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OCULAR DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Topical administration for ocular therapeutics 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 parts of the eye and transcorneal penetration is believed to be the major route for drug absorption. Corneal absorption is much slower process than elimination. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration. Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently it is imperative to optimize ophthalmic drug delivery; one of the way to do so is by addition of polymers of various grades, development of in situ gel or colloidal suspension or using erodible or non erodible insert to prolong the pre corneal drug retention. This review focused on controlled and sustained drug delivery has become the standard in modern pharmaceutical design and several possible routes of drug delivery into the ocular tissues.

KEYWORDS: Ophthalmic drug delivery, Corneal drug delivery, Controlled and sustained drug delivery.

INTRODUCTION

Ocular administration of the drug is primarily associated with the need to treat ophthalmic diseases and is not regarded as a means for gaining systemic drug action. Major classes of drugs are used are miotics, mydriatics/ cyclopegics, anti-inflammatories, anti–infectives (antibiotics, antivirals, antibacterials), surgical adjuvants and diagnostics, which are all meant for local therapy.[1]Ophthalmic preparation are defined in the USP as sterile dosage forms essentially free from foreign particles, suitably compound and packaged for instillation into the eye. They include solution, suspension, ointments, and certain solid dosage forms.[2]

Ophthalmic products are the preparation designed for application to the ethier for the treatment of disease, for the relief of symptoms, for the diagnostic purpose or an adjuvant to the surgical procedure. The conventional ocular preparation are eye drops and the ophthalmic ointments. As soon as the eye drop solution is instilled into cul-de-sac, it is rapidly away from the precorneal cavity by constant tear flow and lachrymal-nasal drainage. Only about 1-2% of instilled dose is absorbed into the target tissues and relatively concentrated solution is required for the instillation to achieve an adequate level of therapeutic effect. The frequent periodic instillation of eye drops becomes necessary to maintain a continuous sustained level of the medication. A basic concept in ophthalmic research and the development is that the therapeutic efficacy of an ophthalmic drug can be greatly improved by perlonging its contact with the corneal surface. The viscosity enhancing agents such as methylcellulose are added to eye drop preparation or ophthalmic drug is formulated in water insoluble ointment formulation to sustain the duration of intimate drug eye contact. But these dosage forms give only marginally more sustained drug – eye contact than eye drop solution and donot yield a constant drug bioavailability s originally hoped.[3]

ADVANCEMENT IN OCULAR DRUG DELIVERY

Ocular drug delivery has remained as one of the most demanding task for pharmaceutical scientists. The unique structure of the eye does not allow the drug molecules at the required site of action. Conventional drug delivery systems;which include solutions, suspensions, gels, ointments and inserts. It leads to development of advanced techniques for ocular therapy those include particulate delivery system which improves the pharmacokinetic and pharmacodynamic properties of various types of drug molecules and novel controlled drug delivery systems such as dendrimers, microemulsions, muco-adhesive polymers, hydrogels, iontophoresisprodrug, collagen shelid, approaches. Other advanced approaches for the treatment of macular degeneration include intravitreal small interfering RNA (siRNA) and inherited retinal degenerations involve gene therapy. This system provides many advantages over

conventional systems as they increase the efficiency of drug delivery by improving the release profile and also reduces drug toxicity. The rapid progress of the biosciences opens new possibilities to meet the needs of the posterior segment treatments.

The examples include the antisense and aptamer drugs for the treatment of cytomegalovirus (CMV) retinitis and age-related macular degeneration, respectively, and the monoclonal antibodies for the treatment of the age-related macular degeneration. These reviews focus briefly on different drug delivery systems for ocular therapy along with their safety evaluation of ocular drug delivery formulations case studies.[3,4]

Ideal ophthalmic drug delivery must be able to uphold the drug release and to remain in the vicinity of front of the eye for protract period of time. Consequently it is imperative to optimize ophthalmic drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gel, development of colloidal suspension or using erodible or non erodible insert to prolong the precorneal drug retention. Bioadhesive systems utilized can be either microparticlesuspension6 or polymeric solution. For petite and medium sized peptides major resistance is not size but charge, it is originated that cornea offers more conflict to negatively charged compounds as compared to positively charged compounds.[5]

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 non-vascular 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 alters 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.[4,6]

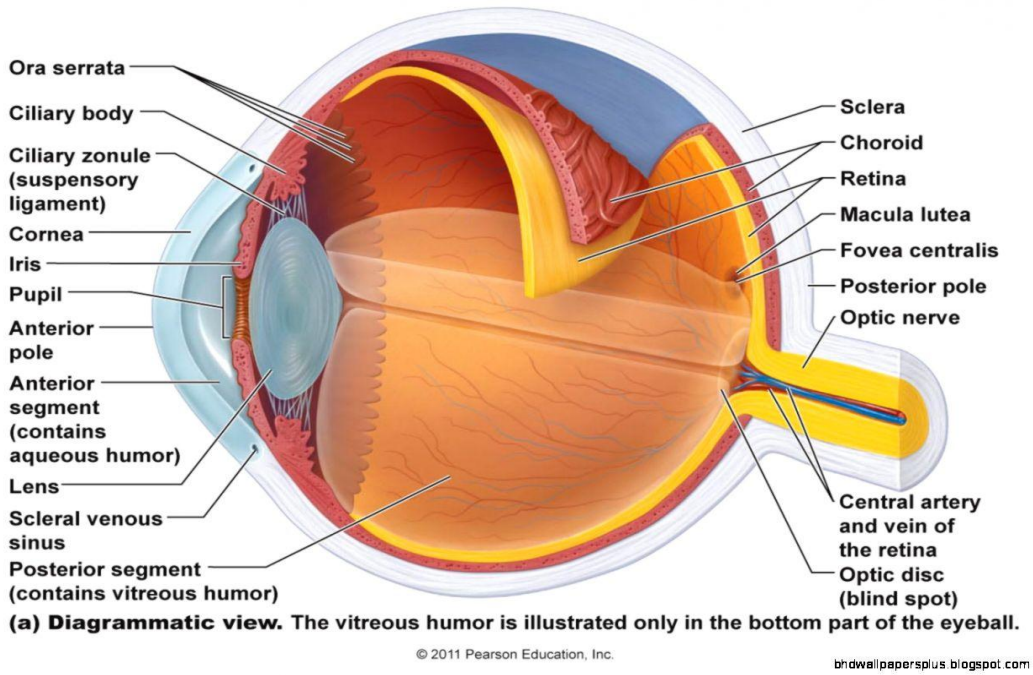

Fig 1: Anatomy Of The Eye.

ANATOMY OF THE EYEBALL

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 bonysocket of the orbit on a cushion of fat and connective tissue.[4] The wall of thehuman eyeball consists essentially of three layers: Fibrous tunic, Vasculartunic and Retina.

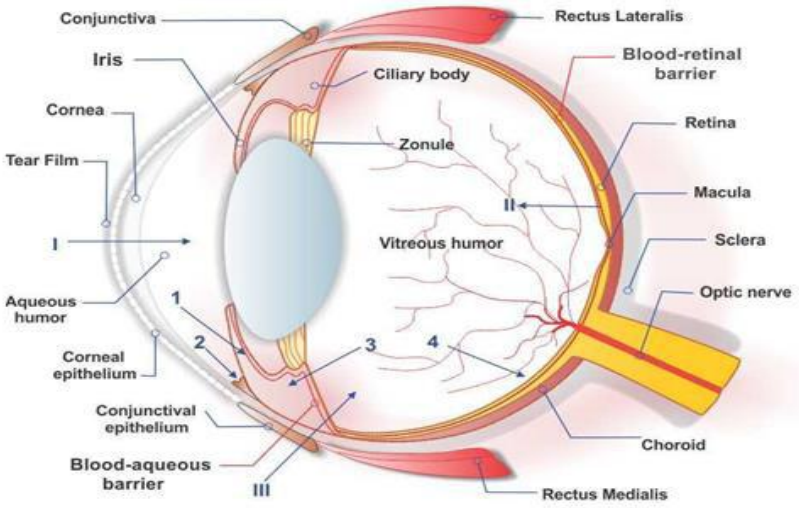

Fig. 2: Anatomy Of The Eye.

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.[6] 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.[4,6] 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.[4]

Lens

Behind the pupil and iris, within the cavity of the eyeball, is the lens. Protein called crystallins, 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.[6,7]

INTERIOR OF THE EYEBALL

The lens divides the interior of the eyeball into two cavities; Anterior cavity and Vitrous 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 glycosaminoglycans, including of hyaluronic acid and proteins such as collagen.[6]

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.[3,6]

PHYSIOLOGY OF EYE

Three types of fluids are present in eye tears (Function of tear lubrication, nourishment, Provide oxygen, protection). Aqueous humour (responsible for the maintenance of shape of the eye ball. It maintains the intraocular pressure 12-20 mm Hg).Vitreous humour (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. Thus the eyeball is continually irrigated by a gentle stream of lachrymal fluid that prevents it from becoming dry and inflamed. The lachrymal fluid in humans has a normal volume of 7µl and is an isotonic aqueous solution of bicarbonate and sodium chloride (pH 7.4) that serves to dilute irritants or to wash the foreign bodies out of the conjunctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjunctival sac. The rate of blinking varies widely from one person to another, with an average of approximately 20 blinking movements per min. During each blink movement the eyelids are closed for a short period of about 0.3 sec.[4,6,8]

ROUTES OF OCULAR DRUG DELIVERY[4,9]:

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue.

Table 1: Routes of Administration for Ocular Drug Delivery.

S.NO	Route	Dosage Forms	Advantages	Disadvantages
1	Topical	Solutions, suspensions, ointments, gels etc.	Ease of administration	Poor bioavailability, suitable only for anterior segment, blurring vision
2	Sub- conjunctival	Injectables	Delivery of large molecular size drugs, sustained release of drug	Patient non-compliance, suitable for only water soluble drugs
3	Retrobulbar	Injectables (used for anesthetization)	-	Perforation of globe, patient non- compliance
4	Peribulbular	Injectables (used for anesthetization)	Avoidance of perforation of globe	Non-compliance in pediatrics patients and patient with mental disorders.
5	Intraviteral	Injectables	Sustained delivery of drug to posterior segment of the eye	Patient non compliance

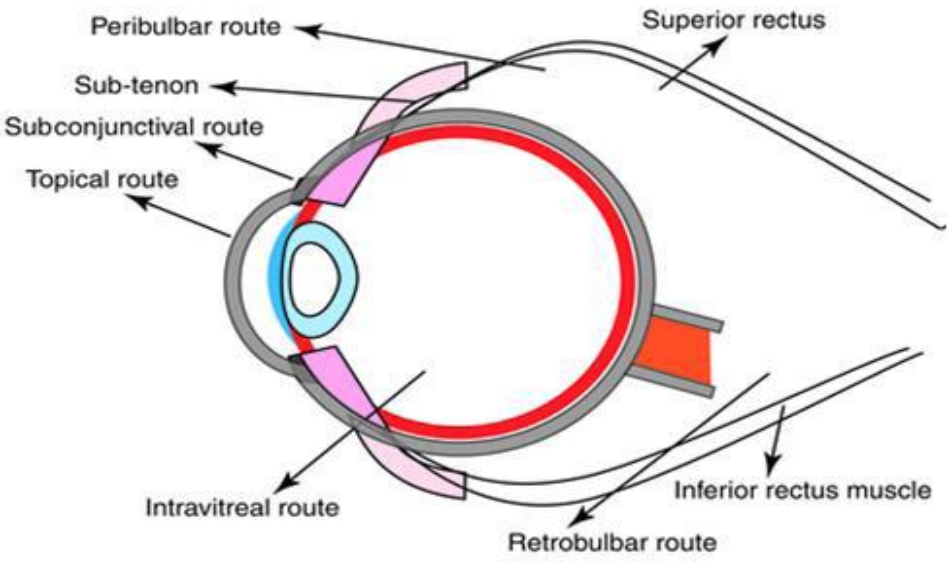

Fig. 3: Different Routes of administration for Ocular Drug Delivery[4]

Table 2: Routes of Absorption of Drugs in Eye.[4,9]

S.NO	Target site	Salient features
1	Cornea	Bowman's capsule is lipophilic, allows diffusion of small lipophilic molecules. Stroma is hydrophilic, allows diffusion of hydrophilic and larger molecules.
2	Conjunctiva	Main barrier for drug absorption, allows absorption of hydrophilic and large molecules. Absorption of peptides is less due to enzymatic degradation.
3	Sclera	Some drugs (β-blockers) diffuse readily. Tran's scleral iontophoresis is used for intravitreal administration.
4	Aqueous Humor	Drugs absorbed through cornea discharge through aqueous humor into systemic routes.

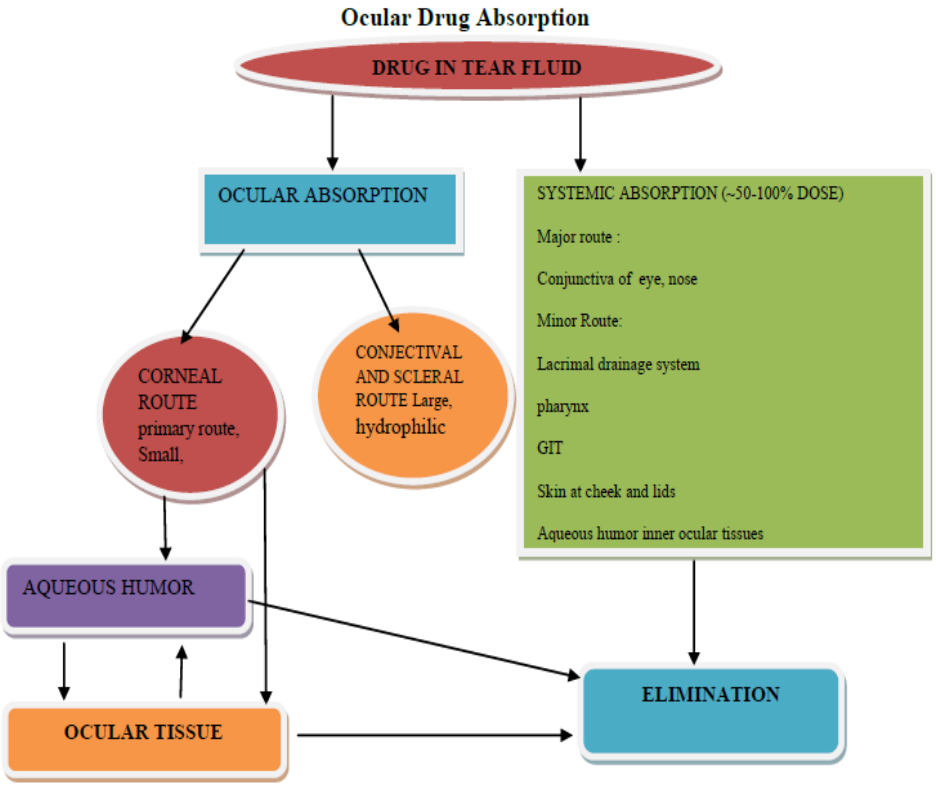

Fig 4: ocular drug absorption.

The topical delivery through ocular route has been extensively used for the local treatment of eye pathologies. Poor bioavailability pertinent to conventional eye drops is attributed to physiological constraints such as limited area of absorption, lipophilic temperament of the corneal epithelium and a series of elimination factors such as nasolacrimal drainage, tear turnover and tear evaporation that reduce the contact time of medication with the corneal surface. A schematic model, depicting the transportation and fate of drug molecule with the challenges is shown in fig.1.3.[10]

The major challenge of ocular delivery is associated with the elimination of instilled dose by a number of elimination factors, which can be resolved effectively by formulation engineering. These desired formulations should be a free-flowing liquid at room temperature to allow easily reproducible administration into the eye as a drop and should undergo *in-situ* phase transition to form a strong gel that is capable of withstanding for prolonged period of time at delivery site. This would result in achieving maximum drug bioavailability is the only solution to this problem.[11]

BARRIERS FOR OCULAR DRUG DELIVERY[14]

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.

Blood-Ocular Barriers

The eye is protected from the xenobiotic in the blood stream by blood-ocular barriers. These barriers have two parts, the anterior blood-aqueous barrier is composed of the endothelial cells in the uvea. This barrier prevents the access of plasma albumin into the aqueous humor and also limits the access of hydrophilic drugs from plasma into the aqueous humor. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extra vascular space, but thereafter distribution into the retina is limited by the RPE and retinal endothelia.

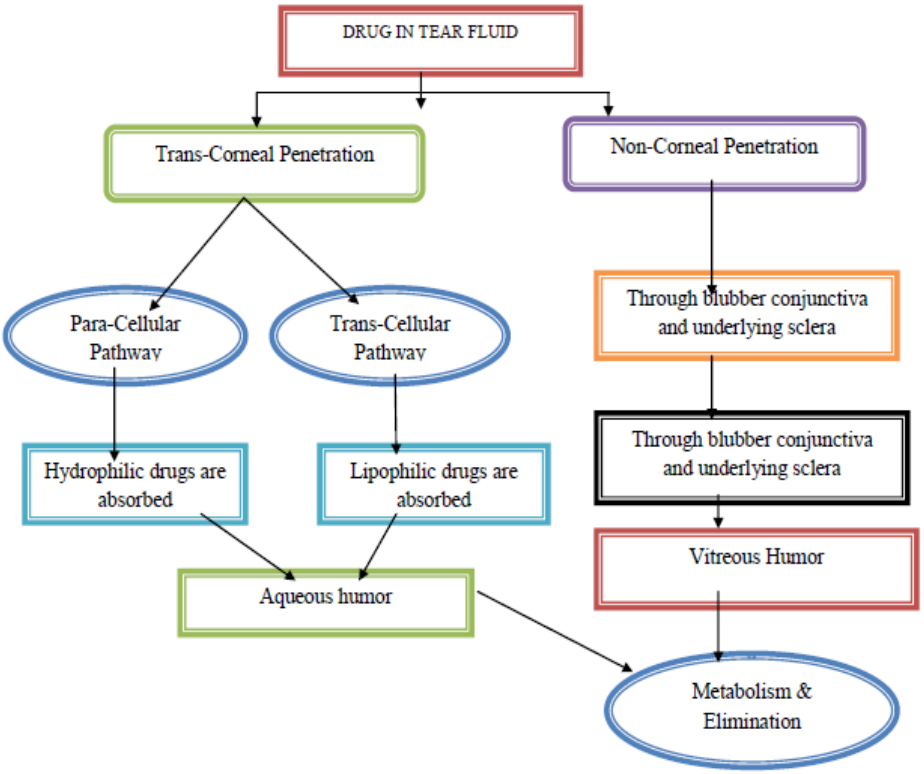

Fig 5: Different drug absorption routes.

FACTOR ATTRIBUTING TO POOR BIOAVAILABILITY OF AN OPHTHALMIC FORMULATION[4,8,9,12]

- Binding by the lachrymal proteins
- Drainage of the instilled solutions
- Lachrimation 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[4,9,11,13]

- 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[14,15,16,17]: 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[16,17]: 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[17]: Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major

drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use.

Inserts

Lacriserts[18,19]: The lacrisert is a sterile rod shaped device made of hydroxylpropyl 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[20]: 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 N-vinylpyrrolidine and ethylacrylate 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[21]: 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[22]: 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[15]: 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[23,24,25]: 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[26,27,28]: 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 preprogmmed to release pilocarpine at constant rate of 20 or 40 µg/hr around the clock for 7 days. The higher release rate of ocusertpilo 40 is achieved by making its rate controlling membrane thinner and by the use of flux enhancer di (2 ethyl – hexyl) phthalate. Although the advantage of precise controlled rate of delivery has been achieved with a number of disadvantage such as patient comfort, placement, and removal of insert which may lead to inadvertent loss of system from the eye. It has been observed that retention of these insert are a function of size and shape. Rod shaped are better retained than oval ones.

Implants[29,30,31]: 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[32,33]: 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[34]: Dendrimers are successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility. Vandamme and co workers have developed and evaluated poly (amidoamine) 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[35]: 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 non irritant to the human and animal eye.

Contact lenses[36]: 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[37]: 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[38]: 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.

Nanosuspensions[39]: Nanosuspensions 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 nanosuspensions, techniques like media milling and high pressure homogenization have been used.

Microneedles[40]: 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[41]: 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[41]: Penetration enhancers increases 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[42]: 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).

Phase Transition Systems/In-situ gel system[43]

Phase transition of the formulation from the liquid form to the gel or solid phase occurs when these systems instilled into the cul-de-sac of eye lead to increase the viscosity of a drug formulation in the precorneal region results in increased bioavailability, due to slower drainage from the cornea. These systems can be influenced by pH, temperature or by ion activation. A sol to gel system with mucoadhesive property to deliver the steroid fluorometholone to the eye was prepared by Middleton and Robinson.

D.PARTICULATE DRUG DELIVERY SYSTEM

Nanoparticles[44]: Nanoparticles are prepared using bioadhesive polymers to provide sustained effect to the entrapped drugs. An optimal corneal penetration of the encapsulated drug was reported in presence of bioadhesive polymer chitosan. Similarly Poly butyl cyanoacrylate nanoparticles, containing pilocarpine into collagen shields, showed greater retention and activity characteristics with respect to the controls.

Microparticles[45]: Microspheres of poly lacto gylcolic acid (PLGA) for topical ocular delivery of a peptide drug vancomycin were prepared by an emulsification/ spray-drying technique.

E. ADVANCED DRUG DELIVERY SYSTEM

Scleral Plug therapy[45]: 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 plugs are effective for treating vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vitrectomy.

Gene Therapy[46,47]: Gene therapy approaches are used to treat blindness arising from corneal diseases, cataract as the leading cause of vision loss. 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. However, the challenge of obtaining substantial gene expression following topical administration has led to the prevalence of invasive ocular administration. Retroviral vectors have been widely used due to their high efficacy; however, they do not have the ability to transduce 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.

siRNA therapy[48]: Feasibility of using siRNA for treatment of choroidalneovascularisation 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. siRNA has become a valuable tool to explore the potential role of various genes in ocular disease processes. It appears that siRNAs may be valuable in the pathogenesis and development of new treatments for several ocular diseases, based on in vivo and in vitro studies. However, its use in vivo remains problematic, largely due to unresolved difficulties in targeting delivery of the siRNA to the tumor cells. Viral gene delivery is very efficient however it currently lacks adequate selectivity for the target cell type.

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.

Stem cell Therapy[49]: 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.

Cell Encapsulation[50]: 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 ciliaryneurotrophic 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 choroidalneovascularisation, anti-inflammatory factors for uveitis.

Protein and Peptide therapy[51]

The intravitreous injection of ranibizumab is an example for the delivery of therapeutic proteins/ peptides. For 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. 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.

Oligonucliotidetherapy[52]: 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 mechanism is the most important. A number of factors have been determined to contribute to the efficacy of antisense ON. One primary consideration is the length of the ON species. Lengths of 17– 25 bases have been shown to be optimal, as longer ONs have the potential to partially hybridize with nontarget RNA species. Biological stability is the major barrier to consider when delivering both DNA and RNA oligonucleotides to cells. Protection from nuclease action has been achieved by modification of phosphate backbones, sugar moiety, and bases.

Aptamer[53]: 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. Pegaptanib sodium (Macugen; Eyetech Pharmaceuticals/Pfizer) is an RNA aptamer directed against VEGFb165, where VEGF isoform primarily responsible for pathological ocular neovascularisation and vascular permeability.

Ribozyme therapy[54,55]: 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. They function by binding to the target RNA moiety through Watson-Crick base pairing and inactivate it by cleaving the phosphodiester backbone at a specific cutting site. 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. Lewin and Hauswirth have worked on in the delivery of ribozymes in ADRP in rats shows promise for ribozyme therapy in many other autosomal dominant eye diseases, including glaucoma.

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