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REVIEW ARTICLE

A REVIEW ON OCULAR DRUG DELIVERY WITH NEW TRENDS

Dipali Suresh Kurade* , Prof. D.G.Joshi,Mrs.Bandgar Anita.A.
Vansantidevi Patil Institute of Pharmacy, Kodoli. Tal. Panhala, Dist. Kolhapur, (M S), India

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****Corresponding Author***

Dipali S. Kurade

Abstract

Eye is a window to the outside world and hence it becomes an important part of our body.

Ocular drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist for past 10-20 years. As an isolated organ, eye is very difficult to study from a drug delivery point of view. Despite these limitations, improvements have been made with the objective of maintaining the drug for an extended period. Recently, controlled and sustained drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been undertaken in achieving much better drug product effectiveness, reliability and safety.

Various diseases occurring in the eye cavity are difficult to treat. Promising management of eye ailments depends on effective concentration of drug at the eye for sufficient period of time. Dosage forms are administered directly to the eye for localized ophthalmic therapy.

Some diseases require continuous use of medicine and other requires surgery. Lacrisert, Vitrasert, Mydriasert, Prosert etc. are patented technologies useful in the treatment of eye disorders. This article review constrains various novel approaches including in-situ gels, colloidal particles, liposomes, nanoparticles, inserts, microparticles, implants to improve the ophthalmic bioavailability of drugs to the anterior chamber of eye. Some approaches are relatively easy to manufacture, but are limited in their ability to provide sustained drug release

INTRODUCTION

Eye is a window to the outside world and hence it becomes an important part of our body.(6) Eye is unique and very precious organ. There are many eye ailments which affect this organ and one can loss the eye sight also. Therefore many ophthalmic drug delivery systems are available. Promising management of eye ailments depends on effective concentration of drug at the eye for sufficient period of time. Dosage forms are administered directly to the eye for localized ophthalmic therapy. This article reviews the constraints for topical ophthalmic drug delivery system, with conventional topical delivery systems and explore various novel approaches including in-situ gels, colloidal particles, liposomes, nanoparticles, inserts, microparticles, implants, minidiscs, pharmacosomes, collagen shields etc to improve the ophthalmic bioavailability of drugs to the anterior chamber of eye.(9) These are classified as conventional and non-conventional drug delivery systems. Most commonly available ophthalmic preparations are eye drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into the cul-de-sac are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage. Only a small amount is available for its therapeutic effect resulting in frequent dosing. So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, intophoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a sustained and controlled manner.(10) Ocular drug delivery has been a major challenge for scientists due to its unique anatomy and physiology which contains various types of barriers such as different layers of cornea,

sclera and retina including blood aqueous and blood–retinal barriers, choroidal and conjunctival blood flow etc. These barriers cause a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment of the eye.(11) Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical companies in the market. Many ophthalmic formulations like solutions, suspensions, ointments suffer from the drawbacks like precorneal elimination, high variability in efficiency and blurred vision. The major problem associated with these conventional dosage forms is the bioavailability of drug.

ANATOMY AND PHYSIOLOGY OF EYE:-

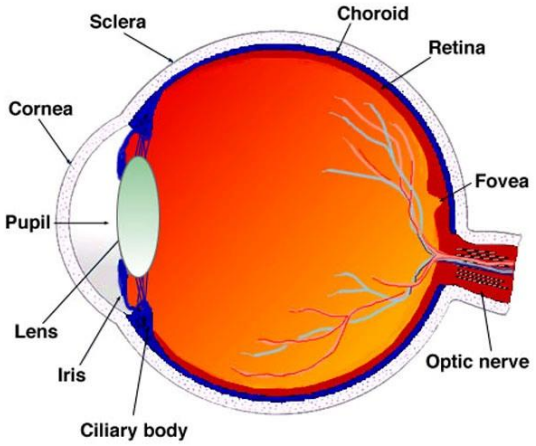

Figure 1 Structure of the eye

The eye is a spherical structure with a wall made up of three layers; the outer part sclera, the middle parts choroid layer, Ciliary body and iris and the inner section nervous tissue layer retina. The sclera is tough fibrous coating that protecting the inner tissues of eye which is white except for the transparent area at the front, and the cornea allows light to enter to the eye. The choroid layer, situated situated in the sclera, contains many blood vessels that modified at front of the eye as pigmented iris the coloured part of the eye (blue, green, brown, hazel, or grey).

The structure of the cornea:-

The clear transparent bulge cornea situated at the front of the eye that conveys images to the back of the nervous system. The adult cornea has a radius of approximately 7-8mm that covers about one-sixth of the total surface area of the eye ball that is a vascular tissue to which provides nutrient and oxygen are supplied via lachrymal fluid and aqueous humour as well as from blood vessels of the junction between the cornea and sclera in fig.1 The cornea is made of five layers as epithelium, bowman's layer, stroma, descemet's membrane and endothelium that is main pathway of the drug permeation to eye . The epithelium made up of 5 to 6 layers of cells. The corneal thickness is 0.5–0.7 mm in the central region. The main barrier of drug absorption into the eye is the corneal epithelium, in comparison to many other epithelial tissues (intestinal, nasal, bronchial, and tracheal) that is relatively impermeable . The epithelium is squamous stratified, (5-6 layer of cells) with thickness of around 50-100 µm and turnover of about one cell layer every day. The basal cells are packed with a tight junction, to forming not only an effective barrier to dust particle and most microorganisms, and also for drug absorption. The transcellular or paracellular pathway is the main pathway to penetrate drug across the corneal epithelium. .the lipophilic drugs choose the transcellular route whereas the hydrophilic one chooses paracellular pathway for penetration (passive or altered diffusion through intercellular spaces of the cells). The Bowman's membrane is an acellular homogeneous sheet with 8-14µm thick situated between the basement membrane of the epithelium and the stroma. The stroma, or substania propria, composed of around 90% of the corneal thickness that contains about 85% water and about 200-250 collagenous lamellae. The lamellae provide physical strength while permitting optical transparency of the membrane. The hydrophilic solutes diffuse through the stroma's open structure. The descemet's membrane is secreted by the endothelium and lies between the stroma and the endothelium.

Conjunctiva:- (2)

The conjunctiva protects the eye and also involved in the formation and maintenance of the precorneal tear film. The conjunctiva is a thin transparent membrane lies in the inner surface of the eyelids and that is reflected onto the globe. The conjunctiva is made of an epithelium, a highly vascularised substantia propria, and a submucosa.(7) The bulbar epithelium contains 5 to 7 cell layers. The structure resembles a pallisadeand not a pavemente corneal epithelium cells are connected by tight junctions, which render the conjunctiva relatively impermeable. The molecules up to 20,000 Da can cross the conjuctiva, while the cornea is restrict to molecules larger than 5000 Da. The human conjunctiva is about 2 and 30 times more absorption of drugs than the cornea and also proposed that loss of drug by this route is a major path for drug clearance. The highest density of conjunctiva is due the presence of 1.5 million globlet cell varying with age depended among the intersujects variability and age. The vernal conjunctivitis and atopic kerato conjunctivitis occurs due to the great variation in goblet cell density results only in a small difference in tear mucin concentration.(8)

Nasolachrymal drainage system :-

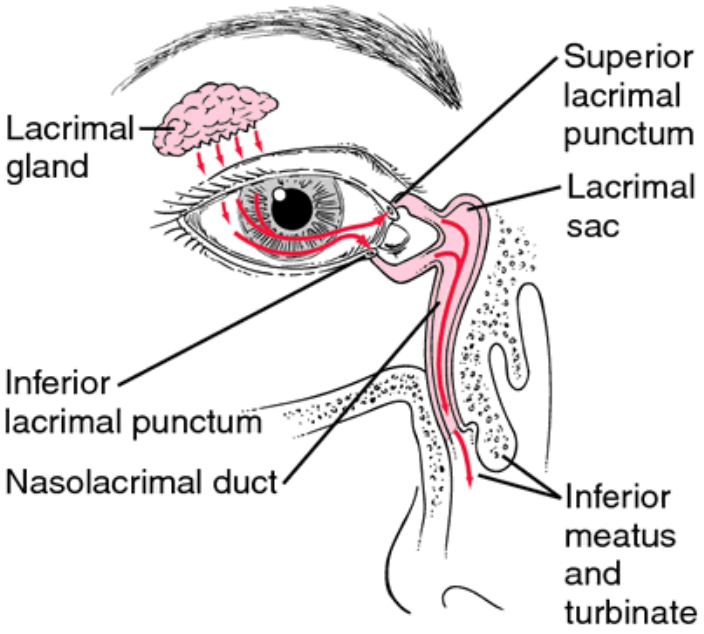

Figure 2 Schematic diagram of nasolachrymation drainage system

Nasolachrymal 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 secretory system is stimulated by blinking and temperature change due to the tear evaporation and reflux secretors that have an efferent parasympathetic nerve supply and secrete in response to physical and emotional state e.g. crying. The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing. The excretory part of the Nasolachrymal drainage system consists of the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac, and the nasochrymal 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 and the lachrymal sac; only a small amount reaches the nasal passage (1)

Tear film:-

A thin fluid layer is covered the exposed part of the eye called as precorneal tear film. The film thickness is about 3–10 Am depending on the measurement method with the resident volume approximately 10 µl. The osmolality of the tear fluid is approx. 310–350 mOsm/kg in normal eyes and is maitained by the monovalent and divalent inorganic ions present in fluid such as Na+, K+, Cl-, HCO3-, and proteins. The mean pH of normal tears is about 7.4. Diurnal

patterns of pH changes the pH of tear, which a general shift from acid to alkaline during the day. The buffer capacity of the tears fluid is determined by bicarbonate ions, proteins, and mucins . Tears exhibit a non-Newtonian rheological behaviour with viscosity is about 3 mPas 12.The mean surface tension of tear film value is about 44 mN/m.

BARRIERS TO OCULAR DRUG DELIVERY:-

Drug loss from the ocular surface:-

After instillation, the flow of lacrimal fluidremoves instilled compounds from the surface of the eye. Even though the lacrimal turnover rate isonly about 1 µl/min the excess volume of the instilled fluid is flown to the nasolacrimal ductrapidly in a couple of minutes. Another source of non-productive drug removal is its systemicabsorption instead of ocular absorption. Systemic absorption may take place either directly from theconjunctival sac via local blood capillaries or afterthe solution flow to the nasal cavity.Anyway, most of small molecular weight drug dose is absorbed into systemic circulation rapidly in fewminutes. This contrasts the low ocularbioavailability of less than 5% . Drugabsorption into the systemic circulation decreases the drug concentration in lacrimal fluid extensively.Therefore, constant drug release from solid delivery system to the tear fluid may lead only toocular bioavailability of about 10%, since most ofthe drug is cleared by the local systemic absorption anyway.

Lacrimal fluid-eye barriers:-

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal barrier is formed upon maturation of the epithelial cells.They migrate from the limbal region towards the centre of the cornea and to the apical surface. The most apical corneal epithelial cells form tight junctions that limit the paracellular drug permeation (12). Therefore, lipophilic drugs havetypically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs (24). Despite the tightness of the corneal epithelial layer, transcorneal permeation is the main route of drug entrance from the lacrimal fluid to the aqueous humor (Fig. 3). In general, the conjunctiva is more leaky epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea (14). Drug absorption across the bulbar conjunctiva has gained increasing attention recently, since conjunctiva is also fairly permeable to the hydrophilic and large molecules.Therefore, it may serve as a route of absorption for larger bio-organic compounds such as proteins and peptides. Clinically used drugs are generally small and fairly lipophilic. Thus, the corneal route is currently dominating. In both membranes, cornea and conjunctiva, principles of passive diffusion have been extensively investigated, but the role of active transporters is only sparsely studied.(25,26)

Blood-ocular barriers:-

The eye is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the uvea.This barrier prevents the access of plasma albumin into the aqueous humor, and limits also the access of hydrophilic drugs from plasma into the aqueous humor. Inflammation may disrupt the integrity of this barrier causing the unlimited drug distribution to the anterior chamber. In fact, the permeability of this barrier is poorly characterised. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space,but thereafter distribution into the retina is limited by the RPE and retinal endothelia. Despite its high blood flow the choroid blood flow constitutes only a minor fraction of the entire blood flow in the body. Therefore, without specific targeting systems only a minute fraction of the intravenous or oral drug dose gains access to the retina and choroid.Unlike blood brain barrier, the blood-eye barriers have not been characterised in terms of drug transporter and metabolic enzyme expression. From the pharmacokinetic perspective plenty of basic research is needed before the nature of blood-eye barriers is understood.(10)

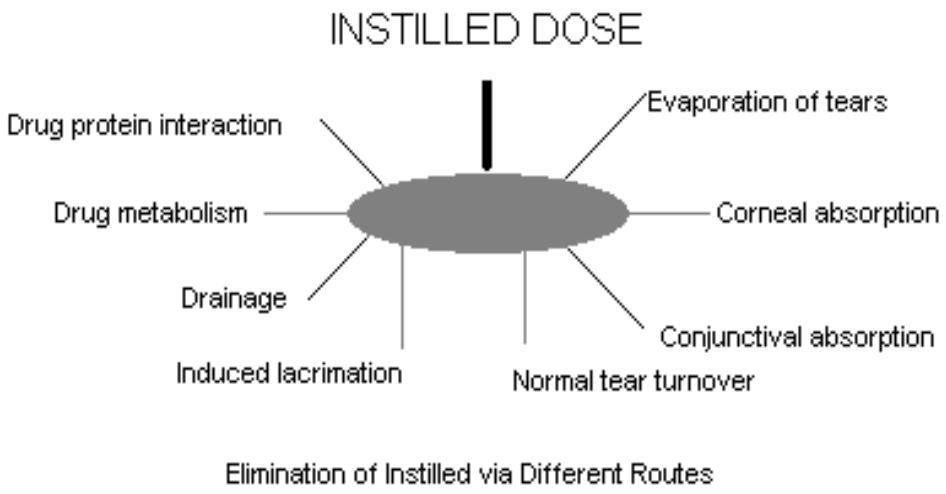

Figure 3 Elimination of Instilled via different routes(15)

Conventional occular drug delivery:-

Ocular drug delivery has been a major challenge to pharmacologists and drug delivery scientists due to its unique anatomy and physiology. Static barriers (different layers of cornea, sclera, and retina including blood aqueous and blood–retinal barriers), dynamic barriers (choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution), and efflux pumps in conjunction pose a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment.(17)

Aqueous solutions:-

Today most of the topical ophthalmic preparations are in the form of aqueous solutions. A sterile homogeneous solution dosage form have many advantages over the other dosage such as formulation, including the easily commercially capability produce on large scale manufacture. There are various factors that must be consider during the formulating aqueous solution includes selection of appropriate salt of the drug, solubility in solvents, therapeutic systemic effect, ocular toxicology, pKa of formulation, and the effect of pH of the formulation. Others stability parameters includes such as solubility(1)

Suspensions:-

Ophthalmic suspensions products is another part of the ocular drug delivery system and have many distinct advantages over others formulation. Recently developed drugs are generally hydrophobic poor solubility in water and aqueous medium. Formulation offers a sterile, preserved, effective, stable and pharmaceutically elegant. Ophthalmic suspensions are more complex and challenging if compare with to ophthalmic (aqueous) solutions. The formulation of a ophthalmic suspension many problem occurred such as non homogeneity of the dosage form, settling of particles, cake formation, aggregation of the suspended particles. The commercial ophthalmic products of should be effectively preserved on storage. To study the surface tension properties, such as wetting, particle size and interaction zeta potential, aggregation, sedimentation rate and rheological characterization of the formulation. Above all criteria are necessary for formulating an effective, elegant suspension ophthalmic formulation(1)

ADVANCED OCULAR DRUG DELIVERY SYSTEMS

Films, erodible and non-erodible inserts, rods and shields are the most logical delivery systems aimed at remaining for a long period of time in front of the eye. From a therapeutical point of view, inserts have been a success in the

improvement of accurate dosing, drug bioavailability and by the reduction of systemic absorption, and consequently side effects. Inserts dissolve and/or erode on contact with the ocular surface and therefore need to be used in addition with other artificial tears to initiate the dissolving process.(13)

Nanotechnology in ocular drug delivery system:-

The word Nanotechnology, arise from the Greek word nano meaning drawf,technology means application to the engineering, electronics, physical, material science medical and manufacturing at a molecular and a submicron level. An early promoter of nanotechnology, Albert franks, defined it as that area of science and technology where dimensions and tolerance are in the range of 0.1-100nm.The nanotechnology based drug delivery system like nanosuspension, solid

nanoparticle microemusion and liposomes have developed to solve the solution of various solubility-related problem of poorly water soluble drugs, likes dexamethsone,budenoside, gancyclovir and so on . Due to relative properties of the particle size charge, surface properties and relative hydrophobicity of (molecules) nanoparticles are developed to be successfully used in crossing the over-coming absorption barriers.(1) In a last few decades, many approaches have been utilized for the treatment of ocular diseases. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability,and ocular tissue compatibility. Several nanocarriers, suchas nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery (Figure 4). Some of them have shown promising results for improving ocular bioavailability.(3)

For ophthalmic delivery, nanoparticles are generally composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan,poly (lactide-co-glycolide) (PLGA), polylactic acid(PLA) and polycaprolactone. Drug loaded nanoparticles can be nanocapsules or nanospheres (Figure 4). In nanocapsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix. From past few decades, nanoparticles have gained attention for ocular drug delivery and several researchers have made attempts to develop drug load ednano particles for delivery to both anterior and posterior ocular tissues.Nanoparticles represents a promising candidate for ocular drug delivery because of small size leading to low irritation and sustained release property avoiding frequent administration. However, like aqueous solutions, nanoparticles may be eliminated rapidly from precorneal pocket.Hence, for topical administration nanoparticles with mucoadhesive properties have been developed to improve precorneal residence time. Polyethylene glycol (PEG),chitosan and hyaluronic acid are commonly employed to improve precorneal residence time of nanoparticles.Chitosan coating is most widely explored for improving precorneal residence of nanoparticles. The chitosan is positively charged and hence it binds to negatively charged corneal surface and thereby improves precorneal residence and decreases clearance. (3)

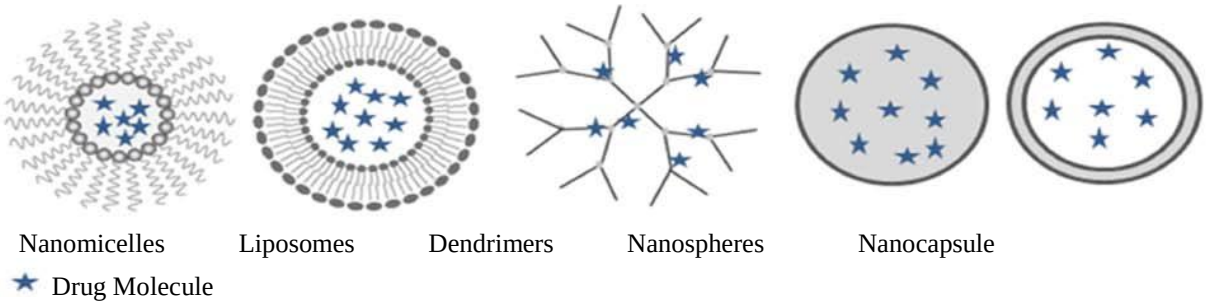

Figure 4 Nanocarriers for ocular drug delivery.

Nanoparticles are solid, submicron, colloidal particles ranging in dimension from 10 to 1000 nm, in that drug molecules may be present in dissolved, entrapped, adsorbed or covalently attached form. Based on formulation approaches nanoparticles can be acquired with distinct properties and release attributes for the capsulated drug. These colloidal particles can be assigned in the liquid form just like eye drops and diminishes uneasiness provoked by application of semisolid ointments. They are patient friendly owing to less frequent application, extended duration of retention in the extra ocular portion deprived of blurring vision.Nanoparticles have been established to be the most promising of all the formulations developed over the past a couple of years of marked navigate in ocular

therapeutics, payable to their sustained release and prolonged therapeutic concern. Polymeric nanoparticles are additionally capable in the targeting of ailments in the posterior segment of the eye . Nanoparticles made of biodegradable polymer that combines the capabilities of stimulus response and molecular recognition hold a pronounced aptitude in ocular drug delivery. Biodegradable polymers formulated as colloidal systems hold significant promise for ophthalmic drug delivery. Supplementally, surface altered nanoparticulate carriers may utilize to acclimatize a sort of actives.

The serious concerns with regard to the formulation of nanoparticles comprehend stability, particle size homogeneity, control of drug release rate, and sizeable production of uncontaminated preparations. Nanocarries possessing polyethylene glycol or surface-segregated chitosan have been established to be correspondingly stable as well as proficient at overcoming mucosal barriers.(20)

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 inserts(15)

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In Ocusert the drug reservoir is a thin disc of pilocarpine-alginate complex sandwich between two transparent disc of micro porous membrane fabricated from ethylene-vinyl acetate copolymer. (11) Ocusert® provides uniform controlled release (20 or 40 g/hour for 7 days) of pilocarpine as an ocular hypotensive drug, and has been commercialized in 1974.

Ocusert® consists of two outer layers of ethylene-vinyl acetate copolymer (EVA), and an inner layer of pilocarpine in alginate gel within di-(ethylhexyl)phthalate for a release enhancer, sandwiched between EVA layers . However, Ocusert® has not become widely used because of unsatisfactory IOP control due to various causes, including difficulty of inserting the device, ejection of the device from eye, and irritation during insertion (29)

Lacrisert:-(29)

Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca and was introduced by Merck, Sharp and Dohme in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea. It dissolves in 24 hours. Lacrisert® (Aton Pharma, Inc., Lawrenceville, NJ, U.S.) is a rod-shaped, water-soluble cul-de-sac insert composed of hydroxypropyl cellulose without preservatives and other ingredients (1.27 mm diameter, 3.5 mm long), and is indicated in moderate to severe dry eye syndrome (30). Lacrisert® has not been applied as a drug delivery carrier as yet.

Prosert:-(32,33)

It is an ophthalmic placebo insert which is insoluble, sterile and biocompatible. This system can contain one or several active components and allow its releasing in programmed or controlled way. Prosert is constituted of a matrix able to contain one or several active components, surrounded by a dyalisantic membrane of a changeable thickness which allows the releasing controlled by the tears. The entirety has the shape of a small oblong cylinder (reservoir) with rounded forms. When PROSERT is inserted in the cul-de-sac, the tears enter into the device and saturate the mesh net intended to contain the active component. When the osmotic equilibrium is achieved the active component is released through the dyalisantic membrane and then is spread in the conjunctiva. The releasing curve

has an ascending phase up to achieve the equilibrium and then its stable; the releasing of the active component is done at constant speed.

SODI:-

Soluble ocular drug insert (SODI) is a small oval wafer which was developed by Soviet scientist for cosmonauts who could not use eye drops in weightless condition.(5) It is sterile thin film of oval shape made from acrylamide, N-vinylpyrrolidone and ethylacrylate called as ABE. It is used in the treatment of glaucoma and trachoma. It is inserted into the inferior cul-de-sac and gets wets and softens in 10-15 seconds. After 10-15 min the film turn into a viscous polymer mass, after 30-60 mins it turns into polymer solutions and delivers the drug for about 24 hours(11)

Iontophoresis:-

Ocular iontophoresis has gained significant interest recently due to its non-invasive nature of delivery to both anterior and posterior segment. It requires a mild electric current which is applied to enhance ionized drug penetration into tissue. This mode of delivery can overcome the potential side effects associated with intraocular injections and implants mentioned earlier. OcuPhor™ system has been designed with an applicator, dispersive electrode and a dose controller for transscleral iontophoresis (DDT) (18) For iontophoresis the ions of importance should be charged molecules of the drug. 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 manner at the ocular site.(19)Iontophoresis is the process in which direct current drives ions into cells or tissues. When iontophoresisis used for drug delivery, the ions of importance arecharged molecules of the drug. If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged,at the cathode. Ocular iontophoresis offers a drug delivery system that is fast, painless and safe; and in most cases, it results in the delivery of a high concentration of the drug to a specific site.Increased incidence of bacterial keratitis, frequently resulting in corneal scarring, offers a clinical condition that may benefit from drug delivery by iontophoresis. Iontophoretic application of antibiotics may enhance their bactericidal activity and reduce the severity of disease; similar application of anti-inflammatory agents could prevent or reduce vision threatening side effects .But the role of iontophoresis in clinical ophthalmology remains to be identified.

Ophtha coils:- (6,34)

It can be placed in the lower conjunctival fornix, where it releases its drug. The device consists of a metal coil, coated with a hydrogel. The drug is entrapped in the hydrogel coating. The device is non biodegradable to prevent disintegration of the device or leakage of the drug and hence the device has to remove after the drug is released. Release of drug is by diffusion into the tear fluid. The coil can potentially serve as an alternative to the administration of drugs to the eye via eye drops.

Microneedle:-

A goal of ophthalmology researchers is to deliver medication to the back of the eye in a selective and minimally invasive way. An Emory Eye Center scientist and two fellow researchers have investigated opportunities and have recently been awarded a U.S. patent for application of microneedle technology.(27) Filed for in 2007 and awarded in April 2011, the patent (US 7,918,814) was awarded to Henry F. Edelhauser, Emory Eye Center's former director of research, along with Mark Prausnitz, professor of chemical and biomedical engineering at the Georgia Institute of technology, and Ninghao Jiang. Because of its smaller size than the currently used intravitreal needles there may be less discomfort for the patients. Many patients with age related macular degeneration have injections on a regular basis. In the future, the same microneedle technology may be used to inject medication directly into the eye for many other ocular conditions, such as glaucoma, eliminating the need to put drops in the eyes every day a real chore for some patients. This hollow tubed microneedle can serve as a route for targeted drug delivery for retinal disease using an array of delivery suspensions such as microbeads and microbubbles.(6)

Liposomes- The use of liposomes as atopically administered ocular drug delivery system began in the early stage of research into ophthalmic drug delivery. Drug's physicochemical properties have significant influence on the effectof liposomes. Favorable result with liposomes found essentially with lipophilic drugs as hydrophilic drug escape rapidly out of the liposomes than lipophilic drugs. Charge on liposomes also influence drug concentration inocular tissues.Corneal epithelium is covered by negatively charged mucin thus positively charged liposomes increase drug concentration in ocular tissues. Coating with bioadhesive polymers to liposomes, prolong the precomea retention of liposomes. Carbopol coated pilocarpine containing liposomes were shown to produce a longer duration of action.(9)

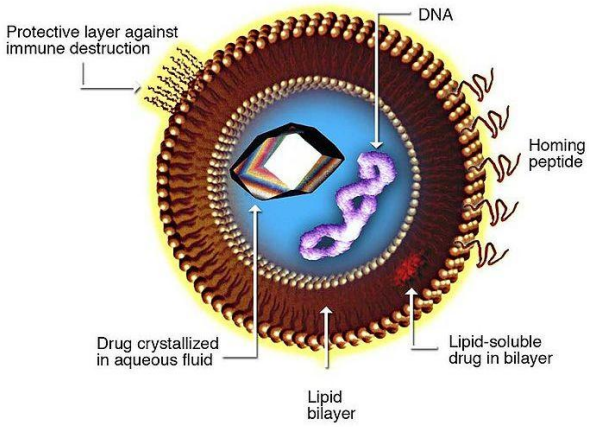


Figure 5 Liposome for drug delivery

Liposomes are phospholipid-lipid vesicles for targeting drugs to the specific sites in the body.
They provide controlled and selective drug deliveryand improved bioavailability and their potential inocular drug delivery appears greater for lipophilic than hydrophilic compounds. Liposomes 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 a potential delivery system for administration of a number of drugs to the eye.

Implants:-

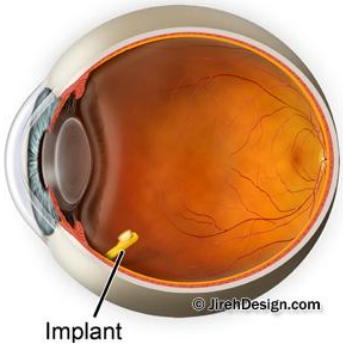


Figure 6 Intraocular Implant

Intraocular implants are specifically designed to provide localized controlled drug release over a extended period.These devices help in circumventing multiple intraocular injections and associated complications. Usually for drug delivery to posterior ocular tissues, implants are placed intravitreally by making incision through minor surgery at pars plana which is located posterior to the lens and anterior to the retina. Though implantation is invasive procedure, these devices are gaining interest due to their associated advantages such as sustained drug release,
local drug release to diseased ocular tissues in therapeutic levels, reduced side effects and ability to circumvent blood retina barrier. Several implantable devices
have been developed for ocular drug delivery especially
for the treatment of chronic vitreoretinal diseases.Ocular implants are available as biodegradable andnon-biodegradable drug releasing devices. Non-biodegradable implants offer long-lasting release by achieving near zero order release kinetics. Polymers such aspolyvinyl alcohol (PVA), ethylene vinyl acetate (EVA), andpolysulfone capillary fiber (PCF) are being employed for fabricating non-biodegradable implants. Vitrasert® and Retisert® are the examples of marketed non-biodegradable implants.
Vitrasert® (Bausch and Lomb Inc., Rochester, NY,United States) is a controlled-release intraocular implant of ganciclovir approved by Food and Drug Administration(FDA) for the treatment of acquired immune deficiency syndrome-associated cytomegalovirus retinitis.(22) It is

composed of a ganciclovir tablet of 4.5 mg surrounded by PVA/EVA that slowly release the drug over an extended period of 5-8 mo. The device provides long term sustained release without systemic toxicity at reduced cost. Retisert® (Bauschnd Lomb Inc., Rochester,
NY, United States) is approved by FDA for the treatment of chronic uveitis which affects the posterior segment ofthe eye. It is the first marketed silicone laminated PVA implant. It provides sustained release of fluocinolon eacetonide up to 3 years.(23) The implant had effectively controlled inflammation, reduced uveitis recurrences and improved vision acuity. The associated side effects are cataracts and elevated IOP[Long term drug release may be achieved with these non-biodegradable implants but are associated with certain short comes. These devices
have to be surgery implanted and removed after drug depletion, which makes the treatment expensive and patient non-compliance. Also, adverse events such as endophthalmitis,
pseudoendophthalmitis, vitreous haze and hemorrhage, cataract development and retinal detachment limit their applications(3) Another category of ocular implant includes biodegradable
implants. These implants are gaining muchattention and are being studied at large due to their biocompatibleproperty and sustained drug release properties.Because of biodegradable nature, these implants arenot required to be surgically removed which signify a distinctive
advantage over the non-biodegradable implants.(3)Polylactic acid (PLA), polyglycolic acid (PGA), PLGA,and polycaprolactones are the most commonly used polymers
for the fabrication of biodegradable implants Examples of biodegradable implants for ocular delivery include Surodex™ and Ozurdex® which are designed for the sustained delivery of dexamethasone for the treatmentof intraocular inflammation and macular edema(3)

Vitrasert :-It is an ocular implant for delivering ganciclovir for the treatment of cytomegalovirus. This implant was developed under Vitrasert Dr. Smith This implant delivers the drug directly to the retina for over 5 months. It is useful for patients with AIDS associated cytomegalovirus retinitis. The device was prepared by coating a ganciclovir pellet with PVA. The pellet was then coated with ethylene vinyl acetate except on its top surface, and again coated with PVA. It is surgically implanted into the pars plana and attached to the sclera by a suture. The device lasted 4-5 months. (21)

Retisert:-

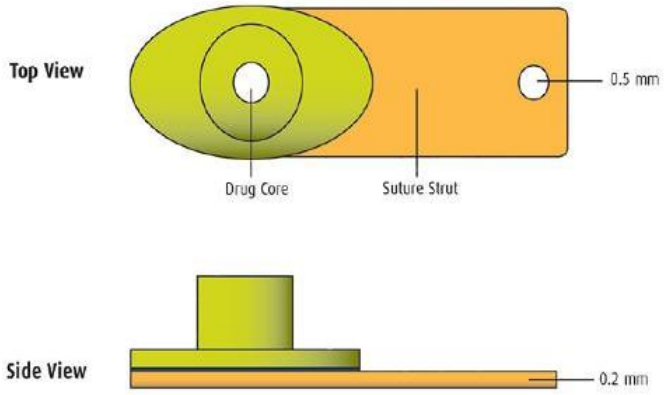


Figure 7 Schematic view of retisert and its delivery system

The Retisert implant was also developed under Dr. Smith, using the same technology as Vitrasert. (16)They developed an intraocular sustained release steroid implant capable of maintaining anti inflammatory intravitreal drug levels for periods of up to 3 years from single implantation. (6)

Artificial tear inserts

A rod shaped pellet of hydroxypropyl cellulose without preservative is commercially available (Lacrisert). This device is designed as a sustained release artificial tear for the treatment of dry eye disorders. It was developed by Merck, Sharp and Dohme in 1981(17)

In-situ gelling systems

In-situ hydrogels refer to the polymeric solutions which undergo sol-gel phase transition to form viscoelastic gel in response to environmental stimuli. Gelation can be elicited by changes in temperature, pH and ions or can also be

induced by UV irradiation. For ocular delivery, research studies have been more focused toward development of thermo sensitive gels which respond to changes in temperature.(4)

Advanced Delivery System

Cell Encapsulation:-

The entrapment of immunologically isolated cells with hollow fibres or microcapsules before their administration into the eye is called Encapsulated Cell Technology (ECT) which enables the controlled, continuous, and long-term delivery of therapeutic proteins directly to the posterior regions of the eye. The polymer implant containing genetically modified human RPE cells secretes ciliary neurotrophic factor into the vitreous humour of the patients' eyes. ECT can potentially serve as a delivery system for chronic ophthalmic diseases like neuroprotection in glaucoma,anti-angiogenesis in choroidal neovascularization, anti-inflammatory factors for uveitis.

Gene Therapy:-

Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications. Topical delivery to the eye is the most expedient way of ocular gene delivery. Retroviral vectors have been widely used due to their high efficacy; however, they do not have the ability to transducer nondividing cells, leads to restrict their clinical use. The advanced delivery systems that prolong the contact time of the vector with the surface of the eye may enhance transgene expression, thereby facilitate non-invasive administration.

Stem cell Therapy:-

Emerging cell therapies for the restoration of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina. The most successful ocular application has been the use of limbal stem cells, transplanted from a source other than the patient for the renewal of corneal epithelium. The sources of limbal cells include donors, autografts, cadaver eyes, and (recently) cells grown in culture. Stem-cell Therapy has demonstrated great success for certain maladies of the anterior segment.(11)

Protein and Peptide therapy:-

The designing of optimized methods for the sustained delivery of proteins and to predict the clinical effects of new compounds to be administered in the eye, the basic knowledge of Protein and Peptide is required. However, several limitations such as membrane permeability, large size, metabolism and solubility restrict their efficient delivery. A number of approaches have been used to overcome these limitations. Poor membrane permeability of hydrophilic peptides may be improved by structurally modifying the compound, thus increasing their membrane permeability. Ocular route is not preferred route for systemic delivery of such large molecules. Immunoglobulin G has been effectively delivered to retina by trans scleral route with insignificant systemic absorption.

Scleral Plug therapy:-

Scleral plug can be implanted using a simple procedure at the pars plana region of eye, made of biodegradable polymers and drugs, and it gradually releases effective doses of drugs for several months upon biodegradation. The release profiles vary with the kind of polymers used, their molecular weights, and the amount of drug in the plug. The plugs are effective for treating vitreoretinal diseases such as proliferative vitreo retinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vitrectomy.

siRNA therapy:-

For various angiogenesis-related diseases, the use of siRNA is considered as a promising approach. Feasibility of using siRNA for treatment of choroidal neovascularization has been demonstrated using siRNA directed against vascular endothelial growth factor (VEGF) or VEGF receptor 1 (VEGFR1), and both of these approaches are being tested in clinical trials. Topical delivery of siRNAs directed against VEGF or its receptors has also been shown to suppress corneal neovascularisation. New encapsulated siRNA have been developed using liposomes, coupled-antibodies or others polymer vesicles. Therapeutic approach using siRNA provides a major new class of drugs that will shed light the gap in modern medicine.

Oligonucliotide therapy:-

Oligonucleotide (ON) therapy is based on the principle of blocking the synthesis of cellular proteins by interfering with either the transcription of DNA to mRNA or the translation of mRNA to proteins. Among several mechanisms by which antisense molecules disrupt gene expression and inhibit protein synthesis, the ribonuclease H mechanisms are the most important. A number of factors have been determined to contribute to the efficacy of antisense ON.

Aptamer:-

Aptamers are oligonucleotide ligands that are used for high-affinity binding to molecular targets. They are isolated from complex libraries of synthetic nucleic acid by an iterative process of adsorption, recovery, and reamplification. They bind with the target molecules at a very low level with high specificity.

Ribozyme therapy:-

RNA enzymes or ribozymes are a relatively new class of single-stranded RNA molecules capable of assuming three dimensional conformations and exhibiting catalytic activity that induces site-specific cleavage, ligation, and polymerization of nucleotides involving RNA or DNA. A disease named, Autosomal dominated retinitis pigmentosa (ADRP) is caused by mutations in genes that produce mutated proteins, leading to the apoptotic death of photoreceptor cells.(11)

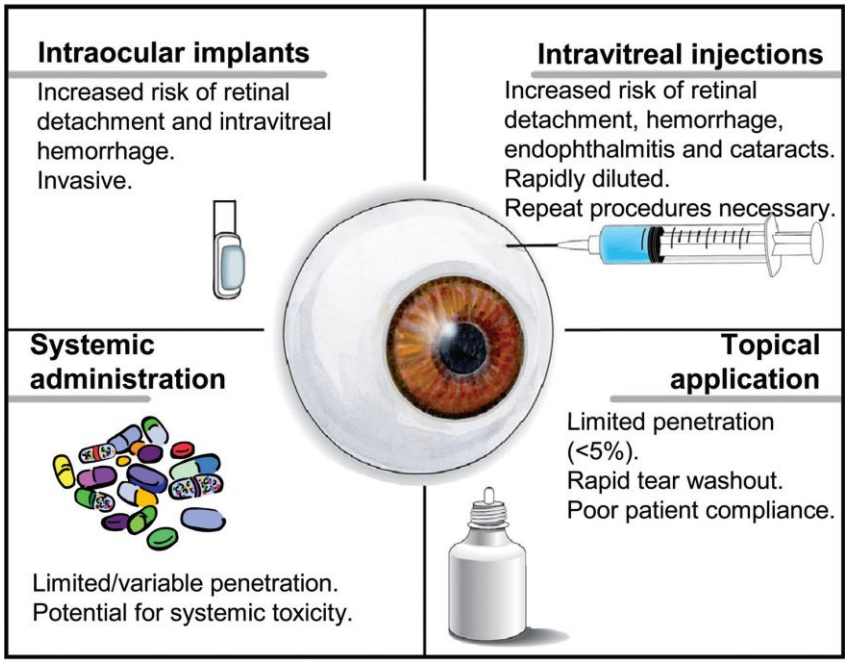
Conclusion:-

Effective treatment of ocular diseases is a formidable challenge for scientists in the field especially because of the nature of diseases and presence of the ocular barriers especially in posterior ocular segments. An ideal therapy should maintain effective levels of drug for the longer duration following a single application. Drug delivery by topical and intravitreal routes cannot be considered safe, effective and patient friendly.

A few new products have been commercialized as a result of the research into ophthalmic drug delivery.

The performance of these new products, however, is still far from being perfect. An ideal system should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure. In addition, the system should be both comfortable and easy to use. Patient acceptance will continue to be emphasized in the design of

future ophthalmic drug delivery systems. Major improvements are required in each of the technologies discussed in this review. Some approaches are relatively easy to manufacture, but are limited in their ability to provide sustained drug release.



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