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Review Article

# CURRENT TRENDS AND CHALLENGES FACED IN OCULAR DRUG DELIVERY SYSTEMS

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**ABSTRACT**

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. The effective dose of the medication which is administered opthalmically may be altered by varying the strength, volume, or frequency of administration of medication or the retention time of the medication in contact with the surface of the eye. This article reviews the constraints with conventional ocular therapy and explores various novel approaches being used to improve the corneal penetration of drug, along with their advantages to improve the Opthalmic bioavailability of drugs.

**Keywords:** Ophthalmic, Precorneal, Constraints, Ocular therapy.

## INTRODUCTION

Eye is the index of our soul. The eye is unique organ from anatomical and physiological point of view. Without eye we cannot enjoy the beauty of nature. The eye has special attributes that allows local drug delivery and non invasive clinical assessment of disease but also makes understanding disease pathogenesis and ophthalmic drug delivery challenges. Many parts of the eye are inaccessible to systemically administered drugs and thus topical drug delivery remains the preferred route in most cases. Drugs may be delivered to treat the precorneal region for such infections such as conjunctivitis, blepharities or to provide intraocular treatment via cornea for diseases such as glaucoma and uveitis[1].Topical delivery of eye drops in to the lower cul-de-sac is most common method of drug treatment in ocular diseases and diagnostics. The site of action of most ophthalmic drugs is located in inner eye. Although the external eye structures are readily accessible, the biological barriers mainly the corneal epithelium, limit ocular drug absorption. Consequently after instillation of an eye drop, typically less than 5% of an applied dose reaches the intraocular tissue. This is due to tightness of corneal barrier and rapid loss of instilled solution from the pre corneal area[2, 3]. The goal of ophthalmic drug delivery systems has traditionally been to maximize the ocular drug absorption rather than to minimize systemic absorption. Systemic absorption of ocularly applied drug is often nearly complete. This has caused systemic side effects varying from mild to life threatening events[4]. In case of ophthalmic drugs that may cause systemic side effects, it is important to make formulation changes that improve oculoselectivity of drug rather than only ocular absorption[3]. This review mainly focus on anatomical features-structural barriers of eye in topical drug delivery, various types of ocular

drug delivery systems and their advances advantages and disadvantages.

## ANATOMY AND PHYSIOLOGY OF EYE

Eye is a spherical structure with a wall consists of three layers. Namely outer sclera, middle choroid layer, inner retina. The schematic diagram of which is shown in fig.[1][6] .Sclera is a tough fibrous coating that protects the inner layers. It is white except for the transparent area at the front, the cornea, which allows the light to enter the eye. The choroid layer, situated inside the sclera contains many blood vessels and is modified at the front of the eye as the pigmented iris. The biconvex lens is situated behind the pupil. The chamber behind the lens is filled with vitreous humor, a gelatinous substance occupying 80% of the eyeball. At the back of the eye the light detecting retina[5].

### Cornea

The cornea, which is the optically transparent tissue that conveys image to the back of the eye and covers about one sixth of the total surface area of the eye ball. The cornea is considered to be the main path way for permeation of drugs in to the eye[3]. It is approximately 0.5mm thick in the centre and 0.7mm thick at periphery and composed of five layers as shown in fig.[2][7]

- Epithelium is stratified, consisting of 5-6 layers of cells.(8-10layers at periphery)and has a total thickness of 50-100 µm.the tight junctions and hydrophobic domains in this layer make it the most important barrier to drug delivery.
- Bowman's membrane is an acellular homogenous sheet, about 8-14µm thickness. This is positioned between basement membrane of epithelium and stroma.
- The stroma or substantia propria, accounts for around 90% of corneal thickness. It contains approximately 85% of water, and about 200-250 collagenous lamellae that are superimposed on to one another and run parallel to the surface. Stroma has a relatively open structure and will normally allow the diffusion of hydrophilic solutes.
- The descement membrane, which is secreted by endothelium lies below endothelium and stroma.
- The corneal endothelium is responsible for maintaining normal corneal hydration. For a drug to cross the cornea effectively, it has to have both hydrophilic and lipophilic properties, and be sufficiently small to pass through tight junctions.

### The conjunctiva

Conjunctiva involves in the formation and maintenance of pre corneal tear film and in the protection of eye. It is a thin vascularised mucous membrane that lines the posterior surface of the eye lids and outer regions of the cornea. The conjuctival epithelium differs somewhat from the cornea, in that it is thicker and posses mucous secreting goblet cells. The human conjunctiva is 2-30 times permeable to drugs than the cornea and it has been proposed that loss by this route is a major path of drug clearance [8].

### The nasolacrymal drainage system

It consists of three parts. Secretory system, distributive system and excretory system, which are shown in fig.[3][9].the secretory system consists of basic secretors that are stimulated by blinking and temperature. Change due to evaporation and reflex sectors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulations. The distributive system consists of the eye lids and the tear meniscus around the lid edges of the open eye. The excretory part of nasolacrymal system consists of the lachrymal puncta; the superior, inferior and common canaliculi, the lachrymal sac and the nasolacrymal duct[5].

## NEED FOR THE IMPROVEMENT IN OCULAR DRUG DELIVERY SYSTEMS

Eye is the most accessible site for topical administration of a medication. Drugs are commonly applied to the eye for localized action on the surface or in the inferior eye. A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action poor bioavailability of drugs of drugs from ocular dosage forms is mainly due to precorneal loss factors. Which includes tear dynamics, non-productive absorption, transient residence time in cul-de-sac, and relative impermeability of the corneal epithelial membrane? Due to these constraints only a small fraction of drug .effectively 1% or even less of the instilled dose is ocularly absorbed. Normal dropper used with conventional ophthalmic solution delivers 50-75µl per drop and portion of these drops quickly

drain until the eye is back to normal resident volume of 7µl.because of this drug loss in front of eye, very little drug is available to enter in to the eye. Actual corneal permeability of drug is quite low and very small corneal contact time of about 1-2min in humans for instilled solution commonly less than 10%[10-12] consequently very small amount actually penetrates the cornea and teaches intraocular tissue[13,14].Ideal ophthalmic drug delivery must be able to sustain the drug release and remain in the vicinity of the 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 viscous gels, development of colloidal suspension or using erodible/non-erodible insert to prolong the pre-corneal drug retention[15,16]. Cornea offers more resistant to negatively than positively charged compounds[17].

**Following characteristics are required to optimize ocular drug delivery system[18]:**

- Good corneal penetration
- Prolong contact time with corneal tissue.
- Simplicity of instillation for the patient.
- Non irritant and comfortable form. (Viscous solution should not provoke lachrymal secretion & reflux blinking.)
- Appropriate rheological properties & concentration of the viscous system.

**DRUG DELIVERY SYSTEMS FOR THE EYE**

Most commonly used are drops in the lower cul-de-sac, which are usually drained quickly, aided by blinking reflex and the precorneal region returns to the normal resident volume of 7µl.as stated previously in the requirements efficient ocular drug absorption requires good corneal penetration as well as prolonged contact time with corneal tissue. Iontophoresis, prodrugs, ion pair formation and cyclodextrins have been used as means of drug absorption an ideal topical ophthalmic formulation would enhance bioavailability by sustaining drug release, while the remaining in contact with front of the eye for prolonged periods of time; modern formulations attempts to achieve this[19]. There is wide variety of ophthalmic drug delivery systems in the market[20]. Nevertheless about 70% of prescriptions for eye medications are for conventional eye drops. This is due to factors including expense, difficulty in bulk manufacture, patient compliance. In all cases the formulations should sterile. Following are the recent developments in topical ocular drug delivery systems, the characteristic advantages and limitations of each system.

**(1)LIQUIDS-Eye drops and lotions**

Eye drops may be solutions or suspensions and are comparatively convenient, safe, immediately active and acceptable to patients. An eye drop is a sterile and contains a preservative .it is isotonic and having a $p^H$ of 7.4 and has limited shelf life after opening[20]. Drops provide pulse entry of drug followed by rapid decline of drug concentration and shows first order kinetics. Polymers are frequently added to ophthalmic solution as viscosity modifiers which prolong contact time with cornea and often enhance bioavailability[21]. The polymers used are high molecular weight hydrophilic molecules that are unlikely to cross biological membranes. E.g. includes cellulose, poly vinyl alcohol, and poly acrylic acid and poly saccharine such as xantnum gum found to increase viscosity and delays the clearance by tear flow. Patton and Robinson[15] reported that increase in the corneal penetration of drug is maximum at viscosity about 15-150cps; further increase causes burning of vision and resistance to eye lid movement. This techniques increases contact time but no sustaining effect is reported.

Colloidal system, encompassing Liposomes and micro and nano particles has been studied as drug carries in ophthalmic drug delivery over many years. Liposomes and nano particles found to be useful to prolong the corneal contact time and hence more and more tested in ocular drug delivery[22]. Smolin et al[23]. For the first time studied application of Liposomes for O.D.D. Favorable results with Liposomes found essentially with lipophilic drugs[24]. Reason for this suggested that hydrophilic drugs escape from Liposomes faster rate than lipophilic ones. Charge on Liposomes also influence drug concentration in ocular tissue. The potential of Liposomes as a topical O.D.D system is restricted by their stability and limited drug loading capacity. In addition large scale manufacturing of Liposomes is expensive and technically challenging[25].

Micro particles have an average particle size less than 1um and may be microcapsules or microspheres. Microspheres are monolithic particles, perhaps of insoluble drug or drug disappeared in a polymer matrix, where as micro capsules consists of polymeric membrane surrounding by liquid/solid drug reservoir up on instillation the particles resides in ocular cul-de-

sac and drug is released from the particles through diffusion/polymer degradation[26].
Nano particles are polymeric colloidal particles ranging from 10-100 nm. Various polymers like polyacrylamide, polymethyl methacrylate, albumin gelatin, poly alkyl cyanoacrylate and caprolactone used in the preparation of nano particles[27-33]. First study using nanosphere done on system constituted of pilocarpine-loaded nanosphere of gurny et al. (Developed $p^H$ sensitive latex nano particles for pilocarpine and result found to be promising)

**(2) Eye ointments**
Eye ointments are semisolid preparations intended for external application. They are usually formulated using mixtures of semisolids and solids which have melting or softening points close to body temperature and are nonirritating to eye. Ointments may be simple bases or compound bases. Upon instillation in to eye the ointments breaks into small droplets and remain as a depot of drugs in the cul-de-sac for extended periods. Ointments are thus useful in improving drug bioavailability and in sustaining drug release. Although safe and well tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation[34]. For this reason they are often used as night time medication.

**(3) Aqueous gels**
Hydro gels consist of high molecular weight hydrophilic cross linked polymers or copolymers that form three-dimensional network in water. The gels have been shown to combine significantly longer residence times in the cul-de-sac with increased drug bioavalibility.typical gelling agents includes cellulose derivatives, PVA, hyaluronicacid and carbomer. These systems are more acceptable to patients since they are administered into the eyes as solution after which they undergo transition in to gels. The polymers used in these systems exhibits reversible phase transition. The change in viscosity can be due to change in $p^H$, temperature and ionic strength[36,37].

- $P^H$ triggered systems: cellulose acetate hydrogen phthalate latex, typically shows very low viscosity up $p^H$ 5, and forms a clear gel in few seconds when in contact with tear fluid $p^H$ 7.2-7.4 and hence release contents over prolonged periods of time[37].
- Temperature sensitive systems: poloxomerF127 in the form of solution at room temperature and when this solution is instilled in to eye, phase t transition occurs from a solution to gel at temperature of eye, prolonging its contact time with ocular surface[38].
- Ion activation: Gel rite is a polysaccharide; a low acetyl gellan gum shows phase transition in presence of mono or divalent cations[39, 40].

**(4) Solid matrices and devices**
A number of solid polymeric inserts and discs have been developed as ophthalmic drug delivery systems. Inserts allow for accurate drug dosing, reduced systemic absorption and in some cases, better patient compliance resulting from reduced frequency of administration and a lower incidence of visual and systemic side effects. Inserts are less affected by nasolacrymal drainage and tear flow than more conventional dosage forms[41]. The major drawback of this is the resistance of the patients to place the solid object in the precorneal region. Ocusert®, pilocarpine ocular therapeutic system is the first product marketed by Alza incorporation, USA from this category[42]
Currently under development is an encapsulated cell technology in which cells transferred with human growth factor genes are surgically implanted into the vitreous cavity, in phase-1trial using human ciliary neurotrophic factor in patients with retinitis pigmentosa, the implants were productive for six months and there were no substantive safety issue.

**(5) Iontophoresis**
It is the process in which direct current drives ions into cells/tissues. When iontophoresis is used for drug delivery, the ions of importance are charged molecules of drug. If the drug molecules carry a positive charge, they are driven into the tissue at anode; if negatively charged, at cathode. Ocular iontophoresis offers a drug delivery system that is fast, painless, safe and in most cases result in the delivery of high concentration of drug at specific site. But there were some findings of neutralization effects of drug adversely affecting the optimum zeta potential.
Along with all the above delivery systems some advanced drug delivery systems like cell encapsulation, stem cell therapy, protein and peptide therapy, sclera plug therapy, oligo nucleotide therapy, aptomer technology and ribosome therapy also available and all are having their own limitations.

## CONCLUSION

The ocular systems which are developed even today are facing with one or other drawbacks. It's really essential & challenging to develop novel ocular drug delivery system to overcome the above mentioned drawbacks .Given the problems associated with their use, it may be surprising that eye drops remain a major choice of medication for ophthalmic disorders.

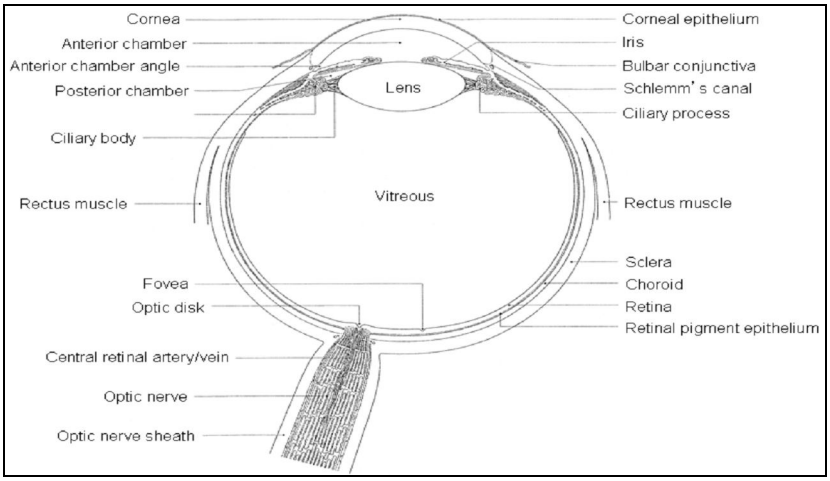


**Fig. 1: The schematic diagram of eye**

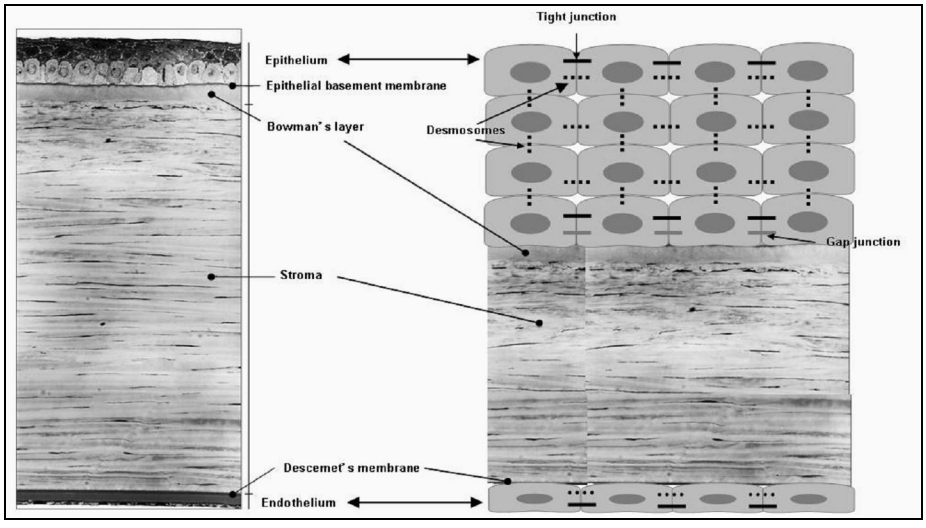


**Fig. 2: The schematic structure of cornea**

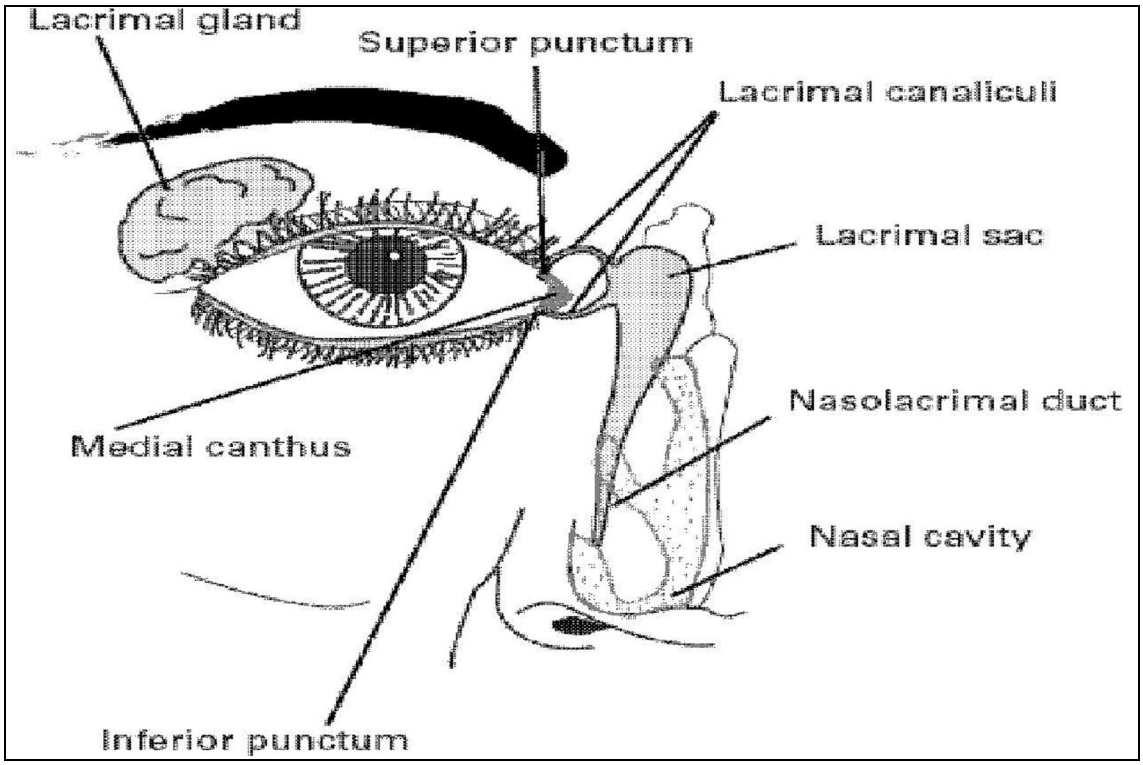


**Fig. 3: The Naso-lachrymal system**

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