A Review On Ocular Drug Delivery System

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ABSTRACT
The ocular drug delivery is one of the most challenging & interesting endeavors facing the pharmaceutical companies in the market. To circumvent the protective barriers of the eye without causing permanent tissue damage is the challenge to the formulator. Hence to improve the bioavailability of ocular drug considerable amount of research has been focused in developing the controlled drug delivery systems. The main aim of preparing the ocular insert is to increase the bioavailability of ocular drug. The Ocular inserts maintain the concentration of drug within the desired range. The Ideal ophthalmic drug delivery must be able to sustain the release of drug & to remain in the vicinity of front of the eye for the prolong period of time. In this review, we have focused on the Barriers for Ocular drug delivery system, mechanism of action, classification of ocular insert.

Keywords: Ocular drug delivery, eye, sustain release.

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INTRODUCTION

For the treatment of various eye diseases like eye flu, dryness, conjunctiva, etc the topical application of drugs to the eye is the well established route of administration. The protective mechanisms of the eye such as the blinking, baseline & reflexlachrymation & drainage decreases the bioavailability of the drug & also help to remove therapidly foreign substances like the dust particles, bacteria including the drugs from thesurface of the eye. There are different eye diseases which can be affected to the eye & also the vision of eye. Therefore the marketed ophthalmic dosage formulations are classified as the conventional &non-conventional [newer] drug delivery systems.\textsuperscript{1-4} There are most commonly available ophthalmic preparations such as the ointments & dropsabout 70 percent of the eye dosageformulations in market. But when instilled into eye these preparations are rapidlydrained away from the ocular surface due to the tear flow, blinking& lacrimal nasaldrainage of the eye. Only the small amount of drug is available for its therapeutic effectresulting in the frequent dosing application to the eye. The newerpharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome,nanosuspension, microemulsion, intophoresis and ocular inserts have been developed inlast three decades increase the bioavailability of the drug as a sustained and controlledmanner to overcome these problems.\textsuperscript{5-9}

The Ocular Anatomy & Physiology

A human eye is the complex anatomical devicethat remarkably demonstrates the architectural wonders of the human body. For the topicaladministration of drugs the human eye is the challenging organ. In the anatomical arrangement of thesurface tissues & in the permeability of thecornea the basis of this can be found. The protective function of the eyelids &lachrymal system is such that there is rapidremoval of the material instilled into the eye unless the material is suitably small in the volume&chemically & physiologically compatible with thesurface tissues. The eye is referred as the globe& consists of 2 spheres one set in the other. The front sphere is smaller& is bordered anteriorly by the sclera. Thecombined weight of both the spheres has been givenas 6.7-7.5gm with the volume of the approximately6.5ml. About 75mm is the circumference of the eye. In the bony orbitalcavity of the head the eye is located.

A] The Eyeball

Wall of the human eyeball [globe] is composed of 3 concentric layers.
I. The outer fibrous layer. This fibrous layer is made up of 2 parts.
1) The Anterior [1/6\textsuperscript{th}] is transparent & called the cornea.
2) The Posterior [5/6\textsuperscript{th}] is opaque & called the sclera.
II. The middle vascular layer: the uvea or the uvealtract consisting of a choroid, ciliary body & iris.

III. The nervous layer: The retina.

B] The Sclera
It contains the microcirculation which nourishes the tissues of this anterior segment & usually is white.

C] The Vascular Layer consists of 3 parts
A choroid: It remains just behind the retina forming a posterior 5/6th of the middle coat which is composed of numerous blood vessels & pigmented cells containing melanin.

D] The Ciliary body: It includes the orbicularis ciliaris, ciliary processes & ciliary muscle.

E] The Iris nervous coat is called retina which contains the photosensitive receptors. The eyeball houses the optical apparatus which consists in sequences of a precorneal film, cornea, aqueous humor, pupil, crystalline lens, vitreous humor & the retina. The aqueous & vitreous humors are the layers of the clear fluid or gel like materials that are interposed between the solid structures. The crystalline lens is the refractive element with variable power controlled & supported by the muscle incorporated in the ciliary body.

F] Conjunctiva
The conjunctival membrane covers the outer surface of a white portion of the eye & the inner aspects of eyelids. It is loosely attached & thereby permits free movement of the eyeball. The conjunctiva is the most exposed portion of the eye, except for the cornea.

G] Lachrymal System.
The corneal & conjunctival surfaces are covered & lubricated by the film of the fluid secreted by the lachrymal & conjunctival glands. The secretions of the lachrymal glands the tears are delivered through the number of fine ducts into the conjunctival fornix. The movement of eye helps to spread the tears over the conjunctiva surface. The excess fluid is then directed into the lachrymal lake the small triangular area lying in the angle bound by a inner most portions of the lids. The tears are drained from the lachrymal lake by 2 small tubes, the lachrymal canaliculi which lead into a upper part of the nasolacrimal duct. The act of blinking exerts the suction-force pump action in removing tears from the lachrymal lake & emptying them into a nasal cavity. The Lacrimation is induced reflexly by the stimulation of the nerve ending of the conjunctiva or the cornea the turnover rate of nasolacrimal fluid is about 16 percent. The eyeball is continually irrigated by the gentle stream of the lachrymal fluid which prevents it from becoming dry & inflamed.

H] Composition of tear.

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The secretion is the clear watery fluid containing the numerous glucose, salts, the other organic compounds approximately 0.7% protein & the enzyme lysozyme.

Water- 98.2%
Solids- 1.8%
Organic elements- Protein-0.67%, Sugar-0.65%, NaCl: 0.66%, NPN: 0.05%
Urea: 0.03%

Other mineral elements like potassium, sodium & ammonia: 0.79%.

I) The Precorneal Film
The part of a tear fluid provides the moist surface to the cornea. The film that is compatible with the both aqueous & lipid ophthalmic preparations is composed of the 3 layers, the thin outermost layer is the lipid & is secreted mainly by the meibomian glands. By preventing the evaporation of the underlying layers the lipid layer keeps the cornea moist, the thickest middle aqueous layer, secreted by lachrymal gland it helps in nourishing the cornea. It consists of the salts, water, urea, glucose, proteins, lysozyme [an antibacterial enzyme] & the immunoglobulin, & the thin inner mucous layer. It is secreted by a goblet cells of the tarsal conjunctiva. For tear film stability this layer is necessary. It enhances tear spreading, smooths the corneal epithelial surface, lubricates the eye & helps to trap the debris. It is renewed during each blink & when blinking is suppressed it dries in patches. Though the tear film is typically only about 7μL in volume with the fluid pH 7.4 & if the blinking does not occur the volume can go up to the 30μL without spillage, the cul-desac is sterile due partly to the action of the lysozyme in the tears.

J) The Cornea
The cornea 0.5-1 mm thick consists mainly of the following structures:

a) The Corneal Epithelium.
b) The Substantia Propria [stroma].
c) The Corneal Endothelium.

Because of a special laminar arrangement of the structure the cornea is transparent to ordinary diffuse light, the fibers & because of the absence of the blood vessels. By diffusion the cornea derives its nutrition & must have certain permeability characteristics. An efficient barrier against bacterial invasions is provided by the corneal epithelium. Unless its continuity has been broken by the abrasion the pathogenic bacteria cannot gain the foothold. Any foreign body that either scratches a cornea or the lodges & becomes embedded into the cornea is of the serious concern because of the role it may play in permitting the pathogenic bacteria to gain the foot hold.
Structure & Functions of the Eye

The eye consists of several parts which are as follows:

- The Sclera: The eye's white outer protective coat normally seen as the "white of the eye".
- The Cornea: The transparent curved structure at the front of the eye.
- The Iris: The coloured part of the eye: blue, brown, green, grey etc that can be seen through the cornea.
- The Pupil: The black part of eye in middle of the iris. It constricts or dilates depending on the amount of light passing through it.
- The lens: The transparent disc [with both sides being convex] immediately behind the iris & pupil.
- The Aqueous humour: The fluid which is transparent [with consistency similar to water] that circulates behind the cornea & in front of the lens.
- The Vitreous humour: The material [like transparent jelly] that fills the eyeball between the lens & the retina.
- The Retina: The light-sensitive layer of the millions of nerve cells that line the back of the eyeball. The cells consist of 2 main groups that are called rods & cones due to their appearance under the microscope.
- The Rods: More numerous these spread out over the entire retina with more towards the outer edge respond to low levels of light.
- The Cones: Far fewer they are concentrated around the retina's centre respond to colour & to the details.
- The Macula: It is the small centre of the retinawhich is responsible for reading vision.
- The Retinal pigment epithelium: This is the dark coloured layer of the cells at the back of the retina responsible for providing the oxygen & other nutrients to the rods & cones.
- The Choroid: A large network of the blood vessels [present behind the retina] that transports oxygen & other nutrients to the retinal pigment cells.
- The Optic disc: A small yellow oval structure in the retina to which the nerve cell connections travel from all the rods & cones.
- The Optic nerve & beyond: The "cord" of the nerve cell connections that passes from an eyeball to the destinations throughout the brain.\(^{12-13}\)
DIFFERENT EYE INFECTIONS
From fungi, viruses or bacteria the eyes can get infections. The eye infections can occur in the parts of the eye & can affect just one eye or both the eyes. The common eye infections are Endophthalmitis, Conjunctivitis, Corneal ulcers &

i] The Endophthalmitis
This Endophthalmitis is the severe form of the intraocular inflammation [purulent uveitis] which involves the ocular cavities and inner coats of the eyeball. The causative organisms include the E.coli, Pseudomonas, Streptococci etc. Also the other available antimicrobials that are used in the treatment & prevention of these infections includes the antibacterials, antifungals, antivirals & common topical antibacterials that are used in the treatment of the ocular infectious diseases which include the aminoglycosides, sulfonamides, polymyxin-based combinations & the fluoroquinolones. The fluoroquinolones represent the expanding class of the broad-spectrum antibacterials, which cover the host of the Gram-negative & anaerobic species that are responsible for the ocular infections. These antibacterials have gained the popularity in the ophthalmology field since they have been shown to be equivalent to the combination therapy in the treatment of the many ocular infections. The Fluoroquinolones are also effective against the variety of the Gram-positive organisms which includes the Staphylococcal & Streptococcal species; however the resistance is emerging among some of these organisms.

ii] The Conjunctivitis
The conjunctivitis is the inflammation [swelling] or infection of the membrane lining the eyelids [conjunctiva]. By cellular infiltration & exudation it is characterized. The Staphylococcus aureus is the most common cause of the bacterial conjunctivitis & blepharo-conjunctivitis. Various other organisms like the Streptococcus pneumonia, Haemophilus influenzae also cause the conjunctivitis.
It can be classified as
(2) Allergic Conjunctivitis.
(1) Infective Conunctivitis: Acute, Subacute and Chronic

iii] The Corneal ulcers/ Keratitis
The inflammation of the cornea [Keratitis] is characterized by the corneal oedema, cellular infiltration and ciliary congestion. The cornea is exposed to atmosphere & hence prone to get infected easily, being the most anterior part of the eyeball. The bacterial corneal ulcers are the most commonly caused by the virulent organism. The common bacteria associated with the corneal ulceration are the Pseudomonas pyocyanea, Staphylococcus aureus, Proteus & E.colietc.14-15
THE BARRIERS FOR OCULAR DRUG DELIVERY SYSTEM

The drug Loss from the Ocular Surface

After the infusion of the drug into the eye the lacrimal fluidflow removes the instilled or the infused drug compound from the surface of the eye. Even if the lacrimal turnover rate is only about 1 micro liter/minute. The other method of the nonproductive drug removal is its systemic absorption in the body instead of the ocular absorption.

The Lacrimal Fluid Eye Barriers

The corneal epithelium act as the barrier & limit the drug absorption from the lacrimal fluid into the eyes, therefore typically the lipophilic drugs have a higher permeability in the cornea as that of the hydrophilic drugs.

Generally the conjunctiva has the twenty times greater surface area than that of the cornea.

The Blood Ocular Barriers

The eye prevents from the xenobiotics in the blood stream by the blood ocular barriers. These barriers are mainly divided into 2 parts which are as follows:

The Blood retina barrier: Posterior blood eye barrier
The Blood aqueous barrier: Anterior blood eye barrier.\(^\text{16}\)

CLASSIFICATION OF PATENTED OCULAR INSURTS

[Based on their solubility behaviour]

A] Insoluble inserts
   1] The Diffusion based
   2] The Osmotic based
   3] The Soft contact lenses
B] Soluble inserts
C] Bioerodible inserts

The desired criteria for the controlled release ocular are as follows

The foreign-body sensation presents the challenge to overcome the discomfort which leads to poor-patient compliance, excessive lachrymation that accompanies their irritation, dilutes the drug & causes reduction in its concentration. The properly designed ocular inserts will minimize a sensation caused by its insertion & wear.

i] Sterility
iii] The Non-interference with vision & oxygen permeability.
iv] The ease of insertion & handling
v] Applicability to the variety of drugs
vi] The stability.
vii] Ease of manufacture
viii] The lack of expulsion during wear.17-19

A] **Insoluble ophthalmic inserts**
The insoluble inserts has been classified into 3 groups which are as follows:

1. **The Diffusion systems**
2. **The Osmotic systems**
3. **The Hydrophilic contact lenses.**

First 2 classes include the reservoir in contact with the inner surface of a rate controller & supplying the drug thereto. A reservoir contains the liquid, gel, colloid, semisolid, solid matrix or the carrier-containing the drug heterogeneously or homogeneously dissolved or dispersed therein. The carriers can be made of the hydrophilic, hydrophobic, inorganic, organic, naturally occurring or the synthetic material.

The 3rd class including the contact lenses. A insoluble of these devices is their main disadvantages after use they have to be removed.

1] **The Diffusion inserts**
These diffusion systems are compared of the central reservoir of the drug enclosed in the specially designed semi permeable or the micro porous membranes which allows a drug to diffuse the reservoir at the precisely determined rate. The release of drug from such a system is controlled by alachrymal fluid permeating through the membrane until the sufficient internal pressure is reached to drive a drug out of reservoir. The rate of drug delivery is controlled by the diffusion through the membrane, which one could be controlled.

2] **The Osmotic inserts**
Theses osmotic inserts are generally compared of the central part surrounded by the peripheral part. The 1st central part can be composed of the single reservoir or of the 2 distinct compartments. In the 1st case it is composed of the drug with or without the additional osmotic solute dispersed through the polymeric matrix so that the drug is surrounded by a polymer as the discrete small deposits.12, 20-23 In the 2nd case, the drug & the osmotic solutes are placed in the 2 separate compartments the reservoir of drug being surrounded by the elastic impermeable membrane & a osmotic solute reservoir by the semi permeable membrane. The 2nd peripheral part of this osmotic inserts comprises in all of the cases the covering film made of the insoluble semipermeable polymer. A tear fluid diffuse into the peripheral deposits through a semi permeable polymeric
membrane wets them & induces their dissolution. The solubilized deposits generate the hydrostatic pressure against a polymer matrix causing its rupture under the form of the apertures. The drug is then released through these apertures from the deposits near a surface of the device which is against the eye by a sole hydrostatic pressure. These correspond to the osmotic part that is characterized by the zero order drug release profile.

3] The Soft contact lenses
These are the shaped structures made up of the covalently crosslinked hydrophobic or the hydrophilic polymer that forms the 3-dimensional network or the matrix capable of retaining the aqueous solution, solid or the water components. When a hydrophilic contact lens is soaked in the drug solution it absorbs the drug but does not give the delivery as precise as that provided by the other non-soluble ophthalmic systems. The release of drug from the system is generally very rapid at a beginning & then declines exponentially with the time. The release rate could be decreased by incorporating a drug homogeneously during its manufacture or by adding the hydrophobic component. The contact lenses have certainly good prospects as the ophthalmic drug delivery systems.13, 24-27

B] The Soluble Ophthalmic inserts
The soluble inserts correspond to the oldest class of the ophthalmic inserts. They offer a great advantage of being entirely soluble so that they need not to be removed from their site of the application thus limiting the interventions to only insertion.

Types:
1] Based on natural polymers e.g. collagen.
2] Based on synthetic or semi synthetic polymers.

By soaking the insert in a solution containing the drug, drying and rehydrating in before use on the eye a therapeutic agent is preferably absorbed. The amount of loaded drug will depend upon the amount of the binding agent upon the concentration of solution of drug into which a composite is soaked as well as the duration of soaking.28-29

The soluble ophthalmic inserts that contain semi synthetic/synthetic polymers
They offer the additional advantages of being generally of the simple design.

a) It is based on products that are well adopted for the ophthalmic use.
b) It is easily processed by the conventional methods: slow evaporating extrusion, injection or the molding compression.

The drug release from such a system is by the penetration of the tears into an insert which induces the release of a drug by the diffusion & forms the gel layer around a core of an insert this external
gelification induces a further release but still controlled by the diffusion. The rate of release $J$, is derived from the Fick’s law yields the expression which is as follows:

$$J = \frac{AdkCs}{L}$$

When $A$ - Surface area of the membrane.
$K$ – Diffusion coefficient of the drug
$L$ – Membrane thickness
$CS$ – Drug solubility in water
$D$ – Diffusion coefficient of the Ocusertsmembrane.

As all the terms on the right hand side of the above equation are constant so is the release rate of the device.

Some other factors affecting release of drug from these Ocuserts include:

• The dissolution of the drug & the polymers.
• The swelling of the matrix.
• The relaxation of the polymeric chain.
• The penetration of the inclusion.

The soluble inserts that are made of the cellulose derivatives can be sterilized by the exposure to the gamma radiation without acellulose components being altered. The decreased release rate is obtained by using the component of a matrix thepolymer normally used for the enteric coating or by introducing the suitable amount of the hydrophobic polymer which is capable of diminishing a tear fluid penetration & thus of decreasing a drug release without modifying the solubility of a insert when added in the proper proportion.

**The Biodegradable ophthalmic inserts**

These inserts are composed of the materialhomogeneous dispersion of the drug included or not into thehydrophobic coating which is substantially impermeable to a drug. They are made up of the biodegradable polymers. The successful biodegradable materials for the ophthalmic use are the poly [orthocarbonates] & poly [orthoesters]. The drug release from such a system is a consequence of a contact of the device with a tear fluid inducing the superficial diversion of a matrix. The use of the solid ophthalmic devices will certainly increase owing to a development of the new polymers the emergence of new drugs that having short biological half lives or the systemic side effects & the need to improve the efficacy of the ophthalmic treatment by ensuring the effectivedrug concentration in a eye over an extended period of the time.
THE MECHANISM OF OCULAR DRUG ABSORPTION

The drug administration by instillation must penetrate the eye & do so primarily through cornea followed by the non corneal routes. The non corneal route involves the conjunctiva & sclera & the diffusion occurs mainly across these areas & appears to be the particularly important for the drugs that are absorbed poorly across the cornea.\footnote{1}

**The Mechanism of Drug Release**

The mechanisms of the controlled drug release into the eye are as follows:

- **The Diffusion** - The drug is released continuously at the controlled rate through the membrane into the tear fluid. The drug release can take place via the diffusion through the pores. From a region of higher to lower concentration across the concentration gradient the drug diffuses. \footnote{35}

- **The Osmosis** - The inserts comprise the transverse impermeable elastic membrane by dividing the interior of the inserts into the 1\textsuperscript{st} compartment & the 2\textsuperscript{nd} compartment. The 1\textsuperscript{st} compartment is bounded by a semi permeable membrane & the impermeable elastic membrane & the 2\textsuperscript{nd} compartment is bounded by an impermeable material & the elastic membrane. The drug release aperture in the impermeable wall of the insert

- **The Bioerosion** - The symmetry of the body of the insert is constituted from the matrix of the bioerodible material in which the drug is dispersed. The contact of the insert with the tear fluid results in the controlled sustained release of the drug. \footnote{37-38}

**CONCLUSION**

The ocular drug delivery systems provide the local as well as the systemic drug delivery. The novel advanced delivery systems offer the more protective & effective means of the therapy for the different eye diseases. During the 2 decades the main efforts in the ocular drug delivery has been on the design of the systems, to prolong the residence time of the topically applied drugs at the ocular surface & conjunctival sac. The development of the ophthalmic drug delivery systems is easy because we can easily target the eye to treat the ocular diseases as well as complicated because the eye has the specific characteristics such as the eye protecting mechanism which makes the ocular delivery systems extremely difficult. Currently very few new ophthalmic drug delivery systems have been commercialized in which the ocular inserts have been mostly used.

**REFERENCES**


