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A Novel Approach to Ophthalmic Drug Delivery System: A Review

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ABSTRACT

The purpose of this review is giving a current update of the knowledge in this field of ocular drug delivery. Ideal property of ophthalmic drug delivery must be able to sustain the drug release and should remain in the vicinity of the front of the eye for a prolonged period. Nanotechnology is currently a promising drug delivery way to provide protection and improve the pathway through ocular barriers and deliver the drugs to specific and particular target sites without harming the other cells or tissues. Prolonged drug unleash may be achieved exploitation ophthalmic inserts, solid devices placed in the eye, but the inserts must then be removed when they are no longer needed. The systems typically embody controlled, delayed and or sustained unleash bioerodible implantable parts having multiple layers different [of various] materials and/or different concentrations of materials.

INTRODUCTION

The eye is an important route for drug delivery is generally used for local therapy against systemic therapy to avoid the risk of eye damage from high blood concentration of the drug, which is not intended. A significant challenge to the formulator is to form a formulation that can't harm the protective barriers of the eye without causing permanent tissue damage. Most ocular formulations like eye drops and suspensions are used for the topical administration of ophthalmically active drugs to the tissues around the ocular cavity. These dosage forms are easy to instill but having some drawback that the majority of the medication they contain is immediately diluted in the tear film and they rapidly drained away from the pre-corneal cavity by constant tear flow and lacrimal-nasal drainage. Therefore, the target tissue absorbs a very small fraction of the instilled dose and this is the major drawback of the ophthalmic drug delivery system. [1]

Ointments have the advantages of longer contact time and having greater storage stability, but they also have the disadvantage of producing a film over the eye, thereby causing blurring vision. The typical administration of an ocular drug delivery system has been pulse entry of the drug, followed by a rapid, first-order decline of drug concentration. Adequate therapy from eye drops may be achieved either by providing a sufficient magnitude of the pulse so that its effect is extended for a useful period, or by giving more frequent applications of a less-concentrated pulse. Some of the new ophthalmic drug delivery systems have been reported to have enhanced corneal absorption. While these systems prolong the desired effect with less frequent applications than eye drops require, side effects are also enhanced. Thus, these systems are limited to use with drugs with dose-related side effects that are not serious or that can be tolerated by the patient. [2]

Ophthalmic inserts supply several blessings over typical indefinite quantity form, like accumulated ocular residence, the chance of emotional medication at a slow rate and constant rate, correct dosing, and exclusion of preservatives increased shelf life and reduced systemic absorption.[3] The objective of this paper is to review the antibiotic formulations for an ophthalmic administration. First, the ocular anatomy and physiology and the ocular barriers were described. Finally, recent advances in ocular antibiotic administration are reviewed. [4]

Ideal characteristics of ophthalmic drug delivery system

- Good corneal penetration.
- Maximizing ocular drug absorption through prolonging contact time with membrane tissue.
- The simplicity of installation for the patient**.**
- Reduced frequency of administration.
- Patient compliance.
- Lower toxicity and side effects.
- Minimize precorneal drug loss.
- Should not cause blurred vision.
- Relatively nongreasy.
- Appropriate rheological properties and concentrations of the vicious system.[5]

Anatomy and physiology of the eye for ocular drug delivery

The human eye, elegant in its detail and design, represents a gateway to the process we call vision. The eyeball is spherical and about regarding one in 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 careful description of every eye half is given below. The human eye could be a testing organ for the topical organization of medicines. The premise of this can be found in the anatomical course of action of the surface tissues and the porousness of the cornea.[6] The eye is a spherical structure with a wall consisting of three layers; the outer sclera, the middle choroid layer, the Ciliary body and iris, and the inner nervous tissue layer retina. The sclera is a tough fibrous coating that protects the inner layers. It is white apart from the clear space at the front, the membrane which permits the lightweight to enter the attention. The choroid layer, situated inside the sclera, contains many blood vessels and is modified at the front of the eye as pigmented iris. The iris is the colored part of the eye (in shades of blue, green, brown, hazel, or grey). [7]

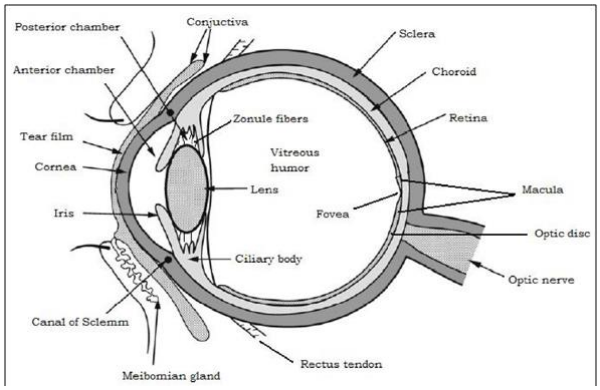

Figure no. 1: Structure of an Eye

A. Eyeball: The mass of the human eyeball (globe) is made out of three concentric layers.

1. The external stringy layer. The sinewy layer is comprised of two sections.

a. Posterior (5/sixth) is obscure and known as the sclera.

b. Anterior (1/sixth) is straightforward and called the cornea.

2. A Centre vascular layer – the uvea or uveal tract comprising of the choroid, the ciliary body, and the iris.

3. An apprehensive layer-the retina.

B. Sclera: Contains the microcirculation, which supports the tissues of this front section and is typically white.

C. Iris: The Iris nervous coat is called the retina, which contains photosensitive receptors. The eyeball homes associate device that includes in successions of the precorneal film, the cornea, the fluid diversion, the student, the crystalline focal point, the vitreous amusingness, and the retina. The watery and vitreous humor squares measure layers of clear liquid or gel-like material that intervened between the study structures. The crystalline focal point is a refractive component with variable power controlled and bolstered by a muscle fused in the ciliary body.

D. Conjunctiva: The conjunctival layer covers the external surface of the white segment of the eye and the inward parts of the eyelids. It is appended freely and consequently allows free development of the eyeball. Aside from the cornea, the conjunctiva is the most uncovered bit of the eye.[6]

E. Pupil: Pupil generally appears to be the dark "center" of the eye, but can be more accurately described as the circular aperture in the center of the iris through which light passes into the eye. The size of the pupil (and thus the number of sunshine that is admitted into the eye) is regulated by the innate reflex (also called as the "light reflex").

F. Lens: The lens is a transparent structure enclosed in a thin transparent capsule. It is situated behind the pupil of the attention and encircled by the ciliary muscles. It helps to refract light traveling through the eye (which first refracted by the cornea).[8]

G. Cornea: The cornea is a strong clear bulge located at the front of the eye. The Surface of the adult membrane incorporates a radius of roughly 8mm. It has a very important optical operation because it refracts lightweight coming into the attention that then passes through the pupil and onto the lens (which then focuses the sunshine onto the retina). The cornea, a non-vascular structure (does not contain any blood vessels) gets the mandatory nutrients from the capillaries that terminate in loops at its circumference. It is equipped with several nerves derived from the ciliary nerves. These enter the laminated tissue of the cornea. It is therefore extremely sensitive.[9]

BARRIERS FOR OCULAR DELIVERY

1. Drug loss from the ocular surface

After installation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is barely concerning 1 µl/min the surplus volume of the instilled fluid is flown to the duct speedily in a very few minutes. Another supply of non-productive drug removal is its general absorption rather than of ocular absorption. Systemic absorption might come about either directly from the mucosa sac via native blood capillaries or when the answer flow to the bodily cavity.

2. Lacrimal fluid-eye barriers

Corneal epithelium tissue limits drug absorption from the lacrimal fluid into the attention. The tissue layer animal tissue cell type tight junctions that limit the paracellular drug permeation. Therefore, lipotropic medicines have usually a minimum of associate degree order of magnitude higher porousness within the tissue layer than the hydrophilic medicines.

In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea.

3. Blood-ocular barriers

The eye is protected from the xenobiotics in the bloodstream by blood-ocular barriers. These barriers have 2 parts: the blood-aqueous barrier and the 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 sclera. It consists of the iris, ciliary body, and choroid). This barrier prevents the simple protein into the liquid body substance and also limits the access of hydrophilic drugs from plasma into the aqueous humor. The posterior barrier between the bloodstream and eye is comprised of retinal pigment epithelial tissue (RPE) and also the tight walls of retinal capillaries. Unlike retinal capillaries, the vasculature of the choroid coat has in-depth blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the retina is limited by the RPE and retinal endothelial.[10]

ROUTES OF OCULAR DRUG DELIVERY

There area unit many attainable routes of drug delivery into the ocular tissues. The selection of the route of administration depends totally on the target tissue.

a) Topical route: Topical administration, mostly in the form of eye drops, is employed to treat anterior segment diseases. For most of the locally applied medication, the site of action is usually different layers of the cornea, conjunctiva, sclera, and the other tissues of the anterior segment such as the iris and ciliary body (anterior uvea). Upon administration, precorneal factors and anatomical barriers negatively affect the bioavailability of topical formulations. Precorneal factors include solution drainage, blinking, tear film, tear turn over, and induced lacrimation.[11]

b) Systemic administration: Following systemic administration, the blood-aqueous barrier and blood-retinal barrier are the major barriers for the anterior segment and posterior segment ocular drug delivery, respectively. Blood–binary compound consists of two distinct cell layers placed within the anterior section of the attention viz. the endothelium of the iris/ciliary blood vessels and the nonpigmented ciliary epithelium. Both cell layers express tight junctional complexes and prevent the entry of solutes into the intraocular environment such as the aqueous humor.[12] Pharmacokinetic studies involving various drugs such as

micafungin, marbofloxacin, and amphotericin B demonstrated that these drugs are distributed in ocular tissues upon intravenous administration.[13]

c) Oral administration: oral delivery was studied as a possible noninvasive and patient preferred route to treat chronic retinal diseases as compared to the injectable route. However, restricted access to several of the targeted ocular tissues limits the utility of oral administration that necessitates high indefinite quantity to look at significant therapeutic efficacy. This can result in systemic side effects. Hence, parameters such as safety and toxicity need to be considered when trying to obtain a therapeutic response in the eye upon oral administration.[14] The oral route is not predominant, and only a limited number of compounds were investigated for ocular drug delivery. These include various classes of drugs such as analgesics, antibiotics, antivirals, antineoplastic agents, and omega-6 fatty acids.[15]

d) Periocular or intravitreal administration: systemic administration may lead to side effects making it a less desirable delivery route for geriatric patients. The periocular route includes subconjunctival, subtenon, retrobulbar, and peribulbar administration and is comparatively less invasive than intravitreal route. The drug administered by periocular injections can reach the posterior section by 3 completely different pathways: transscleral pathway; circulation through the choroid; and therefore the anterior pathway through the tear film, cornea, aqueous humor, and the vitreous humor.[16]

DRUG DELIVERY SYSTEM FOR EYE

Sustained ocular drug delivery through nanoparticles, microspheres, and liposomes has been attempted for the improvement of various ocular diseases.

1. Microspheres:

a. Ease of administration.

b. Biocompatibility and biodegradability.

c. Modulation of drug release rates and durations by carefully manipulating the type of microspheres used in the dispersion.

d. Minimal particle migration in vitreous.

e. Frequent re-administrations possible without the need for removal of previous implants.

Micro-particles smaller than 10 µm in diameter were fabricated by emulsification with poly (lactic-co-glycolic acid) as a core material and, in some cases, poly (ethylene glycol) as a mucoadhesion promoter. Mucoadhesive micro discs adhered better to the simulated ocular surface than did other types of microparticles. When a dry pill embedded with mucoadhesive micro-discs was administered within the cul-de-sac of the rabbit eye in vivo, these micro-discs exhibited longer retention than the opposite formulations tested in this study. More than 40% and 17% of mucoadhesive micro-discs remained on the preocular surface at 10 minutes and 30 minutes after administration, respectively.[17]

2. Nanoparticles: Nanoparticle delivery systems have potential applications for ocular drug delivery. Particulate carriers meet the basic needs of advanced ocular drug carriers, being non-toxic, non- immunogenic, biocompatible, uniform, and biodegradable at a predictable pace. Also, they can protect the delivered molecules while interacting with the ocular surface. Extensive research efforts are underway in the development of ophthalmic particulate delivery systems. The adhesive properties of these polymeric systems contributed to the enhancement of corneal penetration of the drug as a result of the increased residence time of the drug in the precorneal environment.[18]

3. Liposomes: Liposomes are microscopic lipid vesicles designed to entrap drugs. Liposomes composed of natural lipids are perishable, biologically inert, feeble immunogenic, manufacture no substance reactions and possess restricted intrinsic toxicity. Therefore, drugs encapsulated in liposomes are expected to be transported without rapid poly (lactide-co-glycolide) degradation and minimum side effects to the recipients. A method has been developed to target drugs locally in the eye via a light-based mechanism. The method, called laser-targeted delivery.[19-20] The polymer hydrogels used in our preparations ensured a steady and prolonged active ingredient release.[21] The designed liposomes had average particle sizes that ranged from 2.5 to 7.23 µm.[22]

4. Implants: For chronic ocular diseases like cytomegalovirus retinitis, implants are effective drug delivery system. Earlier nonperishable polymers were used however they required surgical procedures for insertion and removal. Presently biodegradable polymers such as Poly Lactic Acid are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs.[23]

CHALLENGES IN OPHTHALMIC DRUG DELIVERY SYSTEM

The specific challenge of planning a therapeutic system is to attain associate degree optimum concentration of a drug at the situation for the suitable length to produce an ocular delivery system with high therapeutic efficacy. The anatomy, physiology, and barrier perform of the tissue layer compromise the fast absorption of medicines. Frequent instillations of eye drop square measures necessary to take care of a therapeutic drug within the tear film or at the location of the action. But the frequent use of extremely focused solutions could induce venomous facet effects and cellular injury at the ocular surface. Poor bioavailability of medicines from ocular dose forms is especially because of the precorneal loss factors that embrace answer emptying, activity, tear dynamics, tear dilution. To be clinically effective, the topical formulation has to possess a balance between lipophilicity and hydrophilicity with higher contact time.[24]

- **Anterior segment delivery challenge**

For ailments of the attention, topical administration is typically most well-liked over general administration, as a result before reaching the anatomical barrier of the tissue layer, any drug molecule administered by the ocular route has to cross the precorneal barriers. These are the primary barriers that slow the penetration of a lively ingredient into the attention and incorporate the tear film and also the mucosa. Poor bioavailability of drugs from ocular dosage forms is mainly due to the precorneal loss factors which are demonstrated in Figure 1.[25]

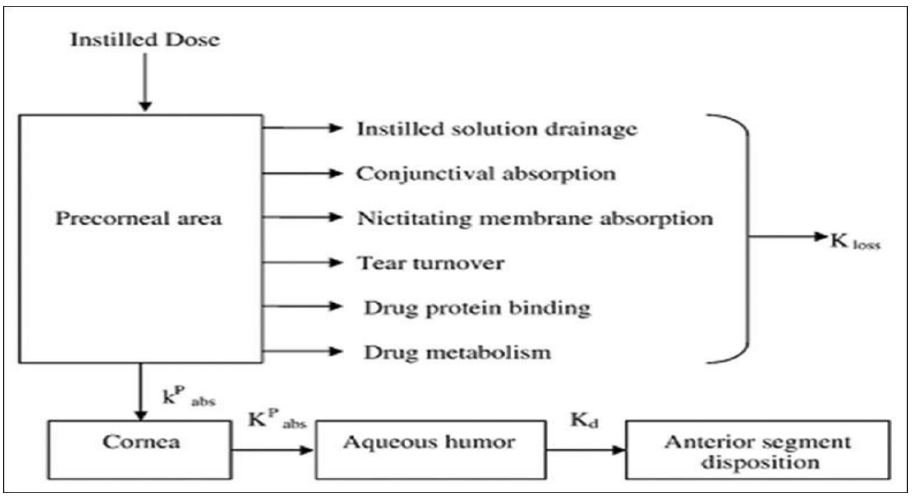

Figure No. 2: Anterior segment delivery

Posterior segment delivery challenge

Topical ocular medications do not reach the posterior phase drug targets due to the high potency of the blood-retinal barrier (BRB). The delivery of medicines to the posterior phase of ocular tissue is prevented by the constant factors that square measure accountable for the poor ocular bioavailability. Also, the BRB limits the effectiveness of the endovenous route in posterior drug delivery.[25] The tight junctions of BRB limit the entry of systemically administered medication into the tissue layer.[26]

High vitreal drug concentrations square measure needed within the treatment of posterior phase diseases. BRB that is by selection leaky to additional lipotropic molecules principally governs the entry of drug molecules into the posterior phase of the attention. This results in frequent administration of high amounts of drugs leading to systemic side effects.[27]

APPROACHES TO IMPROVE OCULAR BIOAVAILABILITY

A. Physical approaches

1. Conventional ophthalmic dosage forms: Solutions are widely used dosage forms for topical delivery of therapeutics to the eye. Factors to be considered in formulating ophthalmic solutions are solubility, ocular toxicity, PKA, the effect of ph, tonicity, buffer capacity, viscosity, compatibility with other ingredients in the formulation, preservatives to be used, comfort when instilled into the eye, and the ease of manufacturing.

a. Viscosity enhancers: Polymers are usually added to ophthalmic drug solutions which increases the viscosity on the premise and corresponds to a slower elimination from the periocular area, which leads to improved precorneal residence time and hence a greater transcorneal penetration of the drug into the anterior chamber. In terms of improvement in bioavailability, it has minimal effects on humans. The polymers used are methylcellulose, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose. Natural polymers such as HA, veegum, alginates, xanthan gum, gelatin, acacia, and tragacanth can also be used as viscosity enhancers. However, these suffer the drawback of harboring bacteria and fungi. [28]

b. Eye ointments: Ointments are usually formulated using mixtures of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to body temperature and are nonirritating to the eye. Ointments may be simple bases, where the ointment forms one continuous phase or compound bases where a two-phased system (e.g., an emulsion) is employed. As a solution or as a finely micronized powder the medicinal agent is added to the base either. Upon installation in the eye, ointments break up into small droplets and remain as a depot of the drug in the cul-de-sac for extended periods. Therefore, in improving drug bioavailability and in sustaining drug release ointments are useful. Although safe and well-tolerated by the attention, ointments suffer from comparatively poor patient compliance thanks to the blurring of vision and occasional irritation. [29]

c. Penetration enhancers: The transport characteristics across the cornea can be maximized by increasing the permeability of the corneal epithelial membrane.[30] By increasing the permeability of the corneal epithelial membrane the transport characteristics across the cornea can be maximized, so to improve ophthalmic drug bioavailability, one of the approach used which lies in increasing transiently the permeability characteristics of the cornea with suitable substances called penetration enhancers or absorption promoters. Like ocular irritation and toxicity are some disadvantages of it. The transport process from the cornea to the receptor site is a rate-limiting step, and permeation enhancers increase corneal uptake by modifying the integrity of the corneal epithelium. [31]

d. Prodrug: The principle of the prodrug is to enhance corneal drug permeability through modification of the hydrophilicity (or lipophilicity) of the drug. Within the cornea or after corneal penetration, the prodrug is either chemically or enzymatically metabolized to the active parent compound. Thus, the best prodrug should not solely have hyperbolic lipophilicity and a high partition constant, however, it should even have high catalyst status.[31] Catalyst systems known in ocular tissues include esterases, ketone reductase, and steroid 6-hydroxylase.[32,33]

For example; antiviral medications ganciclovir and acyclovir are suitable prodrugs. [34]

2. Novel ophthalmic dosage forms:

a. Microemulsions: Microemulsions area unit clear, clear transparent and thermodynamically stable systems of 2 unmixable fluids. Microemulsions are clear, transparent and thermodynamically stable systems of two immiscible fluids. This system is a

dispersion of oil in water stabilized by surfactant and sometimes a cosurfactant. Microemulsions permit the development of drug solubilization (hydrophilic and lipophilic) and dissolution potency of poorly soluble medicines. Its long shelf life, easy preparationtion, and improvement of bioavailability make it a potential ocular delivery system. [35] Microemulsions are novel ocular delivery systems that are mainly dispersions of water and oil along with a surfactant. Microemulsions confer advantages such as higher thermodynamic stability, improved solubility, and improved corneal permeation. [36]

Various drugs for ophthalmic use such as timolol, sirolimus, and chloramphenicol were formulated in various microemulsions with improved stability, solubility, and bioavailability. [37]

b. Nano suspensions: Nano suspensions are submicron colloidal systems made with inert polymeric resins and usually have a poorly water-soluble drug suspended in an appropriate dispersion medium. Advantages of Nano suspension include improved solubility of the drug, enhanced bioavailability, and reduced irritation to the eye. Results indicated that the Nano suspension has shown greater anti-inflammatory activity when compared with micro suspensions. [38]

c. Iontophoresis and sonophoresis: Iontophoresis involves the application of a low-density electrical current to enhance drug transport across various epithelia such as the skin, nail, and eye structures. In Iontophoresis coordinate current drives particles into cells or tissues. Emphatically charged of medication are crashed into the tissues at the anode and the other way around. Visual Iontophoresis conveyance is quick, effortless and protected as well as conveys high grouping of the medication to a particular site. [39]

Sonophoresis or ultrasound involves the application of ultrasound at frequencies higher than 20 kHz to enhance transdermal and ocular permeation. An ultrasound is usually applied over the epithelium through a coupling medium such as emulsion suspension of any formulation that allows the propagation of the acoustic field. In a recent report, sonophoresis was used to enhance intra scleral delivery of fluorescein isothiocyanate conjugated to serum albumin in an ex- vivo rabbit eye model. The frequency used was 1MHz with an intensity of 0.05 W/cm^2 and 30s exposure time. Results have shown that sonophoresis enhanced the transscleral permeation of the protein 1.6-fold without damaging ocular tissues. [37]

B. Chemical approaches:

The objective behind improved ocular drug delivery should not only consider enhanced ocular drug absorption but also reduced systemic absorption. Systemic absorption of drugs is not only nonproductive absorption but also leads to undesirable systemic side effects associated with the drugs. Therefore, it is important to optimize the drug delivery systems, which could offer improved biopharmaceutical properties and have the capability to concentrate on ocular tissues predictably. Chemical modification of drugs to improve therapeutic efficacy and to enhance various physicochemical properties such as solubility, stability, permeability, and evasion of efflux pump is an established approach in therapeutic drug delivery. The metabolic activity of ocular tissues provides an opportunity for the utilization of chemically modified drugs that have a predictable metabolic bioconversion in the eye. The most important strategies in chemical approaches for ocular delivery are

- Designing ocular drugs that are inactive at sites other than the eye (prodrugs).
- Designing drugs that undergo sequential metabolic conversion and finally reach the target (retro metabolic design), and
- Chemical modification of a known inactive metabolite or analog to restore the therapeutic activity that transforms back into the inactive metabolite in predictable one-step biotransformation [40].

SUMMARY

Various approaches have been studied to achieve therapeutically effective concentrations of drugs into the ocular tissues. Recent technological advancement has changed the field of ocular drug delivery from conventional drops to sustained release and targeted ocular delivery systems. In the recent era of technology, the combinatorial approach seems to be a focus of research in the development of safe and efficient ophthalmic drug delivery systems. Ocular drug delivery systems give natives also as general delivery of medicines. The novel advanced delivery systems offer more protective and effective means of the therapy for various diseases of eyes. Increasing the residence time of an ophthalmic formulation on the corneal surface increases the drug bioavailability and therefore reduces the frequency of administration. However, frequent administration is necessary. The efficient and safe delivery of therapeutic agents to the ocular tissues, mainly posterior segment tissues, is a

major challenge for the formulation of scientists due to the presence of various physiological barriers.

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