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A Review on Novel Ocular drug Delivery System

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ABSTRACT

Ocular drug delivery system (ODDS) is one of the most challenging tasks faced by pharmaceutical researchers. For a prolonged duration the major barriers in ocular medication are the ability to maintain a therapeutic level of the drug at the site of action. As drops are easier to administer so the most prescribed dosage form is the eye drop solution. The new drug delivery systems for this type of delivery is ocusert, which are designed to eliminate the frequent administration of the drug by releasing the drug at predetermined and predictable rate. 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

The eye is a unique organ, both anatomically (Figure- 1), and physiologically, containing several widely varied structures with independent physiological functions. The complexity of the eye provides unique challenges to drug delivery strategies. [1-2]

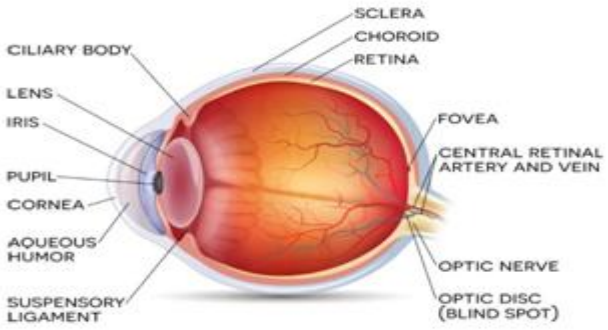


Figure: -1 Cross sectional view of eye

Ophthalmic drug delivery is most interesting and challenging delivery system facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the for the formulator is circumvent the protective barriers of the eye without causing permanent tissue damage. These barriers affect the bioavailability of drugs. [3]

The bioavailability of traditional ocular drug delivery systems such as eye drops is very poor because eye is protected by a series of complex defense mechanisms that make it difficult to achieve an effective drug concentration within the target area of the eye. The anatomy, physiology of the eye is one of the most complex and unique systems in the human body. lachrymation (figure-2), effective drainage by the nasolacrimal system, the inner and outer blood-retinal barrier,

the impermeability of the cornea, and inability of absorption by other non-corneal structures cause the eye to be exceedingly impervious to foreign substances. [4-5]

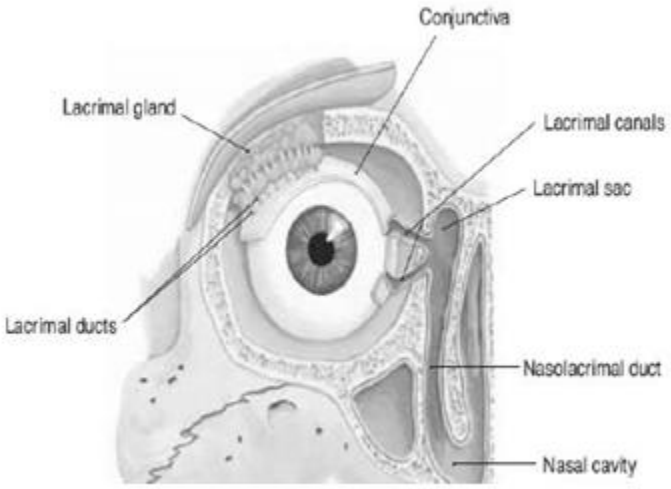


Figure: -2 Lacrimal apparatus shown in an anterior view of the right eye

To optimize ocular drug delivery systems, the following characteristics are required:

- A good corneal penetration.
- A continued contact time of drug with corneal tissue.
- Easiness in installation and removal.
- A non-irritative form.
- Good rheological properties. [6]

Advantages of ocular drug delivery system [7]
The merits of ODDS are followings:

- Increased accurate dosing, to overcome the side effects of pulsed dosing produced by conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
- To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
- To circumvent the protective barriers like drainage, lacrimation and conjunctive absorption.
- To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
- To provide better housing of delivery system.

Disadvantages [8-9]
Various disadvantages of ocular drug delivery system are given below.

- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen.

THE ANATOMY OF THE EYE

The human eye, elegant in its detail and design, represents a gateway to the process we call vision. The eyeball is spherical in shape and about 1 inch across. It houses many structures that work together to facilitate sight. The human

eye is comprised of layers and internal structures, each of which performs distinct functions. The detailed description of each eye part is given below

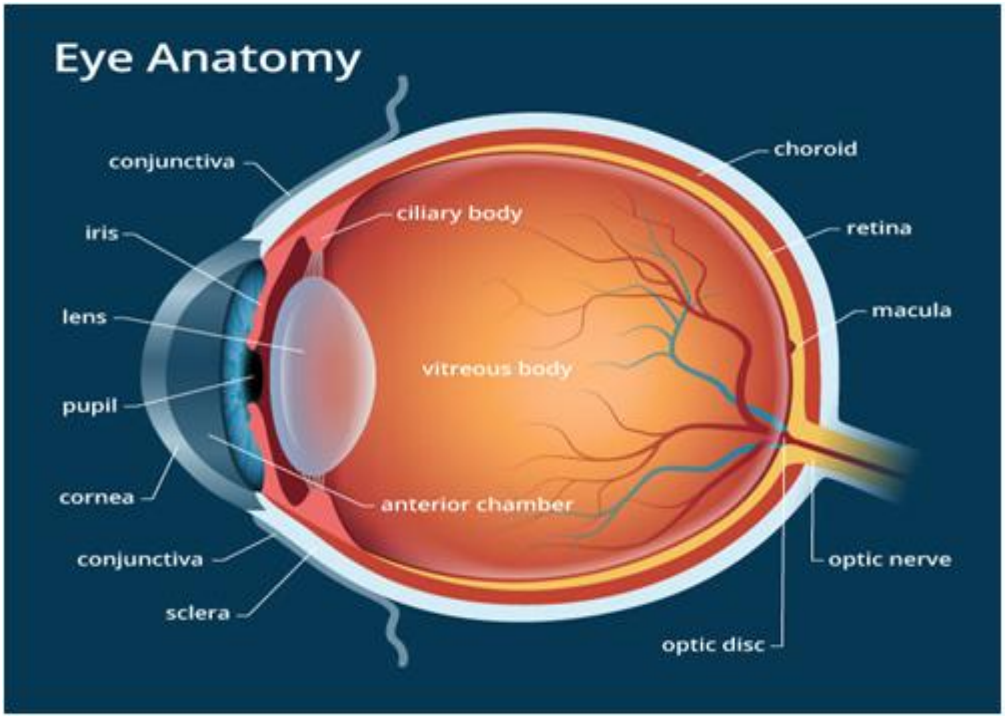


Figure: -3 Anatomy of the eye

A. Sclera

The sclera (white portion of the eye) is the tough white sheath that forms the outer-layer of the ball. It is afirm fibrous membrane that maintains the shape of the eye as an approximately globe shape. [10]

B. 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 respective portion of conjunctiva is referred to as the palpebral and bulbar conjunctiva. 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.

C. Cornea

The cornea is a strong clear bulge located at the front of the eye. Surface of the adult cornea has a radius of approximately 8mm. It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens (which then focuses the light onto the retina). The cornea, a non-vascular structure (does not contain any blood vessels) gets the necessary nutrients from the capillaries that terminate in loops at its circumference.

D. Aqueous humor

The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind the cornea and in front of the lens. The aqueous humor is very slightly alkaline salt solution that includes tiny quantities of sodium and chloride ions. The rate of aqueous formation is approximately 2.5 µl/min. The pressure dependent outflow refers to the trabecular meshwork-schlemm's canal-venous system, while pressure independent outflow refers to any non-trabecular outflow and is called as uveoscleral outflow. [11]

E. Pupil

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. The size of the pupil (and therefore the amount of light that is admitted into the eye) is regulated by the pupillary reflex (also known as the "light reflex").

F. Iris
The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The iris is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye. It is the coloured part of the eye (shades may vary individually like blue, green, brown, hazel, or grey).

G. 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 distances and regulates the flow of aqueous humour into schlemm's canal. The muscle has parasympathetic and sympathetic innervation. Contraction and relaxation of the ciliary muscle alters the curvature of the lens.

H. Lens [12]
The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye (which first refracted by the cornea). This adjustment of shape of the lens is called accommodation and is achieved by the contraction and relaxation of the ciliary muscles.

ROUTES OF OCULAR DRUG DELIVERY

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.

Topical route
Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. m gels, gelifying formulations, ointments, and inserts).

Subconjunctival administration
Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.

Intra- vitreal administration
In recent advancement in the surgical procedures, intra- vitreal administration of therapeutic agents by direct injection into the midvitreous region and sustain and controlled released intra- vitreal implants have become a mainstay treatment option of posterior segment diseases. Longer retention time and higher vitreous concentration of drugs was obtained following this route of administration. However, patient noncompliance, pain and discomfort are major obstacles to the clinical application. In order to overcome the risks related to direct intravitreal injection such as cataract, retinal detachment and vitreous haemorrhage. Vitrasert® is a non- biodegradable GCV intraocular implant. Sustain therapeutic concentration of ganciclovir in to the vitreous humor for a period of 5-6 months can be achieved by this intra- vitreal implant. Removal of implant requires a skillful surgical procedure and possesses risks of retinal detachment and hemorrhage.

Scleral administration
Due to its large surface area, easy accessibility and relatively high permeability to macromolecules, the sclera recently has become a potential vector for posterior segment drug delivery. Scleral drug delivery has been attempted by different ways, such as scleral plugs and implants, sun conjunctival injection, subtenon injection. Trans-scleral administration of drugs offers a promising therapeutic approach for the treatment of various posterior segment diseases.

Barriers to ocular drug delivery systems
The major disadvantage associated with systemic administration ocular therapeutics is its low ocular bioavailability, and only 1%-2% of the administered dose reaches the anterior segment. [13] Therefore, in clinical practices, for ocular diseases related to the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea), topical administration of therapeutics is the preferred route of administration. Even though it seems to be an ideal route of administration, it has to overcome certain physicochemical, metabolic, and biological barriers to reach the intended site of action. [14]

Figure: -4 Barriers avoiding drug delivery (15)

Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of eye. Even though the lacrimal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.

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 paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. Ingeneral, 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: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the uveam (The middle layer of the eye beneath the the sclera. It consists of the iris, ciliary body, and choroid).

MECHANISM OF OCULAR DRUG ABSORPTION

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea [16].

Corneal permeation

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

Various Barriers to drug Absorption

The extent to which the transport or absorption process occurs is also function of physiological mechanism of precorneal fluid drainage or turnover. In terms of transcorneal drug permeation, the cornea can be considered to consist of three primary layers (epithelium, stroma and endothelium).

Non-corneal permeation

Primary mechanism of drug permeation is the sclera is likely to be diffusion across the intercellular aqueous media in the case of structurally similar corneal stroma. Therefore the possibility of partitioning mechanism cannot be eliminated. Although like cornea, the conjunctiva is composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance than does the corneal epithelium.

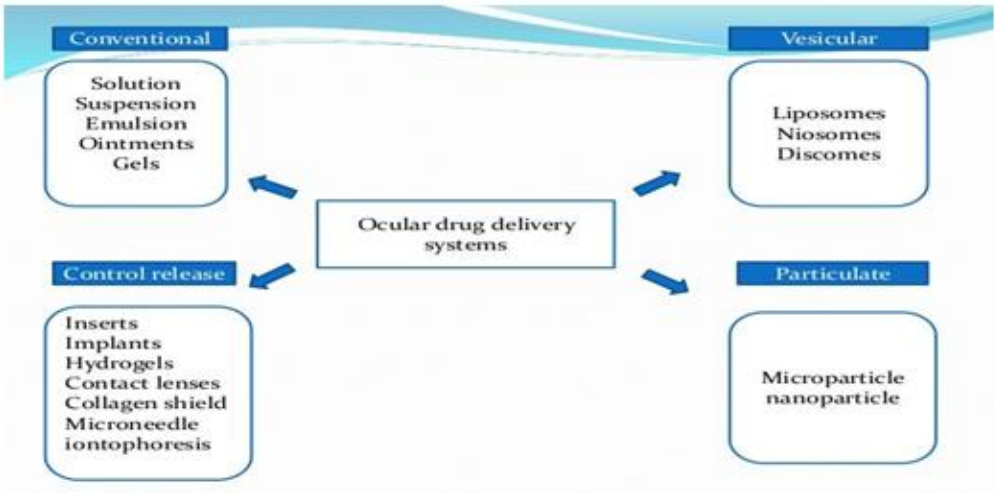
Various factors responsible for disposition of ocular drugs

Bioavailability of drugs administered to the eye is an important consideration. There are physiological factors, which can affect a drug's bioavailability including protein binding, drug metabolism and lachrymal drainage. Protein bound drugs are incapable of penetrating the corneal epithelium due to the size of the protein drug complex. Because of the brief time in which an ophthalmic solution may remain present in the eye (due to lachrymal drainage), protein binding of a drug substance could quickly negate its therapeutic value by rendering it unavailable for absorption.

Nasolacrymal drainage system

The nasolachrymal drainage system consists of three parts: the secretory system, the distributive system and the excretory system. The secretory system consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation. [17]

FORMULATION OF OCULAR DRUG DELIVERY SYSTEM: -



Conventional drug delivery system: -

- These include eye drops containing solutions, suspension or emulsion of drugs and eye ointments.
- These preparations when instilled in the eye are rapidly removed from the ocular cavity by tear flow and nasolacrimal drainage.

Disadvantages: -

- poor bioavailability
- frequent dosing
- interference with vision

Advantages: -

- Ease of bulk scale manufacturing,
- High patient acceptability.
- Drug product efficacy
- Stability and cost effectiveness

1.ointment and gels: -

- 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

2.ocuserts and lacrisert: -

- Occular inserts (ocusert) are sterile preparation that prolong residence time of drug with controlled release manner and negligible or less effected by nasolacrimal damage
- Inserts are available in different varieties depending upon their composition and applications.
- Lacrisert is a sterile rod shaped device for the treatment on dry eye syndrome and keratitis sicca.
- They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea.

3.Vesicular system: -

1. **Liposomes: -**

- Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25-10000nm in diameter.
- They are having an intimate contact with the cornea and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition co-efficient, poor solubility or those with medium to high molecular and thus increases the probability of ocular drug absorption.

2. **Niosomes and Discomes**: -

- The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids.
- To avoid this Niosomes are developed as they are chemically stables as compared to liposome and can interact both hydrophobic and hydrophilic drugs.
- They are 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.
- DISCOMES may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.

3.Control delivery system: -

1.Implants: -

- 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.

2.Iontophoresis: -

- In iontophoresis direct current drives ions into cells or tissues. For iontophoresis the ions of importance should be charged molecules of the drug.
- Positively charged of the drug are driven into the tissues at the anode and vice versa.

3.Microneedles: -

- 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.

4.Particulates: -

1.Nanoparticles and Microparticles: -

- The maximum size limit for microparticles for ophthalmic administration is about 5-10mm above which a scratching feeling in the eye can result upon ocular instillation.
- That is why microspheres and nanoparticles are promising drug carriers for ophthalmic application.
- Nanoparticles are prepared using bioadhesive polymers to provide sustained effect to the entrapped drugs.

EVALUATION OF OCDDS

1. **Thickness of the film: -**

- Measured by dial caliper at different points and the mean value is calculated.

2. Drug content uniformity: -

- The cast film cut at different places and tested for drug as per monograph.

3. Uniformity of weight: -

- Here, three patches are weighed.

4. Percentage moisture absorption: -

- Here ocular films are weighed and placed in a dessicator containing 100ml of saturated solution of aluminium chloride and 79.5% humidity was maintained.
- After three days the ocular films are reweighed and the percentage moisture absorbed is calculated using the formula=%moisture absorbed= final weight-initial weight/ initial weight×100

5. IN- vitro evaluation methods: -

1. Bottle method: -

- In this, dosage forms are placed in the bottle containing dissolution medium maintained at specified temperature and pH.
- The bottle is then shaken.
- A sample of medium is taken out at appropriate intervals and analyzed for the drug content.

2. Diffusion method: -

- Drug solution is placed in the donor compartment and buffer medium is placed in between donor and receptor compartment.
- Drug diffused in receptor compartment is measured at various time intervals.

6. IN-vivo study: -

- Here, the dosage form is applied to one eye of animals and the other eye serves as control.
- Then the dosage form is removed carefully at regular time interval and are analyzed for drug content.
- The drug remaining is subtracted from the initial drug content, which will give the amount of the drug absorbed in the eye of animal at particular time.
- After one week of washed period, the experiment was repeated for two time as before.

CONCLUSION

New ophthalmic delivery system includes ocular inserts, collagen shields, ocular films, disposable contact lens and other Novel drug delivery systems like hiosomes 20 and nanoparticles. Newer trend is a combination of drug delivery technologies for improving the therapeutic response of a non efficacious drug. This can give a superior dosage forms for topical ophthalmic application. Among these drug delivery systems, only few products have been, commercialized. An ideal system should have effective drug concentration at the target tissue for an intended period of time with minimum systemic effect. Patient acceptance is very important for the design of any comfortable ophthalmic drug delivery system. Major Improvements are required in each system like improvement in sustained drug release, large scale manufacturing and stability. Combination of drug delivery systems could open a new directive for improving the therapeutic response of a non-efficacious system. They can overcome the limitations and combine the advantages of different systems.

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