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Review Article

# Occular Drug Delivery System – A Review

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**ABSTRACT**

The unique Anatomy of the eye makes it a highly protected organ and unique structure restricts entry of the drug into the target site of action. Designing an effective therapy for ocular diseases has been considered as a difficult task. Major barriers in eye medication are the ability to maintain a therapeutic level of the drug at the site of action. Therapeutic drug levels are not maintained for a longer duration in target tissues. Limitations of the traditional route of administration have challenged scientists to find an alternative mode of administration like periocular routes. The ophthalmic formulations are available as buffered, isotonic, sterile solution. A number of types of dosage forms are applied as the drug delivery system for the ocular delivery. The topical ocular drop is the most suitable and patient compliant route of drug administration, especially for the management of anterior segment diseases. Ideal ophthalmic drug formulation must be able to prolong the drug release and to remain in the area of the front of the eye for prolong period. It is necessary to optimize ophthalmic drug delivery; one way to do so is by adding polymers, development of in situ gel or using erodible or nonerodible insert or colloidal suspension to extend the precorneal drug retention.

**Keywords:** Novel ocular drug delivery, drug delivery to eyes.

## INTRODUCTION

The eye presents unique opportunities and challenges when it comes to the delivery of pharmaceutical formulations. Ophthalmic drug delivery is one of the most interesting and challenging tasks facing the pharmaceutical scientists[1]. The distinctive structure of the eye restricts the entry of drug molecules at the required site of action. Conventional preparations like suspensions, ointments and eye drops cannot be considered best in the treatment of vision-threatening ocular diseases[2]. Though, more than 90% of the marketed ophthalmic formulations are in the form of eye drops. These formulations mainly target the anterior segment eye diseases[3]. A significant challenge to the formulator is to evade the protective barriers of the eye without causing undeviating tissue damage. The development of newer, more sensitive diagnostic techniques and therapeutic agents renders necessity to the development of most successful and advanced ocular drug delivery systems[1,2]. Conventional ophthalmic preparations like suspension, ointment and solution have several drawbacks which lead to poor bioavailability of the drug in the ocular cavity. The particular aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the suitable period[3]. Most of the topically applied drugs are washed off from the eye by various mechanisms resulting in low ocular bioavailability of drugs. Furthermore, the human cornea comprises of epithelium, substantia propria and endothelium also restrict the entry of drug molecules into ocular cavity. Various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories[4,8]. Former is based on the use of sustained drug delivery systems, which give the controlled and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss[8]. Treatment of posterior segment diseases still remains a herculean task for the formulation scientists. The tight junctions of blood-retinal barrier limit the access of systemically administered drugs into the retina. High vitreous drug concentrations are required in managing the posterior section diseases. This can be made possible only by the local administration. Periocular injections are associated with fairly high patient compliance as compared to intravitreal injections[5,7].

*Anatomy of the eye*

The eye is a complex organ with a unique anatomy and physiology. Broadly we discuss the structure of the eye under two subheadings (a) anterior segment and (b) posterior segment. The Anterior potion consists of front one-third of the eye that primarily includes pupil, cornea, iris, ciliary body, aqueous humor, and lens while the posterior part consists of the back two-thirds of the eye that includes vitreous humor, retina, choroid, macula, and optic nerve[6] (Fig. 1).

*Cornea*

It is the clear front window of the eye that transmits and focuses light into the eye. The cornea is a strong clear bulge located at the front of the eye. It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens. The cornea, a non-vascular structure gets the necessary nutrients from the capillaries that terminate in loops at its circumference[10].

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*Sclera*

The sclera is the tough white sheath that forms the outer-layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape. It is much thicker towards the back/posterior aspect of the eye than towards the front/anterior of the eye[10].

*Iris*

It is colored part of the eye that helps regulate the amount of light that enters. The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The function of the iris is to adjust the size of the pupil to regulate the amount of light admitted into the eye[9,10].

*Ciliary Muscle*

The ciliary muscle is a ring of striated smooth muscles in the eye's middle layer that controls accommodation for viewing objects at varying. Contraction and relaxation of the ciliary muscle alters the curvature of the lens[10].

*Pupil*

It is a dark aperture in the iris that determines how much light is let into the eye. Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye[9,10].

*Lens*

It is a transparent structure in the eye that focuses the rays of light on the retina. It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye. The lens focuses light into an image on the retina. It is able to do this because the shape of the lens is changed according to the distance from the eye of the object(s) the person is looking at[9,10].

*Retina*

It is thin, semitransparent, multilayered sheet of neural tissue that lines the internal portion of the posterior two-thirds of the globe terminates anteriorly at the ora serrata. 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[9,10].

*Macula*

The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cells which convert light into nerve signals. Because of the high concentration of photoreceptors, we are able to see fine details such as newsprint with the macula. At the very center of the macula is the fovea, the site of our sharpest vision[9,10].

*Optic nerve*

It connects the eye to the brain and carries electrical impulses created by retina to the visual cortex of the brain. The optic nerve is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for processing by the brain[9,10].

*Choroid*

The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portions of the retina. It is a thin, highly vascular membrane that is dark brown in colour and contains a pigment that absorbs excess light and so prevents blurred vision[10].

*Vitreous*

It is a clear, jelly-like substance that fills the middle of the eye. The vitreous humour is located in the large area that occupies approximately 80% of each eye in the human body. The vitreous humour is a perfectly transparent thin-jelly-like substance that fills the chamber behind the lens of the eye. It is an albuminous fluid enclosed in a delicate transparent membrane called the hyaloid membrane[9,10].

*Conjunctiva*

The conjunctiva is a thin transparent mucous epithelial barrier, lines the inside of the eyelids, and covers the anterior one-third of the eyeball. The conjunctiva is composed of two layers: an outer epithelium and its underlying stroma (substantia propria). The exposed surface of the eye includes conjunctiva and cornea and is covered with the tear film. The conjunctiva contributes to the formation of the tear film by way of secreting substantial electrolytes, fluid, and mucins[9,10].

*Common eye infections.*[11]

Bacteria are the causative pathogens for a large number of eye infections. In addition virus, fungus and protozoas also cause eye infections. As such, eyes are prone to a number of diseases but more commonly found are mentioned here.

Conjunctivitis

Glaucoma

Keratitis.

Cataract.

Iritis (anterior uveitis).

Blepharitis.

*Routes of ocular drug delivery*

There are various possible routes of drug delivery into the optical tissues. The selection of the route of administration depends on the target tissue.

*Topical route*

The topical administration of ocular drugs is usually carried out with ocular drops, but they have a short contact time on the surface of the eye. The increase in contact with the drug, and therefore the duration of the action of the drug, can be prolonged by the design of the formulation (for example gels, inserts and ointments)[11].

*Subconjunctival administration*

Conventional subconjunctival injections were used to administer drugs at enhanced level in the uvea[11].

*Intravitreal administration*

Direct administration of drugs into the vitreous gives a clear advantage of more direct access to the vitreous body and the retina. It should be noted; however, that delivery from the vitreous to the choroid is more complicated due to the hindrance by the Retinal Pigment Epithelium barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted[11,24].

*Mechanism of ocular drug absorption*

The drugs administered by instillation must penetrate the eye and do it mainly through the cornea followed by non-corneal pathways. These non-corneal pathways involve the spread of the drug through the conjunctiva and the sclera and appear to be particularly important for drugs that are poorly absorbed through the cornea[12].

*Corneal permeation*

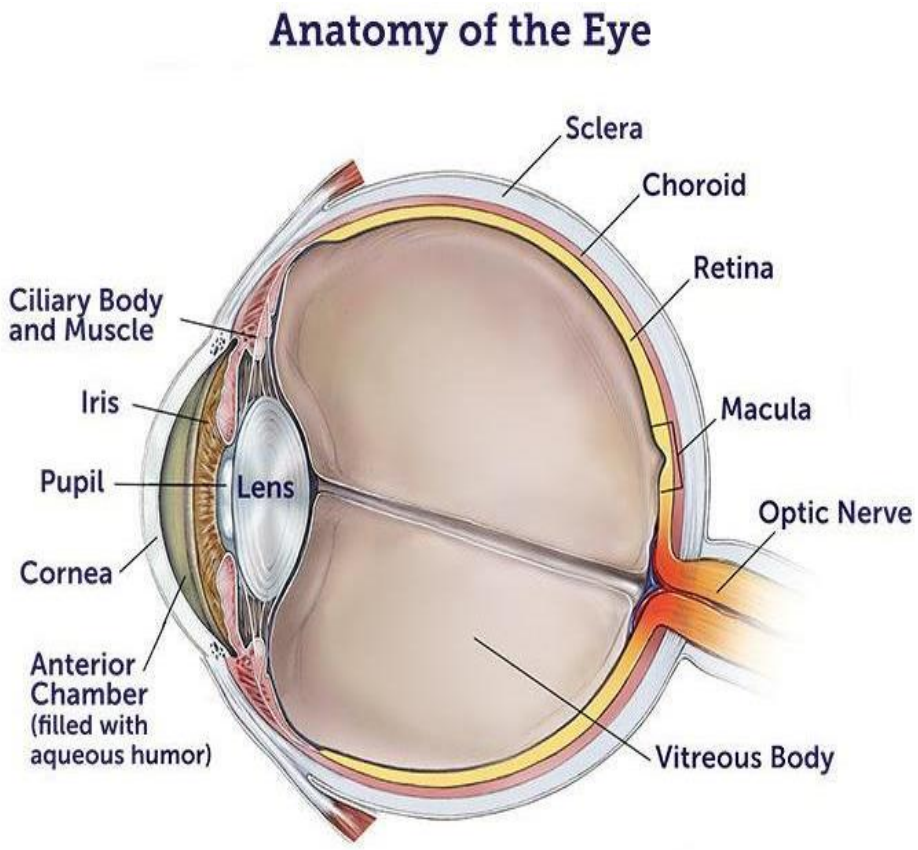


Figure 1: Structure of the eye.

The permeation of drugs across the corneal membrane occurs from the precorneal space.

*Barriers to drug Absorption*

Tears have a direct bearing on the efficiency of drug absorption into the inner eye. The productive absorption of most ophthalmic drugs derives from the diffusion process through the corneal membrane. The efficiency of absorption process is a function of rate and extent at which the transport processes of the eye. The flux of any drug molecule across the biological membrane depends on the physicochemical properties of the permeating molecule and its interaction with the membrane. Depending on the physicochemical properties of a diffusing drug, the resistance offered by the individual layers varies greatly. Epithelium, being lipoidal, represents a diffusional barrier offering high resistance to ionic or other aqueous soluble or polar species[12,25].

*Non-corneal permeation*

The main mechanism of drug permeability is that the sclera is likely to spread through aqueous intercellular media in the case of structurally similar corneal stroma. Therefore, the possibility of a partition mechanism cannot be eliminated. Although like cornea, the conjunctiva is made up of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers significantly less resistance than does the corneal epithelium[12,22].

*Factors responsible for disposition of ocular drugs*

The bioavailability of drugs given to the eyes is an important consideration. There are physiological factors that can influence the bioavailability of a drug, including protein binding, drug metabolism and tear drainage. Drugs bound to proteins are not able to penetrate the corneal epithelium due to the size of the protein drug complex. Because of the short time in which an ophthalmic solution remains present in the eye, protein binding of a drug substance could quickly reduce its therapeutic value by making it inaccessible for absorption. One of the main problems encountered with conventional ophthalmic solutions is the rapid and extensive elimination of drugs from the precorneal tear fluid. It must be noted that this high drainage rate is due to the tendency of the eye to maintain its residence volume (7– 10 µl), while volumes topically instilled range from 20–50 µL[13.23].

*Nasolachrymal drainage system*

The nasolachrymal drainage system comprise of three parts: secretory system, distribution system and excretory system. The secretory system consists of a base secretors that have an efferent parasympathetic nerve flow and secrete in response to physical or emotional stimulation. The distribution system consists of the lacrimal eyelids and the meniscus around the edges of the open eye lid. The excretory part of the nasolachrymal drainage system consists of: lacrimal points, upper, lower and common canaliculi; the lacrimal sac and the nasolacrimal duct. It is believed that tears are absorbed to a large extent by the mucous membrane that lines the ducts and the lacrimal sac only a small amount reaches the nasal passage[13,21].

*Conventional ocular drug delivery systems*

Instillation of topical drops into the precorneal lower pocket is a widely recommended route compatible with the

patient for drug administration. However, most of the topically administered dose is lost due to reflux blinking and only 20% of the instilled dose is retained in the precorneal pocket. To improve corneal permeation prodrugs, iontophoresis, cyclodextrins and ion-pair forming agents are employed[14]. There is a wide range of ophthalmic products available in the market out of which around 70% of prescriptions include conventional eye drops. The reasons may be due to the ease of bulk-scale manufacturing, high patient acceptability, drug product efficacy, stability and cost-effectiveness[20,15].

*Topical liquid eye drops*

Topical ophthalmic drops are the most suitable, safe, immediately active, patient compliant and non-invasive mode of ocular drug administration. The solution of ophthalmic drops provides a permeability of the pulsed drug after instillation of topical drops, after which its concentration decreases rapidly. To enhance the drug contact time, penetration and ophthalmic bioavailability; different excipients may be added to eye drops such as permeation enhancers viscosity enhancers, and cyclodextrins[15].

*Suspensions*

Suspensions are defined as a dispersion of finely divided insoluble drug in an aqueous solvent consisting of a suitable suspending agent. In other words, the carrier solvent system is a saturated solution of API. Suspension particles retain in the precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution. Extent of drug action of suspension is particle size dependent. Smaller the size of particle greater the drug absorbed into ocular tissues from the precorneal pocket. While on the other hand, larger particle size helps retain particles for a longer time and slow drug dissolution. Therefore, an optimal particle size is likely to result in optimal drug activity[14,15].

*Emulsions*

An emulsion-based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. There are two types of emulsions which are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems. For ocular drug delivery, o/w emulsion is common and generally preferred over w/o system. The reasons include less irritation and better ocular tolerance of o/w emulsion[14,15].

*Ointments*

Ophthalmic ointments are one more class of carrier systems developed for topical application. Ophthalmic ointments contain a combination of solid and a semisolid hydrocarbon that has a melting point at ocular temperature (34°C). The selection of hydrocarbon is based on biocompatibility. Ointments help to enhance ocular bioavailability and prolong the drug release[14,15].

*Factor affecting the bioavailability of topically applied formulation*[14]

Continued inflow and outflow of lachrymal fluid.

Sufficient nasolachrymal drainage.

Interaction of drugs with proteins of lachrymal fluid.

*Novel ocular drug delivery systems*

Colloidal carriers have been broadly exploited in the field of drug delivery. It provides a more selective targeting along with the sustained release of molecules at the desired site. Nanotechnology-based ophthalmic preparations are one of the approaches which are presently being used for both anterior, as well as posterior segment drug delivery[16].

*Nanoparticles*

For ocular drug delivery, nanoparticles are normally composed of proteins, lipids, natural or synthetic polymers such as sodium alginate, albumin, chitosan etc. Drug-loaded nanoparticles can be nanosphere or nanocapsules. In nanocapsules, the drug is enclosed inside the polymeric shell while in nanospheres; the drug is evenly distributed all over polymeric matrix[20]. Nanoparticles represents a promising candidate for ocular drug delivery because of small size leading to low irritation and sustained release property avoiding frequent administration. Aqueous solutions of nanoparticles may be eliminated rapidly from the precorneal pocket. Hence, for topical administration of 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[16,19].

*Nanomicelles*

Nanomicelles are frequently used carrier systems to prepare therapeutic agents into clear aqueous solutions. These molecules may be surfactant or polymeric in nature. Ophthalmic research is currently focused to non-invasively deliver therapeutic levels of drugs to both anterior and posterior ocular segments. The advent of nanomicellar technology to deliver drugs in a non-invasive route, topical drop, is gaining interest. Due to their exceptionally small size and hydrophilic corona, nanomicelles may be retained in systemic circulation for a longer time and accumulate at the diseased tissue *via* enhanced permeability and retention effect. Thus, non-specific drug accumulation into normal tissues may be minimized. Proper selection of surfactant/polymer and engineering technique may aid in the delivery of drugs to both the anterior and posterior eye segments[16,19].

*Liposomes*

Liposomes are lipid vesicles with one or more phospholipid bilayers enclosing an aqueous core. The size of liposomes typically range from 0.08 to 10.00μm and based on the size and phospholipid bilayers, liposomes can be classified as small unilamellar vesicles (10–100 nm), large unilamellar vesicles (100–300 nm) and multilamellar vesicles[21]. For ocular applications, liposomes are perfect drug delivery systems due to the exceptional biocompatibility, the cell-like structure and the ability to encapsulate both hydrophobic and hydrophilic drugs[17].

*Nanosuspensions*

Nanosuspensions are a colloidal diffusion of submicron drug particles stabilized by the surfactant(s) or polymer(s). It has emerged as a promising approach for the delivery of hydrophobic drugs. For ophthalmic drug delivery, it provides various advantages such as less irritation, ease of eye drop formulation, increase precorneal residence time sterilization and enhancement in ocular bioavailability of

drugs which are insoluble in tear fluid[25]. The efficiency of nanosuspensions in enhancing the ophthalmic bioavailability of glucocorticoids has been demonstrated in several research studies[17].

*In-situ gelling systems*

*In-situ* hydrogels refer to the polymeric solutions which undergo a sol-gel phase transition to form a 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 the development of thermosensitive gels which respond to changes in temperature. Various thermogelling polymers have been reported for ocular delivery which includes multiblock copolymers made of polycaprolactone, poloxamers, poly (lactide), poly (glycolide), poly (*N*-isopropylacrylamide), polyethylene glycol, and chitosan. These thermosensitive polymers form temperature dependent micellar aggregates which gellify after a further temperature increment due to aggregation or packing. For drug delivery, these polymers are mixed with drugs in the solution state and solution can be administered which forms an *in situ* gel depot at physiological temperature. These thermosensitive gels demonstrated promising results for increasing ocular bioavailability for both posterior segment and anterior[17,26].

*Dendrimers*

Dendrimers are characterized as nanosized, highly branched, star-shaped polymeric systems. These branched polymeric systems are available in different molecular weights with terminal end amine, hydroxyl or carboxyl functional group. The terminal functional group may be utilized to conjugate targeting moieties[27]. Dendrimers are being employed as carrier systems in drug delivery. Selection of size, molecular weight, functional group, surface charge, and molecular geometry are vital to deliver drugs. The highly branched structure of dendrimers allows incorporation of a wide range of drugs, hydrophobic as well as hydrophilic. In ocular drug delivery, few promising results were reported with these branched polymeric systems[28].

Poly amidoamine (PAMAM) dendrimers are widely employed in ocular drug delivery[28]. In order to evade scar tissue formation after glaucoma filtration surgery, conjugates of modified Poly amidoamine dendrimers with glucosamine and glucosamine 6-sulfate were synthesized to exert immunomodulatory and anti-angiogenic activities, respectively[17,28].

*Contact lens*

Contact lenses are thin, and curved shape plastic disks which are designed to cover the cornea. Following application, contact lens adheres to the film of tears over the cornea due to the surface tension. The Drug-loaded contact lens has been developed for ophthalmic delivery of various drugs such as antimicrobials, antihistamines and β-blockers. It is postulated that in presence of contact lens, drug molecules have a longer residence time in the post-lens tear film which ultimately led to higher drug flux through cornea with less drug inflow into the nasolachrymal duct. Usually, the drug is loaded into a contact lens by soaking them in drug solutions. These soaked contact lenses demonstrated high effectiveness in delivering drug compared to conventional eye drops[18,29].

*Implants*

Intraocular implants are specifically designed to provide localized controlled drug release over an extended period. These devices help in circumventing multiple intraocular injections and associated complications. In general, for the administration of drugs to the posterior ocular tissues, the implants are positioned intravitreally by making an incision through minor surgery in the pars plana which is located behind the lens and anterior to the retina. Though implantation is an 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[30].

Ocular implants are available as biodegradable and non-biodegradable drug releasing devices. Non-biodegradable implants propose long-lasting release by achieving near zero order release kinetics. Polymers such as ethylene vinyl acetate, polyvinyl alcohol, and polysulfone capillary fiber are being employed for fabricating non-biodegradable implants[27].

*Recent trends in occular drug delivery system*

From the newer approaches, successful extended duration and controlled release ocular delivery systems like ocular inserts, are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs. Utilization of the principle of controlled release as embodied by ocular inserts therefore offer an attractive alternative approach to the difficult problem of prolonging pre- corneal drug residence time[19.20].

Mucoadhesive dosage forms.
Ocular inserts.
Collagen shields or corneal shields.
Artificial tear inserts.
Drug presoaked hydrogel type contact Lens.
Ocular iontophoresis.
Phase transition systems.
Microspheres and nanoparticles

## CONCLUSION

Treatment of ocular diseases is a difficult challenge especially because of the nature of diseases and presence of the ocular barriers. A best therapy should retain effective levels of drug for the longer period following a single application with minimum systemic effect. Invasive mode of drug delivery cannot be considered safe. Drug delivery by periocular route can overcome several of these drawbacks and also can provide sustained drug levels. Colloidal carriers can substantially improve the current therapy. New ocular drug delivery system includes ocular films, ocular inserts, disposable contact lens and other novel drug carrier systems like Niosomes and nanoparticles. Patient acceptance is important for the design of any ocular drug delivery system. Improvements are necessary in each system like improvement in sustained drug release.

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