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A comprehensive review of ophthalmic drug delivery systems for effective antibiotic therapy

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***Abstract*---Background:** Ophthalmic drug delivery presents a unique challenge due to the complexity of ocular anatomy and the barriers to drug absorption. Current ocular formulations struggle with issues such as low bioavailability and rapid drug elimination, necessitating advancements in drug delivery systems to enhance therapeutic efficacy. **Aim:** This review aims to evaluate various ophthalmic drug delivery systems specifically for antibiotic therapies, addressing their efficacy in overcoming ocular barriers and improving drug retention. **Methods:** A comprehensive literature review was conducted, focusing on different ophthalmic drug delivery systems including topical formulations (eye drops, ointments, hydrogels, and contact lenses), novel systems (in situ gels, nanoparticles, and emulsions), and advanced techniques like intraocular injections. Key developments and challenges associated with each method were analyzed to assess their impact on drug bioavailability and therapeutic outcomes. **Results:** Traditional ophthalmic delivery methods, such as eye drops and ointments, are limited by factors such as rapid drug clearance and poor bioavailability. Innovations such as in situ gelling systems, nanoparticles, and emulsions have shown promise in extending drug residence time and enhancing bioavailability. Specifically, nanoparticles offer targeted delivery and prolonged action, while hydrogels and emulsions improve drug solubility and stability. However, each system has its limitations and potential side effects, which must be considered. **Conclusion:** Advances in ophthalmic drug delivery systems are crucial for addressing the limitations of traditional methods. Innovative formulations such as in situ gels and

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nanoparticles have demonstrated improvements in drug retention and efficacy, though challenges remain in terms of patient comfort and systemic safety. Future research should focus on optimizing these systems and exploring new technologies to further enhance the effectiveness of ophthalmic antibiotic therapies.

***Keywords*---**Ophthalmic drug delivery, antibiotic therapy, bioavailability, in situ gels, nanoparticles, eye drops, emulsions.

Introduction

Ophthalmic drug delivery represents a significant challenge within pharmaceutical and medicinal sciences. Over the past several decades, advancements have been made to enhance existing dosage forms. The treatment of ocular diseases is inherently complex, requiring ocular formulations to be safe, non-allergenic, and sterile. Topical formulations account for 90% of the marketed ophthalmic drugs [1]. However, factors such as tear fluid turnover, nasolacrimal drainage, the corneal epithelium, and blood-ocular barriers reduce the local bioavailability of drugs and limit their residence time on the ocular surface during topical application. Only 5%–10% of the drug penetrates the corneal barriers. Anterior segment diseases, including blepharitis, conjunctivitis, scleritis, keratitis, and dry eye syndrome, are typically managed through topical or periocular administration. Yet, delivering drugs to the posterior segment of the eye for conditions such as glaucoma, endophthalmitis, or uveitis, as well as to the anterior segment, faces similar issues of limited drug bioavailability and barrier challenges. Despite these issues, intraocular administration may be favored, albeit with the risk of complications [2]. Moreover, compared to oral administration, ocular drug delivery has demonstrated equivalent or superior bioavailability within the eye [3]. Several strategies have been developed to improve drug bioavailability, control drug release, and enhance therapeutic efficacy [4].

Antibiotics are a prominent class of medications used in ophthalmic drug delivery due to their effectiveness against various ocular diseases, such as microbial keratitis, conjunctivitis, Meibomian gland dysfunction, and dry eye. Infectious diseases pose a significant public health challenge [5]. Antibacterial therapies can be administered in the eye through topical, subtenon, intraocular, or subconjunctival routes. Commonly used antibiotics for eye infections include tetracyclines, fluoroquinolones, aminoglycosides, and penicillins [6]. However, antimicrobial resistance, the ability of bacteria to withstand the effects of antibiotic treatment, has become a major concern. This reduction in efficacy is largely due to the misuse and overuse of antibiotics, as well as the adaptive responses of bacteria. Ophthalmic antibiotic delivery aims to minimize the frequency of administration and dosing by improving current formulations and developing new ones.

Innovative ocular drug delivery systems are varied, encompassing in situ gelling systems, liposomes, nanoparticles, niosomes, nanoemulsions, and microemulsions. These systems are compatible with both hydrophilic and

lipophilic drugs, can target specific sites, and allow for administration via different routes. In situ gelling systems, when formulated with appropriate excipients, can increase precorneal residence time and reduce drug loss due to tear fluid. Nanoparticles, with their diverse polymers, preparation methods, and compositions, offer solutions for mucoadhesion and enable topical, periocular, or intraocular administration, resulting in stable, effective, and non-irritating formulations for patients.

The objective of this paper is to provide a comprehensive review of antibiotic formulations for ophthalmic administration. Initially, the anatomy and physiology of the eye, along with ocular barriers, are described. The second section focuses on topical formulations, such as eye drops, ointments, hydrogels, contact lenses, and ophthalmic inserts, to introduce ocular administration and discuss currently marketed dosage forms. Finally, recent advancements in ocular antibiotic administration are reviewed. In vitro and in vivo studies have investigated the efficacy of antimicrobial formulations, and various compositions and forms have been developed to improve antibiotic bioavailability, extend ocular residence time, and enhance therapeutic outcomes.

Anatomy and Physiology of the Eye

The eye is a spherical organ housed within the orbital cavity and protected by the eyelids. It has a diameter of 24 mm, a volume of 6.5 cm^3, and weighs approximately 7.5 g. The eyeball is composed of several layers with distinct structures, which are divided into two segments: the anterior segment (including the cornea, conjunctiva, aqueous humor, iris, ciliary body, and lens) and the posterior segment (comprising the retina, choroid, sclera, and vitreous humor) [3,7].

Three Different Layers

The eye is enveloped by three distinct layers: the outer layer, the middle layer, and the inner layer.

- **Outer Layer**: This layer consists of the cornea and the sclera, both of which are fibrous tissues serving a protective function for the eyeball. The sclera, continuous with the cornea, is an avascular, white, strong, and elastic tissue covering 80% of the eye's tunic. The cornea, a thin (0.5 mm) [8], avascular, and transparent layer, allows light to penetrate the eye. The anterior and posterior segments are anatomically separated by the sclera and the cornea.
- **Middle Layer**: Known as the uvea, this vascular envelope comprises the iris, choroid, and ciliary body. The iris is a contractile, circular membrane with an opening at its center, the pupil. Located posterior to the cornea, it is the colored part of the eye. The choroid, a highly vascularized membrane located at the back of the uvea, supplies nutrients and oxygen to the iris and retinal photoreceptors. The ciliary body, situated between the sclera and the retina, secretes aqueous humor through the ciliary processes and contains smooth muscles that control the lens's shape.
- **Inner Layer**: The innermost tissue is the retina, responsible for vision and composed of two types of tissue. The retina and the choroid cover the

inside of the posterior segment from the optic nerve to the ora serrata. The neural tissue consists of photoreceptors (rods for night and peripheral vision and cones for color and detailed vision), bipolar cells, and ganglion cells.

Inside the Globe

The interior of the eye consists of three major components: the crystalline lens, aqueous humor, and vitreous humor.

- **Crystalline Lens**: This biconvex, transparent lens is located behind the iris and the pupil. It is an avascular, elastic organ connected to the optical layer by the ciliary body and separates the aqueous humor from the vitreous humor. Its function is to enable accommodation by focusing light onto the retina through its contraction.
- **Aqueous Humor**: This clear optical fluid with low viscosity is located in the anterior and posterior chambers of the eye and is continuously produced by the ciliary body (2.4 ± 0.6 µL/min in humans) [9]. The anterior chamber and the posterior chamber contain 0.250 mL and 0.060 mL of aqueous humor, respectively. Comprising 99% water, the aqueous humor supplies nutrients to the iris, crystalline lens, and cornea [10], maintains intraocular pressure, and helps maintain the convex shape of the lens.
- **Vitreous Humor**: Also known as the vitreous body, this transparent, gelatinous substance is situated between the crystalline lens and the retina, representing 90% of the eye's volume (4.0 mL). It consists of 99% water and helps maintain the structure of the eyeball and acts as a lens to deliver light rays.

Ocular Annexes

Ocular annexes are external anatomical structures necessary for the proper functioning of the ocular apparatus, including the muscles, eyelids, and lacrimal apparatus.

- **Extraocular Muscles**: These six muscles facilitate eye movement within the orbit and control the superior eyelid movement.
- **Eyelids**: These movable skin folds provide the first line of protection for the eye, hydrating the cornea and cleaning the eye's surface from debris. The superior eyelid regulates light entry using extraocular muscles.
- **Meibomian Glands**: Located inside the eyelid, these small, oily, and sebaceous glands secrete lipids and proteins that cover and protect the eye's surface, reducing tear evaporation.
- **Lacrimal Apparatus**: Responsible for tear secretion, this apparatus clears debris from the ocular surface and hydrates the eye. The lacrimal glands continuously produce lacrimal fluid (0.1 mL/hour), which is evacuated through the lacrimal canaliculus and ultimately cleared by the nasolacrimal duct. Human tears have an average osmolarity of 310 mOsm/kg and a tonicity equivalent to a 0.9% sodium chloride solution [8].

Blood-Ocular Barriers

The blood-ocular barriers consist of the blood-aqueous and blood-retinal barriers. These physical barriers between the blood and the eye play a crucial role in drug penetration, elimination via the ophthalmic route, and maintaining homeostatic control [11].

- **Blood-Retinal Barrier**: Located in the posterior segment, this barrier forms an inner barrier within the retinal vessel endothelium and an outer barrier in the retinal pigment epithelium [11,12]. It prevents drug diffusion into the posterior eye and maintains neuroretina homeostasis through non-leaky tight junctions, which tightly control solute and fluid permeability. The retinal pigment epithelium regulates nutrient exchange with choroidal vessels. Retinal capillary endothelial cells and retinal pigment epithelial cells are interconnected by tight junctions.
- **Blood-Aqueous Barrier**: This anterior segment barrier is a nano-porous (104 Å) and isotonic membrane composed of the ciliary epithelium and iris capillaries. It produces aqueous humor and restricts large plasma albumin molecules and other molecules, such as antibiotics, from entering the aqueous humor. The non-pigmented ciliary epithelium secretes the aqueous humor [13]. The blood-aqueous barrier's permeability is controlled by osmotic pressure resulting from sodium, chlorine, and bicarbonate transport, as well as the physicochemical properties of drugs. Lipophilic molecules pass through passively, while hydrophilic molecules require active transport. The barrier comprises an epithelial barrier, formed by tight junctions between non-pigmented ciliary epithelial cells, and an endothelial barrier, formed by proteins similar to the epithelial tight junctions in iris vessels.

These barriers restrict drug entry from systemic circulation to the posterior eye segment and vice versa. Acute inflammation caused by intraocular surgery, induced ocular hypotony, or inflammatory mediators can disrupt the blood-ocular barrier. Restoration is achieved through the self-limiting action of the inductive drug or the administration of anti-inflammatory or anti-hypotensive medications. The ocular surface is directly exposed to the environment and to pathogens or allergens. It is an epithelial barrier composed of corneal epithelium connected with intercellular junctions, including tight junctions, desmosomes, adherent junctions, and gap junctions. The tear film is the first line of defense for the ocular barrier, washing away debris and protecting against desiccation. Ocular inflammation, intraocular surgery, trauma, and vascular diseases can compromise the ocular barrier.

Ophthalmic Forms

The choice of the drug administration route in ophthalmic treatment is contingent upon the target tissue within the eye. Various administration routes are utilized depending on whether the target is the anterior or posterior segment of the eye. Topical ocular and subconjunctival administration are primarily employed for targeting the anterior segment, while intravitreal and systemic administration are used for the posterior segment. Two types of drug permeation after topical administration are recognized: transcorneal and transconjunctival/transscleral

permeation. Transcorneal permeation allows drugs to move from the lachrymal fluid to the anterior chamber, with lipophilic drugs showing higher permeability due to the corneal epithelium's lipidic composition [14]. On the other hand, the transconjunctival pathway is more suited to hydrophilic drugs and larger molecules, directing them from the external ocular surface to the anterior uvea-ciliary body and iris. Topical administration is common for treating anterior chamber pathologies such as inflammation, allergy, keratoconjunctivitis, infection, or corneal ulceration. Topical forms must meet criteria of efficacy, sterility, stability, and ocular tolerance.

Eye Drops

Eye drops are sterile, often isotonic solutions containing drugs, or simply lubricating or tear-replacing solutions. They account for 90% of marketed ophthalmic formulations due to their simplicity, cost-effectiveness, and good patient acceptance [2]. However, they suffer from a significant drawback: up to 95% of the drug is eliminated within 15 to 30 seconds post-instillation, mainly due to the lachrymal apparatus and various barriers [14]. Despite this, eye drops remain the most commonly used ophthalmic dosage form. Their ocular bioavailability can be enhanced by using excipients like permeation enhancers, viscosity agents, and cyclodextrins [15]. Permeation enhancers, such as polyoxyethylene glycol ester and ethylenediaminetetraacetic acid sodium salt, modify corneal integrity, reducing barrier resistance [3]. Viscosity enhancers like polyvinyl alcohol (PVA) and hydroxylmethylcellulose improve the residence time of the solution on the eye surface, thereby increasing local bioavailability [15]. Cyclodextrins, with their hydrophobic internal cavity and hydrophilic external surface, stabilize drugs in aqueous solutions, reduce local irritation, and enhance drug permeation through the ophthalmic barrier [19].

Ointments

Ophthalmic ointments are sterile, semi-solid, homogeneous preparations meant for application to the eye's conjunctiva or eyelid. They primarily use non-aqueous excipients and must be non-irritating. There are four types of ointment bases: oleaginous, absorption, water-removable, and water-soluble [22]. Unlike eye drops, ointments offer the advantage of slowing down drug elimination by the tear flow, thereby increasing corneal residence time. However, they are associated with blurred vision, so their use is often recommended in the evening. The content is limited to 5 g per package, which can be either single or multidose.

Hydrogels

Hydrogels are used in ocular administration to increase drug residence time on the eye. These are three-dimensional, water-swollen structures composed of a viscosity agent dispersed in water or hydrophilic liquid. They are better tolerated by patients than ointments, reducing the side effects of systemic absorption. Hydrogels come in two types: preformed gels and in situ gels. Preformed gels are simple viscous solutions applied to the eye. They are often used as bioadhesive hydrogels to improve residence time and reduce dosing frequency [2]. Various mucoadhesive polymers are utilized in these gels, such as methylcellulose,

hydroxylethylcellulose, sodium hyaluronate, and sodium alginate [24,25]. Sodium hyaluronate, for example, is commonly used due to its viscoelastic properties and water retention capacity, making it suitable for treating dry eye disease [26,27,28].

In situ hydrogels are instilled as drops into the eye, transitioning from a solution to a gel upon contact with the eye, triggered by changes in pH, temperature, or ionic strength. This formulation enhances ocular bioavailability by prolonging contact with the corneal layer and reducing administration frequency [29]. Thermosensitive gels, pH-dependent systems, and ion-triggered systems are some types of in situ hydrogels, each with specific mechanisms for gelation and drug release.

- **Thermosensitive gels** transition from solution to gel with temperature changes, with polymers like poloxamer being commonly used [38, 34, 39, 40, 41, 42]. However, the high concentration of polymers in these gels can be a disadvantage.

Emulsions

A system of two immiscible fluids that is clear, transparent, and thermodynamically stable is called an emulsion. In this system, an oil dispersion in water is stabilized, sometimes with the help of a co-surfactant, by a surfactant. The enhanced drug solubilization (lipophilic and hydrophilic) and dissolution efficiency of weakly water-soluble medicines is the reason for the interest in this emulsion. Nevertheless, this form has certain drawbacks, like clouded eyesight upon product injection, which may reduce patient compliance. Furthermore, the uniformity of the drug content is correlated with the form's homogeneity, and the emulsion needs to be stable in order to administer the recommended dosage.

It is a viable ocular drug delivery strategy due to its extended shelf life, ease of production (spontaneous synthesis), and increased bioavailability [52, 53]. Because the droplets in micro- and nanoemulsions are so minute, they are preferred for ocular delivery. An aqueous phase, a lipophilic phase, and a surfactant phase make up their structure. In some situations, a co-surfactant could be necessary. The spontaneous creation of this scattered system has the benefit of requiring less energy [54]. This carrier can be sterilized and degrades naturally. A lipid anionic (zeta potential < −40 mV) emulsion with 0.05% cyclosporine, called RestasisTM (Allergan, Irvine, CA, USA), was licensed by the FDA in 2002 [55].

The eye's mucosal surface has a negative charge. Positively charged formulations with a nanoscale structure are called cationic nanoemulsions. Because of the electrostatic attraction between the formulation and the surface of the eye, they are helpful in extending the formulation's residence period in the eye. A cationic (+10 mV) lipid nanoemulsion called Novasorb® (Novagali Pharma, Evry, France) contains cetalkonium chloride or benzalkonium chloride as a cationic agent [56]. The most hazardous surfactants are recognized to be cationic agents [57]. Because these surfactants can dissolve lipid membranes, they are regarded as irritants for the skin and eyes. Selecting a suitable cationic agent with a high positive charge, low toxicity, and good ocular acceptability is necessary for the

formulation of cationic nanoemulsions. Palmatine-containing cationic nanoemulsions were made by means of the emulsifying/high-pressure homogenization technique. A zeta potential of +45 mV and a particle size of 190 nm were obtained by the researchers. They showed an increase in the duration of ocular residence and came to the conclusion that the corneal epithelial cells were the primary site of cellular uptake and internalization [58].

The Ocular Insert

Flexible polymeric materials called ocular inserts are inserted into the space between the eyeball's sclera and the lid, known as the cul-de-sac of the conjunctiva. They were found to be sterile, non-allergenic, insoluble in tear fluid, and biologically inactive in 1971 [59]. This form was created to extend the duration of the medication's contact with the eye's tissues, improving ocular bioavailability and enduring pharmacological effect. Additionally, they enhance patient compliance and lessen systemic absorption. Preservatives do not apply to ocular inserts [60], and they must be taken out when no longer required. They do have several disadvantages, though, like the solid form causing discomfort to the patient, placement challenges, and accidental loss. Additionally, patients could be reluctant to utilize an unknown form of ophthalmic treatment due to its high cost. Three categories of ocular inserts are identified: bioerodible, soluble, and insoluble. Soluble inserts break down in the eye and are composed of natural polymers like collagen as well as synthetic or semi-synthetic polymers like PVA and HPMC. One example of a commercially available soluble ophthalmic medication insert is Lacrisert® (Idis Limited, Weybridge, UK). The purpose of this medicine is to treat dry eyes. The polymer degrades gradually after absorbing tear fluid from the conjunctiva and tears after being placed in the periocular region.

Bioerodible inserts don't need to be taken out after use because they are composed of biodegradable polymers (polyorthoester, polyorthocarbonate). The medicine is released from the hydrophilic matrix gradually when the polymer erodes or disintegrates. Lately, dibutyl phthalate was used as a plasticizer in the development of diclofenac sodium inserts, which used HPMC for the rate-controlling membrane and drug reservoir [61]. Formulations containing 3% HPMC in the rate-controlling membrane and 3% HPMC in the drug reservoir lengthened the residence period and decreased the frequency of administration. Additionally, HPMC was combined with PVA and cyclodextrins to create an ocular lidocaine insert for topical ocular anesthetic [62]. The findings showed that lidocaine with β-cyclodextrin (βCD), 4% HPMC, and 2% PVA had suitable flexibility and acceptable properties. Additionally, the drug content in the aqueous humor increased with the addition of β-cyclodextrins.

There are three types of insoluble inserts, commonly known as Ocusert: hydrophilic contact lenses, diffusion systems, and osmotic systems [60]. After use, this form must be taken out of the eye. In a reservoir, the medication can be dissolved or distributed. This reservoir may consist of nanocarriers (nanoparticles), liquid, semi-solid, or solid. Osmotic inserts are made up of two sections: a peripheral part that surrounds the inner part, which has one or two compartments. The solubilization of the components leads to drug release. The medication is released when they create hydrostatic pressure against the polymer

matrix [63]. A core reservoir (glycerin, ethylene glycol, or propylene glycol) and a semi-permeable or microporous membrane (polycarbonate, polyvinyl chloride) make up dispersible systems. Drug release is regulated by tear fluid, and the system's membrane regulates how quickly drugs are released [64].

Contact Lenses

Contact lenses are circularly shaped systems. They are thin, curved, round pieces of transparent plastic placed directly on the surface of the eye. They are used to increase the residence time of the drug in the eye [65] and allow treatment of anterior eye disorders. The incorporation of the drug is achieved with methods like imprinting, simple soaking, and colloidal nanoparticles [66]. Important settings in lens development are the preservation of oxygen permeability and the transparency of the form. They have many advantages, such as being exempt from preservatives and the control of size and shape. Although contact lenses are a promising ophthalmic drug delivery system, they are an expensive form that requires handling and cleaning. Some limitations of this form include the oxygen permeability of the lenses and its potential issues, the possibility of premature drug release, or the limitations of some methodologies to develop therapeutic contact lenses.

The first contact lenses were made of glass, but the use of polymethylmethacrylate allowed the development of rigid lenses, improving patient comfort without letting oxygen pass. In the last three decades, contact lenses have been mostly made with silicone hydrogel [67]. They are traditionally used to improve vision defects, for cosmetic effects (changing the appearance of the eye, such as color), or more recently for therapeutic reasons. There are two types of therapeutic contact lenses: scleral rigid gas permeable (RGP) lenses and soft lenses. Scleral lenses are large, thin lenses with a diameter ranging from 18 mm to 24 mm. They are used in several indications [68], such as various ocular conditions [69], correction of refractive disorders [70], relief of corneal irregularity [71,72,73], protection of the cornea for chronic ocular diseases [74], and treatment of different ocular conditions such as glaucoma, chronic dry eye, allergies, and infections [75].

Intraocular Injections

Intraocular injections are performed for posterior segment diseases. This technique is used in specific pathologies and requires the presence of trained and competent personnel. The surface of the eye is anesthetized during the procedure. This technique requires a clean room, sterile materials, and takes 15 to 30 minutes. Only solutions or suspensions of drugs can be injected. Medications are injected through the corneal barrier into the vitreous. Clear solutions may contain antibiotics, antifungals, anticancer agents, or antivirals. Avastin® (Roche, Basel, Switzerland) and Lucentis® (Novartis, Basel, Switzerland) are commonly used in the treatment of age-related macular degeneration. Other diseases such as endophthalmitis, uveitis, diabetic retinopathy, and retinal vein occlusion are treated with intraocular injections.

Innovative Forms

For many years, researchers have explored and discovered different forms for ocular administration. Among them, colloidal dispersions such as microemulsions, nanoemulsions, micro- or nanoparticles, and liposomes have been primarily described as innovative systems for ophthalmic delivery in recent decades. They are capable of penetrating the eye via the anterior or posterior segment. Microemulsions are clear, transparent, and thermodynamically stable systems of two immiscible fluids. This system is a dispersion of oil in water stabilized by a surfactant and sometimes a co-surfactant. Microemulsions enhance drug solubilization (both hydrophilic and lipophilic) and dissolution efficiency of poorly water-soluble drugs. Their long shelf life, easy preparation (spontaneous formation), and improved bioavailability make them a potential ocular drug delivery system [52,53].

Nanoemulsions are preferred in ocular administration due to their small size, typically below 1 μm. They consist of an aqueous phase, a lipophilic phase, and a surfactant phase. A co-surfactant may be required in some cases. This dispersed system has the advantage of requiring minimal energy due to its spontaneous formation [54]. Nanoemulsions are biodegradable and can be sterilized by filtration.

Nanoparticles are solid particles with at least one dimension less than 1 μm. These carriers can entrap drugs in different ways. Depending on their composition, nanoparticles can be made from natural or synthetic polymers, metals, lipids, and phospholipids. There are two main types: nanospheres and nanocapsules [76]. Nanospheres are polymeric vesicles where the drug can be entrapped or attached to the surface, while nanocapsules have a hydrophilic or lipophilic core surrounded by a polymeric coating, with active substances dissolved and encapsulated in the core. Nanocarriers offer many advantages, including small size, large surface area, and potential for controlled and sustained release profiles of drugs. They also improve drug therapy, reduce side effects, and allow specific-site targeting [77,78]. However, limitations include potential particle aggregation due to their small size and large surface area, difficulty in handling in liquid and dry forms, and possible systemic toxicity [80]. The systemic toxicity of nanoparticles can be related to oxidative stress, pro-inflammatory gene activation, or their ability to cross ocular barriers, leading to systemic drug diffusion [81,82].

Liposomes, introduced in 1965 as drug delivery carriers [83], are biodegradable and biocompatible vesicular systems composed of phospholipid bilayers surrounding aqueous compartments. They are categorized into small unilamellar vesicles (SUV, 20 nm to 200 nm), large unilamellar vesicles (LUV, 200 to 3000 nm), and multilamellar vesicles (MLV, larger than 1 μm). Liposomes can encapsulate both lipophilic and hydrophilic drugs. In ocular drug delivery, liposomes offer high biocompatibility and tolerance, and can treat both anterior and posterior segment eye diseases via topical, subconjunctival, or intravitreal administration [84,85]. Positively charged liposomes seem to be the most efficient for prolonged adhesion to the corneal surface due to the negatively charged ocular mucus [86]. Niosomes are non-ionic surfactant vesicles and a specific type of liposome. They range in size from 10 to 1000 nm, are biodegradable, bilayered

structures stable, and have low toxicity due to their non-ionic nature. Common surfactants used include sorbitan monooleate (Span), polysorbate (Tween®), and cholesterol [87,88].

Dendrimers are “tree-like” nanostructured polymers. They have nanosize dimensions (1–100 nm) and low polydispersity, structured as a three-dimensional globular shape with a core, branching units in concentric layers (generations), and terminal functional groups [89]. New-generation dendrimers are cationically charged and potentially toxic for ocular delivery, while older generations with anionic or neutral charges have higher ocular biocompatibility [90]. Dendrimers with carboxylic and hydroxyl surface groups have shown increased residence time in the eye [91].

Recent Advances in Ocular Antibiotics Administration
Antibiotics and Ophthalmic Delivery

The discovery of penicillin by Alexander Fleming revolutionized medicine by providing a powerful tool against bacterial infections [92]. Antibiotics, whether naturally produced or synthetically created, are used to treat or prevent infections caused by bacteria and other microorganisms. Their primary mechanisms of action include:

- **Inhibition of Cell Wall Synthesis**: Antibiotics such as beta-lactams (e.g., penicillin, cephalosporins) and other agents like fosfomycin interfere with bacterial cell wall synthesis, preventing cell growth [93].
- **Inhibition of Protein Synthesis**: Aminoglycosides, macrolides, chloramphenicol, and tetracyclines target bacterial ribosomes, disrupting protein production [93].
- **Interference with Nucleic Acid Synthesis**: Fluoroquinolones and other agents inhibit DNA and RNA synthesis [93].
- **Folate Synthesis Inhibition**: Sulfamides and dihydrofolate reductase inhibitors block essential folate synthesis pathways [93].

Antibiotics can be classified based on their spectrum of activity (broad or narrow) and their effect (bactericidal or bacteriostatic). For ocular infections, the choice of administration route—oral, parenteral, or local—depends on the infection site and desired concentration of the drug.

- **Topical Administration**: Eye drops, ointments, and gels are commonly used for the anterior segment of the eye (e.g., cornea, conjunctiva). Each form has specific benefits, such as immediate action (eye drops), decreased administration frequency (gels), or increased drug bioavailability (ointments) [94].
- **Intraocular Administration**: Intravitreal and intracameral injections provide high local drug concentrations and are used for conditions like endophthalmitis, often in combination with vancomycin and ceftazidime [95].
- **Periorbital Administration**: Subconjunctival and retrobulbar injections are employed to achieve high drug concentrations or treat conditions like optic neuritis. Generally, the subconjunctival route allows for higher drug concentrations compared to retrobulbar injections [96].

Systemic administration (oral or parenteral) is used for targeting the posterior segment (retina, choroid, sclera). Oral administration is convenient but limited by the drug's bioavailability and potential systemic toxicity [14]. Parenteral administration is typically reserved for more severe conditions such as preseptal cellulitis or orbital cellulitis [97].

Antibiotics usually have a short half-life and require repeated administration. Their low solubility can make ocular penetration challenging. For example, penicillins, cephalosporins, and aminoglycosides are difficult to deliver effectively to the eye. Dermal application of penicillin can cause allergic reactions, while tetracyclines can disrupt intestinal microflora. Modern beta-lactams and aminoglycosides often need to be administered via injection due to their low oral bioavailability, highlighting the advantages of ophthalmic administration for improved tolerance [94].

Recent Advances in Ocular Delivery of Antibiotics

Improvement of Drug Dissolution and Stability Using Cyclodextrins

Cyclodextrins (CD) are cyclic oligosaccharides with a hydrophobic inner cavity and a hydrophilic outer surface, used to enhance drug solubility and stability [98]. They can improve the ocular delivery of antibiotics by preventing irritation and increasing drug permeability. For instance, hydroxylpropyl-β-cyclodextrin (HPβCD) complexes with ciprofloxacin have shown enhanced stability and biological activity compared to simple aqueous solutions [100][101]. Novel βCD polymers in hydrogels also demonstrated slower drug release profiles compared to dextrose-based gels, with hydrophilic drugs showing less alteration in release profiles [102].

Contact Lens for Antibiotic Delivery

Contact lenses, initially developed for vision correction, can serve as drug reservoirs for ocular delivery. Rigid Gas Permeable (RGP) lenses can trap tear reservoirs and serve as drug containers, potentially aiding in corneal healing and hydration [103]. In cases of severe dry eye disease or toxic epidermal necrolysis, scleral lenses can be used to deliver drugs such as topical corticosteroids and cyclosporine [104]. Studies have demonstrated that scleral lenses loaded with ofloxacin provide higher drug levels in the aqueous humor and cornea compared to other delivery methods [105]. Soft contact lenses, often made from hydrogels or silicone hydrogels, have been investigated for drug delivery using various techniques. The "soaking" technique, where lenses are immersed in antibiotic solutions, showed different drug uptake and release rates among various lens types [107][108]. The supercritical CO2 impregnation/dispersion method and molecular imprinting technology have also been explored, demonstrating effective and controlled drug release [109][110][111][112][113].

Ocular Inserts for Antibiotic Delivery

Ocular inserts are solid or semi-solid devices placed in the eye to provide controlled drug release. Early studies showed that hydrogel inserts with high water content maintained consistent drug elution rates [114]. Collagen-based

inserts with antibiotics like erythromycin and penicillin provided sustained drug delivery and effective treatment of infections [115][116]. Inserts combining gentamicin sulfate with dexamethasone phosphate have also shown prolonged release and improved patient compliance [117]. Recent developments include fluoroquinolone-based inserts that improve ocular bioavailability and reduce administration frequency [118][119]. Chitosan microspheres incorporated into inserts have enhanced drug penetration and release [120]. Additionally, Eudragit®-based inserts and drug reservoir systems have demonstrated prolonged release and improved patient adherence [122][123][124][125][126].

In Situ Gelling Systems for Antibiotic Delivery

In situ gelling systems offer controlled drug release and prolonged ocular contact time. These systems include thermosensitive, ion-activated, and pH-sensitive gels. Studies have shown that formulations with HPMC, alginate, and poloxamer can enhance drug bioavailability and extend ocular residence time [127][128][129][130][131][132][133]. For example, an ion-activated gel with gatifloxacin showed increased ocular retention and bioavailability compared to conventional eye drops [134]. A Gelrite® system for moxifloxacin demonstrated higher retention in the aqueous humor and faster improvement in corneal inflammation compared to standard eye drops [135-136].

Conclusion

Ophthalmic drug delivery remains a challenging field due to the complex anatomy of the eye and the various barriers that impede drug absorption. Traditional methods such as eye drops and ointments often fall short due to rapid drug clearance and limited bioavailability. Eye drops, despite being the most commonly used form, suffer from significant drug loss within seconds of application, while ointments, although improving residence time, cause visual disturbances that limit their use. Recent advancements in ophthalmic drug delivery systems have introduced several innovative approaches aimed at overcoming these limitations. In situ gelling systems have shown potential in increasing drug residence time by transitioning from a liquid to a gel upon contact with the eye, thereby reducing the frequency of administration. Nanoparticle-based systems offer targeted delivery and enhanced bioavailability, proving particularly effective in overcoming ocular barriers and reducing systemic side effects. Emulsions and hydrogels represent another significant advancement, enhancing drug solubility and stability, which further aids in prolonging drug action. However, each of these systems has its own set of challenges, including potential side effects and issues with patient comfort. For instance, emulsions can lead to blurred vision, while hydrogels may not be suitable for all types of drugs due to their specific formulation requirements. Intraocular injections, while effective for treating posterior segment diseases, require specialized procedures and are not suitable for all patients. Nevertheless, they remain a crucial option for certain conditions, such as age-related macular degeneration and diabetic retinopathy. In conclusion, while innovative ocular drug delivery systems have made substantial progress, there is still a need for continued research to refine these technologies and develop new solutions. Addressing the challenges associated with each system will be essential in achieving more effective and patient-friendly

treatments for ocular infections and diseases. Future developments should focus on enhancing the safety, efficacy, and overall patient experience in ophthalmic drug delivery.

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مراجعة شاملة لأنظمة توصيل الأدوية العينية للعلاج بالمضادات الحيوية

الملخص:

الخلفية :يقدم توصيل الأدوية العينية تحديًا فريدًا بسبب تعقيد التشريح العيني والحواجز التي تحول دون امتصاص الأدوية. تواجه التركيبات العينية الحالية مشكلات مثل انخفاض التوافر البيولوجي والتخلص السريع من الدواء، مما يستلزم تحسين أنظمة توصيل الأدوية لزيادة الفعالية العلاجية.

الهدف :تهدف هذه المراجعة إلى تقييم أنظمة توصيل الأدوية العينية المختلفة خصيصًا للعلاجات بالمضادات الحيوية، مع التركيز على فعاليتها في تجاوز الحواجز العينية وتحسين احتفاظ الدواء.

الطرق :تم إجراء مراجعة أدبية شاملة، مع التركيز على أنظمة توصيل الأدوية العينية المختلفة بما في ذلك التركيبات الموضعية (قطرات العين، المراهم، الهلاميات المائية، وعدسات الاتصال)، والأنظمة الجديدة (الهلاميات في الموقع، والجزيئات النانوية، والمستحلبات)، والتقنيات المتقدمة مثل الحقن داخل العين. تم تحليل التطورات الرئيسية والتحديات المرتبطة بكل طريقة لتقييم تأثيرها على التوافر البيولوجي للدواء والنتائج العلاجية.

النتائج :تقتصر طرق التوصيل العينية التقليدية، مثل قطرات العين والمراهم، على عوامل مثل التخلص السريع من الدواء والتوافر البيولوجي المنخفض. وقد أظهرت الابتكارات مثل أنظمة الجيل في الموقع، والجزيئات النانوية، والمستحلبات وعدًا في تمديد زمن بقاء الدواء وتعزيز التوافر البيولوجي. على وجه التحديد، توفر الجزيئات النانوية توصيلًا مستهدفًا وفعلًا ممتدًا، بينما تحسن الهلاميات المائية والمستحلبات من ذوبان الدواء واستقراره. ومع ذلك، فإن لكل نظام حدوده وآثاره الجانبية المحتملة التي يجب أخذها بعين الاعتبار.

الاستنتاج :تعد التقدمات في أنظمة توصيل الأدوية العينية أمرًا حيويًا لمعالجة قيود الطرق التقليدية. لقد أظهرت التركيبات المبتكرة مثل الهلاميات في الموقع والجزيئات النانوية تحسينات في احتفاظ الدواء وفعاليته، على الرغم من أن التحديات لا تزال قائمة من حيث راحة المرضى والسلامة النظامية. ينبغي أن يركز البحث المستقبلي على تحسين هذه الأنظمة واستكشاف تقنيات جديدة لتعزيز فعالية العلاجات بالمضادات الحيوية العينية.

الكلمات المفتاحية :توصيل الأدوية العينية، العلاج بالمضادات الحيوية، التوافر البيولوجي، الهلاميات في الموقع، الجزيئات النانوية، قطرات العين، المستحلبات.