conditions: Recommendations for proper storage to maintain efficacy.
7. Warnings/Precautions: Important safety information or potential side effects.

Adherence to regulatory standards and guidelines is essential in the labeling process to ensure accurate information for users and compliance with laws governing pharmaceutical products.

CONCLUSION

A detailed study was conducted on ocuserts. Ocuserts are defined as sterile, thin, multilayered, drug-impregnated, solid or semisolid consistency devices placed into the cul-de-sac or conjuctival sac, whose size and shape are specially designed for ophthalmic application. In this study, we describe about GMP and GLP requirements of ocuserts. Pre-formulation studies like identification and characterization method of drug, excipient drug compatibility studies, and criteria for excipient selection, formulation optimization techniques and formulation of ocuserts were also studied. The method of preparation was studied and also it includes the evaluation, stability studies, packaging and labelling of ocuserts.

REFERENCE

1) https://intapi.sciendo.com/pdf/10.2478/amma-2021-0032

2) Journal of Drug Delivery and Therapeutics, Ocular Inserts: A Novel Approach in Ocular Drug Delivery by Khan Ahmar, Raza Syed Naiem, Itoo Asif, Sirjohn Bashir, Wani Taha Umair, Khan Nisar Ahmad.

3) ACTA Scientific Pharmaceutical Sciences: Preparation and Evaluation of Ocuserts for Increasing the Bioavailability of an Antifungal Drugs by Kaushal Kumar, Mohd Faeek and Nida Parveen.

4) World Journal of Biology Pharmacy and Health Sciences (WJBPHS): Ocuserts: A novel ocular-drug delivery method: An update Navneet Nagpal, Sukhmanpreet Singh, Prince Ahad Mir, Mandeep Singh Chhina, Manisha Arora.

5) STABILITY STUDIES OF PHARMACEUTICAL PRODUCTS Sneha Aashigari, Ramya Goud G., Sneha S., Vykuntam U. and Naga Raju Potnuri.

6) Ophthalmic Drug Delivery Systems Second Edition, Revised and Expanded; edited by Ashim K. Mitra; MARCEL DEKKER, INC