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AN OVERVIEW OF OCULAR DRUG DELIVERY SYSTEM: REFERENCE TO IMPREGNATE BARRIERS

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ABSTRACT
Eye is the organ of sense of sight, situated in the orbital cavity. It is a delicate organ and which is protected by several structures. Delivery of ocular drugs to the targeted ocular tissues and maintenance of required therapeutic drug concentration is very difficult due to presence of various precorneal, dynamic and static barriers. Ocular bioavailability is usually only 1%-7% of the applied dose. To overcome barriers in ocular drug delivery, the alternate delivery routes to conventional ones allowing for more direct access to intended target sites and development of novel drug delivery systems providing better permeability, treatability and controlled release at target site. Ocular inserts are Convenient, safe, high patient acceptability, non-invasive and cost effective. It increases accurate dosing, overcome the side effects produced by conventional systems, provides sustained and controlled drug delivery, Increase the ocular bioavailability of drug by increasing the corneal contact time, provides targeting within the ocular globe so as to prevent the loss to other ocular tissues, overcome the protective barriers like drainage, lacrimation and conjunctival absorption, provides comfort, better compliance to the patient and to improve therapeutic performance of drug. Although, there are many advantages in the ocular delivery system, there is poor standardization techniques only available to evaluate the pharmacodynamic and pharmacokinetic effects of drugs**.** This study summarizes the challenges of ocular drug delivery preparation and evaluation in the ocular drug delivery system.

KEYWORDS: Ophthalmic inserts, Naso-lacrimal duct, Contact lens, Niosomes, Pharmacosomes, Discomes.

INTRODUCTION
The field of ocular drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical sciences. This field has significantly improved over the past 10 to 20 years. It is very difficult to obtained specimen to eye tissue contain drugs from human, consequently one is compelled to use animal model as guide. The anatomy, Physiology and biochemistry of eye render this organ impervious to foreign substances. It is a challenge to the formulator to circumvent the protective barriers of the eye so that the drug reaches the BioPhase in sufficient concentration physiological barriers to diffusion and protective absorption of topically applied drug exist in the pre - corneal and corneal spaces. The precorneal constrains responsible for poor ocular bio availability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution tear turnover and conjunctival absorption. The ophthalmic dropper delivers 52 to 75 µL of the eye drops if the patient does not blink the eye can hold about 30 µL without spilling into the cheek. The natural tendency of the cul-de-sac is to reduce its volume to 7 to 10 µL. Tears dilute the drug remaining in the cul-de-sac which reduces the trans corneal flux of the drug a basic concept shared by most scientist in optimal research and development is that the therapeutic efficacy the ophthalmic drug can be greatly improved by prolonging its contact with the corneal surface. Recently drug– pre-soaked hydrogel contact lens and pledgets have gained some popularity in an attempt to bypass to need for repetitive drug dosing. However, the prime objective of developing a truly continuous, controlled delivery of opthalmically active drugs to the eye was not satisfactorily accomplished until the development of the ocusert system.[1]

ANATOMY AND PHYSIOLOGY OF EYE
Eye is the organ of the sense of sight, situated in the orbital cavity. It is delicate organ and which is protected by several structures. The cornea, lens and vitreous body are all transparent media with no blood vessels oxygen and nutrients are transported to this non vascular tissue by the aqueous humour. Aqueous humor is a clear fluid fills the space between cornea and lens. It is secreted by

capillaries of ciliary process. From here the fluid reaches to the anterior chamber which finally reaches to the canal of Schlemm. The aqueous humor has a high oxygen tension and above the same osmotic pressure as blood. Interference with drainage of aqueous humor results in an increase of intraocular pressure (glaucoma). This leads to atrophy of the retina, leading to blindness. The cornea also derives part of its oxygen need from the oxygen, and if the oxygen is excluded the anaerobic metabolism results in an increase in the intracorneal lactic acid concentration. The cornea is covered by a thin epithelial layer continuous with the conjunctiva at the cornea – sclerotic junction. Its posterior surface is covered by a layer of endothelium. The eye is constantly cleansed and lubricated by the lacrimal apparatus which consists of four structures. (i) lacrimal gland, (ii) lacrimal canal, (iii) lacrimal sac, and (iv) naso lacrimal duct. The lacrimal fluid in human as a normal volume of 7 µL and is an isotonic aqueous solution of bi carbonate and sodium chloride pH 7.4 that serve to dilute irritant or to wash the foreign bodies out of the conjunctival sac the aqueous humour in human has a volume of approximately 300 µL that fills the anterior chamber of the eye. Aqueous humour is secreted by ciliary process and flows out of the anterior chamber at a turnover rate of approximately 1% per min.[2]

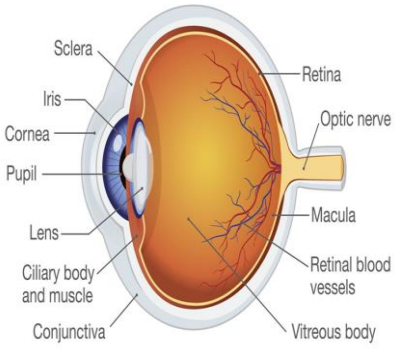

Fig. 1: Anatomy of the eye

BARRIERS TO OCULAR DRUG DELIVERY

Delivery of Ocular drugs to the targeted Ocular tissues and the maintenance of required therapeutic drug concentration is very difficult due to presence of various Precorneal, dynamic and static barriers. As a result, Ocular Bioavailability is usually only 1%-7% of the applied dose. These barriers can also be classified as anatomical and physiological barriers.

A. Anatomical Barriers

1. **Cornea:** The cornea is mainly composed of five sections: Epithelium, Bowman's membrane, stroma, Descemet's membrane and Endothelium. Epithelium act as principle barrier. Stroma, consist of multiple layers of hexagonally arranged collagen fibres containing aqueous pores or channels. It allows hydrophilic drugs to easily pass through but it acts as a significant barrier for lipophilic drugs.
2. **Sclera and Conjunctiva:** The Conjunctiva is more Permeable than Cornea especially for hydrophilic molecules. High vascularity renders this route not suitable for drug delivery as the blood vessels remove a large fraction of absorbed dose. Only a small fraction of the dose reaches the vitreous.
3. **Blood-Ocular Barriers:** These barriers have two parts: blood-aqueous humour barrier and blood-retina barrier. The anterior-blood ocular barrier is composed of the endothelial cells in the uvea. This barrier limits the access of hydrophilic drugs from plasma into the aqueous humour. Inflammation may disrupt the integrity of this barrier. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium and the tight walls of retinal capillaries. Therefore, only a minute fraction of the intravenous or oral drug dose gains access to the retina.

B. Physiological Barriers

The physiological barriers include nasolacrimal drainage of drug solution, reflux blinking, increase lacrimation, and tear turn over, tear dilution, metabolism and non-productive absorption.

Methods to Overcome Barriers

The first approach to overcome barriers involves using alternate delivery routes to conventional ones allowing for more direct access to intended target sites. The second approach involves development of novel drug delivery systems providing better permeability, treatability and controlled release at target site.

NOVEL OCULAR DRUG DELIVERY SYSTEM

1. Particulate system

a) Microspheres and Nanoparticles: These represents promising drug carrier for ophthalmic applications after optimal binding to these particles, the drug absorption in the eye is enhanced significantly in comparison to eye drops solution owing to much slower ocular elimination rate of particles. Smaller particles are better tolerated by patients than larger particles therefore nanoparticles may represent very comfortable ophthalmic prolonged action delivery systems.

b) Nanoparticles: Nanoparticles are defined as particles with a diameter of less than 1µm, comprising of various biodegradable or non-biodegradable polymers, lipids, phospholipids, or metals. Nanoparticles provide sustained release and prolonged therapeutic activity when retained in the cul-de-sac after topical administration and entrapped drug must be released from the particles at an appropriate rate.

2. Vesicular systems

a) Liposomes: Structural diversity of liposomes in terms of size, composition, surface charge, bilayer fluidity and ability to incorporate almost any drug regardless of solubility or to carry on their surface cell specific ligands have been used for the production of formulation that are optimal for clinical use. There are several advantages of liposomes over other delivery systems especially in ocular drug delivery; i) Controls the rate of release of encapsulated drug ii) Relatively non-toxic iii) Non-irritant and do not obscure vision iv) Biodegradable nature. The topical installation is the most convenient and frequent means of administration for ophthalmic therapy and most studies have administered liposomes by this route. Liposomes can enhance or reduce the ocular absorption of encapsulated agents applied to the eye. Several studies have specifically investigated the interaction of liposomes with corneal epithelium. Liposomes and collagen shields have been used as ophthalmic drug delivery devices.

b) Niosomes: Niosomes behave in vivo like liposomes prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. There are many advantages of niosomes in ocular drug delivery as follows; i) They are chemically stable as compare to liposomes ii) They can entrap the hydrophilic and hydrophobic drugs iii) Nontoxic, biodegradable, biocompatible and nonimmunogenic.

c) Pharmacosomes: Most topically applied ophthalmic drugs gain access to their receptor site within eye by transcellular diffusion across the corneal epithelium being lipoidal in nature may present a high resistance to ionic or relatively hydrophilic drug. This resistance can be overcome by pharmacosome approach which produces prolonged drug delivery pattern. Various advantages of pharmacosome approach; i) The problem of drug incorporation, leakage from the carrier on insufficient self-stability is avoided ii) Drug metabolism can be decreased iii) Controlled release profile could be generated.

d) Discomes: Disomes are thus large (12-60 µm) structures formed by solubilization of nisosmes with a non-ionic surfactant solulan C24. Various advantages of discomes in ocular drug delivery include; i) Housing of drug in cul-de-sac becomes easier ii) Increased patient compliance iii) Zero order release can be easily attained iv) Minimal opacity imposes no hindrance to vision.[1]

OPTHALMIC INSERTS

In the recent years, there has been explosion of interest in the polymer-based delivery devices. 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. Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency. The desired criteria for a controlled release ocular insert are: 1. Comfort 2. Lack of explosion 3. Sterility 4. Stability 5. Easy of handling and insertion.

I. Non-Erodible Inserts

A) Ocusert: It is a flat, flexible, elliptical device consisting of three layers. Two outer layers of ethylene vinyl acetate (EVA) ecloses the inner core of pilocarpine gelled with alginate. A retaining ring of EVA Impregnated with titanium dioxide for visibility. The higher release of ocusert pilot 40 is achieved by making its rate controlling membrane thinner and the use of flex enhancer dye (2 ethyl-hexyl) phthalate. The introduction of ocusert there has been a proliferation of erodible inserts. However, none of them are comparable to ocusert with respect to duration of action. Although the advantage of precise controlled rate of delivery has been achieved with ocusert.[2]

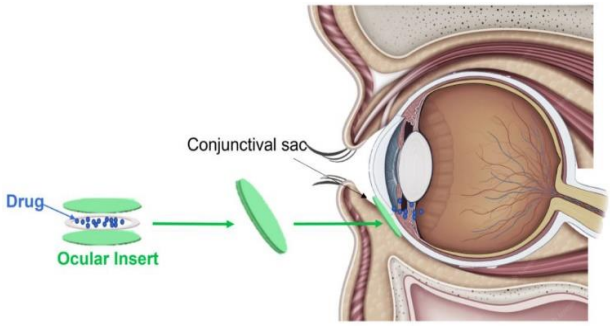

Fig. 2: Impregnation of Ocuserts.

Advantages of ocusert: a) To provide better housing of delivery system. b) Vision and oxygen permeability are not interfered. c) Increased comfort and patient compliance. d) To provide sustained and controlled drug

delivery. e) Less frequent dosing is required unlike conventional dosage form. f) Barriers like drainage lacrimation can be avoided.[3,4]

Disadvantages of Ocusert: a) Leakage can happen. b) Difficult placement and intervention with vision. c) It requires preservatives. d) It suffers loss during sleep or while rubbing eyes. e) Dosage form cannot be terminated during emergency.[5,6,7]

CLASSIFICATION OF OCUSERT

The classification of ocuserts was shown in the Fig. 3.[08]

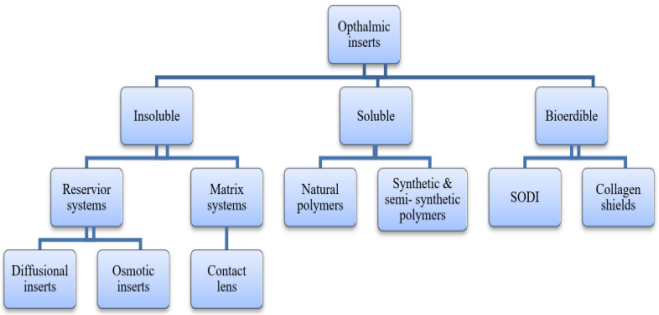

Fig. 3: Classification of Ocuserts.

B. Contact lens

The use of pre-soaked hydrophilic contact lenses for ocular drug delivery has been examined for a drug. Therapeutic soft lenses are often used to aid corneal wound, healing in patients with infection, corneal ulcers, characterized by marked thinning of cornea. Overcoming the disadvantages an alternate approach to pre-soaking soft contact lenses in drug solution is to incorporate the drug either as a solution or suspension of solid particles in the monomer mix. The polymerization is then carried out to fabricate the contact lenses. This technique has demonstrated the promise of longer times of release upto 180h as compared to presoaked contact lenses. The greatest advantage with the use of contact lenses has been the problem of discomfort and difficulty in handling on insertion particularly in case of pre-soaked contact lenses.[2]

II. Erodible Inserts: Erodible inserts containing hydrophobic polycarboxylic acids there is three devices have been marketed such as 1. The Lacrisert 2. Soluble ocular drug insert (SODI) 3. Minidisc

a) Lacrisert: The lacrisert is a sterile rod-shaped device made of hydroxypropyl cellulose without any preservative is used for the treatment of dry eyes syndrome. It is inserted into the inferior fornix were it imbibes water from conjunctiva and cornea forms a hydrophilic film with stabilizes tear film and hydrates and lubricates the cornea. Replacement of four times an hour regimen by once or twice daily regimen by once or twice daily is the benefit achieved by with this dosage form.

b) Soluble ocular drug insert (SODI): It is a small oval wafer in the form of sterile thin films of oval shape after introduction in the inferior cul-de-sac where wetted by the tear film with soft ends in 10-15 seconds and assumes the curved configuration of the globe. A single SODI application has replaced 4-12 drops installation or 3-6 applications of ointment and constitutes a valid once a day therapy for the treatment of glaucoma and trachoma.

c) Minidisc: Minidisc consist of contoured disc with the convex front and a concave back surface in the contact with the eye ball. It is like a miniature contact lens with a diameter of 4-5mm. The in vivo dissolution studies demonstrated a drug was released from minidisc for 170 h.[2]

MECHANISM OF OCULAR INSERT DRUG RELEASE

The three types of mechanism of ocular insert drug release were mentioned as flow chart in the Fig. 4.[09]

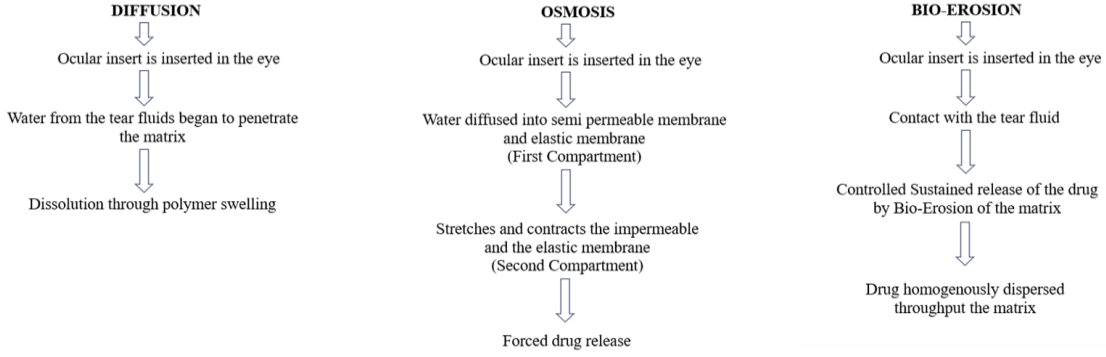

Fig. 4: Mechanism of Ocular Insert Drug Release.

ROLE OF POLYMERS IN OCULAR INSERT

a) **Polyvinyl alcohol (PVA):** some formulations may lead to high dryness so PVA used to relieve and soreness particularly where the is caused by reduced flow of tear.
b) **Polyvinyl pyrrolidine (PVP):** It is used as substitute for PVA and used for temporary relief of burning, irritation, and discomfort due to dryness of eye.
c) **Methyl cellulose:** it is used to increase the solution viscosity from 1 to 100 cps through the incorporation of methyl cellulose reduce the solution drainage rate constant.
d) **Carboxymethyl Cellulose:** This polymer was used in formulation to treat dry eyes and high irritation and also used to lubricate and re-wet soft and rigid gas permeable contact lenses.
e) **Hydroxypropyl Methyl Cellulose:** hydroxypropyl methyl cellulose may also be used to moisten hard contact lenses and artificial eyes. In addition, it may be used in certain eye examination.
f) **Eudagrit 100:** It is selected as a positively charged polymer to prepare muco-adhesive nano particles as it increases the interaction between mucin and nanoparticles such that drug bioavailability increased.
g) **Glycerine:** it is an ophthalmic demulcent forms a soothing film that works by lubricating the eyes mucus membrane surface.
h) **Sodium Hyaluronate:** it helps to relieve dry eyes by increasing tear film stability and reducing tear evaporation. It protects the eye after an injury such as a corneal abrasion.

METHODS FOR PREPARATION OF OCUSERT

1. Solvent casting method: in this method solvent is used to dissolve the polymer. This mixture is continuously stirred with addition of plasticizer. The drug has been precisely weighed and added to the above solution homogenous dispersion produced. After the preparation the liquid is put into a Petri dish with an upside-down funnel so that it can evaporate gradually and uniformly at room temperature until the film dries. Using a cork borer the dry films are then sliced into appropriate shape and size and kept in an air tight container.

2. Glass substrate Method: this method produces a transparent solution by immersing the polymers in a one percentage v/v acetic acid solution for 24 h. filtration is done on the solution for 15 min, the required amount of medication is added and dissolve to the complex in the polymer solution. Plasticizers solution, it is set aside for 30 min to eliminate air bubbles. In order to cast the films, a solution is poured into the centre of a levelled glass mould. And the mould is let dry for 24 h at room temperature. The dry films are cut into specific shape and size.

3. Melt extrusion Met: In this the medication and the polymer are combined, weighed and run through a sieve with 60# Sieve size and plasticizer added to this combination after that the mixture is poured into the melt flow rate device container and extruded. The extrudate was sliced to the proper size, sealed with heat.[10]

EVALUATION OF OCULAR INSERT

1. **Organoleptic properties:** Ocuserts where evaluvated for organoleptic properties colour, appearance, texture.
2. **Thickness of film:** The thickness of occusert was determined by vernier calliper at five separated points of each device of least count of 0.01mm. For each, formulation six randomly selected ocuserts are tested for their thickness. The standard deviation in thickness were computed from mean value.[11]
3. **Uniformity of weight:** All prepared films are weighed individually using electronic balance and then the average weight of film is calculated. The standard deviation is calculated from mean value.
4. **Uniformity of drug content:** The ocuserts were immersed in 5ml of pH 7.4 phosphate buffer saline and shaken at 50 rpm in an orbital shaker incubator to extract the drug. After 24h incubation period, the mixture was filtered using 0.45µm filter, and the resulting filtrate was measured at 254nm.[12]
5. **Moisture uptake:** The percentage moisture uptake was carried out to check the physical stability or integrity of ocuserts. Ocuserts were weighed and placed in a desicator containing 100ml of saturated solution of Aluminium chloride by which a humidity of 79.5% RH maintained. After 3 days ocuserts were taken out and re-weighed.[13] % Moisture uptake = $\frac{final\ weight - Initial\ weight}{initial\ weight} \times 100$
6. **Moisture loss:** The percentage moisture loss done to check the integrity of film in Dry conditions. The ocular inserts are weighed and kept in desiccators containing anhydrous calcium chloride. After few days, the ocular inserts are taken out and reweighed; percentage moisture loss is calculated by following formula.[13] % Moisture loss = $\frac{final\ weight - Initial\ weight}{initial\ weight} \times 100$
7. **Surface pH:** Ocusert placed in closed petri plate in water for half an hour. After this time the swelling of ocusert occurred. Swollen insert is placed in digital pH meter to determine the surface pH.
8. **Folding Endurance:** Folding endurance is expressed as the number of times the insert is folded at the same place, either to break specimen or to develop visible cracks. The specimen was folded in the centre, between the fingers and thumb and then opened. The process is repeated several times till the insert showed breakage or cracks in centre of insert.
9. **Ocular Irritation:** The ocular irritation and damaging effects of ocusert under test were evaluated by observing them for any redness, inflammation, or increased tear production. Formulation is tested on six rabbits by placing the drug in 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 12h.

10. **Sterility Test:** Sterility test is performed according to Indian Pharmacopoeia. 2ml of prepared ocusert solution is removed and is transferred to fluid thioglycolate medium and soyabean-casein digest medium separately. The media are then incubated for not less than 14 days at 30℃ to 35℃ in case of thioglycolate and 20℃ to 25℃ in the case of soyabean-casein digest medium.[14]
11. **Invitro drug release study:** Diffusion cell method was utilized to conduct this study. An open cylinder used as donor compartment is lined with pre-hydrated cellophane membrane. Simulated tear fluid touches the membrane's ocusert. Using a magnetic stirrer, the simulated tear fluid is mixed and kept at 37± 0.5℃. after certain times,1ml of receptor compartment is spectrophotometrically analysed for each sample artificial tear fluid is added.[15]
12. **Stability studies:** In compliance with guidelines stability experiments were performed on ocular inserts. The eyepiece inserts were kept for two months at 40℃ and 75% humidity. The following storage formulations in vitro drug release tests, physical appearance and drug content were assessed.
13. **In vivo drug release study:** Prior to the in-vivo investigation, the ocuserts were sterilized using UV light for one hour. Following an appropriate dilution with pH 7.4 phosphate buffer, the efficacy of pure medication that was sterilized along with the ocuserts was assessed using a UV spectrophotometer. For the experiment, albino rabbits of either sex weighing 2.5-3.0 kg were used. The drug containing ocuserts were removed for the in vivo investigation; they were inserted into the lower conjunctival cul-de-sac after being previously sterilized on the day of the experiment. Each of seven rabbits were received an ocusert while the other seven rabbit eyes function as a control. After carefully removing the ocusert 1, 2, 4, 8, 12, 16 and 20 hours. To determine drug released in the eye, the leftover drug was deducted from the initial drug content of ocuserts.[12]
14. **Swelling Index:** Ocusert weighed and placed 4ml of simulated tear fluid in a beaker. After 5 minutes, the ocusert was removed and excess tear fluid on ocuserts was wiped and it was weighed again.[16] The %swelling index was calculated by following formula; % Swelling index = $\frac{weight\ of\ swollen\ ocusert\ after\ time - original\ weight\ of\ ocusert}{original\ weight\ of\ ocusert} \times 100$
15. **Antimicrobial activity:** The cup-plate technique with agar diffusion medium. The cup was bored at the centre of the plate. The developed film and standard solution of pure drug were taken separately into soyabean casein digest medium earlier seeded with *staphylococcus Aureu*s organism. On placing the film and standard solution in the plate, they were incubated for a day at 37℃. Compared with standard, the zone of inhibition was calculated.[17,18]

DISCUSSION

Ocular drug delivery system has a tremendous challenge, Among the Ophthalmic preparations, ocusert is one of the advanced drug delivery systems. Beyond the complications of ocular delivery, this ocusert provides most advantageous results such as increase in bio availability, long acting, time consuming, easy adaptability and easy to handle. The polymers such as HPMC used in the ocusert increases the viscosity and ails for the dryness over eye. Ocusert delivers with the minimal leakage of drug as compared with of other ocular delivery. In this ocusert, the high therapeutic index is achieved even in minimal dose. In the sensitive tissue part, as it is a sterile preparation, it can deliver the drug without any damage over the tissue and meet the clear vision after application.

CONCLUSION

It is a critical challenge to deliver an ocular drug in sensitive tissue. Although there is enormous formulation over ocular delivery system, it is difficult to evaluate the Pharmacokinetics and Pharmacodynamics of the preparation as it need large animals to carry out the screening, since only less numbers are approved over these ocusert preparation. Future aspects of this study include the relevant standardization of ocular preparation for high therapeutic efficacy with low toxicity and also to increase the commercialization of this preparation.

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