A Review :Ocular Drug Delivery System

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Abstract- *The major challenge faced by today's pharmacologist and formulation scientist is ocular drug delivery. Topical eye drop is the most convenient and patient compliant route of the drug administration, especially for the treatment of anterior segment diseases. Delivery of the drugs to targeted ocular tissues is restricted by various pre corneal, 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 accelerated advanced towards developing a novel, safe and patient compliant formulation and drug delivery devices/techniques, which may surpasses 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. Topical administration for ocular therapeutic is ideal because of smaller doses required compared to the systemic use, its rapid onset of action and freedom from systemic toxicity topically applied ocular drugs have to reach the inner part of the eye and trans corneal penetration is believed to be the major route for the drug absorption.*

Keywords- Opthalmic drug delivery, corneal,anatomy, physiology, retina.

I. INTRODUCTION

In the words of Hughes and Mitra2: "Opthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist… The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances… The challenge to the formulator is to circumvent the protective barriers of the eye without Causing the permanent tissue damage… The primitive Opthalmic solutions, suspensions and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases…" The eye is a complex organ with an unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Eye is a unique and very valuable organ. This is considered a window hinge. We can enjoy it and look at the world body. There are many eye diseases that can affect the body and loss of vision as well.

Advantages of ocular drug delivery systems:

1. Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
2. To provide sustained and controlled drug delivery.
3. To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
4. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
5. To circumvent the protective barriers like drainage, lacrimation and conjunctively absorption.
6. To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
7. To provide better housing of delivery system.

Limitations of ophthalmic drug delivery:

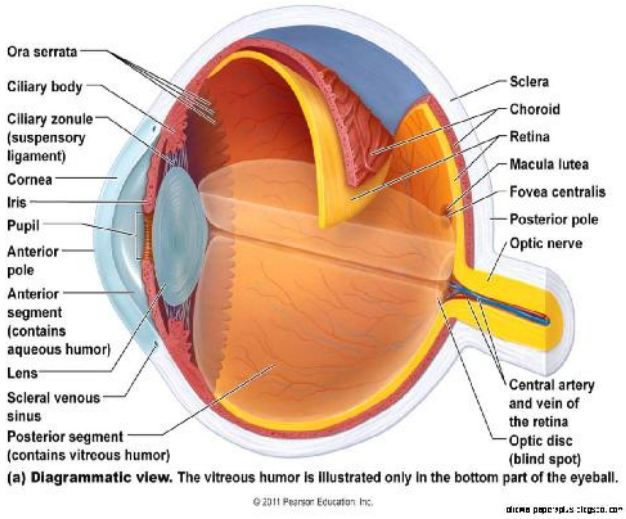
1. Dosage form cannot be terminated during emergency.
2. Interference with vision.
3. Difficulty in placement and removal.
4. Occasional loss during sleep or while rubbing eyes.

Despite these limitations, significant improvements in ocular drug delivery have been made. The improvements have been with objective of maintaining the drug in the bio-phase for an extended period. The anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances.

ANATOMY AND PHYSIOLOGY OF THE EYE:

The human eye is one of the most vital organs in the body which provides vision. After the skin, eye is the most easily accessible site for topical administration of drugs. It contains Sclera which protects the inner layer of eye and also providing integrity to it which help in defining shape and length of the eye. Cornea is a nonvascular structure gets the necessary nutrients from the capillaries. Cornea made up of three principle layers Epithelium (hydrophobic in nature and make it barrier to hydrophilic drugs) Stroma (main barrier for the lipophilic drugs) Endothelium (It consist of Na +/k +-

ATPase pump which depends on the concentration of bicarbonate ion maintains the balance between passive movement of water into the stroma and the active movement of fluid out of it which is responsible for maintaining corneal transparency and thickness). Choroid it contains blood vessels and pigment that absorbs excess light and so prevents blurred vision. Ciliary Body secrets aqueous humor and alter shape of lens for near and far vision. Iris It regulates the amount of light entering the eye by altering the diameter of pupil. Retina is receptor of vision. The function of the retina is not just to be the screen onto which an image may be formed but also to collect the information contained in that image and transmit it to the brain in a suitable form for use by the body. Conjunctiva it protects exposed part of the eye.



(a) Diagrammatic view. The vitreous humor is illustrated only in the bottom part of the eyeball.

ANATOMY OF THE EYEBALLL:

The eyeball measures about 2.5 cm in diameter, only a small portion (about1/6 th part) of the globular eye is exposed in front, the rest is hidden in bony socket of the orbit on a cushion of fat and connective tissue. The wall of thehuman eyeball consists essentially of three layers: Fibrous tunic, vascular tunic and Retina.

Fibrous tunica

Fibrous tunic, the outermost coat of the eyeball, consists of the anterior cornea and posterior sclera.

The cornea is a transparent coat that covers the colored iris. Cornea mainly consists of the following structures from the front to back, (I) Epithelium, (II) Bowman's membrane, (III) Stroma, (IV) Descemet's Membrane, (V)Endothelium. The cornea is 0.5 to 1.0 mm in thickness and normally it possesses no blood vessels except at the corneosclerar junction.

The sclera, the "white" of the eye, is a layer of dense connective tissue made up densely of collagen fibers and fibroblasts. The sclera covers the entire eyeball except the cornea. At the junction of the sclera and cornea is an opening known as the scleral venous sinus (canal of Schelmm).

Vascular tunica

This middle layer is mainly vascular, consisting of the choroid, ciliary body and iris.

Choroid lines the posterior five-sixths of the inner surface of the sclera. It is very rich in blood vessels.

Ciliary body

It is the anterior continuation of the choroids consisting of ciliary muscle and secretary epithelial cells. The major function of the ciliary body is the production of aqueous humor. Systemic drugs enter the anterior and posterior chambers largely by passing through the ciliary body vasculature and then diffusing in to the iris where they can enter the aqueous humor. The ciliary body is one of the major ocular sources of drug-metabolizing enzymes, responsible for drug detoxification and removal from the eye. Iris is the visible colored part of the eye and extends interiorly from the ciliary body lying behind the cornea and in front of the lens. The pigment granules of the iris epithelium absorb light as well as lipophilic drugs. This type of binding is characteristically reversible, allowing release of drug overtime. As a result, the iris can serve as a reservoir for some drugs, concentrating and then releasing them for longer than otherwise expected. The innermost layer is the retina, consisting of the essential nervous system responsible for vision. Retina lines the posterior three quarters of the eyeball and is the beginning of the visual pathway.

Retina

The retina is situated between the clear vitreous humor in its inner surface and the choroids on its outer surface. Retina consists of two distinct chambers, anterior and posterior.

Lens

Behind the pupil and iris, within the cavity of the eyeball, is the lens. Protein called crystallines, arranged like the layers of an onion, make up the lens. The lens is held in

place by the zonules, which run from the ciliary body and fuse into the outer layer of the lens capsule. The lens tends to develop cataract or opacities with age, interfering with vision.

INTERIOR OF THE EYEBALL

The lens divides the interior of the eyeball into two cavities; anterior cavity and Vitreous chamber. The anterior cavity consists of two chambers the anterior chamber that lies between the cornea and the iris. The posterior chamber that lies behind the iris and in front of the lens. Aqueous humor is formed by ciliary bodies and occupies the posterior and anterior chambers, having a volume of about 0.2 ml. The fluid is constantly generated by pigmented and non- pigmented epithelium of ciliary body. The Vitreous chamber is filled with a viscous fluid, vitreous humor, which is a viscoelastic connective tissue composed of small amounts of glycosaminoglycan's, including of hyaluronic acid and proteins such as collagen.

CONJUNCTIVA

The conjunctiva membrane covers the outer surface of the white portion of the eye and the inner surface of the eyelids. In most places it is loosely attached and thereby permits free movement of the eyeball, this makes possible subconjunctival injection. The conjunctiva forms an inferior and a superior sac except for the cornea, the conjunctiva is the most exposed portion of the eye.

PHYSIOLOGY OF EYE

Three types of fluids are present in eye tears (Function of tear lubrication, nourishment, Provide oxygen, protection). Aqueous humor (responsible for the maintenance of shape of the eye ball. It maintains the intraocular pressure 12-20 mm Hg).Vitreous humor (It maintains the shape of eyeball and keeps retina attached to choroid) The cornea, lens and vitreous body are all transparent media with no blood vessels; oxygen and nutrient are transported to this non vascular tissue by aqueous humor. The lachrymal fluid secreted by the lachrymal glands is emptied on the surface of the conjunctiva of the upper eyelid at a turnover rate of 16% per min. It washes over the eyeball and is swept up by the blinking action of the eyelids.

Nasolacrimal drainage system

Nasolacrimal drainage system consists of three parts; the secretory system, the distributive system and the excretory system. The secretory portion is composed of the lacrimal gland that secreted tears are spread over the ocular surface by the eyelids during blinking. The excretory part of the Nasolacrimal drainage system consists of the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac, and the nasolacrimal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that tears are largely absorbed by the mucous membrane that lines the ducts andthe lachrymal sac; only a small amount reaches the nasal passage .

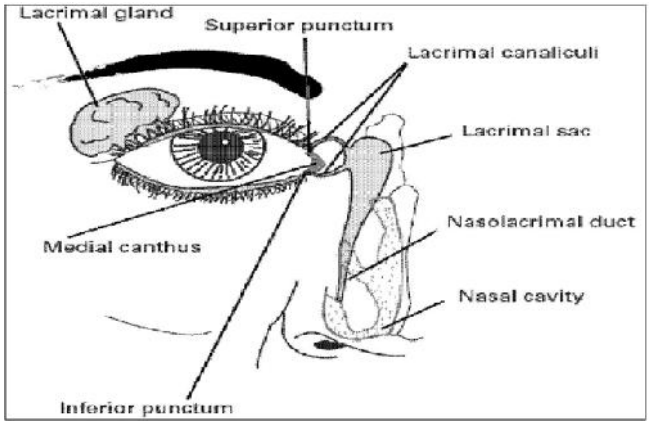


Figure 2: Schematic diagram of naso-lacrimation drainage system

Tear film the exposed part of the eye is covered by a thin fluid layer, the so-called precorneal tear film. The film thickness is reported to be about 3–10 Am depending on the measurement method used. The resident volume amounts to about 10µl. The osmolality of the tear film equals 310–350 mOsm/kg in normal eyes and is adjusted by the monovalent and divalent inorganic ions such as Na+, K+, Cl-, HCO3-, and proteins. The mean pH value of normal tears is about 7.4. Diurnal patterns of pH changes exist, with a general shift from acid to alkaline during the day. The buffer capacity of the tears is determined by bicarbonate ions, proteins, and mucins [16, 17]. Tears exhibit a non- Newtonian rheological behavior. The viscosity is about 3 mPas. The mean surface tension value is about 44 mN/m.

BARRIERS FOR OCULAR DRUG DELIVERY

Drug Loss from the Ocular Surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is drained via the nasolacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption.

Lacrimal Fluid-Eye Barriers

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that limit the Para cellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea.

FACTOR ATTRIBUTING TO POOR BIOAVAILABILITY OF AN OPHTHALMIC FORMULATION

Binding by the lachrymal proteins
Drainage of the instilled solutions
Lacrimation and tear turnover
Limited corneal area and poor corneal penetration
Non- productive absorption/adsorption
Tear evaporation and permeability
Formulation Factor pH, pKa of drug viscosity of formulation

CHARACTERISTICS REQUIRED TO OPTIMIZE OPTHALMIC DRUG DELIVERY SYSTEMS

Good corneal penetration
Prolonged contact time with corneal tissue
Simplicity of installation for the patient
Non- irritative and comfortable form
Minimum protein binding
Sterile, isotonic, pH adjustment

Different Types of Ocular Drug Delivery System

A .CONVENTIONAL DELIVERY SYSTEMS

Solutions, Suspensions, Emulsions:

Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye .16 less than 5 Percent of the dose is absorbed after topical administration into the eye. Ocular absorption is limited by the corneal epithelium, and it is only moderately increased by prolonged ocular contact.

Spray:

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 cycloplegic examination.

Ointment and Gels

Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major 257 drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use.

Inserts

Lacriserts:

The lacrisert is a sterile rod shaped device made of hydroxyl propyl cellulose without any preservative is used for the treatment of dry eye syndrome. This device was introduced by Merck, Sharp and Dohme in 1981.It weighs 5 mg and measures 12.7 mm in diameter with a length of 3.5mm.Lacrisert is useful in patients with keratitis sicca whose symptoms are difficult to treat with artificial tear alone. It is inserted in to inferior fornix where it imbibes water from the conjunctiva and cornea.

SODI/ Wafers:

Ocular drug insert (SODI) is a small oval wafer which was developed by Soviet scientists for cosmonauts who could not use eye drops in weightless conditions. The unit is made from acrylamide Nvinylpyrrolidine and ethyl acrylate designed as ABE. It is in the form of sterile thin films of oval shape weighing 15 to 16 mg. After introduction into cul de sacs where wetted by tear film it softens in 10-15 seconds and assumes the curved configuration of the globe. During the following 10-15 min; the film turns into viscous polymer mass thereafter in 30-60 min it becomes a polymer solution.

B.VESICULAR SYSTEM

Liposomes:

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter. They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increases the probability of ocular drug absorption. To the corneal epithelium which is thinly coated with negatively charged mucin, positively charged surface of the liposomes may combine.

Limitations:

The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids.

Niosomes and Discomes:

Niosomes are chemically stable as compared to liposomes and can entrap both hydrophobic and hydrophilic drugs. They are non-toxic and do not require special handling techniques. Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Non-ionic surface active agents based discoidal vesicles known as (discomes) loaded with timolol maleate were formulated and characterized for their in vivo parameters. In vivo studies showed that discomes released the contents in a biphasic profile if the drug was loaded using a pH gradient technique. Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.

Pharmacosomes:

This term is used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilicprodrug. The amphiphilicprodrug is converted to pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile.

C. CONTROL DELIVERY SYSTEMS:

Mechanism of controlled sustained drug release into the eye,

1. The corneal absorption represents the major mechanism of absorption for the most conventional ocular therapeutic entities.
2. Passive Diffusion is the major mechanism of absorption for nor-erodible ocular insert with dispersed drug.
3. Controlled release can further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solution.

Ocuserts:

The ocusert therapeutic system, developed by Alza corporation.it is flat, flexible, elliptical device consisting of three layers. Two layers of ethylene vinyl acetate (EVA) enclose the inner core of pilocarpine gelled with alginate. A retaining ring of (EVA) impregnated with titanium dioxide for visibility enclose the drug reservoir circumferentially. It is preprogrammed to release pilocarpine at constant rate of 20 or 40 µg/hr.

Implants:

For chronic ocular diseases like cytomegalovirus (CMV) retinitis, implants are effective drug delivery system. Earlier non-biodegradable polymers were used but they needed surgical procedures for insertion and removal. Presently biodegradable polymers such as Poly Lactic Acid (PLA) are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs.

Iontophoresis:

In Iontophoresis direct current drives ions into cells or tissues. Positively charged of drug are driven into the tissues at the anode and vice versa. Ocular Iontophoresis delivery is not only fast, painless and safe but it can also deliver high concentration of the drug to a specific site. Iontophoretic application of antibiotics in eye not only increases their bactericidal activity but also reduce the severity of disease. Similarly application of anti-inflammatory agents can reduce vision threatening side effects.

Dendrimers:

Dendrimers are successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility. Vendome and coworkers have developed and evaluated poly (amid amine) dendrimers containing fluorescein for controlled ocular drug delivery. They determined the influence of size, molecular weight and number of amine, carboxylate and hydroxyl surface groups in several series of dendrimers. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups.

Cyclodextrins:

Cyclodextrins (CDs) are cyclic oligosaccharides capable of forming inclusion complexes with many guest molecules. This complexation of CD does not interrupt the biological membrane compared to conventional permeation enhancer like benzalkonium chloride. Due to inclusion, the free drug is not available, so drugs with inherent irritant properties can be successfully delivered by this approach. CD molecules are inert in nature and were found to be nonirritant to the human and animal eye.

Contact lenses:

For prolongation of ocular residence time of the drugs, hydrophilic contact lenses can be used. Greater penetration of fluorescein has been reported by Bionite lens made from hydrophilic polymer (2-hydroxy ethyl methacrylate) in human.

Collagen Shield:

Collagen shield basically consist of cross linked collagen, fabricated with foetal calf skin tissue and developed as a corneal bandage to promote wound healing. Topically applied antibiotic conjugated with the shield is used to promote healing of corneal ulcers. Tear fluid makes these devices soft and form a thin pliable film which is having dissolution rate up to 10, 24 or 72 hours. Because of its structural stability, good biocompatibility and biological inertness, collagen film proved as a potential carrier for ophthalmic drug delivery system.

Microemulsion:

Microemulsion is dispersion of water and oil stabilized using surfactant and cosurfactant to reduce interfacial tension and usually characterized by small droplet size (100 nm), higher thermodynamic stability and clear appearance. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol for eye diseases.

Nano suspensions:

Nano suspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect. For commercial preparation of Nano suspensions, techniques like media milling and high pressure homogenization have been used.

Micro needles:

Microneedles are developed to deliver drug to posterior segment. Microneedle had shown prominent in vitro penetration into sclera and rapid dissolution of coating solution after insertion while in vivo drug level was found to be significantly higher than the level observed following topical drug administration like pilocarpine.

Prodrugs:

The ideal prodrugs for ocular therapy not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility to such an extent that after corneal penetration or within the cornea they are either chemically or enzymatically metabolized to the active parent compound.

Penetration Enhancers:

Penetration enhancers increase the permeability through corneal epithelial membranes and finally increases transport of drug across the cornea. Examples of enhancers include actin filament inhibitors, surfactants, bile salts, chelators, and organic compounds. But penetration enhancers themselves can penetrate the eye and may lead to unknown toxicological complications e.g., benzalkonium chloride (BAC) was found to accumulate in the cornea for days.

Mucoadhesive Polymers:

They are basically macromolecular hydrocolloids with plentiful hydrophilic functional groups, such as hydroxyl, carboxyl, amide and sulphate having capability for establishing electrostatic interactions.Amucoadhesive drug formulation for the treatment of glaucoma was developed using a highly potent beta blocker drug, levobetaxolol (LB) hydrochloride and partially neutralized poly acrylic acid (PAA).

II. CONCLUSION

The conventional dosage forms for ocular drug delivery is the challenging task for researchers now a day's. Inorder to overcome several disadvantages related to conventional dosage form polymeric in-situ gels are developed, for prolonging the release of drug from the formulation by formation of gels. This provides other advantages over conventional dosage forms such as good stability, biocompatibility and use of biodegradable polymers make the ocular in-situ gelling system more preferable for treatments of ocular disease

REFERENCES

[1] Lee VHL, Robinson JR: Topical ocular drug delivery: recent developments and future challenges. Journal of Ocular Pharmacology 1986; 2: 67–108
[2] Lang J C. Ocular drug delivery conventional ocular formulation. Advanced drug delivery review 1995; 16:39-43.
[3] K Basavaraj, Nanjawade, Manvi FV and Manjappa AS: In situ-forming hydrogels for sustained ophthalmic drug

delivery. Journal of Controlled Release 2007; 122: 119–134.

[4] Sahoo KS, fahima SAD, kumar K: Nanotechnology in ocular drug delivery, Drug delivery today 2008; 13: 144-151.

[5] Weidener J: Mucoadhesive ocular inserts as an improved delivery vehicle for ophthalmic indications. Drug Discovery Today 2003; 8: 906– 907.

[6] Lang JC, Roehrs RTE and Jani R: Ophthalmic preparations, Edition 21, vol-1; Lippincott Williams and Wilkins, 2005.

[7] Andrews GP, Laverty TP and Jones DS: Mucoadhesive polymeric platforms for controlled drug delivery Review article. European Journal of Pharmaceutics and Biopharmaceutics 2009; 71: 505–518.

[8] Alany RG, Rades T, Nicoll J, Tucker IG and Davies NM: W/O micro emulsions for ocular delivery: Evaluation of ocular irritation and precorneal retention. Journal of Controlled Release 2006; 111: 145-152

[9] Binstock EE and Domb AJ: Iontophoresis: A non-invasive ocular drug delivery. Journal of Controlled Release 2006; 110: 479–489.

[10] Gazayerly, E.L., Omaima. N. and Hikal. A H., Int. J. Pharm. 1997; (158); 121.

[11] Nagare R, In Situ gelling System Smart Carrier for Ophthalmic Drug Delivery, International Journal for Pharmaceutical Research Scholars, 2015; 4(2): 10-23

[12] Tortora G, Derrickson B, Principal of Anatomy and Physiology. 11th edition published by John Wiley and Sons, 2006; 579-583.

[13] Gevariya H, Formulation and Evaluation of Sustain Release Ocular Drug Delivery System for An Anti Glucoma Drug. Thesis PhD, 2013; 1-6.

[14] Ross and Wilson, Anatomyand Physiology in Health Education and Illness. 10thedition Published by Churchill Livingstoneelsewire, 2006; 195-204.

[15] Guyton A, Hall J, Textbook of Medical Physiology.10th editionElsevier publication 578-588.

[16] Chien YW: Ocular drug delivery and delivery systems, special edition, 269-296.

[17] Robinson JC: Ocular anatomy and physiology relevant to ocular drug delivery, Ophthalmic Drug Delivery Systems, New York, A.K. Mitra Edition, 1993, 29–57.

[18] Huang AJW, Tseng SCG and Kenyon KR: Paracellular permeability of corneal and conjunctival epithelia. Investigation Ophthalmology of Visual Science 1989; 30: 684– 689.

[19] Nagyova B and Tiffany JM: Components responsible for the surface tension of human tears. Current Eye Research 1999; 19: 4 – 11.

[20] Ahmed L, Gokhale RD, Shah MV and Paton TF: Phytochemical determinants of drug diffusion across the conjunctiva, sclera and cornea. Journal of Pharmaceutical Science 1987: 76: 583-587.

[21] Jani R, Gan O, Ali Y, Rodstrom R, Hancock, Ion exchange resins for ophthalmic delivery. J. Ocul. Pharm. Ther, 1994; 10: 57-67.

[22] Cohen S, A novel in-situ forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. Journal of Controlled Release 1997; 44: 201-08.

[23] Gambhire S, In situhydrogel: Different approaches to the ocular drug delivery. International journal of pharmacy and pharmaceutical science, 2013; 5: 2: 27-36.

[24] Patil A. A novel ophthalmic drug delivery: in situ gel. International Journal of pharmaceutical science and research, 2012; 3: 09: 2938-2946.

[25] Thakur Reeta Rani and KashivMridul Modern Delivery Systems for Ocular Drug Formulations: A Comparative Overview W.R.T Conventional Dosage Form, 2011; 2: 1: 8-10.

[26] Kaur IP, Garg A, Singla AK, Aggarwal D. Vesicular systems in ocular drug delivery; an overview. Int J Pharm, 269, 2004.

[27] Urtti A, Pipkin JD, Rork G, Sendo T, Finne U, Repta AJ. Controlled drug delivery devices for experimental ocular studies with timolol, Ocular and systemic absorption in rabbits. IntJ. Pharm, 1990; 61.

[28] Geroski DH, Edlhausker HF. Drug delivery for posterior segment eye diseases. Invest Opthalmic Vis sci, 2000; 41.

[29] YF Maichuk. Ophthalmic drug inserts. Invest Ophthalmol, 1975; 14: 87–90.

[30] MF Seattone. Solid polymeric inserts/disks as drug delivery devices. In: P Edman, ed.Bio pharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993; 61–79.

[31] A. Fischer, MSc, Thomas M, The future ofOcular drug delivery, email article at, www.google.com.

[32] Benita S, Levy MY. Submicron emulsions as colloidal drug carriers for intravenous administration: Comprehensive physicochemical characterization. J Pharm Sci, 1993; 82(11): 1069– 1079.

[33] Bochot A, Fattal E, Grossiord JL, Puisieux F, Couvreur P. Characterization of a new ocular delivery system based on a dispersion of liposomes in a thermosensitive gel. Int J Pharm, 1998; 162(1–2): 119 – 127.

[34] Plazonnet B. Ophthalmic. In: Bioequivalence of special dosage forms. Kurz nr 442 APV symposium. Berlin, Arbeitsgemeinschaft furl Pharmaceutics Verfahrenstechnike.v., Kurfurstenstrasse 59- D55118, Mainz, 2000.

[35] VHL Lee, JR Robinson. Review: Topical drug delivery. recent developments and future challenges. J Oculus Pharmacol, 1986; 2: 67–108.

[36] Saettone MF, Bucci G, Speiser P. Ophthalmic Drugs Delivery: Biopharmaceutical, Technological, Clinical Aspects. Fidia Research Series, Padova, Italia: Latvian Press, 1987; 11. www.ejpmr.com Kaur et al. European Journal of Pharmaceutical and Medical Research 261
[37] VHL Lee. Review: New directions in the optimization of ocular drug delivery. J OculPharmacol, 1990; 6: 157–164.
[38] Satyajeet al., American Journal of Pharma Tech Research, 2011; 1(4): 72-92. ISSN: 2249-3387 91 www.ajptr.com
[39] Edman P. Biopharmaceutics of Ocular Drug Delivery. Boca Raton, FL: CRC Press, 1993.
[40] AK Mithra. Ophthalmic Drug Delivery Systems. New York: Marcel Dekker, 1993.
[41] M Van Ooteghem. Preparations Ophtalmiques, Paris: Technique & Documentation, 1995.
[42] Frangie JP. Clinical pharmacokinetics of various topical ophthalmic delivery systems. Clin Pharmacokinetic, 1995; 29: 130–138.
[43] Kimura H, Ogura Y, Hashizoe M, Nishiwaki H, Honda Y, Ikad Y. A new vital drug delivery system using an implantable biodegradable polymeric device. Invest Ophthalmol Vis Sci, 1994; 35: 2815-2819.
[44] Hill JM, O'Callaghan RJ, Hobden JA. Ocular Iontophoresis. In: Mitra AK. Ophthalmic Drug Delivery Systems. 2nd Ed. New York: M. Dekker Inc., 1993; 331-354.
[45] Rootman DS, Janssen JA, Gonzalez JR, Fischer MJ, Beuerman R, Hill JM. Pharmacokinetics and safety of transcornealiontophoresis of tobramycin in the rabbit. Invest Ophthalmol Vis Sci 1988; 29:1397- 1401.
[46] Callahan MC, Hobden JA, O'Callaghan RJ, Hill JM. Ocular drug delivery: A comparison of transcornealiontophoresis to corneal collagen shields. Ant J Dharma, 1995; 123: 173- 179.
[47] Usayapant A, Karri AH, Narurkar MM. Effect of 2-Hydroxypropyl-beta-cyclodextrin on the ocular absorption of dexamethasone and dexamethasone acetate. Pharm Res 1991; 8: 1495–1499.
[48] Vainer M, Amidon G, Lindenbaum S, Haslam JL. Thermodynamic studies on the gelsol transition of some pluronicpolyols. Int J Pharma, 1984; 22: 207- 218.
[49] Vasantha R, Sehgal PK, Rao P. Collagen ophthalmic inserts for Pilocarpine drug delivery system. Int J Pharma, 1988; 47: 95-102.
[50] Vandamme TF. Microemulsions as ocular drug delivery systems: recent developments and future challenge. ProgRetin Eye Res, 2002; 21: 15–34.
[51] Patravale VB, Date AA, Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. J Pharm Pharmacol, 2004; 56: 827-840.
[52] Jiang J, Gill HS, Ghate D, McCarey BE, Patel SR, Edelhauser HF, Prausnitz MR. Coated microneedles for drug delivery to the eye. Invest Ophthalmol Vis Sci, 2007; 48: 4038–4043.
[53] Satyajeet al., American Journal of PharmTech Research. 2011; 1(4):72-92. ISSN: 2249-3387 www.ajptr.com 92
[54] Green K, Chapman JM, Cheeks L, Clayton RM, Wilson M, Zehir A. Detergent penetration into young and adult rabbit eyes: comparative pharmacokinetics. J Toxicol Cut OculToxicol, 1987; 6: 89–107.