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OCUSERTS AS SMART OCULAR DRUG DELIVERY SYSTEMS - AN OVERVIEW

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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 retention time with conjunctiva tissue to provide consistent drug release. Uniform ocular medication levels decrease systemic side effects, minimizes dose, boosting patient compliance. The significance of ocuserts, their polymers, preparation methods were elaborated in this review. By overcoming the ocular barriers they provide 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. Ocuserts have wide applications in both local as well as systemic affects of drug.

KEYWORDS: Ocuserts, Minidiscs, Glaucoma, Bioerosion, Diffusion.

INTRODUCTION

Ocusert system was firstly developed in 1975 by Alza corporation in the united state of America. The eye is one of the most soft and most valuable of all the sense organs. The ocusert is inserted in the upper or lower-cul-de-sac of the eye which releases the drug at a predetermined rate constant. It is have been developed in which the drug is delivered on the basis of diffusional mechanism. Such a solid dosage from delivers an ophthalmic drug at near constant rate minimizing side effects by avoiding absorption peaks. The near zero-order rate delivery is based on the selection of on non-eroding copolymer membrane enclosing the drug reservoir. In ocusert drug reservoir is a thin disc of drug complex sandwiched between two transportation discs of microporous membrane from ethylene-vinyl acetate copolymer.[1,2] Most ocular treatments like eye drops and suspensions call for the topical administration of ophthalmically active drug to the tissues around the ocular cavity.

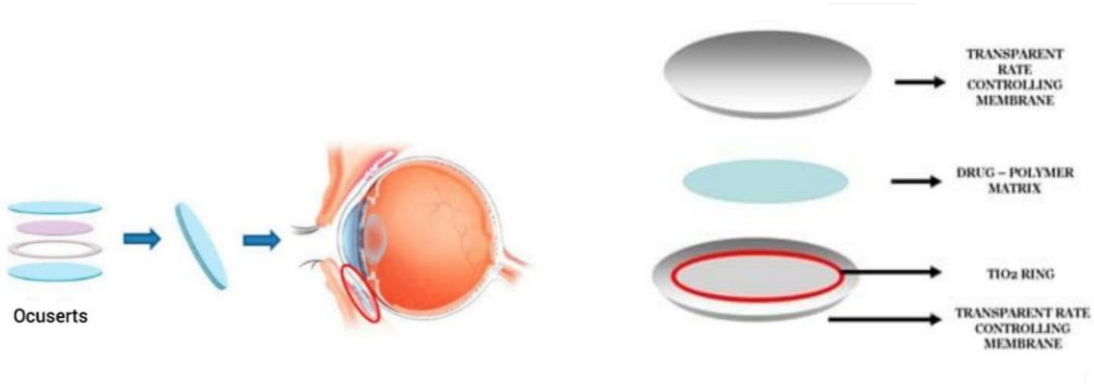


Fig. 1: Schematic diagram of ocuserts a. piol-20 b.piol-40.

Ocular inserts are as preparations with a solid or semisolid consistency whose size and shape These inserts are placed in the lower fornix and less frequently in the upper fornix on the cornea. They are usually

composed of a polymeric vehicle containing the drug and are mainly used for topical therapy Two types of ocusert are available.

The former deliver the drug at a rate of 20p.g/hfoe7days. The former deliver the latter at a rate of 40^g/h for 7days. This device consists of reservoir containing pilocarpine alginate enclosed above and below by thin EVA (ethylene-vinyl acetate) membranes. The insert is encircled by a retaining ring of the same material impregnated with titanium dioxide.[3,4] The dimension of the elliptical device are (for the(20p.g/h system). Major axis 13.4mm.minor axis 5-7mm thick ness 0.3mm The membranes are the same in both system but to obtain higher release rate. The reservoir of the 40.p.g/h system contains about 90mg of di ethylhexyl phthalate as a flux enhancer incorporated in form of dispersion or a solution.

The main purpose of the use of ophthalmic inserts is to enhance the retention time of active form of drug between in eye to ensure a sustained release suited. Dosing frequency can also be reduced and risk of systemic adverse effects is decreased. A mixture of pilocarpine and alginic acid as the drug reservoir provides the drug for almost one week The thin membrane of ethylene-vinyl acetate (EVA) copolymer encloses drug reservoir circumferentially. Ocusert there has been a proliferation of erodible inserts prepared.[5] They are comparable to ocusert with respect to duration of action The pilocarpine molecules dissolved in the lacrimal fluid are released through the rate controlling membranes at predefined rates.

Advantage

1. Increased contact time and thus improved bioavailability
2. Possibility of provided a prolonged drug release and thus a better efficacy
3. Administration of an accurate dose in the eye and thus a better therapy
4. Reduction of the number of administration and thus better patient compliance & Comfort
5. Lack of explosion
6. Ease of handling and insertion
7. Better stability
8. Reproducibility of release kinetics
9. Non-interference with vision and oxygen permeability
10. Sterility
11. Exclusion of preservatives
12. Increased shelf-life with comparison to aqueous solutions due to absence of water
13. Increased possibility of internal ocular tissue targeting through non-corneal(conjuctival and sclera) penetration routes
14. Minimal systemic absorption
15. Accurate dosing
16. Releasing drugs at slow and constant rate
17. Provides better housing of delivery system
18. Circumvent the protective barriers like drainage lacrimation and conjuctival absorption

Disadvantages

1. Perceived by patient as foregin body
2. Movement around the eye
3. Occasional loss during sleep or while rubbing eyes
4. Interference with vision
5. Difficulty in placement and removal
6. Dislocation of the device in front of the pupil
7. Irritation to eye
8. Expensive
9. Retention in the eye for full 7 days
10. Sometimes the insert twists to form a figure eight which diminished the delivery rate
11. Interference with vision
12. Unwanted migration of inserts to upper formix.

SIGNIFICANCE

Ocuserts also known as ocular inserts or ocular drug delivery systems are medical devices designed to deliver drugs to the eye over an extended period. They have several significances in the field of the ophthalmology and pharmaceuticals.

Controlled drug release: Ocuserts can provide a controlled and sustained release of medication to the eye over an extended period, ensuring that the drug remains at therapeutic levels for longer durations.

Improved patient compliance: They eliminate the need for frequent eye drops, which can be challenging for patients to administer correctly. This can improve patient compliance with their treatment regimen.

Enhanced bioavailability: Ocuserts can enhance the bioavailability of drugs by delivering them directly to the target site in the eye, reducing systemic side effects.

Prolonged drug action: These devices can extend the duration of drug action, reducing the frequency of administration and potentially improving treatment outcomes.

Reduced side effects: Ocuserts can reduce the systemic absorption of drugs, minimizing the potential for systemic side effects that can occur when using traditional eye drops. This is especially important when using medications that may have adverse effects on other parts of the body.

Treatment of chronic eye conditions: Ocuserts are particularly valuable for chronic eye conditions such as glaucoma and certain forms of conjunctivitis where long term medication management is necessary.

Enhanced therapeutic efficacy: By delivering drugs directly to the eye and maintaining consistent drugs levels, Ocuserts can enhance the therapeutic efficacy of medications. This is particularly important for conditions

such as glaucoma, where consistent intraocular pressure control is crucial.

Prolonged duration of action: Depending on the design of the Ocusert, it can provide sustained drug delivery for days or even weeks, offering convenience for both patients and healthcare providers.

Targeted delivery: Ocuserts can be designed to target specific ocular tissues, or structures, allowing for prescriptions in drug delivery. This is particularly beneficial for treating conditions affecting specific eye parts.

Reduction in dosage frequency: Ocuserts can reduce the frequency of drug administration which can be advantages for patients with chronic eye conditions who would otherwise need to use eye drops multiple times a day.

Treatment of various ocular conditions: Ocuserts are used to treat a wide range of ocular conditions, including glaucoma, dry eye syndrome, uveitis, and certain infections of the eye.[6]

Research and development: Ocuserts are also valuable tools in pharmaceutical research and development, as they can be used to assess the effectiveness of new drugs in preclinical and clinical trails.

Stable drug concentrations: They help in maintaining a stable concentration of the drug in the eye, which can be critical for treating certain eye conditions.

Minimized fluctuations: Ocuserts can help minimize fluctuations in drug concentrations levels, which is important for conditions, where consistent drug levels are required for optimal treatment outcomes.

Improved patient comfort and convenience: For patients, Ocuserts may be more convenient than the frequent application of eye drops. They reduce the need of repeated administrations throughout the day.

Potential for combination therapies: Ocuserts can be designed to release multiple drugs simultaneously. This can be beneficial for conditions that require combination therapies.

Customization: Ocuserts can be tailored to the specific needs of a patient and the requirements of a particularly eye conditions, allowing for a personalized approach to treatment.[7]

Versatility: Ocuserts can be prepared by various techniques like solvent casting, a glass substrate and melt extrusion technique.

Improved contact: The goal of Ocuserts is to improve medication contact with conjunctiva tissue to sustain consistent dosage release.

BARRIERS

There are different types of barriers. They are

- Ocular surface barriers
- Ocular wall barriers
- Retinal Barriers
- Vitreous body
- The lachrymal fluid
- Solubility of the drug
- Lipophilicity of the drug
- Molecular weight and size of the drug

Ocular surface barriers

The corneal and conjunctiva superficial layers from the ocular surface, i.e. in contact with the tear film. These create a defense barrier against permeation form undesired molecules. corneal surface- 5%, conjunctival surface-95%.Out of corneal five layers only, the outer most squamous epithelium layer forms a barrier. Eventhough the ocular turnover rate is only about 1 /min the excess of instilled fluid is flow to the nasolacrimal duct rapidly in a couple of minutes. The ocular surface provides a barrier to noxious stimuli, thus protecting the vision apparatus In addition, the barrier function keeps the cornea relatively dehydrated and hence preserves transparency for transmission of light. Dysfunction of this barrier leads to disease.[8] Clinical diseases that involve barrier impairment include dry eye, infectious keratitis, allergic keratoconjunctivitis, chemical injury, and persistent epithelial defects. These collectively contribute to a very significant portion of ocular morbidity and cornea-related blindness.

Ocular wall barrier: Two main blood-ocular barriers are proposed: the blood-aqueous barrier and the blood-retinal barrier. The blood-aqueous barrier is formed by an epithelial barrier located in the nonpigmented layer of the ciliary epithelium and in the posterior iridial epithelium, and by the endothelium of the iridial vessels.

SCLERA AND CHOROID

Sclera

- It contains stroma made up of bundles of collagen and fibroblasts covered by vesicular episclera.
- Occupies 80% of eye globe.
- Thickness is 0.3 to 1.0mm.

Choroid

- Beneath sclera and highly vesicular tissue, thickness is 0.25mm.

Retinal barriers

The blood retina barrier (BRB) is composed of both an inner and outer barriers. Blood retinal barriers restricts drug transport from the blood into the retina. BRB is composed of tight junctions of retinal capillary

endothelial cells and RPE, called iBRB for the inner and oBRB, respectively. The function of iBRB is supported by Miller cells are not fenestrated and have a paucity of vehicles. Miller cells are known to support the neuronal activity and maintain the proper functioning of the iBRB under normal conditions. The astrocytes originate from the optic nerve and migrate to the fibre layer during development. the inner BRB, similar to the blood brain barrier (BBB) is located in the inner retinal microvasculature and comprises the microvascular endothelium which line these vessels.[9] The tight junctions located between these cells mediate highly selective diffusion of molecules from the blood to the retina and the barrier is essential in maintaining retinal homeostasis.

Vitreous barriers

It occupies volume about 4.5 ml and is the largest single structure in the eye. Drugs are rapidly eliminated from the vitreous by first order kinetics. Vitreous decreased the cellular uptake of DNA complexes 2-30 times, and GFP expression was also impaired. In hyaluronan solutions the cellular uptake of the complexes was also decreased significantly in most cases. In vitreous, cellular uptake of all FITC-dextrans decreased slightly, and uptake of poly-L-lysines was decreased substantially, whereas in hyaluronan solutions the effects were mild or nonexistent.

The lachryaml fluid

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelium cells from tight junctions, that limit the paracellular drug permeation. Lipophilic drugs are have typically at least an order of magnitude high permeability. Rapid clearance of precorneal area by lacremation and nasolachrymal drainage and spillage- decrease in bioavailability. The lacrimal gland is located within the orbit above the lateral end of the eye.[10] It continually releases fluid which cleanses and protects the eye's surface as it lubricates and moistens it. These lacrimal secretions are commonly known as tears.

Solubility of the drug

Solubility is dependent on the pka of the drug and pH of the solution. Usually unionised drugs permeate rapidly than ionised drugs. As the corneal epithelium bears negative charge cationic species penetrate fast. Drug solubility depends on the pH of fluid, temperature, volume, and contents of fluid. The lipophilicity of a drug is also correlated with water solubility. The rate and extent of absorption can be altered by food.

Factors that increase the amount of drug solubilized are particularly important for BDDCS class 2 and 4 drugs, whose absorption is limited by their poor solubility. Foods can increase solubility by increasing the volume into which a drug can be solubilized, changing the pH of the fluid.

Lipophilicity of the drug

The role of lipophilicity in determining the overall quality of candidate drug molecules is of paramount importance. Recent developments suggest that, as well as determining pre-clinical ADMET (absorption, distribution, metabolism, elimination and toxicology) properties, compounds of optimal lipophilicity might have increased chances of success in development.[11]

Outermost corneal epithelium is tend to permeate lipophilic drugs where as inner stromal layer of cornea permeate hydrophobic drugs. partition coefficient value ranging from 2-4 is found to be optimum.

Molecular weight and size of the drug

Molecular weight less than 500 Daltons can permeate readily in corneal epithelium. Conjunctiva has larger paracellular pore diameter this allow permeation of larger molecules such as small and medium size peptides (5000-10000d). Permeation through sclera is by aqueous pores. Sclera permeability is half of the conjunctiva but much Higher than the choroid.

Table 1: Parameters for ocular absorption.

Parameters	Conjunctiva	Cornea	Sclera
Surface area	17.65+/2.12cm	1.04+/-0.12	16-17
Thickness	-	0.57mm	0.4-0.5
Structural composition	Mucus membrane epithelium vasculature	5 layers epithelium Bowman's membrane stomata Descements membrane endothelium	Collagen fibres water proteoglycons monopolysaccharides Elastic fibres fibroblast

Polymer used for ocusert classification

Ocular inserts

1) Soluble inserts

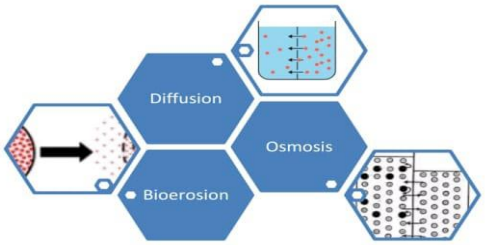
i. Natural polymer
ii. Synthetic and semi synthetic polymer

2) Insoluble inserts

i. Reservoir system
ii. Matrix system

3) Biodegradable inserts

i. SODI(soluble ocular drug inserts)
ii. collagen shields
iii. minidisc



- This section is devoted to solid devices delivering drugs to the anterior segment of the eye that are denoted by the general name **"insert",** originating from the **"Latin",** to introduce.
- **The British pharmacopoeia 1948** describe an atropine in gelatin "wafer" and not with standing all the formulation possibilities as well as biopharmaceutical properties.
- Ophthalmic inserts are defined as preparation with a solid / semisolid, whose size and shape are especially designed for ophthalmic application.
- Two products, Alzaocusert and Merck Lacrisert has been marketed although ocusert is no longer sold.
- Ophthalmic inserts are classified according to their solubility behaviour and their possible biodegradability.

A. Soluble inserts

- Soluble inserts are the most frequently investigated class of ophthalmic inserts.
- True dissolution occurs mainly through polymer swelling.[12]
- The major problems of these soluble inserts are the rapid penetration of the lacrimal fluid into the device.
- Soluble inserts are devided into two categories according to their polymer composition.

1. Natural polymer

- Inserts containing collagen were first developed by "Fyodoror"as corneal bandage following surgical operations and eye disease.
- Collage shields are manufactured from porcine scleral tissue and commercially available.
- The main advantage of collagen shields over contact lens is their solubility.
- They have been shown to improve the management pupillary dilution in humans as well as the delivery of pilocarpine.
- Natural polymers include collage, which was the first ophthalmic insert excited described in the literature.

2. Synthetic and semi synthetic polymers

- Ophthalmic inserts containing synthetic, i.e. PVA and semi synthetic cellulose based polymers.
- A decrease of release rate can be obtained by using Eudragit.[13]
- Ethyl cellulose, a hydrophobic polymer can be incorporated in the formulation decrease insert deformation.
- The device weight-5 mg, measure- 1.27 mm, length with diameter- 3.5mm.
- Lacrisert is a soluble insert that was successful commercialized by "Marck shape" and " Dohme in 1981".

B. Insoluble inserts

It can be classified into two categories.

2. Reservoir system

- Reservoir system can be release drug either by diffusion/ by an osmotic process.
- Reservoir controlled release system may be manufactured in a wide range of geomatrical including tablets / pellets laminated films / other define shapes (eg.hemispheres, cylinders, rods).
- The peripheral part of these **"osmotic inserts"** comprises in all case of a covering film made of an insoluble semipermeable polymer.
- The osmotic pressure against the polymer matrix cause it's rupture in the form of apertures.
- The drug is surrounded by the polymer as discreate small deposits.
- Drug release from the delivery system occurs by the **"Diffusion".**
- A sufficient internal pressure is achieved to drive the drug out from the reservoir.
- Advantage of the insert is that this method requires only two simple measures.

One to insert and one to withdraw the device.

2. Matrix system

- The Matrix insoluble inserts are typically represented by the contact lenses.
- Contact lenses are composed of a hydrophilic polymer of which swells by absorbing water.
- "**Refojo "** has proposed classifying contact lenses according to give groups.[14]

*Rigid
*Semi rigid
*Elastomeric
*Soft hydrophilic
*Biopolymeric

- Soft hydrophilic contact lenses were developed for proloy release of drugs. Such as pilocarpine, chloramphenicol and tetracyline.

- These are very popular because they are easy to fit and are tolerated better.
- The main drawback of contact lenses as a therapeutic lens is their high cost of manufacture and the low drug loading capacity.
- Invitro release studies exhibited drug release profiles compatible with a first order reaction model with a temperature rate constant.

C. Bio degradable inserts

- In resent years, systems that control and prolong the action of therapeutic agents with the development of biodegradable polymers.
- The drug delivery for the ocular route should be sterile, isotonic and non irritant.
- Biodegradable polymers are the polymers of choice for retinal drug delivery.
- The great advantage of these insert is the possibility of bulk erosion and drug diffusion may change according to the errosion rate of the polymer matrix.[15]
- The degradation products/ residual solvents used during the polymer preparation can cause inflammatory reaction.
- The emergency of New drugs short biological half-lives / systemic side effects.
- Sustained release of bovine serum albumin was achieved during an 11day period in neutral phosphate buffer.
- Micro and Nano structured poly(capro lactone)films studied in terms of ocular tolerance and structural integrity while residing in rabbits eye exhibiting acceptable results.

SODI (soluble ophthalmic drug inserts)

- It is a small oval wafer
- It is developed by sovit scientists for cosmonauts who could not use eye drop in weightless conditions.
- The SODIS are the result of vast collaborative effot between eminent Russian chemists and opthalmogists, led eventually (in 1976).
- The development of a new soluble copolymer of acrylamide, N-viny pyrrolidone.
- A comparision of medicated eye films prepared with different polymers.
- The sensation of an “extrenous body” in the eye disappers in 5-15 minutes .

Advantages

Single SODI application replaces 4-12 eye drops instillation or 3-6 applications of ointments.
Once a drug treatment of glaucoma and traucoma.

Collagen shields: Collagen is the structural protein of the bones, tendons, ligaments and skin and comprises more than 25%of the total body protiens in mammals.
This protein which is derived from intestinal collagen.
Bloomfield et al are credited for first suggesting in 1977 and 1978.
The compare the level of gentamicin in tears, cornea, sclera.
The authors included the use of collagen shields impregnated with gentamicin -dexamethasone a new preparation is referred to as collasomes consisit of small pieces (1mm X2mmX0.1mm) of collagen suspended in a 1% methylcellulose vehicle.[16]

Minidisc: It is made up of counter disc with convex front and concave back surface in contact with eye ball 4-5mm in diameter

COMPOSITION: Silicon based prepolymer
Drug release from 170hrs
Example: Pilocarpine, chloramphenicol.

Table 2: Ocular inserts devices.

NAME	DESCRIPTION
Soluble ocular drug insert	Small oval wafer, composed of soluble co polymers of acetyl amide,N-vinyl pyrrolidine and ethylacetate, soften on insertion
New ophthalmic drug delivery system	Medicated solid polyvinyl alcohol flag that is attached to a paper covered with handle. On application, the flag detaches and gradually dissolves, releasing the drugs
Collagen shields	Erodible disc consists of crosslink porcine scleral collagen
Ocusert	Flat, flexible elliptical insoluble device consisting of two layers ,enclosing reservoir, use commercially to deliver pilocarpine for 7 days
Minidisc or ocular therapeutic	System 4-5mm diameter contoured either hydrophilic or hydrophobic disc
Lacrisert	Rose-shape device made from hydroxy propyl cellulose use for the eye syndrome as an alternative to tears
Gelfoam	Slabs of gel foam impregnated with a mixture of drug and cetyl ester wax in chloroform
Dry drops	A preservative free of hydrophilic polymer solution that is freeze dried on the tip of soft hydrophobic carrier strip ,immediately hydrate in tear strip

PREPARATION OF OCUSERTS

Ocuserts are sterile preparations in form of solid or semisolid whose size and shape are specially designed to be applied to the eyes.

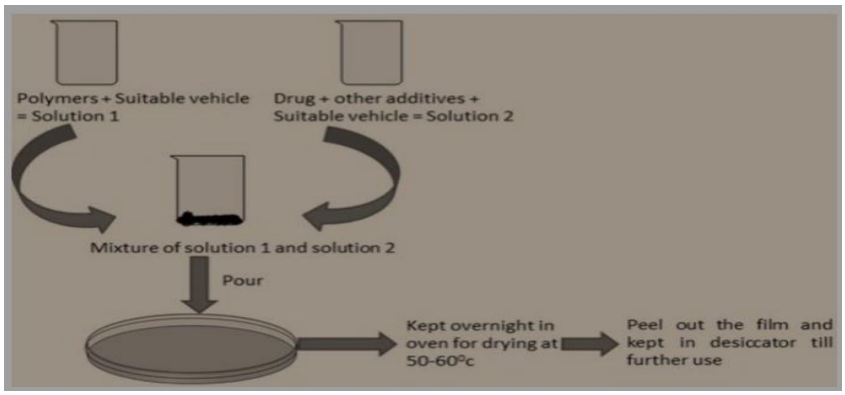
Enhance the drug absorption by increasing its contact time and by reducing drug wastage to the absorption time.

There are three (3) different methods for preparation of ocuserts:

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

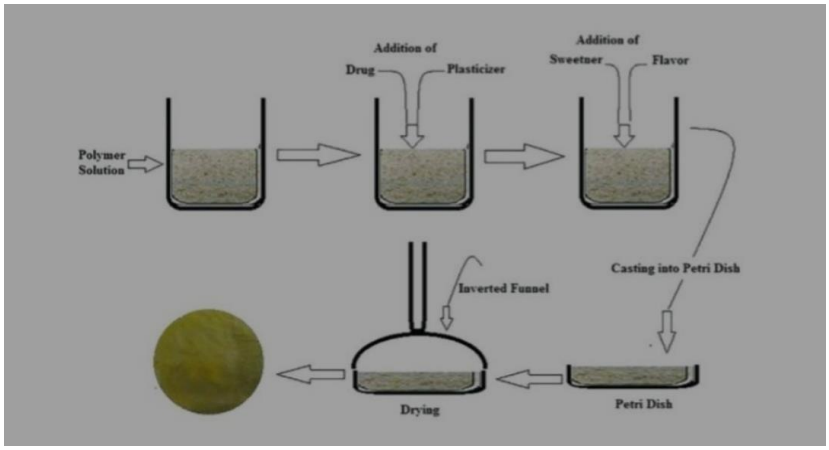
Solvent casting method

Due to its cost effectiveness and simplycity solvent casting is utilised to make ococuserts. In this procedure, rheological properties of polymers are examined since they impact ocusert thickness, drying rate, homogeneiety etc. Deaceration 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 evoparates, leaving the ocusert film. Then, ocusert films are trimmed to size.



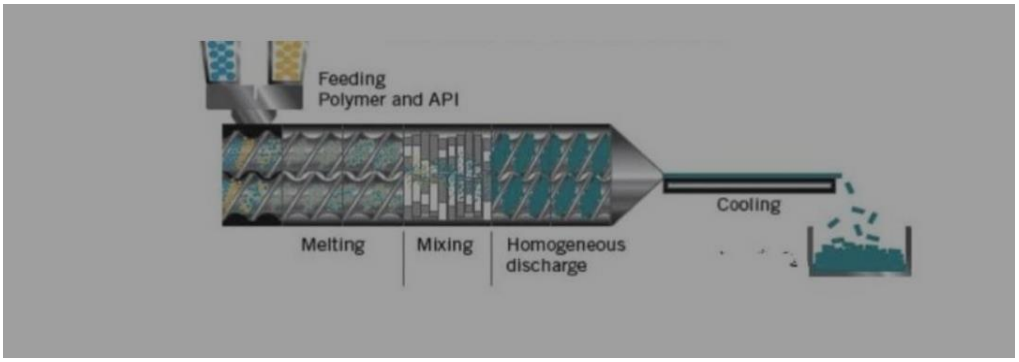
Glass substrate method

Glass substrate technique is used to produce thin films. A transperant 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 adde to glass mould and dried. Drying at rom temperature takes 24 hours. Dried films are then trimed and dried.



Melt extrusion method

Melt extrusion technique is an alternative for solvent csting. It is utilised for non-organic solvents. In this process, Polymers and other components are melted and the passed through dye to prepare film. This films are not for the thermoliable substances.[17,18]

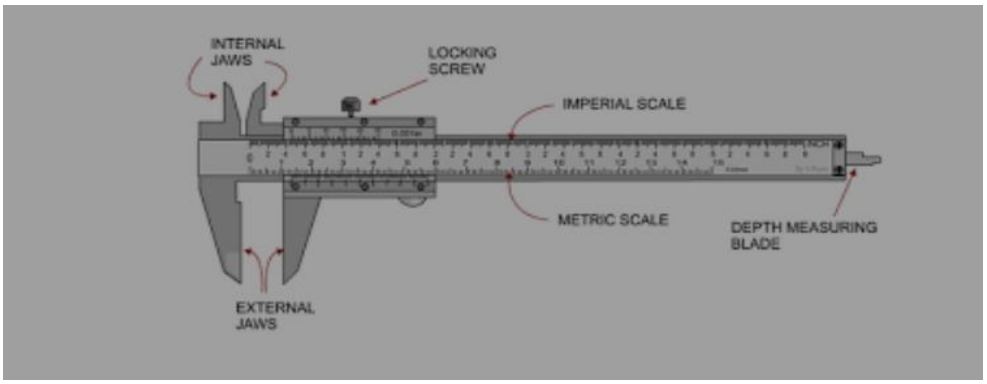


EVALUATION PARAMETERS FOR OCUSERTS

Prepared ocuserts were evaluated by following parameters:

Weight variation: The weight variation tests were carried out by individually weighing balance and average weight variation of 20 ocuserts were calculated and ANOVA (analysis of variance) was applied for stastistical evalution. The least count of ocusert was 0.1mg.

Thickness of ocuserts: The thickness of ocuserts was measured by digital vernier calipers (having least count 0.01mm)at different points of ocuserts and average thickness of 20 ocuserts was calculated and variations in thickness were analysed stastistically by ANOVA (analysis of variance).[19]



Folding endurance: This test measures the ocuserts folding resistance. Folding endurance is the a number of times a film can be folded without breaking. After breaking the endurance is calculated as hoe folds and is determined.

Surface pH: Surface ph of ocuserts was determined by allowing them to swell in a petridish at room temperature for 30minutes in 10ml of distilled water. The swallowen devices were removed and placed on sensing electrode of pH of ocuserts was calculated.

Theoritical drug content of each ocusert: For calculating average drug content in each formulation, first of all theoretical amount of drug in each ocusert reservoir was calculated by measuring area of casted film, amount of drug loaded in ir and then calculating the average area of an ocusert applying following formula.[20]

Theoretical amount of drug =
Drug loaded in casted film **x** area of ocusert in each ocusert reservoir /area of casted film

Average drug content: Accurately weighed three ocuserts were dissolved in phosphate buffer solution of pH 7.4 and the solution was stirred up to 15 minutes. After stirring drug solution was filtered through whatmann filter paper No 40 and drug content of ocusert was calculated from developed U.V spectrophotometric method of drug estimation the whole procedure was done in triplicate and average was reported.

Moisture content

The prepared ocusert s were accurated weighed individually and kept in a desicator containing calcium chloride at room temperature, after a specific time interval 3,6,12,24 and 48 hours ocuserts weighed again until they showed a constant weight and average % moisture content of ocuserts was calculated % moisture content= initialweight-final weight/initial weight x 100

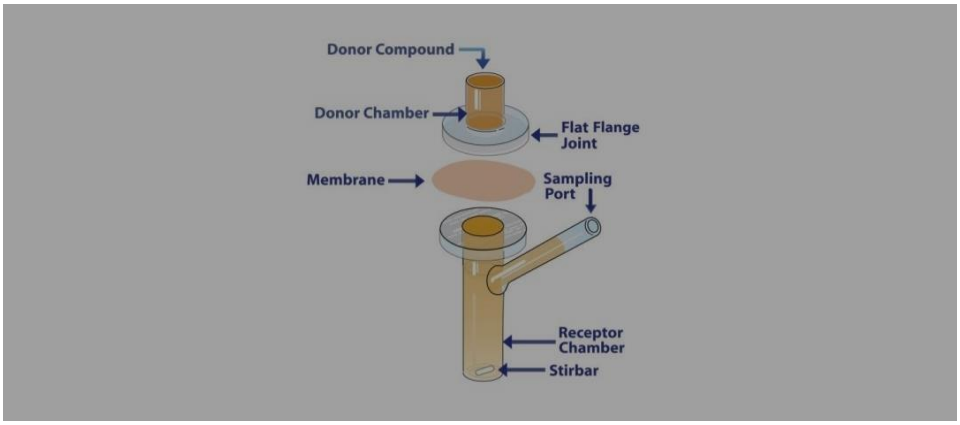
Moisture uptake

The prepared ocuserts are weighed individually and kept in a desicator containing a 100ml, saturated potassium chloride solution at room temperature and relative humidity 82.65% +/- 0.25%. After a specific time interval 3,4,12,24 and 48 hours they were taken out and weighed again and exposed at room temperature and relative humidity 82.65% +/-0.25% using a saturated solutionof potassium chloride in a desicator until a constant weight was obtained and then average % moisture uptake was calculated.[21]

%moisture uptake=final weight-initial weight /intial weight.

In-vitro drug release studies: In-vitro release of drug in phosphate buffer 7.4 pH (ophthalmic stimulated media) from prepared ocuserts was carried out using self assembled modified diffusion. We fabricated diffusion cell assembly by using a standard test tube open on both end and the diameter of 15mm.We tied corneal membrane of goat eye at the one end of the glass tube which acted as a donar compartment. The ocusert was placed inside the donar compartment of the diffusion cell with 0.2ml of phosphate buffer 7.4 PH ophthalmic saline media. Then the glass tube was suspended in the beaker such that entire surface of the membrane was in contact with the receptor compartment containing 20ml of phosphate buffer PH 7.4 and after that the whole assembly was placed on the magnetic stirrer with the constant agitation speed (50rmp) at 37^{o} c temperature. The receptor fluid was removed for drug analysis by replacing fresh receptor fluid. The concentration of drug

was determined by developed U.V spectrophotometric method of drug analysis.[22]



Ex-vivo penetration studies: The study utilizes diffusion of cells. Goat cornea is taken from the eye 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 at 37+/-0.5^{0}C 1ml of receptors compartment is spectrophotometrically analysed after particular times each sample is replaced with artificial tear fluid.

Sterility studies: The test uses Indian pharmacopeia, 2ml of ocuserts solution is aseptically transferd to fluid thioglycolate and soyabean casine, digest media. During 14 days, fluid thioglycolatemedia must be kept at 30^0 for 35^{0}c and digest soyabean casine at 20^0 to 25^{0}c.

Stability studies: Stability studies is done following ICH guidelines. Increasing the product temperature speeds up its breakdown, determining its shelf life, variation in medication concentration , colour , folding endurance etc may be tracked during stability experiments.

Applications of ocuserts

These are the device could release pilocarpine at controlled rate for a week, as opposed by conventional formulations which needed multiple daily application.[23,24]

- Treatment of glaucoma.
- Management of Conjuctivitis.
- Post_operative inflammation control.
- Treatment of dry eye syndrome.
- Delivery anti_VEGF agents.
- Treatment of retinal disease.
- Delivery of antibiotics.
- Delivery of antifungal agents

Table-1: List of ocuserts of different ophthalmic drugs (all categories) available in market

S. No	Drug	Category of drug	Polymer/Bases
1	Ciprofloxacin	Anti-Infective Agent	HPMC, MC, EC and PVP
2	Ofloxacin	Antibacterial agent	Poly ethylene oxide and EUD L100
3	Ciprofloxacin	Anti-Infective agent	Eudragit and Polyvinyl acetate
4	Norfloxacin	Antibacterial agent	HPMC, EC and PVP K-30
5	Pefloxacin	Antibiotic agent	EUD RS100, EUD RL100 and PVP K-30
6	Ofloxacin	Antibacterial agent	HPMC, PVP and PVA
7	Acyclovir	Antiviral agent	MC, HPMC, HPC and Starch
8	Acyclovir	Antiviral agent	PVA, MC, EC and Carbapol 934
9	Levofloxacin	Antibacterial agent	EC, PEO and sodium alginate
10	Brimonidine Tartrate	Intraocular pressure lowering agent	PVA, EC and PVP K-30
11	Fluconazole	Antifungal agent	HPMC, PVP and PVA
12	Natamycin	Polyene antibiotic agent	EUD L100, EUD S100, EUD RL100, HPMC and EC
13	Indomethacin	Non-steroidal anti-inflammatory agent	EUD L100, EUD RL100, HPMC and EC
14	Levobunolol	β-blocker agent	MC, PVP and HPMC
15	Levobunolol	β-blocker agent	EC and EUD RL100
16	Timolol Maleate	Anti-glaucoma agent	MC, HPC, EUD RL100, EUD RS100, EC and PVP
17	Aceclofenac	Non-steroidal anti-inflammatory agent	HPMC and EC
18	Moxifloxacin	Antibacterial agent	EUD RL100, EUD RS100 and NaCMC
19	Ketorolac Tromethamine	Non-steroidal anti-inflammatory agent	Gelatin, HPMC and EC
20	Natamycin	Polyene antibiotic agent	MC, Sodium alginate and Gelatin
21	Diclofenac Sodium	Non-steroidal anti-inflammatory agent	HPMC, and EUD L100
22	Moxifloxacin	Antibacterial agent	Chitosan, MC and HPMC K4M

Durasert technology system

Durasert technology system uses a drug core with one or more surrounding polymer layer and delivers drug for predetermined periods of time ranging from days to years.[25]

Novadur technology

Ozurdex is an intravitreal implant containing 0.7mg of daxamethosone composed of PLGA(length6.5mm, Diameter 0.45mm) approved by FAD. Ozurdex is administred by specially designed injector with a 22 gauge needle into vitreous cavity.

I-vation TA

I-Vation technology is used to delivery triamcinolone acetonide(TA) into the eye. This implants can sustain in vivo minimum for two years.[26]

NT-501

Encapsulated cell technology (neurotech pharmaceutical Inc..,) provide extracellular delivery of ciliary neutropic factor (CNTF) through long term and stable intraocular release at constant doses through a device imanted in the vitreous.

CONCLUSION

Ocular inserts are characterized as clean, thin, multilayered, medicate impregnated, strong or semisolid consistency gadgets set into the cul-de-sac or conjuctival sac, whose size and shape are particularly intended for ophthalmic application. They are made out of a polymeric bolster that might possibly contain a medication. Expanding contact time and along these lines enhancing bioavailability. Conceivable diminishment of systemic absorption and in this manner lessened systemic antagonistic impacts. Lessened recurrence of organizations and therefore better patient consistence with lower occurrence of visual side effects. In this survey, we have focused on the advanced approaches in ocular drug delivery system. Advantages with ocuserts such as, Accurate dosing Capacity to provide at constant rate and prolong drug release thus a better efficacy. Increasing contact time and thus improving bioavailability. Possible reduction of systemic absorption and thus reduced systemic adverse effects. Reduced frequency of administrations and thus better patient compliance with lower incidence of visual side effects. Advantage of inserts as dosage form Ease of handling and insertion Lack of expulsion during wear. Reproducibility of release kinetics Applicability to variety of drugs Non-interference with vision and oxygen permeability. Sterility. Stability. Ease of manufacture.

The ocular insert represents a significant advancement in the therapy of eye disease.

REFERENCES

1. Rajesh, A., Poonam, D., & Sangeeta, A. Ocular Drug Delivery System: Ocular Insert. International Journal of Universal Pharmacy and Bio Sciences, 2012; 1(2): 30-38.
2. Vasantha R, Sehgal P K, Rao P. Collagen ophthalmic inserts for pilocarpine drug delivery system. Int. J. Pharm., 1988; 47: 95-102.
3. Ashaben Patel, Kishore Cholkar et al. World Journal of Pharmacology, 2013; 2(2): 47-64.
4. Saettone M I, Toracca M T, Pagano A. Controlled release of pilocarpine from coated polymeric ophthalmic inserts prepared by extrusion. Int. J. Pharm., 1992; 86: 159-166.
5. Jacob-La, Baure J T, Kaufman H E. Investigation of pilocarpine-loaded polybutyl cyanoacrylate nanocapsules in collagen shields as a drug delivery system. Invest Opthalmol Vis. Sci., 1990; 31: 485.
6. Maichuk Y F. Ophthalmic drug Inserts. Invest. Ophthalmol, 1975; 14: 87-90.
7. La Motte J, Grossman E, and Hersch J. The efficacy of cellulosic ophthalmic inserts for treatment of dry eye. J. Am. Optom. Assoc, 1985; 56(4): 298.
8. Shirsand, S. B., Kumar, G. R., Keshavshetti, G. G., Bushetti, S. S., & Swamy, P. V. Formulation and evaluation of clotrimazole niosomal gel for topical application. RGUHS J Pharm Sci., 2015; 5(1): 32-38.
9. Rastogi SK, Vaya N, Mishra B. Ophthamic inserts: An overview. The 53. Eastern Pharmacist, February, 1996; 41-4.
10. Tangri P. Khurana S. Basics of Ocular Drug Delivery Systems, I.J.R.P.B.S. 2229-3701, Oct-Dec. 2011; 2(4): 1541-1548.
11. N.L Setala et al – Dry eye symptom are increased in mice deficient in phospholipid transfer protein (PLTP).
12. J.A.KO et al – UP regulation of ZO-1 expression and barrier function in cultured human corneal epithelial cells by substance-P.
13. K-Kimura et al – Protective effect of dexa methasone against nypoxia induced disruption of barrier function in human corneal epithelial cells.
14. Patravale VB, Data AA, Kulkarni RM – Nanosuspensions: a promising drug delivery strategy, journal of pharmacy and pharmacology, 2004.
15. Gupta H, Aqil M – Contact lenses in occular therapeutics, Drug discovery today, 2012.
16. Gulsen D, Licc, Chauhan A – Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery, current eye research, 2005.
17. Cholkar K, Patel A, Vadlapudi DA, Mitra AK – Nanomicellar formulations approaches for anterior and posterior segment occular drug delivery, recent patent on nanomedicine, 2012.
18. Watrad K, Mitra A – Drug delivery in occular disesase; Barrier and strategies. World Journal of Pharmacology, 2013.
19. Sovadinova I, Palmermo EF, Urban M, Mpiga P, Caputo GA – Activity and mechanism of antimicrobial peptide-mimetic amphilic polymethacrylate derivatives, polymers.

20. Soni V, Pandey V, Jiwari R, Asati S, Tekade RK - Design and evaluation of ophthalmic delivery formulations.
21. Lancina MG III, Yang H, Dendrimers for occular drug delivery Can Jchem.
22. Fan X, Tuures – Lunac, Azadi M, Domszy R, Hu N, Yang A, et al. evalution of commercial sof contac lenses for ocular drug delivey.
23. Prasannan A, Tsai HC. Formulation and evalution of loaded polymers [acrylic acid-co-N-isopropyl acryl amide]gel for stustained ophthalmic drug delivery.
24. Yavuz B, buzdag phelivan S. Dendrimeric system and their applications.
25. Cousery TG, Henriksson JT, Marcano DC, Shin CS, Isenhart LC, Ahmed F. An effective therapy of dry eye disease.
26. Sarath C.C., Shirwaikar A., Devi S.A. International Journal of PharmTech Research, 2010; 2: 24-26.