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Ocular Drug Delivery System: An Overview

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ABSTRACT

Delivery of drugs to the targeted ocular tissues is restricted by various precorneal, dynamic and static ocular barriers. Also, therapeutic drug levels are not maintained for longer duration in target tissues. In the past two decades, ocular drug delivery research acceleratedly advanced towards developing a novel, safe and patient compliant formulation and drug delivery devices/techniques, which may surpass these barriers and maintain drug levels in tissues. Anterior segment drug delivery advances are witnessed by modulation of conventional topical solutions with permeation and viscosity enhancers. Also, it includes development of conventional topical formulations such as suspensions, emulsions and ointments. On the other hand, for posterior ocular delivery, research has been immensely focused towards development of drug releasing devices and nanoformulations for treating chronic vitreoretinal diseases. These occuserts formulations may help to surpass ocular barriers and associated side effects with conventional topical drops. Also, these novel devices and/or formulations are easy to formulate, no/negligibly irritating, possess high precorneal residence time, sustain the drug release, and enhance ocular bioavailability of therapeutics. An update of current research advancement in ocular drug delivery necessitates and helps drug delivery scientists to modulate their think process and develop novel and safe drug delivery strategies.

Keywords: Cornea, Drug delivery, Formulations, Implants, Liposomes, Nanomicelles, Occuserts.

1. INTRODUCTION

The eye is unique organ from anatomical and physiological point of view. The eye has special attributes that allows local drug delivery and noninvasive clinical assessment of disease but also makes understanding disease pathogenesis and ophthalmic drug delivery challenges. Eye ailment can cause distress and angst in patients, with the ultimate fear of loss of vision or even facial disfigurement. Many parts of the eye are relatively inaccessible to systemically administered drugs and as a result, topical drug delivery remains the preferred route in most cases. Drugs may be delivered to treat the precorneal region for such infections as conjunctivitis and blepharitis or to provide intraocular treatment via the cornea for disease such as glaucoma and uveitis¹.

With conventional ophthalmic solution normal dropper used which delivers about 50-75µl per drop and portions of these drops rapidly drain until the eye is back to normal resident volume of 7 µl. Due to this drug loss in front of the eye, very small drug is available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is relatively low and very small corneal contact time (about 1-2 min) in humans for instilled solution usually less than 10%. Therefore only small amount of drug actually penetrates the cornea and reaches intraocular tissue. Due to these limitations, controlled drug delivery to the eye is restricted imposed by the efficient protective mechanism.

It is necessary to optimize drug delivery by adding polymers of various grades, development of colloidal suspension or using erodible or non-erodible insert, development of viscous gel to prolong the precorneal drug retention. Micro particle suspension or polymeric solution can be bioadhesive system. In situ activated gel forming systems provide better sustained release properties than drops. This type of dosage form are used now a day in various type of eye disease like combat glaucoma, dry eye syndrome, eye infection, etc.²

2. ANATOMY AND PHYSIOLOGY OF EYE

The human eye is a complex anatomical device that remarkably demonstrates the architectural wonders of the human body. The human eye is a challenging organ for topical administration of drugs. The basis of this can be found in the anatomical arrangement of the surface tissues and in the permeability of the cornea. The protective function of the eyelids and lachrymal system is such that there is rapid removal of material instilled into the eye unless the material is suitably small in volume and chemically and physiologically compatible with surface tissues. The eye is referred as a globe and consists of two spheres, one set in the other, as shown in Fig 1. The front sphere is smaller and is bordered anteriorly by the sclera. The combined weight of both spheres has been given as 6.7-7.5gm, with a volume of approximately 6.5ml. The circumference of the eye is about 75mm. The eye is located in the bony orbital cavity of the head.³

2.1 Eyeball

The wall of the human eyeball (globe) is composed of three concentric layers.

The fibrous layer is made up of two parts

- Posterior (5/6th) is opaque and called the sclera.
- Anterior (1/6th) is transparent and called the cornea.

In middle vascular layer, the uvea or uveal tract consisting of the choroid, the ciliary body and the iris.

A nervous layer consists the retina.

2.1.1 Sclera

It contains the microcirculation, which nourishes the tissues of this anterior segment and is usually white.

2.1.2 The choroid

It remains just behind the retina forming the posterior 5/6th of the middle coat, composed of numerous blood vessels and pigmented cells containing melanin.

2.1.3 The ciliary body

It includes orbicularis ciliaris, ciliary processes, and ciliary muscle.

2.1.4 The Iris nervous coat

Called retina, which contains photosensitive receptors. The eyeball houses an optical apparatus which consists, in sequences of the precorneal film, the cornea, the aqueous humor, the pupil, the crystalline lens, the vitreous humor and the retina. The aqueous and vitreous humors are layers of clear fluid or gel like material interposed between the solid structures. The crystalline lens is a refractive element with variable power controlled and supported by a muscle incorporated in the ciliary body.

2.2 Conjunctiva

The conjunctival membrane covers the outer surface of the white portion of the eye and the inner aspects of the eyelids. It is attached loosely and thereby permits free movement of the eyeball. Except for the cornea, the conjunctiva is the most exposed portion of the eye.

Drugs can be incorporated up to single dose of 15 mg.¹⁷ Mechanical properties of the films, such as shifting the glass transition temperature to lower temperature, formulation considerations have been reported as important factor.

2.3 Lachrymal System

The conjunctival and corneal surfaces are covered and lubricated by a film of fluid secreted by the conjunctival and lachrymal glands. The secretion of the lachrymal glands, the tears are delivered through a number of fine ducts into the conjunctival fornix. The movement of the eye helps to spread the tears over the conjunctival surface. The excess fluid is directed into the lachrymal lake a small triangular area lying in the angle bound by the inner most portions of the lids. Tears are drained from the lachrymal lake, by two small tubes, the lachrymal canaliculi which lead into the upper part of the nasolacrimal duct. The act of blinking exerts a suction-force pump action in removing tears from the lachrymal lake and emptying them into the nasal cavity. Lacrimation is induced reflexly by stimulation of nerve ending of the conjunctiva, the turnover rate of nasolacrimal fluid is 16%. The eyeball is continually irrigated by a gentle stream of lacrimal fluid which prevents it from becoming dry and inflamed.

2.4 Composition of tear

The secretion is a clear watery fluid containing numerous salts, glucose, other organic compounds, approximately 0.7% protein and the enzyme, lysozyme. Water: 98.2% Solids: 1.8%

Organic elements- Protein-0.67%, Sugar-0.65%, NaCl-0.66%, NPN-0.05% Urea-0.03%. Other mineral elements sodium, potassium and Ammonia-0.79%.

2.5 Precorneal Film

Part of the tear fluid provides the moist surface to cornea. The film, compatible with both aqueous and lipid ophthalmic preparations is composed of three layers, the thin outermost layer is lipid and is secreted mainly by the meibomian glands. The lipid layer keeps the cornea moist by preventing evaporation of the underlying layers, a thicker middle aqueous layer, Secreted by the lacrimal gland, it helps in nourishing the cornea. It is renewed during each blink and when blinking is suppressed, it dries in patches. Although the tear film is typically only about 7 μ L in volume with fluid pH 7.4 and if blinking does not occur, the volume can go up to 30 μ L without spillage, the cul-de-sac is sterile due partly to the action of lysozyme in the tears.

2.6 Cornea

The cornea 0.5-1 mm thick consists mainly of the following structures.

- Corneal Epithelium.
- Substantial Propria (stroma)
- Corneal Endothelium.

The cornea is transparent to ordinary diffuse light because of a special laminar arrangement of the above structure, fibers and because of the absence of blood vessels. The cornea derives its nutrition by diffusion and must have certain permeability characteristics. The corneal epithelium provides an efficient barrier against bacterial invasions. Unless its continuity has been broken by an abrasion, pathogenic bacteria cannot gain a foothold. Any foreign body that either scratches the cornea or lodges and becomes embedded in the cornea is of serious concern because of the role it may play in permitting pathogenic bacteria to gain a foothold.^{4,5}

3. OCULAR DRUG DELIVERY SYSTEMS⁶⁻⁹

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:

- Liquids: - Solutions, Suspensions, Sol to gel systems, Sprays
- Solids: - Ocular inserts, Contact lenses, corneal shield, artificial tear inserts, Filter paper strips
- Semi-solids: Ointments, Gels
- Miscellaneous: Ocular iontophoresis, Vesicular systems, Muco-adhesive dosage forms, Particulates.

3.1 Liquids

Liquids are the most popular and desirable state of dosage forms used for the eye. This is because the drug absorption is fastest from this state. The slow release of the drug from the suspended solids provides a sustained effect for a short duration of time.

3.2 Solutions and Suspensions

Solutions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. The drug in the solution is in the dissolved state and may be immediately active. This form also has disadvantages; the very short time the solution stays at the eye surface, its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage), the instability of the dissolved drug, and the necessity of using preservatives. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. This rapid elimination is due to solution state of the preparation and may be influenced by the composition of the solution. The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume.

Extensive work has been done to prolong ocular retention of drugs in the solution state by enhancing the viscosity or altering the pH of the solution⁷

Suspensions are called as dispersion of finely divided relatively insoluble drug substances in an aqueous vehicle which contains suitable amount of suspending and dispersing agents. Because of a tendency for the particle to be retained in the cul-de-sac, the contact time and duration of action of a suspension exceed those of a solution. While the retention increases with an increase in the particle size, so does the irritation of the eye. The rate of the dissolution of the suspended drugs increases with decreasing particle size. Thus an optimum particle size has to be selected for each type of drug, and it is recommended that the particles in an ophthalmic suspension should be not more than 10 μ m in size.

3.3 Sol-Gel Systems

The new concept of producing a gel in situ (e.g. in the cul-de-sac of the eye) was suggested for the first time in the early 1980s. It is widely accepted that increasing the viscosity of a drug formulation in the precorneal region will lead to an increased bioavailability, due to slower drainage from the cornea. Several concepts for the in situ gelling systems have been investigated. These systems can be triggered by change in pH, temperature or by ion activation.⁸

3.4 Sprays^{9,10}

Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for cycloplegics examination.

3.5 Solids

The concept of using solids for the eye is based on providing sustained release characteristics.

3.5.1 Ocular inserts

Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system. The eye drops provided pulse entry pattern of drug administration in the eye which is characterized by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of under dosing. The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the function of controlled release systems. Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane ruptures etc.). A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, non-erodible, and hydrogel inserts¹¹⁻²⁵.

3.5.2 Insoluble insert

These are solid or semisolid sterile preparations of appropriate size and shape, designed to be inserted behind the eyelid or held on the eye and to deliver drugs for topical or systemic effects these are polymeric systems into which the drug is incorporated as a solution or dispersion.

3.5.3 Ocular therapeutic system (OTS) or minidisc

These are controlled – release monolithic matrix-type devices consisting of a contoured disc with a convex front and a concave back surface, designed so as to fit the eyeball. The OTS can be made hydrophilic or hydrophobic to permit extended release of both water-soluble and water-insoluble drugs. They were reported to be very comfortable when placed behind the top or bottom of the eyelid.

3.5.4 Contact lenses

Contact lenses can absorb water soluble drugs when soaked in drug solutions. These drug saturated contact lenses are placed in the eye for releasing the drug for long period of time. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs. In humans, the Bionite lens which was made from hydrophilic polymer (2- hydroxyethyl methacrylate) has been shown to produce a greater penetration of fluorescein.²⁶

3.5.5 Corneal shield

A non-cross-linked homogenized, porcine scleral collagen slice is developed by a company (Bio-core (Bausch and Lomb pharmaceuticals)). Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers. Collagen shields are fabricated with fetal calf skin tissue and originally developed as a corneal bandage.²⁷

3.4 Semi solids

A wide variety of semisolids vehicles are used for topical ocular delivery which falls into two general categories: simple and compound bases. Simple bases refer to a single continuous phase. These include white petrolatum, lanolin and viscous gels prepared from polymers such as PVA, carbopol etc. Compound bases are usually of a biphasic type forming either water in oil or oil in water emulsions. A drug in either a simple or compound base provide an increase in the duration of action due to reduction in dilution by tears, reduction in drainage by way of a sustained release effect, and prolonged corneal contact time. The most commonly used semisolid preparation is ointments consisting of dispersion of a effects. The primary purpose of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface. But they present a disadvantage of causing blurring of vision and matting of eyelids. Ophthalmic gels are similar in viscosity and clinical usage to ophthalmic ointments. Semi-solids vehicles were found to prolong the ocular contact time of many drugs, which ultimately leads to an enhanced bioavailability.²⁸⁻³⁰ solid drug in an appropriate vehicle base. Semi-solids dosage forms are applied once or twice daily and provide sustained.

3.5 Miscellaneous

3.5.1 Vesicular systems

Vesicular systems have been developed to provide improvement in ocular contact time, providing sustained effect and reducing side effects of the drug(s) entrapped.

3.5.2 Liposomes

Liposomes are phospholipids-lipid vesicles for targeting the drugs to the specific sites in the body. Because of their structural versatility they can incorporate any kind of drug substance regardless of its solubility. They provide the controlled and selective drug delivery and improved bioavailability and their potential in ocular drug delivery appears greater for lipophilic than hydrophilic compounds. Liposomes are vesicles composed of a lipid membrane enclosing an aqueous volume. Liposome's offer the advantage of being completely biodegradable and relatively nontoxic but are less stable than particulate polymeric drug delivery systems. Liposomes were found to be potential delivery system for administration of a number of drugs to the eye.³¹⁻³³

3.5.3 Niosomes

In order to circumvent the limitations of liposome's as chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids, niosomes are developed as they are chemically stable as compared to liposome's and can entrap both hydrophilic and hydrophobic drugs. They are non-toxic and do not require special handling techniques.³⁴

3.5.4 Pharmacosomes

This is the term used for pure drug vesicles formed by the amphiphilic drugs. Any drugs possessing a free carboxyl group or an active hydrogen atom (-OH, NH₂) can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug.³⁵

4. MECHANISM OF DRUG RELEASE³⁶

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

- Diffusion
- Osmosis
- Bio-erosion

4.1 Diffusion

In the Diffusion mechanism, the drug is released continuously at a controlled rate through the membrane into the tear fluid. If the insert is formed of a solid non-erodible body with

pores and dispersed drug. The release of drug can take place via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions.

4.2 Osmosis

In the Osmosis mechanism, the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into a first compartment and a second compartment; the first compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable membrane and the second compartment provides a reservoir for the drug which again is in liquid or gel form. When the insert is placed in the aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

4.3 Bioerosion

In the Bio-erosion mechanism, the configuration of the body of the insert is constituted from a matrix of bio-erodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bio-erosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix.

5. OCUSERTS

Ophthalmic insert defined as sterile preparation with solid or semisolid consisting and whose size and shape are especially designed for ophthalmic application. They offer several advantages as increase ocular residence, possibility of releasing drug at a slow constant rate, accurate dosing and increased shelf life with respect to aqueous solutions. Ocusert®, pilocarpine ocular therapeutic system is the first product marketed by Alza incorporation USA from this category.³⁷

5.1 Advantages of Ocuserts³⁸⁻³⁹

Ocular inserts offer several advantages, which can be summarized as follows

- Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles;
- Possibility of releasing drugs at a slow, constant rate;

- Accurate dosing (contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a Precise dose which is fully retained at the administration site);
- Reduction of systemic absorption (which occurs freely with eye drops via the naso-lacrimal duct and nasal mucosa);
- Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects;
- Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes;
- Increased shelf life with respect to aqueous solutions;
- Exclusion of preservatives, thus reducing the risk of sensitivity reactions;
- Possibility of incorporating various novel chemical/technological approaches such as pro-drugs, mucoadhesives, permeation enhancers, microparticulates, salts acting as buffers, etc.

The potential advantages offered by inserts clearly explain why an active interest has been dedicated to these dosage forms in recent years, and why efforts to introduce them on the pharmaceutical market continue. Of course, not all of the benefits listed above can be present in a single, ideal device. Each type of insert represents a compromise between the desirable properties inherent to solid dosage forms and negative constraints imposed by the structure and components of the insert itself, by fabrication costs, as well as by the physical/physiological constraints of the application site.

5.2 Disadvantages of Ocular Inserts

The disadvantages of ocular inserts are as follows:

- A capital disadvantage of ocular inserts resides in their 'solidity', i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye. This may constitute a formidable physical and psychological barrier to user acceptance and compliance.
- Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix,

- The occasional inadvertent loss during sleep or while rubbing the eyes,
- Their interference with vision, and
- Difficult placement of the ocular inserts (and removal, for insoluble types).

REFERENCES

1. Rathore KS, Nema RK., An insight into ophthalmic drug delivery system, *International Journal of Pharmaceutical Sciences and Drug Research*, (2009) 1(1) 1-5.
2. Kumar KPS, Bhowmik D, Harish G, Kumar PB. Ocular Inserts: A Novel Controlled Drug Delivery System *The Pharma Innovation – Journal* 1;(12): 2013
3. Chrai SS, Makoid MC, Erikson SP, Robinson JR. Drop size and initial dosing frequency problems of topically applied ophthalmic drugs. *J Pharm Sci*. 1974; 64:333–8.
4. Rewar S, Bansal BK, Singh CJ. Review on Intraocular Drug Delivery System. *International Journal of Research and Development in Pharmacy and Life Sciences* October - November, 2014 Vol. 3, No.6, pp 1236-1243.
5. Khokhar P, Shukla V. Ocular Drug Delivery System-A Review Based on Ocular Inserts *International Journal of Pharma Research & Review*, August 2014; 3(8):29-41
6. Mohd D. *Advances in Ophthalmic Drug Delivery System: Part I &II*. 12th April 2005 (<http://www.Pharmainfo.Net>).
7. Oyekoya OK, Stentford FWM, 2003, "Exploring the Significance of Visual Attention by Eye Tracking". *Proceedings of the London Communications Symposium, UCL, London*, pp. 149-152.
8. Mueller W H, Deardroff DL. Ophthalmic vehicles: The effect of methyl cellulose on the penetration of Homatropinehydrobromide through the cornea. *J. Am. Pharm. Assoc.* 1956; 45: 334
9. Eva M, Amo D, Urtti A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. *Drug Discov Today* 2004; 13:135-143.
10. Aqil, *Advances in Ophthalmic Drug Delivery System: Part I &II*. 12th April 2005 (<http://www.Pharmainfo.Net>)

11. Mueller WH, Deardroff DL. Ophthalmic vehicles: The effect of methyl cellulose on the penetration of Homatropinehydrobromide through the cornea. *J. Am. Pharm. Assoc.* 1956; 45: 334.
12. Saettone MF, Giannicini B, Teneggi A, Savigini P, Tellini N. Vehicle effects on ophthalmic bioavailability: the influence of different polymer on the activity of pilocarpine in rabbit and man. *J. Pharm. Pharmacol.* 1982; 34: 464- 466.
13. Kumar S, Haglund BO, Himmelstein KJ. In-situ forming gels for ophthalmic drug delivery. *J. Ocular Pharmacol.* 1994; 10 (1): 47-56.
14. Trueblood JH, Rossmando RM, Carlton WH, Wilson LA. Corneal contact times of ophthalmic vehicles. *Arch ophthalmol.* 1975; 93: 127-130
15. Vadnere M, Amidon G, Lindenbaum S, Haslam JL. Thermodynamic studies on the gel-sol transition of some pluronicpolyols. *Int. J. Pharm.* 1984; 22: 207- 218.
16. Maichuk YF. Ophthalmic drug Inserts. *Invest. Ophthalmol.* 1975; 14:87-90.
17. Katz IM, Blackman WM. A soluble sustained- release ophthalmic delivery unit. *Am J Ophthalmol.* 1977; 83: 728.
18. Hosaka S, Ozawa H, Tanzawa H. Controlled release of drug from hydrogel matrices. *J. Appl. Polym. Sci.* 1979; 23: 2089.
19. Harwood R J, Schwartz JB. Drug release from compression molded films: preliminary studies with pilocarpine. *Drug Dev. Ind. Pharm.* 1982; 8: 663.
20. Ozawa H, Hosaka S, Kunitomo T, Tanzawa H. Ocular inserts for controlled release of antibiotics. *Biomaterials.* 1984; 4 (3): 170-174.
21. Urtti A, Juslin M, Miinalainen O. Pilocarpine release from hydroxypropyl cellulose-polyvinylpyrrolidone matrices. *Int. J. Pharm.* 1985; 25:165- 178.
22. Attia MA, Kassem MA, Safwat SM. *In vivo* performance of [3H] dexamethasone ophthalmic film delivery systems in the rabbit eye. *Int. J. Pharm.* 1988; 47: 21-30.
23. Vasantha R, Sehgal PK, Rao P. Collagen ophthalmic inserts for pilocarpine drug delivery system. *Int. J. Pharm.* 1988; 47: 95-102.
24. Finne V, Ronkko K, Urtti A. Timolol release from matrices of monoesters of polyvinyl methyl ether-maleic anhydride : Effects of polymer molecular weight and a basic additive. *J. Pharm. Sci.* 1991; 80: 7.
25. Kyyronen K, Hume L, Benedetti L, Urtti A., Topp E, Stella V. Methyl prednisolone esters of hyaluronic acid in ophthalmic drug delivery: in vitro and in vivo release studies. *Int. J. Pharm.* 1992; 80: 161-169.
26. Fitzgerald P, Wilson CG, Greaves JL, Frier M, Hollingsbee D, Gilbert D, Richardson M. Scintigraphic assessment of the precorneal residence of a new ophthalmic delivery system (NODS) in man. *Int. J. Pharm.* 1992;83: 177-185.
27. Saettone MI, Toracca MT, Pagano A. Controlled release of pilocarpine from coated polymeric ophthalmic inserts prepared by extrusion. *Int. J. Pharm.* 1992; 86: 159-166.
28. Kamath R, Singh UV, Udupa N. Evaluation of Ciprofloxacin hydrochloride ocular preparations . *Ind. J. Pharm. Sci.* 1993; 55: 148- 150.
29. Weiner AL, Darougar S, Siddiqui M, Raul V. A sustained release ocular insert (OCUFIT SRTM) with long term retention in the fornix of humans. *Proceed. Intern. Symp. Control. Rel. Bioact. Mater. Controlled Release Society Inc.* 1993; 20: 384-385.
30. Hume LR, Lee HK, Benedetti L, Sanzgiri YD, Topp EM, Stella VJ. Ocular sustained delivery of prednisolone using hyaluronic acid benzyl ester films. *Int. J. Pharm.* 1994; 111: 295-298.
31. Saettone MF, Chetoni T, Bianchi LM, Giannacinni B, Conte U, Sangalli M E. Controlled release of timolol maleate from coated ophthalmic mini-tablets prepared by compression. *Int. J. Pharm.* 1995; 126: 79-82.
32. Barath S, Hiremath SR. Ocular delivery system of pefloxacinmesylate. *Pharmazie.* 1999; 54(1): 55-58. 34. Saisivam S, Manikandav RVM, Nagarajan M. Design and evaluation of ciprofloxacin hydrochloride ocuserts. *Ind. J. Pharm. Sci.* 1999; 61(1):
33. Saisivam S, Manikandav RVM, Nagarajan M. Design and evaluation of ciprofloxacin hydrochloride ocuserts. *Ind. J. Pharm. Sci.* 1999;61(1): 34-38.

34. Sakanaka K, Kawakami S, Nishida K, Nakamura J, Ichikawa N, Iwashita J, Nakamura T, Nakashima M, Sasaki H, Nagano T. One-side- coated insert as a unique ophthalmic drug delivery system. *J Control Release*. 2003;92(3):241-7.
35. Kumari P, Jain R.,Choukse R., Dubey PK, Agrawal S. Ocusert as A Novel Drug Delivery System *International Journal of Pharmaceutical & Biological Archives* 2013; 4(4): 614 – 619
36. Sharma JPK, Banik A, Dixit S. A New Trend: Ocular Drug Delivery System. *International Journal of Pharmaceutical Sciences* 2011; 2(3):1-2
37. Chien YW. Ocular drug delivery and delivery systems. In: *Novel drug 1. delivery systems*. 2nd ed. New York: Marcel Dekker; 1992. pp. 269-70.
38. Saettone MF, Salminen L. Ocular inserts for topical delivery. *AdvDrug 2. Del Rev* 1995; 16:95-106.