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ETHOSOMES DOXYCYCLINE: A PROMISING NANOCARRIER FOR ENHANCED OPHTHALMIC DRUG DELIVERY

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ABSTRACT

Ocular medication delivery research has advanced significantly over the past half-century, forcing researchers to assess the benefits and drawbacks of this delivery method. The most widely utilised preparation for ocular medication delivery is still topical eye drops. This type mainly targets anterior ocular illnesses and has a significant precorneal drug loss because to tear production and natural ocular barriers, even though patients tolerate it well. In ocular therapies, antibiotics are frequently given as ointments or solutions. Their local bioavailability is still below ideal, though, requiring frequent dosing, which may result in adverse effects and diminished therapeutic effectiveness. Sustained-release formulations for the ocular administration of antibiotics have been created in order to get around these restrictions.[1] Ocular barriers and traditional topical forms are the main topics of this review's discussion on ocular administration. It showcases experimental strategies intended to get beyond the restrictions on antibiotic distribution by utilising cutting-edge technology such drug-loaded contact lenses, implants, colloidal systems, and in situ gelling systems. Systems based on nanotechnology, especially Ethosomes, have become a viable tactic among them. An inventive nanocarrier technique that improves ocular medication retention, permeability, and targeted administration is Ethosomes loaded with doxycycline. To treat a variety of eye infections and inflammatory diseases, their lipid-based flexible vesicles may efficiently cross ocular barriers and deliver prolonged release and enhanced bioavailability of doxycycline. This study highlights how these nano systems can preserve labile medications, lower dosage frequency, and provide site-specific delivery, creating new opportunities for efficient antibiotic treatment in the eyes.[1]

KEYWORDS: Ophthalmic Drug Delivery, Doxycycline, Ethosomes, Ocular Bioavailability, Topical Antibiotics, Sustained Release Ethosomes, Nanotechnology, Ocular Barriers, Anterior Eye Diseases, Colloidal Drug Carriers, Targeted Ocular Therapy.

1. INTRODUCTION

Ophthalmic drug delivery is a complex and evolving area of pharmaceutical and medicinal sciences due to the unique anatomy and physiology of the eye. Despite decades of research and progress, achieving efficient and targeted drug delivery to ocular tissues remains a major challenge.

The eye is protected by several dynamic and static barriers—such as tear fluid turnover, nasolacrimal drainage, the corneal epithelium, and blood-ocular barriers—which significantly limit the absorption, bioavailability, and residence time of topically applied drugs. As a result, only about **5%–10%** of the administered drug actually reaches intraocular tissues.[2]

Most marketed ophthalmic formulations—approximately **90%**—are in the form of topical applications like **eye drops, ointments, and gels**. These are primarily used for anterior segment diseases such as **blepharitis, conjunctivitis, scleritis, keratitis, and dry eye syndrome**. However, the treatment of **posterior segment diseases** like **glaucoma, endophthalmitis, and uveitis** is even more challenging due to deeper anatomical positioning and restricted drug permeability. While intraocular injections can deliver drugs directly to target tissues, they come with risks such as infection, retinal detachment, and patient discomfort. Interestingly, in some cases, ocular administration can offer **equivalent or even better bioavailability** than systemic oral administration.[2]

Antibiotics play a crucial role in the treatment of ocular infections such as **microbial keratitis, conjunctivitis, Meibomian gland dysfunction**, and **dry eye**. Commonly used antibiotic classes include **tetracyclines, fluoroquinolones, aminoglycosides**, and **penicillins**. However, the effectiveness of these drugs is increasingly compromised by **antimicrobial resistance (AMR)**, largely due to their overuse, misuse, and bacterial adaptation. This has made it essential to improve existing ophthalmic formulations to enhance therapeutic efficacy while minimizing resistance and side effects.[2,3]

To overcome these limitations, innovative drug delivery systems are being developed. These include **in situ gelling systems, Ethosomes, liposomes, nanoparticles, Niosomes, nano emulsions**, and **microemulsions**. Such systems can encapsulate both hydrophilic and lipophilic drugs, provide controlled or sustained release, and improve site-specific delivery while enhancing precorneal retention. For example, the presence of ethanol helps to fluidize the corneal epithelium, enhancing drug penetration through ocular barriers. Their lipid-based structure allows better adhesion to the eye surface, which increases the contact time of the formulation. This prolonged residence time leads to sustained and targeted drug release, reducing the frequency of administration.[3,4] As a result, **doxycycline-loaded Ethosomes** significantly improve ocular bioavailability, minimize side effects, and are effective in treating both anterior and posterior segment eye infections**. Nanoparticles** can be designed for mucoadhesive properties, enabling better interaction with ocular surfaces and improved penetration.[4]

The objective of this review is to provide a comprehensive overview of **antibiotic formulations used in ophthalmic drug delivery**. It begins with a discussion on **ocular anatomy, physiology, and barriers**, followed by an evaluation of **conventional topical formulations** like **eye drops, hydrogels, contact lenses**, and **ophthalmic inserts**. The review then focuses on **recent advancements** in antibiotic-loaded delivery systems, highlighting **in vitro and in vivo studies** that demonstrate improved drug bioavailability, extended residence time, and enhanced therapeutic response. These novel

approaches offer promising solutions to overcome the long-standing challenges in ocular drug delivery and set the foundation for more effective treatment of eye infections.[4,5]

2. Anatomy and Physiology of the Eye for Ocular Drug Delivery

The human eye is a highly specialized and sensitive organ, and its unique anatomy and physiology present several challenges for efficient ocular drug delivery.

The **cornea**, being the transparent front part of the eye, acts as a major physical and permeability barrier. Its tightly packed epithelial cells allow only small, lipophilic, and non-ionized molecules to penetrate, which limits the absorption of most hydrophilic drugs.

Surrounding the eye is the **conjunctiva**, a vascularized membrane that, while allowing some absorption, often leads to systemic drug loss and reduces local bioavailability.

The **tear film**, constantly refreshed by blinking and lacrimal drainage, further dilutes and clears topically applied drugs within minutes, significantly reducing their contact time with the ocular surface.

Beneath these layers lies the **sclera**, the white fibrous tissue of the eye, which is permeable to hydrophilic drugs but still poses resistance due to its thickness and composition.

The **aqueous humor**, filling the anterior chamber, is responsible for maintaining intraocular pressure and nutrient exchange; however, its rapid turnover clears drugs quickly from the anterior segment.

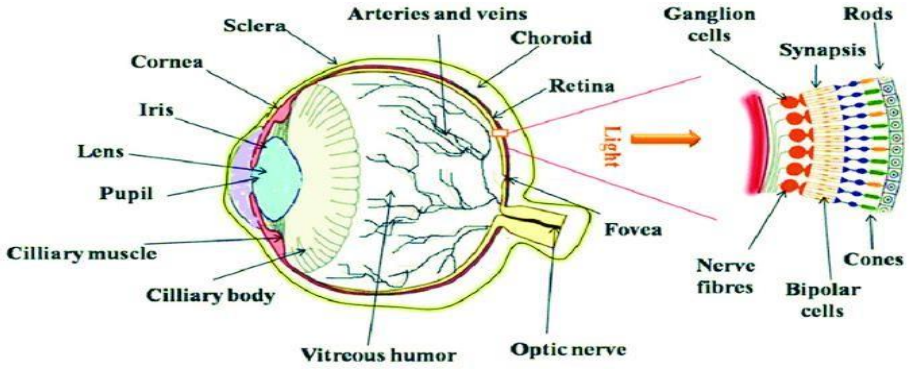
The **iris and ciliary body**, which regulate pupil size and aqueous humor production, are also richly vascularized, potentially increasing systemic absorption and side effects.

The **lens**, located behind the iris, helps focus light but also acts as a barrier between the anterior and posterior segments, making drug diffusion to the back of the eye even more difficult.

The **vitreous humor**, a gel-like substance filling the posterior chamber, further slows down drug movement, especially for large molecules. The ultimate target for many posterior eye diseases is the **retina**, a complex neural tissue responsible for vision.

However, the **blood-retinal barrier**, much like the blood-brain barrier, restricts the entry of most therapeutic agents, whether administered systemically or topically.

Together, these features form the **blood-ocular barriers**—specifically, the blood-aqueous and blood-retinal barriers—which, while essential for protecting the eye, greatly hinder drug penetration. As a result, only about 5–10% of topically applied drugs manage to reach intraocular tissues. These anatomical and physiological obstacles make treating both anterior and posterior segment diseases highly challenging. Therefore, the development of advanced ocular drug delivery systems such as **Ethosomes, liposomes, nanoparticles, in situ gels, and ocular inserts** has become essential. These novel carriers aim to enhance drug retention time, increase penetration, reduce dosing frequency, and deliver drugs more effectively to specific ocular tissues.[6,7,8]



3. Various Ophthalmic Form

Ophthalmic drug delivery includes a wide range of dosage forms, each designed to overcome specific anatomical and physiological barriers of the eye. Among the most commonly used are…

a. **Eye drops**, which are sterile aqueous solutions ideal for treating anterior segment disorders such as conjunctivitis or dry eyes. While they are easy to administer and act quickly, they suffer from rapid tear drainage and low bioavailability, requiring frequent dosing.

b. **Ophthalmic suspensions** are preferred for drugs that poorly water-soluble, these consist of fine drug particles suspended in a liquid medium and offer prolonged drug action, although they require shaking before use and may cause irritation if not properly formulated.

c. **Eye ointments**, made with semi-solid petroleum bases, provide extended contact time with the eye, making them ideal for nighttime application in bacterial infections, but they can cause blurred vision and discomfort during the day.

d. **In situ gelling systems** offer the benefit of transitioning from liquid to gel upon contact with the ocular surface, thereby enhancing precorneal residence time and allowing sustained drug release, although some may cause temporary visual disturbance.

e. **Ophthalmic inserts** is another advanced form, which are solid or semi-solid devices placed in the conjunctival sac to deliver drugs over an extended period. While these reduce dosing frequency and offer controlled release, they may be uncomfortable for some patients.

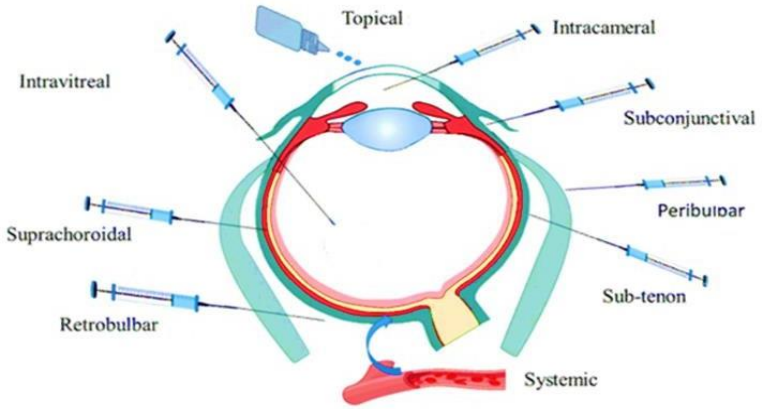
f. **Contact lenses** have also been explored as drug carriers, especially for continuous drug release while correcting vision, although they are more expensive and require careful patient adherence.

g. **Ophthalmic emulsions** is used for hydrophobic drugs, such as microemulsions and nano emulsions, are used to improve solubility and bioavailability, although their stability remains a challenge.

h. **Suspension sprays**, which are sprayed over closed eyelids, offer a non-invasive option suitable for children or sensitive individuals, but drug absorption through the eyelid skin is less predictable.

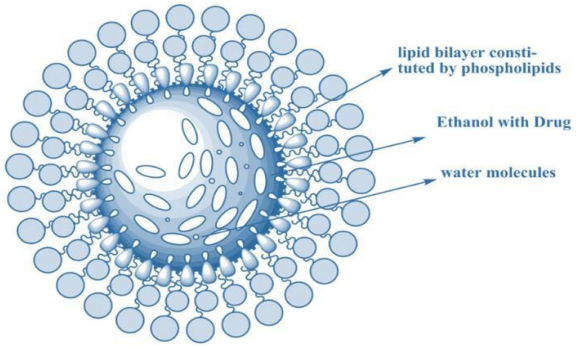
i. **Intravitreal injections** is used for treating diseases of the posterior segment, such as diabetic retinopathy or macular degeneration, it provides direct drug delivery into the vitreous humor, ensuring high local concentration but involving invasive administration and associated risks.

j. **Ocular implants** is work Similarly, which may be biodegradable or non-biodegradable, are surgically inserted to provide long-term controlled drug release in chronic conditions like glaucoma or uveitis, although their use is limited by surgical complexity and cost.[9,10,11]



k. **Niosomes,** on the other hand, are similar to liposomes in structure but are composed of **non- ionic surfactants** instead of phospholipids, making them more stable and cost-effective. They also enhance drug bioavailability and sustain drug release, making them suitable for both anterior and posterior ocular drug delivery. Niosomes can improve precorneal retention time and reduce dosing frequency, although they may still face limitations in corneal penetration without additional modifications.[12,13]

l. **Ethosomes** represent an advanced form of lipid vesicles composed of **phospholipids, a high concentration of ethanol (20–45%), and water**. The presence of ethanol imparts high deformability to the vesicles and enhances their ability to penetrate through ocular barriers like the corneal epithelium. Ethosomes not only improve drug permeation but also increase ocular bioavailability and retention time. They are especially useful for delivering drugs like **doxycycline, cyclosporine**, and other antibiotics or anti-inflammatory agents directly to both anterior and posterior segments of the eye.[13,14]



O Mechanism of Action

Ethosomes enhance drug delivery primarily through:

- **Ethanol-induced lipid fluidization**: Ethanol disrupts the lipid organization of the stratum corneum or corneal epithelium, increasing permeability.
- **Flexible vesicle penetration**: The high ethanol content makes Ethosomes vesicles ultra- deformable, allowing them to squeeze through small openings in biological membranes.
- **Enhanced retention**: After penetration, Ethosomes release the drug into deeper tissues, increasing local concentration and therapeutic effect.[14,15]

4. Ethosomes Gel's benefits for ocular delivery

Ethosomes gels combine the advantages of **Ethosomes** and **gel-based delivery systems**, making them highly beneficial for ocular drug delivery. The ethanol-rich Ethosomes vesicles are ultra-deformable, allowing them to penetrate the corneal epithelium more effectively than conventional vesicles [16]. When incorporated into a gel base, these vesicles offer **prolonged retention on the ocular surface**, reducing drug loss due to tear drainage and blinking. The gel matrix helps in **sustained and controlled release** of the drug, ensuring a consistent therapeutic effect over an extended period. Ethosomal gels enhance **ocular bioavailability**, minimize dosing frequency, and improve patient compliance. Additionally, they reduce systemic absorption and related side effects, and are well-suited for delivering both **hydrophilic and lipophilic drugs**. These formulations are particularly effective for treating anterior segment infections, inflammation, and may even be explored for posterior segment targeting, making ethosomal gels a promising platform for future ophthalmic therapies.[17]

5. Most recent advances and research findings on using **doxycycline-loaded Ethosomes** as a novel ocular drug delivery approach:

i. Superior Penetration and Retention

Because of their high ethanol concentration, ethersomes improve drug penetration and fluidise the corneal epithelium. The same method is currently being used for ocular usage, despite the fact that much of this work is in cutaneous administration. These holds promise for greater retention, decreased dose frequency, and higher doxycycline penetration.[18,19]

ii. Comparative Advantage Over Other Vesicles

Ethamomes are superior to liposomes and Niosomes in terms of ocular bioavailability, extended surface retention, enzymatic protection, and the capacity to distribute drugs hydrophilically and lipophilically, according to a 2024 assessment of vesicular ocular systems, which includes Ethosomes.[20]

iii. Doxycycline-Loaded Niosome Precedent

Doxycycline hyclate niosomes, which have several characteristics in common with ethosomes, were created in a 2019 research and demonstrated ocular safety, excellent encapsulation efficiency, and prolonged drug release in vivo. This promotes comparable ethosomal delivery methods for doxycycline.[21]

iv. Hydrogel-Ethosome Hybrid Formulations

Researchers are investigating ethosomal gels, which combine ethosomes with in situ gelling devices, albeit this study is still in its early phases. Building on the success of existing ethosomal gels in ocular therapy, these hybrids seek to improve patient compliance, maintain doxycycline release, and increase corneal residence.

v. Broader Nano-Vesicular Trends

The emergence of sophisticated vesicles—ethosomes, transfersomes, and niosomes—for targeted ocular administration and their capacity to encapsulate a variety of medications is highlighted in recent work. These technologies have the potential to provide regulated release, shield labile substances like doxycycline, and get past ocular obstacles.[22,23]

5. Future Perspectives

a. Targeted Delivery to Posterior Eye Segment

The majority of topical ophthalmic formulations are now restricted to the anterior segment (e.g., dry eye, conjunctivitis). In order to deliver medications to the posterior segment (such as the retina or choroid) non-invasively for conditions including macular degeneration, diabetic retinopathy, and uveitis, future research will try to alter ethosomal gels to enter ocular tissues more deeply.

b. Gene and Peptide Delivery

Ethosomes have demonstrated the ability to transport sensitive macromolecules like genes, peptides, and proteins in addition to tiny compounds like doxycycline. Gene therapy for hereditary retinal disorders or peptide-based treatments for inflammation and neuroprotection could be investigated in future formulations.

c. Personalized Medicine and Smart Gels

Ethosomal gels might be tailored to meet the needs of individual patients thanks to developments in precision medicine and bio responsive gels. Depending on the state of the eye, smart gels that react to environmental cues (such as pH, temperature, or enzymes) may release the medication at the ideal rate.

d. Combination Therapy Platforms

Future ethosomal gels may be made to provide many medications at once, such an anti- inflammatory and antibacterial. This might improve therapy outcomes with a single formulation and be particularly helpful in post-surgical eye care or multi-targeted infections.

e. Long-Acting and Once-Weekly Gels

The requirement for regular dosage is one of the primary drawbacks of contemporary ophthalmic treatment. Once-daily or even once-weekly application of ethosomal gels with ultra-sustained release profiles is being researched in order to greatly increase patient compliance, particularly in chronic illnesses like glaucoma.

f. Enhanced Patient Acceptability and Packaging Innovations

In order to solve issues like visual blockage, future advancements may also concentrate on making ethosomal gels more comfortable, non-blurring, and simple to administer. Their utility and shelf- life can be further extended by advancements in sterile delivery applicators and multi-dose packaging devoid of preservatives.

g. Clinical Translation and Regulatory Approvals

Large-scale clinical trials and regulatory guidelines are necessary to introduce ethosomal gels into standard clinical practice, notwithstanding the encouraging preclinical research. Future efforts will concentrate on increasing production, guaranteeing stability, and obtaining FDA and EMA clearance.[24,25,26,27]

6. CONCLUSION

Ocular drug delivery remains a significant challenge due to the eye's complex anatomical barriers and dynamic protective mechanisms. Conventional formulations like eye drops and ointments suffer from low bioavailability and short residence time. Ethosomes, with their ethanol-enhanced flexibility and penetration capabilities, offer a novel and effective approach for overcoming these limitations.[28] When incorporated into gels, Ethosomes provide sustained drug release, improved corneal retention, and enhanced therapeutic outcomes. Doxycycline-loaded ethosomal gels, in

particular, show great promise in the treatment of various anterior and potentially posterior segment eye infections. With ongoing advancements in formulation science, characterization techniques, and clinical research, ethosomal gels are expected to become a next-generation solution for safe, efficient, and patient-friendly ocular therapy.[29]

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