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A Review on Ocuserts for Ocular Drug Delivery

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ABSTRACT

An ocuserts represents an advanced technology in eye disease therapy. In case of conventional dosage form has several limitations leading to poor ocular availability. To improve ocular drug bioavailability, there are significant guidelines have been directed towards administration. By means of ocuserts, the films are directly applied in cul-de-sac, increasing duration of contact with corneal tissue, thereby reducing frequency of administration of drug. Ocuserts are defined as preparation with solid or semisolid consistency, whose size and shapes are especially designed for ophthalmic application. In the recent years there has been explosion of interest in the polymer-based delivery device. Utilization of the principles of controlled release as embodied by ocuserts offers an attractive approach to the problem of prolonged pre-corneal drug resident time. The study focuses on introduction, mechanism and method of preparation, evaluation, recent advances of ocuserts.

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INTRODUCTION

The eye is a unique organ, both anatomically and physiologically, containing several widely varied structures with independent physiological functions. The complexity of the eye provides unique challenges to drug delivery strategies [1]. Ocular drug delivery system (ODDS) for the treatment of eye diseases has become popular and feasible in the past few years. Improving ocular contact time, enhancing corneal permeability and site specificity are the key points for the optimization of ocular drug delivery [2]. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents like iontophoresis, bio-adhesive gels, microsphere, contact lenses, and ocuserts have been demonstrated to the harmless and tolerated in the human eye and are efficient delivery systems [3]. The ocuserts represent significant advancement in therapy of eye disease [4].

Ocuserts system was firstly developed in 1975 by Alza Corporation in the United States of America. It is a flat, flexible, solid and semisolid which consists of drug reservoir and rate controlling membrane by using various polymers. The prime objective of development of ocuserts is continuous controlled delivery of ophthalmologically active drug to the eye. The ocuserts is inserted in the upper or lower cul-de-sac of the eye, which releases the drug at a predetermined rate constant. Thus, improved patient compliance by reduced dose frequency, better therapeutic outcomes by reduced over or under dosing, lesser local side effects or toxicity and increased bioavailability by increased drug eye contact time is observed [4].

ANATOMY OF EYE

The human eye, elegant in its detail and design, represents a gateway to the process we call vision. The eyeball is spherical in shape and about 1inch across. It houses many structures that work together to facilitate sight. The human eye is comprised of layers and internal structures. Each of which perform distinct functions [5].

The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optical nerve and vitreous humor [6].

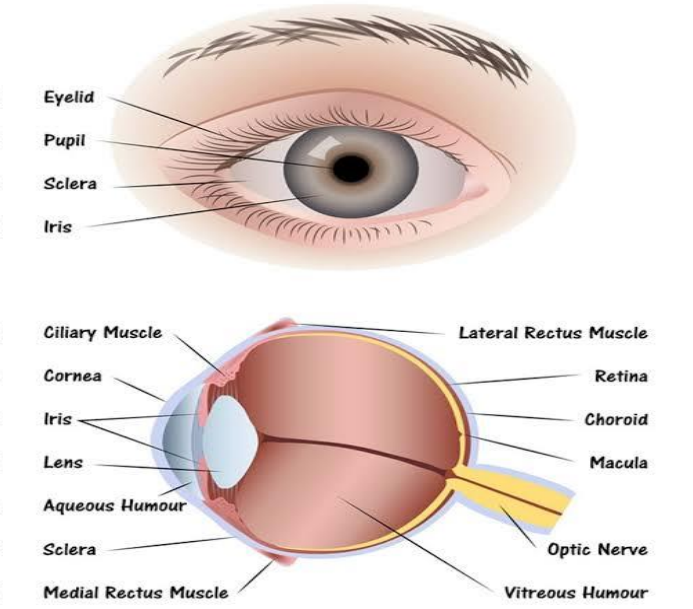


Figure No. 1: **Anatomy of the eye**

- **SCLERA**

Sclera is the white visible part of the eye. A tough covering with which the cornea forms the external protective coat of the eye. The muscles that move the eyeball are attached to the sclera [5].

- **CONJUNCTIVA**

The conjunctiva is a thin, transparent layer of tissues covering the front of the eye, including the sclera and the inside of the eyelids. The conjunctiva prevents the entry of bacteria and foreign material from getting behind the eye [7].

- **CORNEA**

The transparent circular part of the front of the eyeball. It refracts the light entering the eye on to the lens, which then focuses it onto the retina. The cornea contains no blood vessels and is extremely sensitive to pain [5].

- **AQUEOUS HUMOUR**

It is a clear watery fluid that fills the anterior chamber of the eye which is located immediately behind the cornea and In front of the lens. It is secreted by ciliary process at the

rate of 2-2.5 µL/min. It supplies most nutrition and oxygen to a vascular tissues (lens and cornea) [8].

- **PUPIL**

The circular opening in the centre of the iris through which the light passes into the lens of the eye. The size if the pupil is regulated by light reflex [5].

- **IRIS**

It is the colored part of the eye, controls the amount of light that enters the eye. The iris controls widening and narrowing of the pupil [7].

- **CILIARY MUSCLE**

Ciliary muscles are a ring of striated smooth muscle in the eye's middle layer that controls accommodation for viewing objects at varying distances and regulates the flow of aqueous humor into Schlemm's canal. When ciliary muscle relaxed, enable eye to focus on distant objects and the ciliary muscle contracted, enable eye to focus on near objects [8].

- **LENS**

A transparent layer situated behind the pupil and encircled by the ciliary muscles. It is enclosed in a thin transparent capsule and helps to refract incoming lights and focus it onto the retina [8].

- **VITREOUS HUMOR**

It is also known as the vitreous body. It is a clear, jelly like substance between the retina and lens [8].

- **RETINA**

It is the light sensitive layer that lines the interior of the eye. It is composed of light sensitive cells known as rods and cones. Rods are necessary for seeing in the dim light and cones are essential for receiving a sharp accurate image and for distinguishing colors. The retina senses light and creates impulses that are sent through the optic nerve to brain [7].

- **MACULA**

The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cell which convert light into nerve signals [8].

- **FOVEA**

Center part of the macula is called fovea which is the site of our sharpest vision. When the eye is directed at an object, the part of the image that is focused on the fovea is the image most accurately registered by the brain [8].

- **CHOROID**

The thin, blood rich membrane that lies between the retina and the sclera and its major function is to provide nourishment to the photoreceptor cell in the retina. It is dark brown in color and it contains a pigment that absorbs excess light and so prevents blurred vision [7].

- **OPTIC DISC**

Visible portion of the optic nerve, also found on the retina. The optic disc identifies the start of the optic nerve where messages from rod and cone cells leave the eye via nerve fibers to the optic center of the brain. It is also known as blind spot [8].

- **OPTIC NERVE**

It is responsible for transmitting nerve signals from eye to the brain [8].

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEM [9]

➢ It provides sustained and controlled drug delivery.

➢ It provides increased accurate dosing to overcome the side effects of pulsed dosing produced by conventional systems.

➢ It improves the ocular drug availability of drug by increasing the corneal contact time by effective adherence to corneal surface.

➢ It provides targeting within the ocular globe to prevent the loss to other ocular tissue.

➢ It bypasses the protective barriers of the eyes like drainage, lacrimation and conjunctival absorption.

➢ It enhances the therapeutic efficacy of the drug.

- It provides less visual and systemic side effects.
- It can be easily administered by patients himself.
- It shows quick absorption.
- It provides comfort and improved patient compliance.

DISADVANTAGES OF OCULAR DRUG DELIVERY SYSTEM [9]

- The drug solution stays in the eye surface for a very short time.
- It shows poor bioavailability.
- It shows instability of the dissolved drug.
- It requires preservatives.
- Dosage form cannot be terminated during emergency.
- It causes interference with vision.
- Its placement and removal are difficult.
- It suffers occasional loss during sleep or while rubbing eyes.

MECHANISM OF OCUSERTS

Ocuserts is a flat, flexible, solid and semisolid device which consists of drug reservoir and rate controlling membrane by using various polymers. The ocuserts is inserted in the upper or lower cul-de-sac of the eye, which releases the drug at a predetermined rate constant [4].

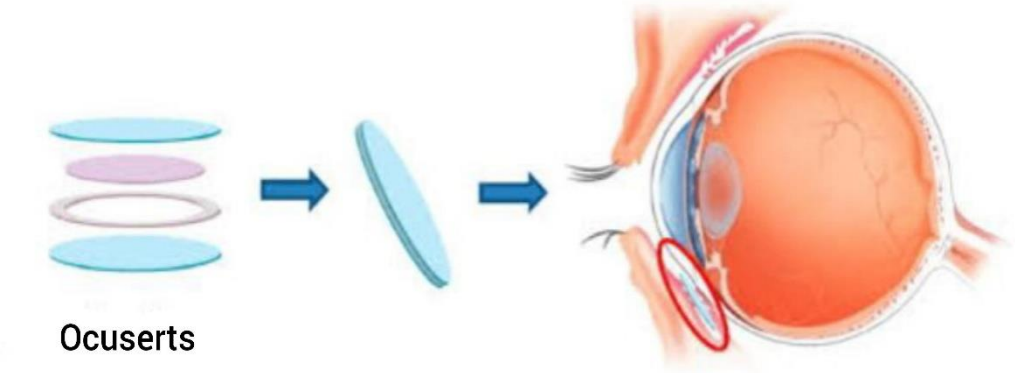


Figure No. 2: Ocuserts

Generally, all type of ocuserts consist of three layers.

- A central drug reservoir - thin disc of drug complex. Here the drug is incorporated in a polymer which allows diffuse the drug from reservoir.

- Rate controlling membrane – two transparent discs of micro porous membrane typically composed of ethylene vinyl acetate, a copolymer which allow the controlled release of medicament from drug reservoir.

- An outer annual ring - help to easy handling and proper insertion [10].

In Ocuserts system, zero order release is achieved by diffusion of drugs from a reservoir through a rate-controlling membrane over a specific lifespan till the drug reservoir is depleted. The technology used in this is an insoluble delicate sandwich technology. The reservoir containing drug complex is sandwiched between the micro porous membranes containing drug reservoir which permit tear fluid to penetrate into drug reservoir compartment to dissolve the drug from complex. The insert is encircled by a retaining ring of the same material, impregnated with titanium dioxide which allows patients to easy to visualize [10].

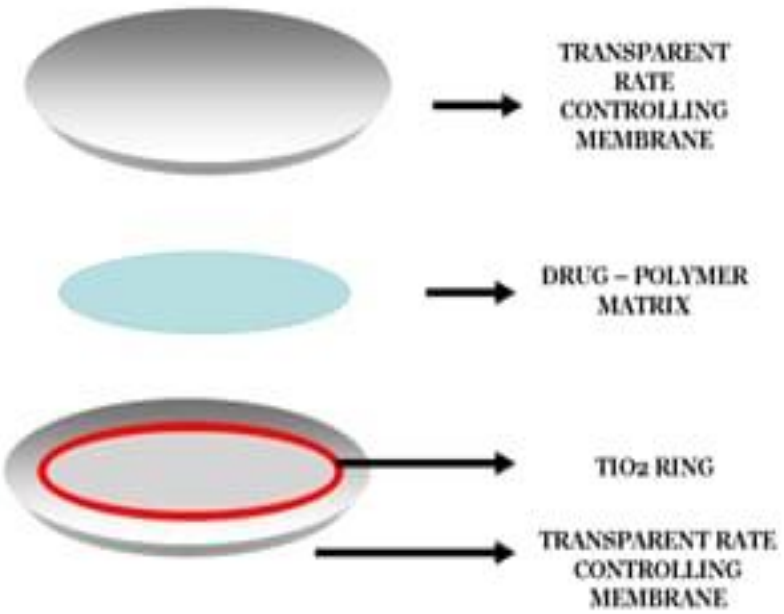


Figure No. 3: **Schematic diagram of ocuserts**

Controlled drug release of ocuserts is based on the following mechanisms:

1. Diffusion
2. Osmosis
3. Bio-erosion

- **DIFFUSION**

In the diffusion mechanism the drug is released continually at a controlled rate through the membrane into the tear fluid. If the insert is consisting of a solid non erodible body with pores and dispersed drug, the release of drug occurs through the pores via diffusion. Controlled drug release can be further regulated by gradual dissolution of solid dispersed drug and thus this matrix as a result of directed diffusion of aqueous solutions. In a soluble device, true dissolution mainly occurs through polymer swelling. In swelling controlled devices, the active ingredient is homogeneously dispersed in a glassy polymer. These glassy polymers are essentially drug impermeable; no diffusion occurs through the dry matrix. When the ocular insert is inserted in the eye, the water from the tear fluids begins to penetrate the matrix, then swelling and thus polymer chain relaxation and drug diffusion occurs. The dissolution of the matrix follows the swelling process which depends on polymer structure [11].

- **OSMOSIS**

In the osmosis mechanism, the insert consists of a transverse impermeable elastic membrane dividing the interior of the insert in to a first compartment and second compartment, the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by impermeable and elastic membrane. There is a drug release aperture in the impermeable wall of insert. The first compartment contains a solute which cannot pass through the semi permeable membrane and the second compartment provides a reservoir for the drug which a gain is in liquid or gel form. When the insert is inserted in the aqueous environment of the eye then water diffuse into the first compartment and stretches and contract the second compartment so that the drug is forced through the drug release aperture [11].

- **BIO-EROSION**

In the Bio-erosion mechanism, the insert is made up from a matrix of bio-degradable material in which the drug is dispersed. When insert contact with tear fluid and gives results in controlled sustained release of the drug by bio-erosion of the matrix. The drug may be homogeneously dispersed throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix [11].

ADVANTAGES OF OCUSERTS [12]

➢ It increases ocular residence time, which results in prolonged drug activity.

➢ Increases the bioavailability of the drug.

➢ Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes.

➢ The release rate of drug is in a controlled manner.

➢ Accurate dosing.

➢ Reduction in systemic absorption.

➢ Shelf life is increased when compared with aqueous solutions.

➢ Exclusion of preservatives, thus reducing the risk of sensitivity reactions.

➢ Improved patient compliance, due to the reduction of frequency of administration.

➢ Reduction of visual and systemic side effects.

DISADVANTAGES OF OCUSERTS [12]

➢ The major disadvantage of ocuserts is their solidity. The patients felt it as an extraneous body in the eye which result in inconvenience in patients.

➢ Discomfort due to their movement around the eye.

➢ Interference with vision.

➢ The occasional unintentional loss during sleep or while rubbing the eyes.

- Difficulty in placement and removal of ocuserts.

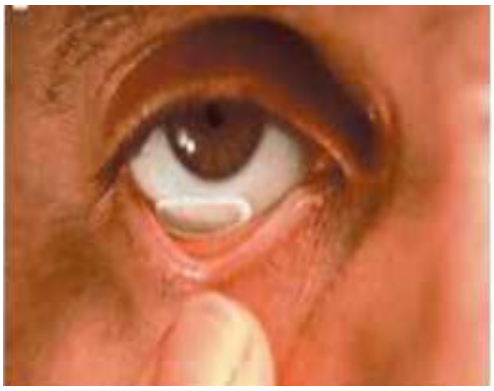
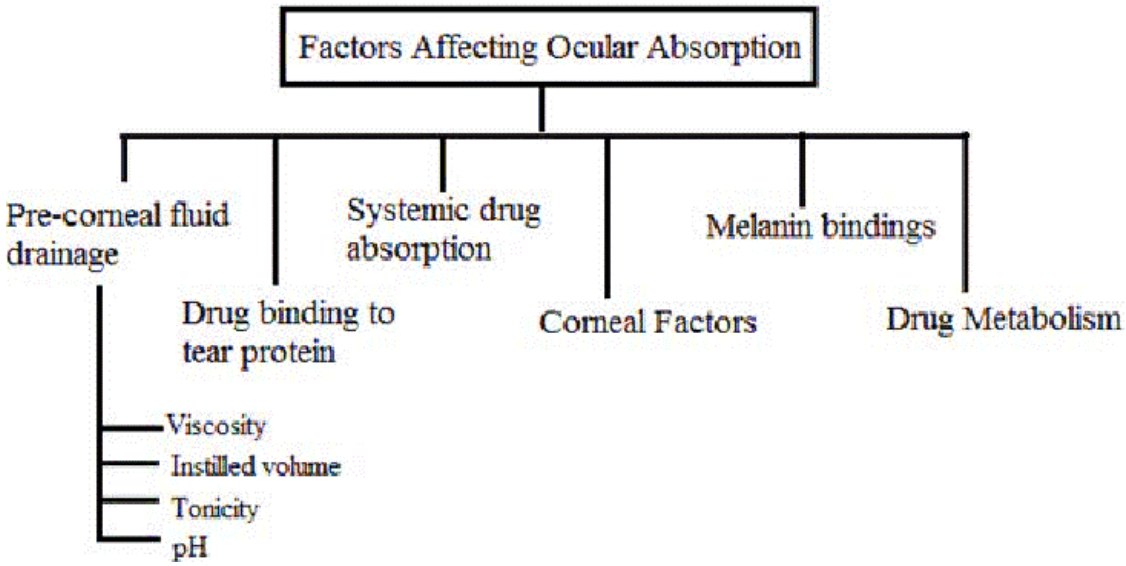


Figure No. 4: **Placement of ocuserts into eye**

FACTORS AFFECTING OCULAR DRUG ABSORPTION



PRE-CORNEAL FLUID DRAINAGE

Pre-corneal fluid drainage is one of the main reasons for low ocular drug absorption. After instillation, a major portion of an instilled volume (approx. 80-90%) is drained out through nasolacrimal duct. This natural protective physiological mechanism causes loss of any excess fluid present. Factors influencing drainage rate are instilled volume, viscosity, tonicity, PH [13].

1. Instilled volume

Higher instilled volume more will be the rate of solution drainage from conjunctival sac [13].

2. Viscosity

Increasing viscosity of an instilled dose can extend the residence time of solution in the conjunctival sac [13].

3. pH

The physiological pH of tear fluid is 7.4. Instillation of acidic or alkaline solution results in excessive tear secretions and loss of drug. The ophthalmic solutions are usually pH adjusted in the range of 7.0-7.7 [13].

4. Tonicity

Ophthalmic formulations for topical delivery should be isotonic with tear. If the tonicity of ophthalmic drugs varies from tonicity of tears, they will adjust it by diffusion or osmosis [13].

1. DRUG BINDING TO TEAR PROTEIN

Tear fluid contain approximately 0.7% of total body protein. Drug binding to this tear protein may result in the reduction in concentration of total available free drug for required pharmacological action at the target site [13].

2. SYSTEMIC DRUG ABSORPTION

Systemic absorption may take place either directly from the conjunctival sac or through the nasal cavity (nasolacrimal duct drainage) which may lead to the potential systematic side effects. It can cause significant drug loss in the ocular delivery into the thereby lowering ocular bioavailability [13].

3. CORNEALFACTORS

The epithelial layer of cornea is lipoidal in nature while stroma is hydrophilic nature which comprises 90% of the corneal thickness. Endothelium is the inner most layer separating the barrier between the stroma and aqueous humor. This layer helps to maintain the aqueous humor and corneal transparency due to its selective carrier mediated transport and secretory function and thus maintain the ocular availability of drugs [13].

4. MELANIN BINDING

The melanin pigment present in the iris and ciliary body may also change the ocular bioavailability of topically administered drug. Drug such as ephedrine and timolol have a high binding capacity for melanin, and only a small portion of the bound drug can release at a very slow rate [13].

5. DRUG METABOLISM

Many enzymes (cytochrome p450, aldehyde oxidase, aldo/ketone, reductase, cyclooxygenase, monoamine oxidase, hydrolase, and transferase) are expressed in ocular tissues such as cornea, lens, iris-ciliary body and retina. These enzymes can metabolize the active drug, leading to decrease in ocular drug bioavailability [13].

METHOD OF PREPARATION OF OCUSERTS

The following methods are commonly used for formulation of ocuserts.

1. Solvent casting method
2. Glass substrate technique
3. Melt extrusion technique

1. SOLVENT CASTING METHOD

In this method no. of batches are prepared using different proportion. The polymer is dissolved in suitable solvent. Into this solution plasticizer is added following continuous stirring the accurately weighed amount of drug is added to above solution and a uniform dispersion is obtained. When the proper blend is formed the solution is casted into the petridish using inverted funnel to allow slow and uniform evaporation at room temperature until the film is dried. The dried films thus obtained the film is cut into proper size and shape using cork borer. The ocuserts are prepared and stored in air tight container [14].

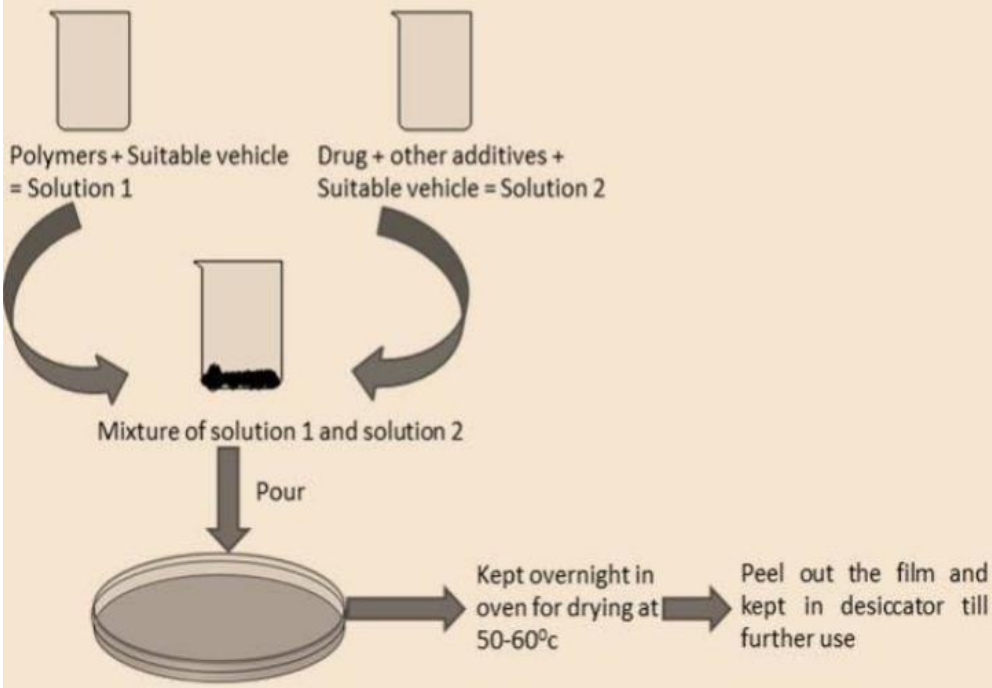


Figure No. 5: Solvent casting method

2. GLASS SUBSTRATE TECHNIQUE

In this method the polymer is soaked in 1%v/v Acetic acid solution for 24hrs, to get a clear solution. The solution is filtered. Required amount of drug is added and stirred for 15minutes to dissolve the complex in polymer solution. Plasticizer is added to the above solution. The viscous solution is obtained and kept aside for 30 minutes until air bubbles are removed. The rate controlling films are formed. The films are casted by discharging solution into the centre of leveled glass mould and allowing it to dry at room temperature for 24 hrs. The dried films are cut to form ocuserts in definite shape and size. Then, the matrix is sandwiched between the rate controlling membranes using gum which is non-toxic, non-irritating, and water insoluble. They are wrapped in aluminum foil separately and stored in a desiccators [14].

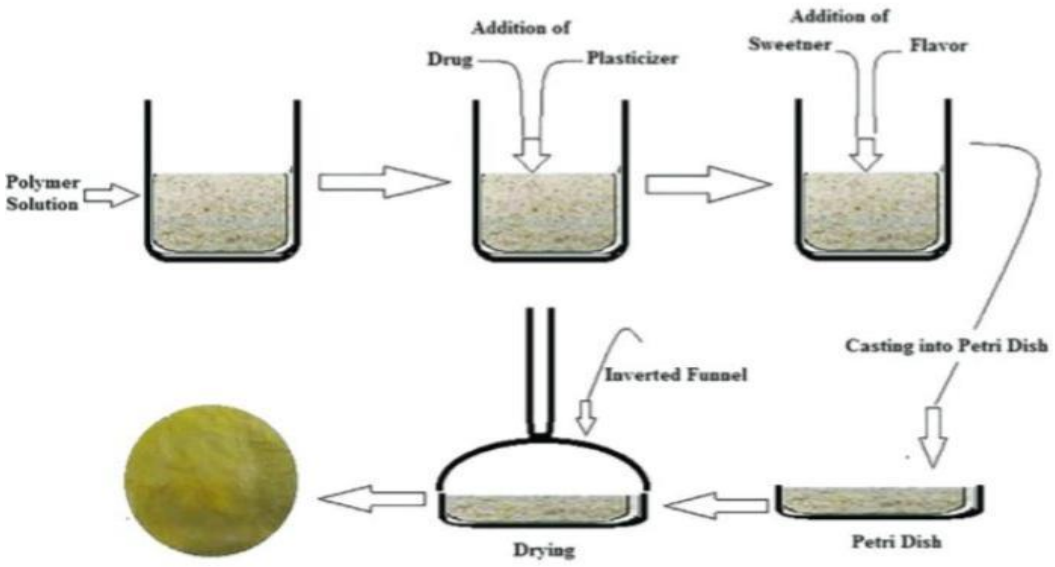


Figure No. 6: Glass substrate technique

3. MELT EXTRUSION TECHNIQUE

Drug and the polymer are passed through sieve having mesh size of 60#, weighed and blended. In this mixture plasticizer is added. The blend is then discharged to the container of Melt flow rate apparatus and extruded. The extrudate was cut into appropriate size and packed in polyethylene lined Aluminium foil, heat sealed and sterilized by gamma radiation [14].

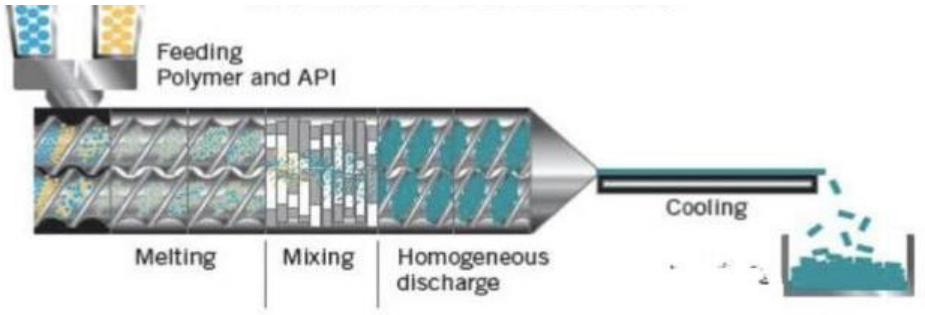


Figure No. 7: Melt extrusion process

EVALUATION TEST FOR OCUSERTS

1. Surface pH
2. Uniformity of thickness
3. Uniformity of weight

4. Swelling index
5. Folding endurance test
6. Drug content uniformity
7. *In-vitro* drug release study /*In-vitro* diffusion study
8. Percentage moisture absorption
9. Accelerated stability studies
10. Sterility studies

1. SURFACE pH

Ocuserts is placed in closed petridish in 1ml distilled water for 30min at room temperature. The swollen device was removed and placed under digital pH meter to determine the surface pH [10].

2. UNIFORMITY OF THICKNESS

The thickness of ocuserts was determined using a Vernier caliper at five separated points of each device. For each formulation, five randomly selected ocuserts are tested for their thickness [15].

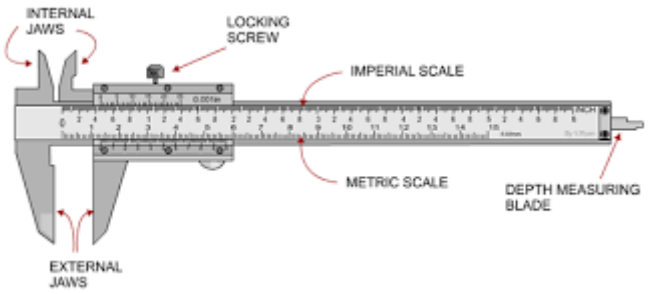


Figure No. 8: Vernier calliper apparatus

3. UNIFORMITY OF WEIGHT

From each batch, five ocuserts were taken out and weighed individually using digital balance. The mean weight of the ocuserts was noted [10].

4. SWELLING INDEX

Small amount of film is cut and weighed initially, and then it is soaked in pH 7.4 tear fluid for 1hour. After 1hour, film is reweighed. [14]

Swelling index is calculated by,

Swelling index = initial weight / final weight * 100

5. FOLDING ENDURANCE TEST

Folding endurance was determined by repeatedly fold the film at the same place till breaking or first sign of breaking. The number of fold occurred in film is its folding endurance till its breakage. The folding endurance of all the film is measured [10].

6. DRUG CONTENT UNIFORMITY

To check the uniformity if drug in an ocuserts, each ocuserts was placed in a glass vials containing 10ml of artificial tear fluid. Then ocuserts was dissolved by aid of a magnetic stirrer, the solution was then filtered. 1ml from filtrate was withdrawn and diluted up to 10ml distilled water and absorbance was measured by using UV-Visible spectrophotometer [10].

7. *IN-VITRO* DRUG RELEASE STUDY / *IN VITRO* DIFFUSION STUDY

An *in-vitro* diffusion studies or *in-vitro* drug release study of ocuserts was done by using Franz diffusion cell. It is the instrument used to study the permeability study of drug. It consists of two compartments, one is donor compartment in which dosage form i.e., ocuserts is added and another is receptor compartment which is filled with 7.4 tear fluid to stimulate the tear fluid in the eye. Both compartments are separated by membrane which may be permeable dialysis membrane or egg membranes. The instrument is started, RPM and Temperature is adjusted. Ocuserts is placed in donor compartment and tear fluid in receptor compartment. 1ml sample is withdrawn after fixed time interval (upto 6 hour) and after making suitable dilution Sample is analyzed in UV spectrophotometer. Sample is withdrawn until a constant absorbance is not obtained and then drug release is calculated [14].

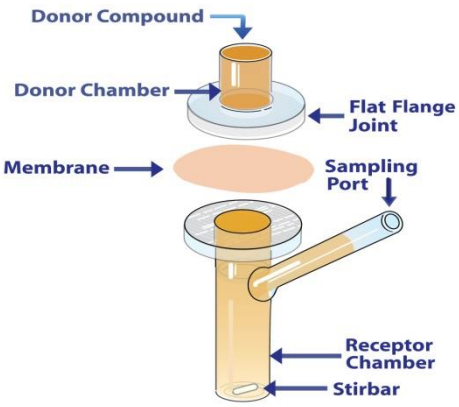


Figure No. 9: Franz diffusion cell

8. PERCENTAGE MOISTURE ABSORPTION

This is carried out to check the physical stability and integrity at wet condition. The prepared ocuserts was accurately weighed and placed in desiccators containing 100ml of saturated solution of Aluminium chloride and it was kept for 3days. The ocuserts are taken out and reweighed after 3days [15].

The percentage of moisture absorbed by the ocuserts was calculated using the following formula:

Percentage moisture absorption = Final weight – initial weight / initial weight* 100

9. ACCELERATED STABILITY STUDY

Stability studies done as per ICH guidelines, to ensure that the drug products retain their fitness for use until the end of their expiration date. Ocuserts are wrapped in aluminum foil stored in a glass bottle at 40^0c and 75% relative humidity (RH) in the stability chamber. The samples are tested for drug content after 0, 7, 15, 21 and 30 days respectively were evaluated for drug concentration, color, folding endurance etc [10].

10. STERILITY STUDY

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

- **Culture media**- Alternate thioglycolate medium and soya bean digest casein medium was used as a culture medium for bacteria and fungi respectively. Media were prepared according to IP 2014 and taken into 20ml boiling test tube, properly plugged with cotton and sterilized by autoclaving at 121^0c at 15ib/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 media for bacteria and fungi were incubated t 30^0c-35^0c and 20^{0c} -25^0c respectively in incubator for not less than 14 days [10].

LIST OF OCUSERTS OF DIFFERENT OPTHALMIC DRUGS AVAILABLE IN MARKET

The first marketed ocuserts is pilocarpine ocuserts by Alza Corporation, USA in 1973. It was the first relatively successful product for delivery of pilocarpine for the treatment of ocular hypertension. Pilocarpine ocuserts consists of a pilocarpine-alginate reservoir sandwiched between thin ethylene-vinyl acetate films. The devices are designed to deliver pilocarpine at either 20µg/hr. or 40µg/hr. It releases pilocarpine continuously at a steady rate for 7days [7].

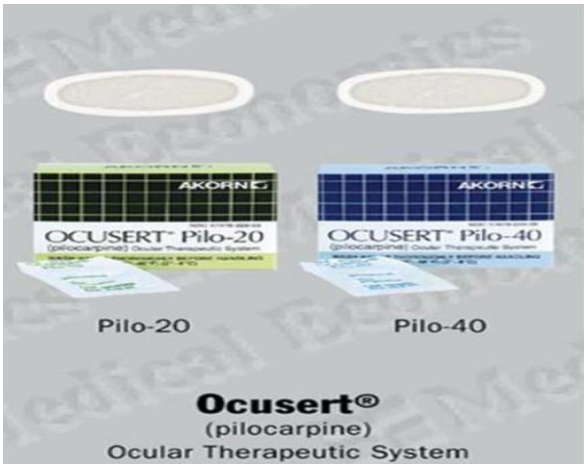


Figure No. 10: Pilocarpine ocuserts (Pilo -20 & Pilo- 40)

The other drugs such as Ofloxacin, Norfloxacin, Moxifloxacin, Acyclovir, Timolol, and Aceclofenac as ocuserts are also available in the market. But these are not popular. In recent days, various researches are conducted in drug delivery through ocuserts [11].

SL. NO	DRUG	CATEGORY OF DRUG
1	Pilocarpine nitrate	Mitotic agent
2	Ciprofloxacin	Antibacterial agent
3	Ofloxacin	Antibacterial agent
4	Moxifloxacin	Antibacterial agent
5	Acyclovir	Antiviral agent
6	Fluconazole	Antifungal agent
7	Brimonidine tartrate	Intra ocular pressure lowering agent
8	Aceclofenac	NSAID
9	Levobunolol	Betablocker agent
10	Timolol maleate	Anti-glaucoma agent

CONCLUSION

As challenges are more for eye as compared to skin, so there is a need to focus more on non-invasive sustained drug release for eye disorders in both segments [16]. The main aim of the novel ocular drug delivery systems during the past two decades is to prolong the ocular residence time of the drugs [7]. Ocuserts should be able to administer an effective drug concentration at the targeted site for a prolonged period of time, while lowering systemic exposure. The output resulted from such systems, makes the system comfortable and easy to use. Ocuserts are prepared with different method and can be evaluated with different parameters [16]. Ocuserts are novel approaches in the era of ocular drug delivery compliance with ethical standards. The advantages gained by ocuserts are many for the treatment of eye-related problems, but only a few gain commercial acceptances [7]. Future work is in progress to establish the therapeutic utility of these systems by pharmacokinetic and pharmacodynamics in human beings this said to be promising formulation.

REFERENCES

1. Dr Dheeraj, T Baviskar *et al*. Novel Drug Delivery System, Nirali publication: 7.1-7.20.
2. Nikhil Gulati, Vanya Dwivedi. International Journal of Drug Regulatory Affairs, 2014; 2(3):79-82.
3. Yadav Tejpal, Jat R. K. Journal of Drug Delivery and Therapeutics, 2013; 3(1): 114-123.
4. Nida Praveen, Himanshu Joshi, Saudi Journal of Medical and Pharmaceutical Sciences, 2020; 6(5); 420-425.
5. Ramaiyan Dhanapal, J Vijaya Ratna. International Journal of Innovative Drug Discovery, 2012; 2(1):4-15.
6. Ashaben Patel, Kishore Cholkar *et al.* World Journal of Pharmacology, 2013; 2(2) 47-64.
7. Dr. B. Arul, Dr. R. Kothai Current trends in novel drug delivery systems, PV Publication: 201-221.

8. Deepika Sharma, Shubham Tyagi, Bhavna Kumar. Asian Journal of Nanoscience and Materials, 2019; 2(3): 356-366.
9. Dr. Shailesh Thanaji Prajapati, Dr. R. Manivannan, *et al.* Novel drug delivery system, Thakur publication: 186-205.
10. Thakur Richa, Swami Gaurav. Journal of Drug Delivery and Therapeutics, 2012; 2(2): 18-25.
11. Kaushal Kumar, Lakshyaveer Singh. Journal of Emerging Technologies and Innovative Research, 2014; 1(3): 1221-1229.
12. Anitha Kumari, Pramod ksharma *et al.* Journal of Advanced Pharmaceutical Technology and Research, 2010; 1(3): 291-296.
13. Vibhuti Agrahari, Abhirup Mandal, *et al.* Drug Delivery and Translational Research, 2016; 6(6): 735-754.
14. Dabral Kriti, Uniyal Yashika. GSC Biological and Pharmaceutical Sciences, 2019; 7(3): 1-7.
15. S D Mankar, S S Siddheshwar, *et al.* Inventi Rapid: NDDS, 2014; 2014(4) 1-6.
16. Vishal Kumar Raj, Rupa Mazumder *et al.* International Journal of Applied Pharmaceutics, 2020; 12(5): 49-57.