TOPOCAL DRUG DELIVERY FOR EFFECTIVE TREATMENT OF BACTERIAL INFECTIONS OF THE ANTERIOR SEGMENT OF THE EYE

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ABSTRACT

Anterior parts of the eye are susceptible to infections caused by different bacterial species. The use of suitable therapeutic measures in case of ocular infections can be sight saving. The appropriate therapy depends on selecting the right antibacterial as well as an efficient drug delivery system. Despite their accessibility, topical delivery of the selected antibiotic into the anterior ocular parts is still a challenging issue due to the complex nature of the eye. Ocular therapy would be significantly improved by modifying the physicochemical properties of the drug and by prolonging its pre-corneal residence time. This review will help pharmaceutical formulators to identify different parts of the eye and the corresponding bacterial infections, ocular barriers to drug delivery, and general consideration when formulating ocular drug delivery systems for the treatment of eye infections.

Keywords: Ocular drug delivery, Antibacterials, Ocular infections.

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INTRODUCTION

Bacterial infections of the eye are caused by different bacterial species and require effective treatment as early as possible to avoid any complication on vision. Moreover, proper antibacterial treatment is needed as pre-operative prophylaxis in ocular surgeries. Systemic administration of drugs for these purposes is not ideal because of the systemic adverse effects and low ocular bioavailability. Topical administration, mostly in the form of eye drops, is therefore preferred for ocular antibacterial drugs. Despite its accessibility, relative safety, and faster action, topical drug delivery to the eye stills problematic due to the unique physiology and anatomy of the eye as well as the need for frequent administration. Several techniques and delivery systems have been therefore developed to overcome such obstacle (e.g., nanocarriers, microemulsions, and collagen shields) and ocular drug delivery stills the topic of many researches. Regardless the fact that, only a limited number of these delivery systems are commercially available, and there is a great potential for some of them for commercial use in the future.

ANATOMY OF THE EYE

Eye is a unique and sophisticated structure with complex anatomy and physiology which makes ocular drug delivery a big challenge to formulation scientists. The simple and almost sole function of this organ is to deliver light signals to the brain [1]. The eye serves as the window to our surrounding environment. In general, the eye can be divided into two segments: Anterior and posterior. These segments achieve their function together [2]. The anterior segment consists of the cornea, iris, pupil, conjunctiva, ciliary body, anterior chamber, aqueous humor, trabecular meshwork, and lens. The posterior segment consists of vitreous humor, sclera, choroid, retina, macula, and optic nerve as shown in Fig. 1 [3].

Cornea

It is a transparent tissue with no blood vessels and called the window of the eye. The outer surface of the cornea is covered with a thin film of tear which helps to protect the eye from irritants and harmful substances. The cornea constitutes about two-thirds of the refractory power of the eye where the shape of the cornea provides strong refractive power that, along with the lens, allows focusing of the light and image on to the retina. It forms one-sixth of the anterior eyeball which is supplied with oxygen and nutrients through the aqueous humor, lacrimal fluid, and the blood vessels at the cornea/sclera junction. Regardless of its small surface area, the cornea constitutes the conventional site of drug entry into the eye, particularly for drugs administered as eye drops. It is consisted of five layers which, from outside to inside, are epithelium, Bowman's membrane, stroma, Descemet's membrane, and the endothelium. Such structure makes the cornea like a lipid-water-lipid sandwich. The tight cellular structure of the cornea together with the tear film constitutes a barrier for both lipophilic and hydrophilic compounds [1,4].

Conjunctiva

It is a highly vascularized mucus-secreting membrane, which lines the posterior layer of the eyelids, the anterior sclera, and the superior and inferior conjunctival fornices. It borders the white part of the eye and coats the rest of the anterior surface of the eye. The conjunctiva consists of two layers: The epithelium layer and an underlying stroma layer. Although its permeability is 2-30 times more than that of the cornea [5], the conjunctiva has a critical role in reducing drug penetration [6]. Ocular lubrication by the mucus produced from the goblet cells of the conjunctiva is an important role of this membrane [4,7] which can also modify the composition of the tear film by absorbing or secreting water, electrolytes, and mucin [6].

Iris

The iris is a pigmented circular muscular structure with a circular aperture at its center known as the pupil [4,8]. The pupil enlarges or constricts to control the light entry into the eye. It is this which makes the iris a target for drug delivery to control the pupil size by acting on the adrenergic or cholinergic receptors found there [1].

Ciliary body

The ciliary body is a ring-shaped thickened tissue that is anterior to the lens. It consists of non-pigmented ciliary epithelium, pigmented ciliary epithelium, ciliary muscle, and stroma. The inner layer of the ciliary body faces the vitreous body and is non-pigmented till up to the iris; it is pigmented then. The arterial blood supply to the ciliary body is mainly came from the long posterior and the anterior ciliary arteries [9]. The capillaries in this region are leaky and fenestrated [10,11]. The ciliary body secretes aqueous humor [4,12] and helps in lens accommodation...
by attaching it and changing its shape [1]. The ciliary body and lens loss their flexibility with aging leading to presbyopia: A diminished capability of focusing on near objects.

Drug diffusion into the aqueous humor can be achieved through the blood supply of the ciliary body. However, there are many metabolic enzymes in the ciliary body that can pose problems for certain drugs [1].

**Aqueous humor**

It is a clear water fluid continuously produced by filtrating the blood crossing through the capillaries of the ciliary body and continuously removed at a rate of about 5 ml/day. This fluid is excreted into the posterior chamber (behind the iris) and flows through the pupil into the anterior chamber (between the iris and the cornea). It consists fundamentally of water, glucose, amino acids, high levels of ascorbic acid, and low levels of proteins. It maintains normal intraocular pressure (IOP) through achieving a balance between secretion and discharge, preserves the integrity of the eyeball, provides dioptric power to the cornea, supplies nutrition to the cornea and lens, and transports waste substances away from surrounding tissues [1,7,12-14].

**Lens**

The lens is a transparent biconvex structure consisting of water and proteins with no blood supply and no connective tissue. It connects with iris anteriorly, fits into a cavity of the anterior vitreous surface posteriorly, and floats in the aqueous humor. The basic components of the lens are capsule, lens fiber cells, and epithelium. The lens capsule is a modified basement membrane entirely surrounding the lens. The inner part of the anterior capsule contacts directly with lens epithelium, while the posterior part is in contact with fiber cells of the most superficial layer. Membrane transport proteins in the lens perform an important function in nutrition supply, regulation of cell volume, and transparency of the lens [12,15,16].

**Sclera**

The sclera is a sponge-like white structure with an average surface area of 17 cm², which connects frontally to the cornea at the limbus and coats about five-sixths of the eyeball surface. It consists mainly of collagen (~28.8%), water (~68%), elastin (~1-2%), and proteins (~3%) [8]. It is divided into three layers: Episclera, stroma, and lamina fusca. The random arrangement of the collagen fibrils in the sclera results in its opacity. The sclera has dissimilar thickness varies from about 0.4 mm at the equator of the eye to about 1 mm near to the optic nerve [4,13,14].

**Vitreous humor**

About 80% of ocular volume is made of a transparent gel-like fluid called as vitreous humor [8]. It is a clear gel consisted mostly of water (99%), whose function is to maintain ocular size and shape while allowing the light to pass to the retina. Tiny amounts of collagen fibers and other large molecules are present in the vitreous humor. It is called also the vitreous body and occupies the central chamber of the eye (between the lens and the retina). In addition, the vitreous humor plays important roles in comprising, supporting the lens and retina, maintaining the neural part of the retina in place, acting like a reservoir for nutrients, and acting like a barrier between the anterior and posterior segments of the eye. More than 50% of the vitreous can liquefy with aging (80-90s) and detachment of the posterior vitreous [4,14].

The vitreous humor is one of the primary targets for ocular drug delivery, which provides access to both anterior and posterior parts of the eye as the retina [1].

**Retina**

The retina is a multi-layered circular tissue lining the back of the eye globe. It contains millions of cells packed together and consists of the retinal pigment epithelium and the neural retina. The neural retina is composed of rod- and cone-shaped photoreceptor cells, second-order cells, and ganglion cells. The retinal pigmented epithelium constitutes the external coat of the retina which along with endothelial cells of retinal vessels forms the blood retinal barrier (BRB). BRB limits transport of drugs into the eye, especially those with hydrophilic characters. The innermost membrane of the retina prevents the passage of molecules larger than about 100 kDa [13,14].

The function of the neural retina is light detection, which is similar to the photographic film of camera in taking pictures. The retina converts the image to an electrical signal and sends it to the brain which converts the signal again to a visual image [1].

**Choroid**

The choroid is a highly vascularized layer located in the inner part of the sclera and in the outer part of the retina (between the retina and the sclera). It supplies oxygen and nutrition to the outer layers of the retina and consists of the vessel layer, choriocapillaris, and the vessel layer Bruch's membrane. The choroid assists in light absorption, thermoregulation, and IOP regulation. The thickness of the choroid decreases from about 0.2 mm at birth to about 0.08 mm by age of 90s resulting in a decrease in the transport of nutrients and metabolites [3,4,14].

**BACTERIAL INFECTIONS OF THE EYE**

Eye infections are caused by a wide range of pathogens, including bacterial, viral, fungal, and parasitic organisms. Antimicrobials are commonly used in the treatment or prophylaxis of such conditions. Although topical installation of these drugs is mostly preferred, systemic administration might be necessary. Microbial infections of the eye can be classified according to the involved structure into conjunctivitis, keratitis, and endophthalmitis [15,16].

**Bacterial conjunctivitis**

Bacterial conjunctivitis is an inflammation of the conjunctiva caused by bacterial pathogens, most commonly *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. Conjunctivitis can also be caused by viral or fungal infections, allergen, or an irritant. Common manifestations of all forms of conjunctivitis include itching, redness, tearing, and foreign body sensation. Bacterial conjunctivitis is characterized by the presence of mucopurulent drainage and a papillary reaction causing a velvety appearance. Other causative pathogens for bacterial conjunctivitis are *Neisseria gonorrhoea*, *Corynebacterium diphtheriae*, *Mycobacterium tuberculosis*, *Francisella tularensis*, *Treponema pallidum*, *Bartonella henselae*, *Chlamydia trachomatis*, and *Pseudomonas aeruginosa*. Bacterial conjunctivitis may be self-limiting, but the possibility may proceed to keratitis; this condition should be treated properly with a suitable antibiotic [17].

**Bacterial keratitis**

Keratitis is an inflammation of the cornea caused by bacterial, viral, or fungal infection. Bacterial keratitis accounts for about 65% to 90%...
The corneal infections and most commonly caused by *P. aeruginosa*, *S. aureus*, *Streptococcus pyogenes*, and *S. pneumoniae*. Other causative agents include *Neisseria gonorrhoeae* and *M. catarrhalis* [17].

This infection is commonly linked to contact lenses and may be developed from untreated conjunctivitis. There is no manifestation to reliably differentiate bacterial keratitis from other forms of keratitis. Signs include red eye, ocular pain, light sensitivity, infiltrates or cloud/opaque cornea, corneal perforation, and loss of visual acuity. Bacterial keratitis is potentially sight-threatening and requires rapid diagnosis and use of a suitable antibiotic therapy for the infectious organism [13,18,19].

Corneal ulcer is an infection that gives rise to breakdown of the corneal stroma and corneal thinning. It is similar to keratitis but considered to be more serious and sight threatening due to the possibility of corneal scarring [18].

**Bacterial endophthalmitis**

Bacterial endophthalmitis is a serious condition involving an inflammation of the deep eye components (e.g. the aqueous humor) commonly caused by the entry of contaminating pathogen after intraocular surgery or penetrating trauma. It can also be caused by endogenous spread of microorganisms through the bloodstream. Causative bacterial species include *Escherichia coli*, *P. aeruginosa*, *S. aureus*, and *Streptococcus faecalis*. In general, to prevent and reduce endophthalmitis, topical antibiotic prophylaxis is administered immediately after and on the next day of surgery [18,20-22]. Signs of bacterial endophthalmitis include pain, blurred vision, corneal edema, conjunctival hyperemia, and hypopyon.

**BARRIERS TO TOPICAL OCULAR DRUG DELIVERY**

Topical drug delivery into the eye is the most accepted route to treat ocular infections due to formulation simplicity, minimum systemic drug exposure, and ease of administration. However, effective topical drug delivery into the eye is still a challenging issue due to its restrictive barriers known as ocular barriers. These barriers limit the distribution of the drugs in the ocular components and decrease their bioavailability to 1–5% [23]. These barriers are classified into anatomical and physiological barriers [24]. Anatomical barriers are further classified into static and dynamic. The static barriers are the corneal epithelium, stroma, and blood-aqueous barrier (BAB), whereas dynamic barriers comprise tear drainage and the conjunctival blood and lymph flow [24]. Physiological barriers are tear turnover, nasolacrimal drainage, and blinking.

Tear film is the first physiological barrier which greatly alters drug distribution into the ocular tissues. It covers the anterior surface of the eye with a thickness of about 3µm, a volume of only 6–8 µl, and a turnover rate of 0.5–2.2 µl/min. Drug administration in the form of eye drops results in a sudden increase in the tear volume, reflex eye blinking, lacrimal drainage, and ultimately high drug loss [25]. The complex composition of the tears further complicates drug delivery into the eye where tear film composed of three main layers: Aqueous, lipid, and mucous [3].

The cornea is the rate-limiting membrane for the absorption of drugs administered locally into the eye. The epithelial layer of the cornea constitutes to about 90% of the barrier to the hydrophilic drugs which pass the cornea mainly by petitioning between the epithelial cells (paracellularly). On the other hand, lipophilic compounds enter mainly through epithelial cell membranes (intracellularly). The tight structure of the epithelial corneal cells makes the paracellular route of penetration available only for drugs with low molecular weight (<350 Da) [25].

Drug penetration through the conjunctival/scleral (non-corneal) pathway is a less restrictive parallel route for drug absorption into the eye. Due to the larger pores and higher pores density, the conjunctival permeability to hydrophilic drugs is 15–25 fold that of the cornea [25]. Drugs permeation through the sclera is nearly half that of the conjunctiva [3].

The endothelial cells lining the blood vessels of the iris and the non-pigmented layer of the ciliary epithelium constitutes the BAB which inhibits the movement of macromolecules and solutes. However, hydrophobic drugs having small sizes can penetrate this barrier [26].

**GENERAL CONSIDERATIONS FOR DESIGNING OCULAR DRUG DELIVERY FORMULATIONS FOR EFFECTIVE TREATMENT OF EYE INFECTIONS**

For the treatment of ocular infections, the selected drug should retain its concentration at the site of infection above the minimum inhibitory concentration for a sufficient period of time to kill the causative bacteria. Hence, the amount of the concentration per dosage unit, the effect of tear dilution, the clearance, and corneal permeability, are all important factors to determine the efficacy of the formulated antibacterial.

The development of effective ophthalmic drug delivery systems is simple and hard to achieve at the same time. It is simple because the eye easily targeted where the drugs are administered directly to the eye for rapid action to treat ocular diseases. However, the specific properties of the eye that make the development of ocular drug delivery systems are very hard. Bacterial infection of the anterior segment of the eye is mostly treated by topical application of eye drops of a suitable antibiotic agent [27]. Eye drops provide the advantages of ease of formulation and patient’s acceptance. Factors to be considered when formulating ocular preparations include drug antibacterial activity, solubility, molecular weight, pKa as well as formulation pH, viscosity, buffering capacity, concentration, tonicity, sterility, clarity, comfort on application, and ease of manufacturing [28]. Formulation development for ocular drug delivery could be divided into two major pathways. One is the enhancement of drug penetration through the cornea. The other is the increase of drug contact time with ocular surface.

As mentioned previously, a drug with optimal oil to water partition will show maximum corneal penetration. This is attributed to the structural complexity of corneal layers. Inclusion of penetration enhancers (e.g., benzalkonium chloride, ethylenediaminetetraacetic acid, Tween 20, Brij® 35, and dodecylmaltoside [29,30]), Cycloedextrins [31], and dendraimers [32,33] in ocular formulations has been reported to increase corneal penetration of the tested antibacterial agents [34].

Ocular therapy would be significantly improved if the pre-corneal residence time of drugs could be increased [35-37]. Addition of viscosity enhancing agent or muco-adhesive polymers to the formulation increases the contact time of the drug with the ocular surface, thereby improving its bioavailability in the anterior ocular compartments. Commonly used viscosity enhancing agents are polyvinylpyrrolidone and hydroxypropyl methylcellulose (HPMC) [38].

Numerous ocular delivery systems were developed to increase the bioavailability of ocular antibacterial drugs by prolonging their contact time with ocular surface [27,59] such as minitablets [40], ointments [41-43], occlusets [44], microparticles [45], nanocarriers [46,47], collagen shields [48], in situ gel [49,50], microemulsions [51,52], contact lenses [53], and films [54-56]. Each system has its own advantages and limitations.

Ophthalmic ointments resist the effect of tear dilution and nasolacrimal drainage and hence increase the contact time of the contained drugs with eye tissues [28], but they are associated with blurred vision and patient’s discomfort [27].

Similar to other solid dosage forms, ocular minitablets, films, and occlusets provide many advantages such as ease of manufacturing, cost-effectiveness, accurate dosing, ease of application, reliable drug release and low risk of flushing out, and lower incidences of visual
The ability of microparticles and nanocarriers to prolong drug release depends on the presence of sustained release polymers as Eudragit RS, HPMC, and ethylcellulose in the formulation. Polymers with mucoadhesive properties will further increase the residence time of the formulation in the ocular cavity. Nanocarriers studied for their potential for oculur drug delivery include polymeric nanoparticles, solid lipid nanoparticles, liposomes, niosomes, dendrimers, nanosuspensions, and emulsions [28]. Such systems have been reported to increase drug concentration in different ocular compartments, reducing drug dose and administration frequency [57-59].

Collagen shields are curved discs made of porcine or bovine collagen, which were originally developed as protective corneal bandages supports to wound healing. They are provided in dehydrated form and intended to be rehydrated for 5–10 min before use. In spite of their discomfort and vision interference, collagen shields have been attractive for drug delivery purposes. Drugs could be loaded on these devices either during their manufacturing or when soaked before their application. When coming in contact with ocular surface, these shields start to dissolve at different rates depending on the degree of collagen crosslinking while releasing their drug content in an extended release manner for up to 72 h [8,27].

Contact lenses are curved shaped discs, which are prepared from silicon-containing hydrogels or polyvinyl alcohol hydrogels to be inserted into the eye and come in contact with the cornea [3,60]. These devices have been mainly used for vision correction and cosmetic purposes. Although the use of contact lenses for oculur drug delivery was early reported in the literature [3,61], such drug delivery systems have not reached the market yet [62]. This might be attributed to the low drug loading capacity and burst drug release from the modified lenses [63]. The interest in contact lenses as drug delivery systems was recently renewed by the development of new technologies for drug loading onto the devices other than soaking such as molecular imprinting and the use of nanotechnology [8]. Drug bioavailability was reported to increase from less than 5% to up to 50% using contact lenses [3].

Ocular in situ gels are liquid systems, which changed to gels when exposed to the physiological conditions of the ocular environment, and thus increase the drug residence time in the ocular surface. These conditions are temperature, pH, and ionic strength. Ideally, minimum changes in these conditions would result in the solution to gel transition of the formulation due to the presence of stimuli-responsive polymers. Recently, formulations containing combinations of different stimuli-responsive polymers have been developed and found to be interesting. In addition, in situ gel has been used as a platform for other drug delivery systems as liposomes, niosomes, nanoparticles,... etc. Such strategies have resulted in exponential increase in the bioavailability of the ophthalmic drugs [49,64-66].

CONCLUSION

Effective treatment of bacterial infections of the eye can be sight saving. Topical oculur drug delivery systems of antibacterial agents have gotten considerable attention in the pharmaceutical research in the past decades, but only small number of such systems is commercially available. The main advantages of these systems are to attain sufficient antibacterial concentration in the ocular tissues and to overcome the need of frequent drug administration.

AUTHORS CONTRIBUTIONS

The three authors contributed equally to this work.

CONFLICTS OF INTERESTS

The authors report no conflict of interests and are responsible for the content and writing of this article.

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