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A Review On Ocular Drug Delivery System

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ABSTRACT

The ocular drug delivery is one of the most challenging & interesting endeavors facingthe 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, conjuctiva, 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.[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.[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 unlessthe 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] iscomposed of 3 concentric layers.

I. The outer fibrous layer.This fibrous layer is made up of 2 parts.

1) The Anterior [1/6th] is transparent & called the cornea.

2) The Posterior [5/6th] 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 nourishesthe tissues of this anterior segment & usually iswhite.

C] The Vascular Layer consists of 3 parts

A choroid: It remains just behind the retinaforming a posterior 5/6th of the middle coatwhich is composed of numerous blood vessels &pigmented cells containing melanin.

D] The Ciliary body: Itincludes the orbicularisciliaris, ciliary processes & ciliary muscle.

E] The Iris nervous coat is called retina whichcontains the photosensitive receptors.The eyeball houses the optical apparatus whichconsists in sequences of a precorneal film,cornea, aqueous humor, pupil, crystalline lens, vitreous humor & theretina. The aqueous& vitreous humors are thelayers of the clear fluid or gel like materials that areinterposed between the solid structures. Thecrystalline lens is the refractive element withvariable power controlled & supported by themuscle incorporated in the ciliary body.

F] Conjunctiva

The conjunctival membrane covers the outersurface of a white portion of the eye & theinner aspects of eyelids. It is loosely attached& thereby permits free movement of the eyeball. The conjunctiva isthe most exposed portion of the eye, except for the cornea.

G] Lachrymal System.

The corneal & conjunctival surfaces arecovered & lubricated by the film of the fluid secretedby the lachrymal & conjunctival glands. Thesecretions of the lachrymal glands the tears aredelivered through the number of fine ducts into theconjunctival fornix. The movement of eyehelps to spread the tears over the conjunctivalsurface. The excess fluid is then directed into the lachrymal lake the small triangular area lying inthe angle bound by a inner most portions of thelids. The tears are drained from the lachrymal lakeby 2 small tubes, the lachrymal canaliculiwhich lead into a upper part of the nasolacrimalduct. The act of blinking exerts the suction-forcepumpaction in removing tears from thelachrymal lake & emptying them into a nasalcavity. The Lacrimation is induced reflexly by thestimulation of the nerve ending of theconjunctiva or the cornea the turnover rate of nasolacrimal fluid is about 16 percent. The eyeball is continually irrigatedby the gentle stream of the lachrymal fluid whichprevents it from becoming dry & inflammed.

H] Composition of tear.

The secretion is the clear watery fluid containing thenumerous glucose, salts, the other organic compounds approximately 0.7% protein & theenzyme 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 thecornea. The film that is compatible with the both aqueous& lipid ophthalmic preparations is composed ofthe 3 layers, the thin outermost layer is the lipid &is secreted mainly by the meibomian glands. By preventing theevaporation of the underlying layers the lipid layer keeps the cornea moist, the thickermiddle aqueous layer, secreted by lachrymalgland it helps in nourishing the cornea. Itconsists of the salts, water, urea, glucose, proteins, lysozyme [an antibacterial enzyme]& theimmunoglobulin, &the thin inner mucous layer.It is secreted by a goblet cells of the tarsalconjunctiva. For tear filmstability this layer is necessary. It enhances tear spreading, smoothes the corneal epithelialsurface, lubricates theeye & helps to trap the debris. It is renewed duringeach blink & when blinking is suppressed itdries inpatches. Though the tear film istypically only about 7µL in volume with the fluid pH7.4 & if the blinking does not occur the volumecan go up to the 30µL without spillage,the cul-desac is sterile due partly to the action of the lysozymein the tears.

J] The Cornea

The cornea 0.5-1 mm thick consists mainly of thefollowing structures:

a) The Corneal Epithelium.

b) The Substantia Propria [stroma].

c) The Corneal Endothelium.

Because of a special laminar arrangement of thestructure the cornea is transparent to ordinary diffuse light, the fibers & because of the absenceof the blood vessels. By diffusion the cornea derives its nutrition& must have certain permeabilitycharacteristics. An efficient barrier against bacterial invasions is provided by the corneal epithelium.Unless its continuity has been broken by the abrasion thepathogenic bacteria cannot gain thefoothold. Any foreign body that either scratches a cornea or the lodges & becomes embedded inthe cornea is of the serious concern because of the role it may play in permitting the pathogenic bacteriato gain the foot hold.[10-11]

Structure & Functions of the Eye

The eye consists of several parts which are as follows:

- TheSclera: The eye's white outer protectivecoat normally seen as the "white of theeye".
- The Cornea: The transparent curved structureat the front of the eye.
- The Iris: The coloured part of the eye: blue,brown, green, grey etc that can be seenthrough the cornea.
- The Pupil: The black part of eye in middle of the iris. It constricts or dilatesdepending on the amount of light passingthrough it.
- The lens: The transparent disc [with both sidesbeing convex] immediately behind the iris& pupil.
- The Aqueous humour: The fluid which is transparent[with consistency similar to water] thatcirculates behind the cornea & in frontof the lens.
- The Vitreous humour: The material [liketransparent jelly] that fills the eyeballbetween the lens & the retina.
- TheRetina: The light-sensitive layer of themillions of nerve cells that line the backof the eyeball. The cells consist of 2main groups that are called rods & cones due totheir appearance under the microscope.
- TheRods: More numerous these spread out overthe entire retina with more towards the outeredge respond to low levels of light.
- The Cones: Far fewer they are concentrated aroundthe 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 thedark coloured layer of the cells at the back ofthe retina responsible for providing theoxygen & 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 pigmentcells.
- The Optic disc: A small yellow oval structurein the retina to which the nerve cellconnections travel from all the rods &cones.
- The Optic nerve & beyond: The "cord" of thenerve cell connections that passes from a eyeball to the destinations throughout thebrain.[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 thetreatment& prevention ofthese 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 Conjuctivitis: 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 fromthe surface of the eye.Even if the lacrimal turnover rate is onlyabout 1 micro liter/minute. The other method of the nonproductive drug removal is its systemic absorption in thebody instead of the ocular absorption.

The Lacrimal Fluid Eye Barriers

The corneal epithelium act as the barrier & limit the drugabsorption from the lacrimal fluid into the eyes, thereforetypically the lipophilic drugs have a higher permeabilityin the cornea as that of the hydrophilic drugs.

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

The Blood Ocular Barriers

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

The Blood retina barrier: Posterior blood eye barrier

The Blood aqueous barrier: Anterior blood eye barrier.[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 asfollows

The foreign-body sensation presents the challenge toovercome the discomfort which leads to poor-patientcompliance, excessive lachrymation that accompanies theirritation, dilutes the drug & causes reduction in itsconcentration. The properly designed ocular inserts willminimize a sensation caused by its insertation &wear.

i] Sterility

ii]The Reproducibility of release kinetics [Zero-order drug delivery]

iii]The Non-interference with vision & oxygenpermeability.

iv]The ease ofinsertion& 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 3groups 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 withthe inner surface of a rate controller & supplying the drugthereto. A reservoir contains the liquid, gel, colloid,semisolid, solid matrix or the carrier-containing the drugheterogeneously orhomogeneouslydissolved ordispersed therein. The carriers can be made of the hydrophilic,hydrophobic,inorganic, organic, naturallyoccurring or the synthetic material.

The 3 rd class including the contact lenses. A insolubleof these devices is their main disadvantageas after use theyhave to be removed.

1] The Diffusion inserts

These diffusion systems are compared of the central reservoirof the drug enclosed in the specially designed semi permeable or themicro porous membranes which allowsa drug to diffuse the reservoir at the precisely determined rate.Therelease of drug from such a system is controlled by alachrymal fluid permeating through the membrane until thesufficient internal pressure is reached to drive a drugout of reservoir. Therate of drug delivery is controlledby the diffusion through the membrane, which one could becontrolled.

2] The Osmotic inserts

Theses osmotic inserts are generally compared of the centralpart surrounded by the peripheral part. The 1 st centralpart can be composed of the single reservoir or of the2distinct compartments. In the1 st case it is composed of the drug with or without theadditional osmotic solute dispersed through the polymericmatrix so that the drug is surrounded by a polymer as the discrete small deposits.[12, 20-23] In the 2 nd case, the drug& the osmotic solutes are placed in the 2 separate compartments the reservoir of drug being surrounded by theelastic impermeable membrane &a osmotic solutereservoir by the semi permeable membrane. The 2 ndperipheral part of this osmotic inserts comprises in all of thecases the covering film made of the insoluble semipermeable polymer.A tear fluid diffuse into the peripheral deposits through asemi permeable polymeric

membrane wets them &induces theirdissolution. The solubilized deposits generate thehydrostatic pressure against a polymer matrix causingits rupture under the form of the apertures. Thedrug is thenreleased through these apertures from the deposits neara surface of the device which is against the eye by asole hydrostatic pressure. These correspond to theosmotic part that is characterized by the zero order drug releaseprofile.

3] The Soft contact lenses

These are the shaped structures made up of the covalently crosslinkedhydrophobic or thehydrophilic polymer that forms the 3-dimensional network or the matrix capable of retaining theaqueous solution, solid or the watercomponents.When a hydrophilic contact lens is soaked in the drugsolution it absorbs the drug but does not give the deliveryas precise as that provided by the other non-solubleophthalmic systems. Therelease of drug from the systemis generally very rapid at a beginning & then declinesexponentially with the time. The release rate could bedecreased by incorporating a drug homogeneouslyduring its manufacture or by adding the hydrophobiccomponent. 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 theophthalmic inserts. They offer a great advantage ofbeing theentirely soluble so that they need not to beremoved from their site of the application thus limiting theinterventions toonly insertion.

Types:

1] Based on natural polymers e.g. collagen.

2] Based on synthetic or semi synthetic polymers.

By soakingthe insert in a solution containing the drug, drying and rehydratingin before use on the eye a therapeutic agents is preferably absorbed. The amount ofloaded drugwill depend upon the amount of the binding agentupon the concentration of solution of drug into whicha composite is soaked as well as the duration of soaking.[28-29]

The soluble ophthalmic inserts that containsemi synthetic/ synthetic polymers

They offer the additional advantages of being generally of thesimple design.

a) It is based on products that are well adopted for the ophthalmic use.

b) It is easily processed by the conventional methods: slowevaporating extrusion, injection or the molding compression.

Thedrug release from such a system is by thepenetration of the tears into a insert which induces the releaseof a drug by the diffusion & forms the gel layer around acore of a insert this external

gelification induces afurther release but still controlled by the diffusion. Therate ofrelease J, is derived from the Fick's law yields theexpression which is as follows:

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

When A - Surface are 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 aboveequation are constant so is the release rate of the device

Some other factors affecting release of drug from theseOcuserts include:

• The dissolution of the drug & the polymers.

• The swelling of the matrix.

• The relaxation of the polymeric chain.

• The penetration of the inclusion. [28-30]

The soluble inserts that are made of the cellulose derivatives can besterilized by the exposure to the gamma radiation without acellulose components being altered. The decreased releaserate is obtained by using the component of a matrix thepolymer normally used for the enteric coating or byintroducing the suitable amount of thehydrophobic polymer which iscapable of diminishing a tear fluid penetration & thusof decreasing a drug release without modifyingthe 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 impermeableto a drug. They are made up of the biodegradablepolymers. The Successful biodegradable materials for the ophthalmic use are thepoly [orthocarbonates] & poly [orthoesters]. Thedrug release from such asystem is a consequence of a contact of the devicewith a tear fluid inducing the superficial diversion of amatrix.The use of the solid ophthalmic devices will certainlyincrease owing to a development of the new polymers theemergence of new drugs that having short biological halflivesor the systemic side effects & the need to improve theefficacy of the ophthalmic treatment by ensuring the effectivedrug concentration in a eye over an extended period of thetime.[31-34]

THE MECHANISM OF OCULAR DRUG ABSORPTION

The drug administration by instillation must penetrate theeye & do so primarily through cornea followed bythe non corneal routes. The non corneal route involves theconjunctiva & sclera &the diffusion occurs mainly acrossthese areas & appears to be the particularly important forthe drugs that areabsorbedpoorly across the cornea.[35]

The Mechanism of Drug Release

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

 The Diffusion-The drug is releasedcontinuously at the controlled rate through themembrane into the tear fluid. Thedrug release cantake place via the diffusion through the pores. From a region of higher to lowerconcentration across the concentration gradient the drug diffuses. [36]

 The Osmosis-The inserts comprise thetransverse impermeable elastic membrane by dividingthe interior of the inserts into the 1st compartment &the 2nd compartment. The 1stcompartment isbounded by a semi permeable membrane & theimpermeable elastic membrane & the 2ndcompartment is bounded by a impermeablematerial & the elastic membrane. The drug releaseaperture in the impermeable wall of the insert

 The Bioerosion- The symmetry of thebody of the insert is constituted from the matrix of thebioerodible material in which the drug is dispersed. Thecontact of the insert with the tear fluid results in thecontrolled sustained release of the drug.[1, 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 & conjuctival 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.

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