



## OCCULAR DRUG DELIVERY SYSTEM – EMERGING TRENDS

R.B Desireddy, Taraka Lalitha Kumari.Ch, Naga Sowjanya.G, Sowjanya.T, Lavanya Latha Reddy.K  
 Nalanda Institute of Pharmaceutical Sciences, Siddhath nagar, Kantepudi, Sattenapalli, Andhra Pradesh, India.  
 \*Corresponding author's E-mail: [sweetty.reddy04@gmail.com](mailto:sweetty.reddy04@gmail.com)

Accepted on: 26-06-2012; Finalized on: 31-08-2012.

### ABSTRACT

Ophthalmic drug delivery is one of the most interesting and challenging endeavors being faced by the pharmaceutical companies in the market. The major problem associated with the conventional dosage forms is the bioavailability of drug. In Ophthalmic formulation to the eye like solutions, suspensions and ointments are available in the market shows drawbacks such as increased pre-corneal elimination, high variability in efficiency, and blurred vision. To overcome the conventional dosage formulations there were a drug-eluting contact lens to provide controlled release of drug for a longer period of time using Liposomes, Niosomes, Pharmacosomes and Discomes. This review focuses on recent development in ophthalmic dosage formulations and products used to achieve prolonged contact time of drug with the cornea and increase their bioavailability. Currently, the knowledge in this field is rapidly expanding, and many concept and drug delivery strategies are emerging out.

**Keywords:** Eye, Ophthalmic formulations, Polymers, Sustained release.

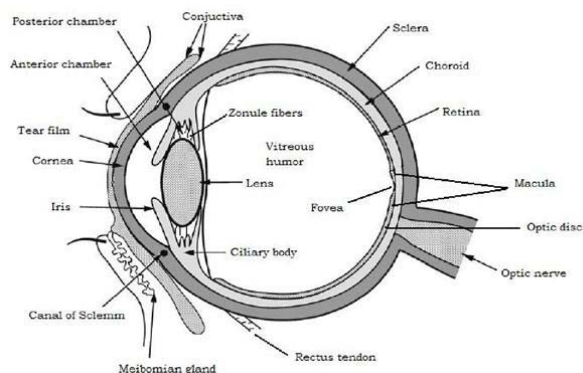
### INTRODUCTION

Ocular drug delivery is the maintenance of an adequate concentration of drug in the pre-corneal area. Ocular administration of the drug is primarily associated with the need to treat ophthalmic diseases.<sup>1</sup> Topical application of drugs to the eye is the well established routes of administration for the treatment of various eye diseases like dryness, conjunctiva, and eye flu etc.<sup>2</sup> Conventional topical ocular delivery systems include various dosage forms such as solutions, suspensions, emulsions, ointments, gels, erodible inserts, non-erodible inserts which shows drawbacks such as rapid pre-corneal elimination, blurred vision, abrasion, irritation to eye, tissue fibrosis, matted eyelids after use and patient discomfort etc. In order to overcome these, vesicular system for drug delivery are used such as Liposomes, Niosomes, Pharmacosomes and discomes. Various ocular drug delivery devices are used that can deliver drug to eye such as Matrix-type drug delivery systems, Capsular-type drug delivery systems, Implantable drug delivery pumps etc.<sup>1</sup>

### STRUCTURE AND PHYSIOLOGY OF 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 protects 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.<sup>2</sup>

The choroid layer, situated in the sclera, contains many blood vessels that modified at front of the eye as pigmented iris, the colored part of the eye ( blue, green, brown, hazel, or grey).<sup>2</sup>



**Figure 1:** Schematic cross section through a human eye

#### The structure of the cornea

The clear transparent bulge cornea situated at the front of the eye 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 which provides nutrient and oxygen, supplied via lachrymal fluid and aqueous humour as well as from blood vessels of the junction between the cornea and sclera.<sup>5</sup>

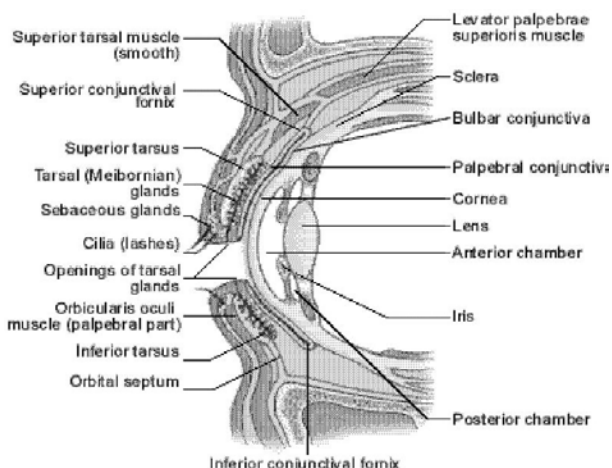
The cornea is made of five layers as epithelium, bowman's layer, stroma, descemet's membrane and endothelium that is main pathway of the drug permeation to eye.<sup>6,7</sup> The epithelium made up of 5 to 6 layers of cells. The corneal thickness is 0.5-0.7 mm in the central region. The main barrier 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.<sup>6</sup>

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 thickness situated between the basement membrane of the epithelium and the stroma. The stroma, or substantia 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.<sup>4,5</sup>

**Conjunctiva**

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. The bulbar epithelium contains 5 to 7 cell layers. The structure resembles a palisade and not a pavement corneal epithelium cells are connected by tight junctions, which render the conjunctiva relatively impermeable. The molecules up to 20,000 Da can cross the conjunctiva, while the cornea is restrict to molecules larger than 5000 Da. The human conjunctiva is about 2-30 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 to the presence of 1.5 million goblet cells varying with age depended among the inter subject 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.<sup>3</sup>

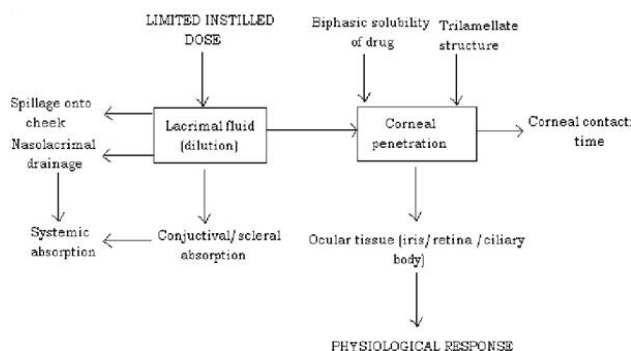


**Figure 2:** The Conjunctiva

**Ocular absorption of drug**

The common method of ocular drug delivery is topical administration of ophthalmic dosage formulation drops into the lower cul-de-sac. Such drops are outflow quickly due to the eye blinking reflex, and the precorneal region returns to maintain resident volume of around 7µl. The available concentration of drug in precorneal fluid provides the driving force for passive transport of drug across the cornea. However, the epithelium is the predominant, rate limiting barrier for hydrophilic drugs and where as stroma is rate limiting step for most of the lipophilic drugs. Recent studies suggest that the non-corneal routes of absorption are across the sclera and conjunctiva have significant role for drug molecules with poor corneal permeability. Studies with inulin, timolol maleate, gentamycin, anesthetic and autonomic drug and PGF2α, PGF2α-1-methyl ester, and PGF2α-1-isopropyl ester suggest that these drugs gain access through the non-corneal route.

Thus the topical application of the formulation to the surface of ocular is an extremely complicated issue because of the numerous protective mechanisms of the eye that protects the visual pathway from foreign materials. Design of modern ocular drug delivery systems is based on the drug application pathways and absorption mechanism in the eye and the overall ocular pharmacokinetic/pharmacodynamic profile. Thus for efficient drug absorption require more prolonged contact time of the formulation within the eye is required.<sup>8-10</sup>



**Figure 3:** Fate of ophthalmic drug delivery systems

**NEW DRUG DELIVERY SYSTEM**

The various vesicular system used for ocular drug delivery are Liposomes, Niosomes, Pharmacosomes, Nanoparticles, Nanosuspensions, Microspheres, Microemulsions, discomes and ocusets. There are certain advantages of new drug delivery systems over other delivery systems especially in ocular drug delivery, using liposomes i.e. it controls the rate of release of encapsulated drug, protects the drug from the metabolic enzymes present at the tear corneal epithelium interface, relatively nontoxic, biodegradable nature, non-irritant, and ability to form intimate contact with the corneal and conjunctival surfaces thereby increase in the possibility of ocular drug absorption. Whereas, Niosomes are chemically stable, can entrap both hydrophilic and



hydrophobic drugs and they can improve the performance of drug molecule via delayed clearance from circulation, better bioavailability and controlled drug delivery at the desired site. In case of Niosomes the problem of drug incorporation, leakage from the carrier on insufficient self-stability is avoided, drug metabolism can be decreased and controlled release profile could be generated. Discomes are found in its place by increased patient compliance, minimal opacity imposes no hindrance to vision, disc shape result in better adherence of the system to the cornea and large size (12-60 $\mu$ m) prevents their drainage in to systemic pool.<sup>1</sup>

### 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 nanosuspention, solid nanoparticle microemulsion and liposomes have developed to solve the solution of various solubility-related problem of poorly water soluble drugs, like dexamethsone, budenoside, gancyclovir and so on. Due to relative properties of the particle size, charge, surface properties and relative hydrophobicity of (molecules) nananoparticles are developed to be successfully used in crossing the over-coming absorption barriers.

Furthermore, nanocarriers are critical in order to exploit the emerging in pharmaceutical field of drug delivery systems and new gene therapies for the treatment of ocular Disorders.<sup>2</sup>

Different nanoparticles based drug delivery systems are:

#### Microemulsion

Microemulsions were first described by Hoar and Schulman. Microemulsion is a dispersion of water and oil that formulated with surfactants and co-surfactants in order to stabilize the surface tension of emulsion. The ophthalmic o/w Microemulsion could be advantageous over other formulation, because the presence of surfactants and co-surfactants increase the drug molecules permeability, thereby increasing bioavailability of drugs. Due to, these systems act as penetration enhancers to facilitate corneal drug delivery. The mechanism is based on the adsorption of the nanodroplets representing the internal phase of the microemulsions, which act as a reservoir of the drug on the cornea and should decrease their drainage in limit. Indeed, in 2002 the FDA approved the clinical use of an anionic emulsion containing cyclosporine A 0.05% for the treatment of chronic dry eye. A similar formulation (anionic emulsion containing difluprednate 0.05%, Durezol™, Sirion Therapeutics) has recently been approved

for the treatment of ocular inflammation. In the same field, a non-medicated anionic emulsion for eye lubricating purposes, in patients suffering from moderate to severe dry eye syndrome (Refresh Dry Eye Therapy®, Allergan), and two lipidic emulsions, indicated for the restoration of the lipid layer of the lacrimal fluid (Lipimix™, Tubilux Pharma, and Soothe XP® Emollient, Bausch and Lomb), have been launched in the US and European markets. The cationic nanoemulsions have also made their way onto the market. Namely, the product Cationorm® (Novagali Pharma, France) was launched in the European market for the treatment of dry eye symptoms and two more products, based upon the same technology and intended to deliver cyclosporine A, are currently under registration or under clinical evaluation (Phase III). Water-in-oil microemulsions (w/o ME) capable of undergoing a phase-transition to lamellar liquid crystals (LC) or bicontinuous ME upon aqueous dilution were formulated using Crodamol, sorbitan mono-laurate and polyoxyethylene 20 sorbitan mono-oleate, an alkanol or alkanediol as cosurfactant and water. A w/o ME formulated without cosurfactant showed a protective effect when a strong irritant (0.1 M NaOH) was used as the aqueous phase.<sup>2,8</sup>

#### Nanoparticles

Nanoparticles are the particle with a diameter of less than 1 $\mu$ m, containing of various biodegradable materials, such as natural and synthetic polymer, liposomes, lipids, phospholipids and even inorganic material. Biodegradable nanoparticles of polymers like polylactides (PLAs), polycyanoacrylate, poly (d,l-lactides), natural polymers can be used effectively for efficient drug delivery to the ocular tissues.

The movement of nanoparticles in the internal limiting membrane (ILM) because of the modification of the vitreous interface structure secondary to the presence of the PLA and poly (d,l-lactide-co-glycolide) (PLGA) . The encapsulated nanospheres may also increases when in such bioavailability of ophthalmic delivery. Recently, it reported that non-biodegradable polystyrene nanospheres observed within the neuroretina. Generally nanoparticles act at the cellular level and followed to endocytosed/phagocytosed by cells, then resulting cell internalization of the encapsulated drug. The surface charge and the binding of the drug to the particles were found to be more important factors in the drug loading in case of nanoparticles. The albumin nanoparticles was used to a very efficient ocular delivery system for like CMV retinitis, they are biodegradable, non-toxic and have non-antigenic effects. Since high content of charged amino acids, albumin nanoparticles allow the adsorption of positively charged gancyclovir or negatively charged particles like oligonucleotides that increased the bioavailability. However nanoparticles of natural polymers which are made up of like sodium alginate, chitosan, are very effective in intraocular penetration for some specific drugs, because of contact time with corneal





and conjunctival surfaces. Studies results show the bioavailability of encapsulated indomethacin doubled when Poly(epsilon-caprolacton) (PECL) nanoparticles were coated with Chitosan. Greater corneal penetration enhancement was occurred, when PECL nanoparticles were coated with polyethylene glycol (PEG). All these studies lead us to believe that nanoparticles have great potential ophthalmic delivery systems for ocular tissues.<sup>2,3</sup>

### Nanosuspensions

Nanosuspension contains of pure, hydrophobic drugs (poorly water soluble), suspended in appropriate dispersion medium. Nanosuspension technology are utilised for drug components that form crystals with high energy content molecule, which renders them insoluble in either hydrophobic or hydrophilic media.

Although nanosuspensions offer advantages such as more residence time in a cul-de-sac and avoidance of the high tonicity created by water-soluble drugs, their performance depends on the intrinsic solubility of the drug in lachrymal fluids after administration. Thus, the intrinsic solubility rate of the drug in lachrymal fluid controlled its release and increase ocular bioavailability. However, the intrinsic dissolution rate of the drug after application will vary because of the constant inflow and outflow of lachrymal fluids. However, a nanosuspension, by their inherent ability to improve the saturation solubility of the drug in media, also represents an ideal approach for ophthalmic delivery of hydrophobic drugs in eye. Moreover, in earlier nanoparticulate nature of the drug allows to prolonged residence (ocular surface) in the cul-de-sac, giving sustained release of the drug. To achieve sustained release of the drug, nanosuspensions can be incorporated or formulated with a suitable hydrogel or mucoadhesive base (*in-situ gel*) or even in ocular inserts.

A recently approaches been develops desired release the drug is the formulation formulated with polymeric nanosuspensions particles loaded with the drug. The bioerodable as well as water soluble/permeable polymers could be used to sustain and control the release of the medication. The nanosuspensions can be formulated by using the quasi-emulsion and solvent diffusion method. The using acrylate polymers such as Eudragit RS 100 and Eudragit RL 100 in polymeric nanosuspensions of flurbiprofen and ibuprofen have been successfully formulated, and these have been characterized for drug loading, particle size, zeta potential, in-vitro drug release, ocular tolerability and in-vivo biological performance in animal. The flu is a non-steroidal anti-inflammatory drug (NSAID) that using in inflammation and antagonizes papillary construction during intraocular surgery. Since the flu-loaded Nanosuspension are formulated by the quasi emulsion solvent diffusion (QESD) method in which generally avoids using of toxic chemical. They are proved to great potential for ophthalmic application.<sup>2</sup>

**Table 1:** Ocular insert devices<sup>2,14</sup>

Name	Description
Bioadhesive Ophthalmic Drug Inserts (BODO)	Adhesive rods based on mixture of hydroxypropyl cellulose, ethyl cellulose, polyacrylic acid cellulose acetate phthalate
Collagen Shields	Erodable discs composed of cross-linked porcine sclera collagen
Dry drops	A Preservative-free drop of hydrophilic polymer solution(hydroxypropyl methyl cellulose) that is freeze-dried on the tip of a soft hydrophobic carrier strip, immediately hydrates in the tear film
Gel foam	Slabs of gel foam impregnating with a mix of drug and Cetyl ester wax in chloroform
Lacriset	Rod-shaped device made from hydroxypropyl cellulose used in the treatment of dry eye syndrome as an alternative to artificial tears
Minidisc (or) Ocular Therapeutic System (OTS)	4-5mm diameter contoured either hydrophilic or hydrophobic disc.
NODS (New or novel ophthalmic delivery system)	Medicated solid polyvinyl alcohol flag that is attached to a paper-covered handle. On application, the flag detaches and gradually dissolves, releasing the drug.
Ocuserts	Flat flexible elliptical insoluble device consisting of 2 layers enclosing a reservoir, used commercially to deliver pilocarpine for 7 days.
Ophthalmic Inserts	A Cylindrical device containing mixtures of silicone elastomer and sodium chloride as a release modifier with a stable polyacrylic acid(PAA) (or) polymethyl acrylic acid(PMA) interpenetrating polymer network grafted onto the surface.
SODI (Soluble Ocular Drug Insert)	Small oval wafer, composed of a soluble co-polymer consisting of acrylamide, N-vinyl Pyrrolidone and ethyl acrylate, softens on insertion.

### CONCLUSION

Ocular drug delivery has to overcome unique barriers. To improve ocular drug bioavailability, there are a significant efforts have been directed towards development of new drug delivery systems for ophthalmic administration. The liposomes were found to be safe as a drug delivering agent. It seems that new tendency of research in ophthalmic drug delivery systems is directed towards a combination of several drug delivery technologies.

### REFERENCES

1. S.P Vyas and Roop K.Khar, Controlled Drug Delivery- Concepts and Advances, 383-410.
2. Jitendra, Sharma P.K, Banik.A, Dixit S, A NEW TREND: Ocular drug delivery system, IJPS, 2, July 2011, 457-461.
3. Rathore K.S, Neema R.K, An Insight into Ophthalmic drug delivery system, IJPDR, 1(1), 2009, 34-37.
4. Waugh A and Grant A: The special senses Ross and Wilson Anatomy and physiology in Health and Illness, Churchill Livingstone, 197-207.
5. Chien YW, Ocular drug delivery and delivery systems, special edition, 1998, 269-296.



6. Greaves JL and Wilson CG, Treatment of diseases of the eye with mucoadhesive delivery systems, *Advance Drug Delivery Review*, 11, 1993, 349– 383.
7. Robinson JC, Ocular anatomy and physiology relevant to ocular drug delivery, *Ophthalmic Drug Delivery Systems*, Mitra Edition, New York, A.K., 1993, 29–57.
8. Bodor N, *Advances in Drugs Research*, 13, 22-30.
9. Alder C. A, Maurice D. M., Ocular drug delivery system, *Exp. Eye Res*, 1971, 11-34.
10. Bawa R, *Ophthalmic Drug Delivery Systems*, Marcel Decker(Ed), Mithra A.K, New York, 46-50.
11. Roopal L Jain, JP Shastry, Study of ocular drug delivery system using drug-loaded liposomes, *IJPI*, 1, Jan 2001, 39-55.
12. Gulsen D, Chauhan A, Ophthalmic Drug delivery through Contact lenses, *IOVS.*, 45, 2004, 2342-2345.
13. Jain MR, Drug Delivery through soft contact lenses, *Br J Ophthalmal*, 5(4), 1988, 568-570.
14. Galvain S, Andre C, Vatrinet C, Villet B, Safety and efficacy studies of liposomes in specific immunotherapy, *Curr Therap Res*, 6, 1999, 278-294.

\*\*\*\*\*

