



Ocular Drug Delivery System - An Overview Entrenched on Ocuserts

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ABSTRACT

Human eye is the incredible design of almighty among all the sense organs in the human body as it makes us aware of various objects all over. The domain of ocular delivery of drugs is one of the most emerging and interesting challenges of pharmaceutical researchers. This speciality has considerably refined over the past three decades. The local application to the eye is the well-prominent way of administering drugs for the therapy of various eye diseases such as eye dryness, eye infection, eye flu, cataract, conjunctiva, etc. The major problem encountered with conventional eye drops is a rapid precorneal drug loss. The ocuserts symbolizes a momentous innovation in the therapy of eye disease. Ocuserts are sterile, thin, multi-layered, drug-impregnated, solid or semisolid consistency devices placed into the cul-de-sac or conjunctival sac, whose size and shape are designed for ophthalmic application. There are three major ways to prepare ocuserts such as solvent casting, glass substrate, and melt extrusion techniques and drug release characteristics principally based upon the bioerosion, osmosis, and diffusion of the drug and this review paper is an effort to deliver an outline about this novel ocular drug delivery system-ocuserts.

Keywords: ODDS, NDDS, Ocuserts, Diffusion, Osmosis, Bioerosion.

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INTRODUCTION

The eye is a vital and intricate sensory organ that we humans are gifted with. It aids us in envisioning things and also assists us in color, depth, and light perception. In addition, this sense organ is quite similar to a camera, and it helps us to see by taking light from outside and sending visual information to the brain. Of course, it is absolutely intriguing to discern the anatomy and physiology of the human eye. There are hundreds of different eye disorders and vision problems that can affect the eye and loss of vision as well. Ocular drug delivery meets prime challenges owing to distinctive anatomical and physiological characters of the eye which is delineated to shield itself from outside perilous and toxic substances.¹ They are classified as conventional and novel drug development systems. Generally, topical route of drug administration to the eye is a desired and well-accepted method for the therapy of a variety of eye illnesses. Ophthalmic dosage forms such as eye drops and eye ointments are consistently available in the market.

Eye drops are the most commonly used conventional topical ophthalmic dosage form due to the ease of administration and patient compliance. Most of the topically applied drugs are washed off from the eye by

various mechanisms (blinking, lacrimation, tear dilution and tear turnover) resulting in low ocular bioavailability of drugs.² These barriers have been taken into consideration in increasing the effectiveness of the topical ophthalmic dosage form.³

New advancements are required for ocular drug delivery systems to develop an extended period and controlled release approach in order to eliminate the shortcomings of conventional ocular drug delivery systems. Novel pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner.

Jain⁴ wrote that there has been an explosion of interest in polymer-based delivery devices in recent years. Adding further dimension to topicals thereby is the use of polymers such as collagen and fibrin fabricated into erodible inserts for placement in cul-de-sac. Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging precorneal residence times. Ocular inserts with improved ocular bioavailability and drug retention are being developed using a variety of polymeric systems.

The development of an ocular drug delivery system that will not only extend the vehicle's contact time with the ocular surface but also stymie the drug's elimination has been the focus of prior research. Ocular inserts would be the most novel approach in this field.



2. ANATOMY OF EYE^{5,6}

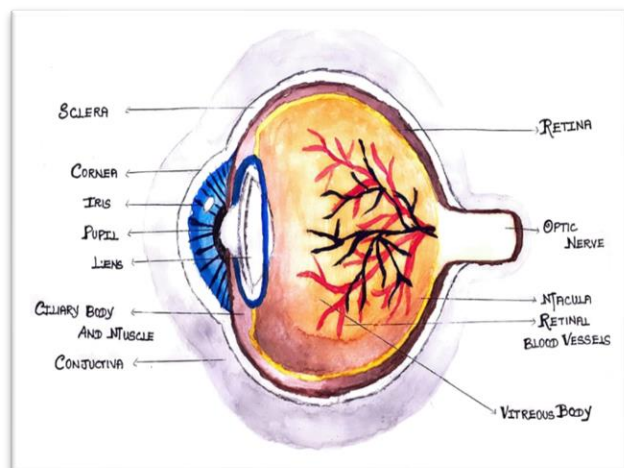


Figure 1: Structure of human eye

The human eye can be partitioned into the anterior and posterior segments. The anterior segment contains the cornea, iris, lens, and ciliary muscle, whereas the posterior segment encompasses aqueous/vitreous humor, choroid, macula, retina and optic nerve. This complex structure of the eye including the presence of static and dynamic barriers in conjunction with the efflux pumps generates a challenge for delivery of the treatment.

Vision occurs when light enters the eye through the pupil. With the help of other important structures in the eye, such as the iris and cornea, the appropriate amount of light is directed to the lens.

2.1. Iris: It regulates the amount of light entering the eye. It is the colored, visible part of the eye, located in front of the lens. Light enters through a central opening, the pupil.

2.2. Pupil: the circular opening in the center of the iris through which light enters the lens of the eye. The iris controls the dilation and constriction of the pupil.

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

2.4. Lens: a transparent structure located behind the pupil. It is surrounded by a thin transparent capsule and helps refract and focus incoming light onto the retina. During cataract surgery, the clouded lens is replaced with an artificial lens made of plastic.

2.5. Choroid: the middle layer of the eye between the retina and the sclera. It also contains a pigment that absorbs excess light, preventing blurred vision.

2.6. Ciliary body: the part of the eye that connects the choroid to the iris.

2.7. Retina: a light-sensitive layer that lines the inside of the eye. It consists of light-sensitive cells called rods and cones. The human eye contains about 125 million rods, which are necessary for seeing in dim light. The cones, on

the other hand, function best in bright light. There are between 6 and 7 million cones in the eye, which are essential for receiving a sharp, accurate image and for distinguishing colors. The retina works much like the film in a camera.

2.8. Macula: It is a yellow spot on the retina at the back of the eye that surrounds the fovea.

2.9. Fovea: It forms a small indentation in the center of the macula and is the area with the greatest concentration of cone cells. When the eye is focused on an object, the part of the image that is focused on the fovea is most accurately registered by the brain.

2.10. Optic disc: The visible (when examining the eye) portion of the optic nerve, which is also located on the retina. The optic disc refers to the beginning of the optic nerve where messages from the cone and rod cells leave the eye via nerve fibers to the visual center of the brain. This area is also called the 'blind spot'.

2.11. Optic nerve: It leaves the eye at the optic disc and transmits all visual information to the brain.

2.12. Sclera: The white part of the eye, a tough shell with which the cornea forms the outer protective covering of the eye.

2.13. Rods: They are one of the two types of light-sensitive cells in the retina of the eye. There are about 125 million rods, which are necessary for vision in low light.

2.14. Cones cells: They are the second type of light-sensitive cells in the retina of the eye. The human retina contains between six and seven million cones; they function best in bright light and are essential for sharp vision (receiving a sharp, accurate image). There are thought to be three types of cones, each sensitive to the wavelength of a different primary color - red, green, or blue. Other colors are perceived as combinations of these primary colors.

3. CONVENTIONAL OPHTHALMIC FORMULATIONS⁷

3.1. Eye drop:

It is a liquid preparation in which all ingredients are completely dispersed in solution. Absorption in the eye is limited via the corneal epithelium. When eye drops are administered topically, only less than 5% of the administered dose is absorbed. The residence time of the ophthalmic solution in the eye may be influenced by various properties of the ophthalmic solution such as hydrogen ion concentration, viscosity, etc.

3.2. Eye gel:

This is a semi-solid preparation consisting of either small or larger molecules permeated with a liquid. When applied to the ocular region, this preparation results in increased drug absorption, longer contact time, prolonged duration of action/therapeutic effect, and reduced dosing frequency compared to solutions.

3.3. Eye ointment:

It is a sterile, semi-solid, anhydrous preparation in which the drug is dispersed in a suitable, non-irritating base such as mineral oil and white petroleum. Ophthalmic ointment remains popular as a pediatric dosage form. The ointment provides longer contact time and higher bioavailability of the drug after application to the eye, but its use is limited to night time application because its greasy nature impairs vision.

3.4. Eye suspension:

Eye suspensions are preparations in which the active ingredients, insoluble in an aqueous carrier, are dispersed with the aid of a suitable suspending and dispersing agent. The ophthalmic suspensions contain small particles that are non-irritating to the eye. These particles are retained in the cul-de-sac region, resulting in increased bioavailability of the drug.

4. LIMITATIONS OF CONVENTIONAL OPHTHALMIC DOSAGE FORMS ⁸

Ocular drug administration is subject to the following limitations:

- They show poor bioavailability due to;
 - ÷ conjunctival absorption
 - ÷ efflux of solution via the nasolacrimal route
 - ÷ Rapid precorneal excretion
 - ÷ Normal tear turnover
- Viscous vehicles may cause blurred vision
- Frequent instillation is required to achieve therapeutic effect of concentrated drug
- Adverse effects following instillation of ophthalmic formulations due to systemic absorption of the drug and nasolacrimal drainage of the additives
- Delivery of the drug is generally not correct due to inconsistency in drop size of ophthalmic drugs
- Discontinuation of the dosage form is not possible in the event of an emergency
- Impairment of vision
- Difficulty in placing and removing the dosage form
- Loss of the drug may occasionally occur during sleep or when rubbing the eyes

5. NOVEL OPHTHALMIC DELIVERY SYSTEM ⁹

To overwhelm the limitations of conventional ophthalmic dosage forms, various approaches have been consummated to better pre-corneal drug absorption and minimizing pre-corneal drug elimination.

5.1. Mucoadhesives:

They are the formulation which is retained in the eye by virtue of noncovalent bonds accomplished with the corneal conjunctival mucin for improving the precorneal residence time.

5.2. Phase transition system:

It is a liquid formulation that converts into the gel when instilled into the cul-de-sac of the eye and remains in contact with the cornea of the eye for a prolonged period of time.

5.3. Liposomes:

Liposomes are nano-sized to micro-sized vesicles comprising a phospholipid bilayer that surrounds an aqueous core. The lipophilic drug is entrapped in a bilayer of lipids and hydrophilic drug in aqueous phase and thus the residence time of a drug in the eye can be increased.

5.4. Niosomes:

Niosomes are vesicular systems consisting of non-ionic surfactant bilayer, in which both hydrophilic and lipophilic drugs can be enclosed in aqueous or in vesicular lipid membranes. It prevents the enzymatic metabolism of the drugs and improves the precorneal residence time of the drug.

5.5. Nanoparticles:

Nanoparticles are spherical, polymeric particles composed of natural or artificial polymers. They range in size between 10 and 500 nm, in which the drug is entrapped to provide a sustained effect.

5.6. Contact lenses:

The drug saturated contact lenses are placed in the eye which releases the drug in the eye for a prolonged period of time. Hydrophilic or water-soluble drugs soaked in drug solution can be absorbed through contact lenses and thus hydrophilic contact lenses can be used for improving ocular residence time of drug.

5.7. Vesicular systems

They are developed to provide enhanced ocular contact time and sustained effect of the drug.

5.8. Ophthalmic inserts:

Ocuserts are flexible, solid and flat devices that consist of drug reservoir and rate controlling membrane by using various polymers and can overcome the limitations of conventional ophthalmic dosage forms such as aqueous solutions, ointments and suspensions. In most cases, all sorts of ocusert are made up of three components: "a central drug reservoir," in which the drug is embedded in a polymer; rate-controlling membrane, which makes certain that the medication is released from the drug reservoir in a controlled manner; and "an outer annular ring" for convenient handling and placement.

5.8.1. Advantages:

Ocuserts offer the following advantages over conventional ophthalmic dosage forms ^{4, 10, 11}

- + Increased eye contact time and thus improved bioavailability of the drug
- + Increased ocular permeation compared to the standard formulation, resulting in prolonged drug activity and thus increased ocular bioavailability of the drug
- + Administration of a precise dose in the eye allows for better therapy
- + Better patient compliance by reducing the number of doses administered
- + Better efficacy due to consistent drug release
- + Increased ability to target internal ocular tissue through non-corneal penetration routes
- + chances of targeting internal ocular tissues via conjunctiva and sclera routes
- + The prohibition of the use of preservatives to minimize the risk of sensitivity reactions
- + Longer shelf life compared to standard formulation due to the absence of water
- + Lower systemic absorption and therefore lower adverse effects. diminished number of doses for better patient compliance

6. MECHANISM OF CONTROL DRUG RELEASE INTO THE EYE ^{11, 12, 13, 14}

The mechanism of controlled release of drugs into the eye is as follows:

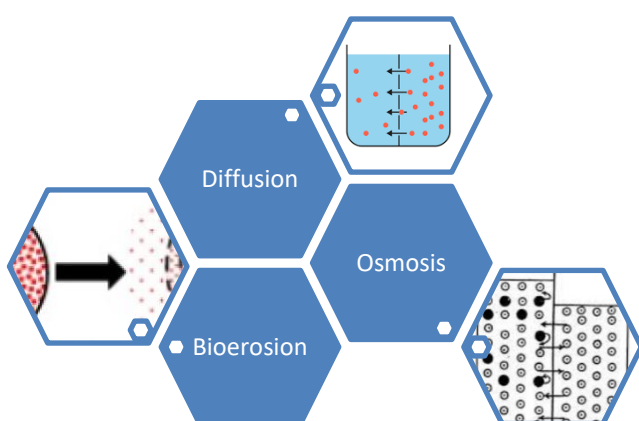


Figure 2: A Schematic Representation of Mechanism of Controlled Release of Drugs

6.1. Diffusion

In the diffusion mechanism, the active ingredient is released unceasingly and at a controlled rate through the membrane into the tear fluid, when the insert consists of a solid, non-erodible body with pores and dispersed drug. The drug is released through the pores by diffusion. The

controlled release of the drug can be further regulated by the gradual dissolution of the solid dispersed drug and thus the matrix as a result of the directional diffusion of aqueous solutions. In a soluble device, the actual dissolution occurs mainly as a result of swelling of the polymer. In swelling-controlled products, the drug 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 into the eye, water from the tear fluid begins to penetrate the matrix, whereupon swelling occurs, resulting in relaxation of the polymer chain and diffusion of the drug. The dissolution of the matrix follows the swelling process, which depends on the polymer structure.

6.2. Osmosis

In the osmosis mechanism, the insert consists of a transverse impermeable elastic membrane dividing the interior of the insert in to a first and second compartments, the first compartment bounded by a semipermeable membrane and the impermeable elastic membrane, and the second compartment being bounded by an impermeable and elastic membrane. The impermeable wall of the insert contains an opening for release of the drug. The first compartment contains a solute that cannot penetrate the semipermeable membrane, and the second compartment provides a reservoir for the drug, which is in liquid or gel form. When the insert is introduced into the aqueous environment of the eye, water diffuses into the first compartment and expands and contracts the second compartment, forcing the drug through the drug release orifice.

6.3. Bioerosion

In the bio-erosion mechanism, the insert consists of a matrix of bio-erodible material in which the drug is dispersed. When the insert comes into contact with the tear fluid, there is a controlled, sustained release of the drug by bio-erosion of the matrix. The drug may be homogeneously dispersed in the matrix, but it is believed that a more controlled release is achieved when the drug is concentrated superficially in the matrix.

7. FORMULATION METHODS OF OCUSERTS ^{15, 16, 17}

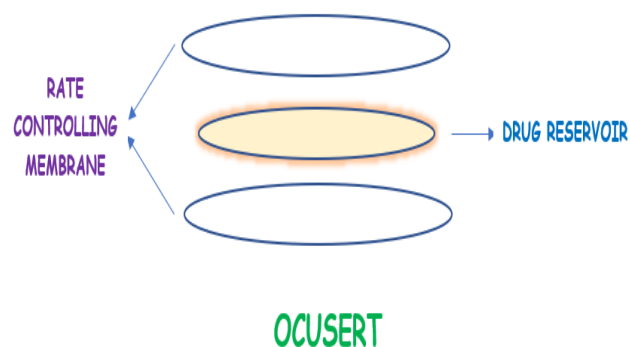


Figure 3: A Schematic Diagram of Ocusert

7.1. Solvent casting method

In this method, several batches are prepared in different ratios. The polymer is dissolved in a suitable solvent. The plasticizer is added to this solution with constant stirring. The accurately weighed amount of the drug is added to the above solution and a uniform dispersion is obtained. When the proper mixture is formed, the solution is poured into a Petri dish with an inverted funnel to allow slow and uniform evaporation at room temperature until the film is dried. The dried films thus obtained are cut into the correct size and shape with a cork borer and stored in an airtight container.

7.2. Glass substrate technique

In this method, the polymer is soaked in a 1% acetic acid solution for 24 h until a clear solution is obtained. The solution is filtered. The required amount of drug is added and shaken for 15 min to dissolve the complex in the polymer solution. A plasticizer is added to the above solution. The resulting viscous solution is set aside for 30

min until the air bubbles are removed and the rate-controlling films are formed. The films are cast by pouring the solution into the centre of a leveled glass mold and allowing it to dry at room temperature for 24 h. The dried films are cut so that they have a specific shape and size. The matrix is then sandwiched between the speed-controlling membranes using a non-toxic, non-irritating and water-insoluble gum. They are wrapped separately in aluminium foil and stored in a desiccator.

7.3. 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 is cutted into appropriate size and packed in polyethylene lined aluminium foil, heat sealed and sterilized by gamma radiation.

The following hierarchical information shows the list of various classes ocuserts.

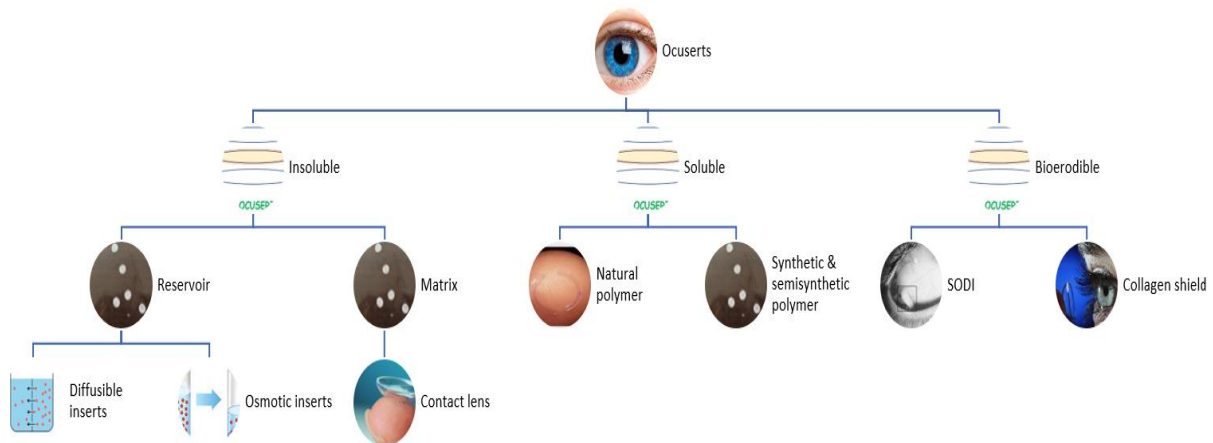


Figure 4: A hierarchical Model of Classification of Ocuserts

8. EVALUATION PARAMETERS OF OCUSERTS 10, 18-26



Figure 5: A Schematic Representation of Evaluation of Ocuserts

8.1. Physical Characterization

The ocuserts are evaluated for their physical characteristics such as shape, colour, texture, and appearance. Thickness Ocuserts are evaluated using a vernier caliper at different spots of the patches. The average of 6 readings is taken at different points and the mean thickness is calculated. The standard deviations in thickness are computed from the mean value.

8.2. Weight variation

Six ocuserts are taken from each batch and their individual weights are determined by using a digital electronic balance. Then the mean and standard deviation are calculated.

8.3. Thickness of film

Film thickness is measured by using the Dial caliper at different points of the formulation and the mean value is calculated.

8.4. Folding Endurance

Folding endurance was determined by repeatedly fold the film at the same place till breaking or first sign of breaking. The number of times the film could be folded at the same place without breaking gives the folding endurance value.

8.5. Swelling index

A small amount of the film is first cut and weighed and then soaked in tear fluid with a pH of 7.4 for 1 h. After 1 h, the film is weighed again. The swelling index is calculated according to the following formula.

$$\text{Swelling index} = \frac{\text{initial weight} - \text{weight of swollen insert}}{\text{initial weight}} \times 100$$

8.6. Surface pH

The inserts are allowed to swell in a closed petri dish at room temperature for 30 min in 1 mL of distilled water. The swollen device is removed and solution is placed under a digital pH meter to determine the surface pH.

8.7. Moisture Absorption

The percentage moisture uptake test is carried out to check physical stability or integrity of ocuserts. Ocuserts are weighed and placed in a desiccator containing 100 mL of saturated solution of aluminium chloride by which a humidity of 79.5 % RH is maintained. After three days the ocuserts are taken out and reweighed, the percentage moisture uptake is calculated by using formula.

$$\% \text{ Moisture Uptake} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

8.8. Moisture Loss

The percentage moisture loss is carried out to check integrity of the ocuserts at dry condition. Ocuserts are weighed and kept in a desiccator containing anhydrous calcium chloride. After 3 days, the ocuserts are taken out and reweighed; the percentage moisture loss is calculated using the formula.

$$\% \text{ Moisture loss} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

8.9. Content Uniformity

The ocuserts are placed in 5 mL of pH 7.4 STF and are shaken in orbital shaker incubator at 50 rpm to extract the drug from ocuserts. After incubation for 24 h, the solution is filtered through a 0.45 µm filter and the filtrate is suitably diluted with STF solution. The absorbance of the resulting solution is measured using a UV-spectrophotometer.

8.10. Ocular Irritation

The potential ocular irritation of the ocusert under test are evaluated by observing them for any redness, inflammation, or increased tear production. Formulation is tested on five rabbits by placing the inserts in the cul-de-sac of the left eye. Both eyes of the rabbits under test were examined for any signs of irritation before treatment and were observed up to 12 h.

8.11. In Vitro Studies

Whole eyeball of the goat is transported from a local butcher shop and the cornea is carefully isolated along with 2 to 4 mm of surrounding tissue and washed with cold normal saline free from proteins. Isolated cornea is mounted between clamped donor and receptor compartments of Franz diffusion. A strip of film (1cm) placed in the donor compartment and the solution (pH 7.4 STF) in the receptor compartment were stirred at 100 rpm using a magnetic stirrer and the temperature should be maintained at 37 °C ± 5 °C. At 15, 30, 45, 60, 90, 120 and 150 min time intervals 0.5 mL of test sample is removed from the receptor and the volume is replaced by adding a fresh buffer. The test samples are filtered and the absorbance of each sample is measured using UV spectrophotometer and reagent blank (pH 7.4 STF). The absorbance is converted into concentration by using the standard curve. The release rates are calculated and the graphs were plotted taking time on X- axis & cumulative amount on Y- axis.

8.12. In Vivo Drug Release Study

The ocuserts were sterilized by using UV radiation before *in vivo* study. After sterilization, ocuserts are transferred into a polyethylene bag with the help of forceps inside the sterilization chamber itself. Albino rabbits of either sex, weighing between 2.5– 3.0 kg, are used for the experiment. The ocuserts are taken for *in vivo* study is placed into the lower conjunctival cul-de-sac. The ocuserts are inserted into each of the six rabbits and at the same time the other eye of six rabbits serves as control. Ocuserts were removed carefully at 30, 60, 90, 120, and 150 min and analyzed for drug content. The drug remaining was subtracted from the initial drug content of ocuserts that will give the amount of drug released in the rabbit eye.



9. LIST OF OCUSERTS ^{10,15}

The following table shows the list of ocuserts of different drugs with their polymer base.

Table 1: List of Ocuserts of different classes of drugs with their polymer base

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

CONCLUSION

It is obvious that administering medications to the eye is connected to serious and substantial consequences. The pH-dependent solubility of the traditional dosage form, which is very low, necessitates repeated administration every 4 h and the development of crystalline deposits on the cornea. Ocular inserts represent a significant advance in the treatment of ocular diseases. Ocular Inserts were created to cater to the increasing number of patients who need less invasive treatments. Ocular inserts are clean, thin, multi-layered, drug-impregnated gadgets of solid or semi-solid consistency. They are inserted into the cul-de-sac or conjunctival sac and whose size and shape are specifically designed for ophthalmic use. They are made of a polymeric carrier that may contain a drug. They prolong contact time and thus improve bioavailability. Ocuserts promote patient compliance by reducing the number of dosage administrations. It is possible to lessen systemic side effects, which will lessen negative effects. To lower the danger of hypersensitivity responses, preservatives may be banned. Ocular inserts can be evaluated using a variety of

factors and are produced using a variety of processes. Ocuserts are innovative methods in the era of the ocular drug delivery system.

In this review, we have concentrated on novel methods of ocular medication administration. Ocuserts have the following benefits: precise dosing, consistent dosing, and delayed drug release, which leads to improved efficacy. lengthening of the contact period, improving bioavailability. Perhaps less systemic absorption, which would mean less systemic adverse effects. Less frequent administration results in improved patient compliance and less frequently occurring visual side effects.

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