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A Review On:-Nanoparticle-Based Drug Delivery for Ocular Antibiotherapy

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APSTRCT ;

Nanoparticle-based drug delivery systems represent a promising approach for enhancing ocular antibacteriotherapy, addressing challenges such as poor bioavailability, rapid clearance, and limited penetration of therapeutic agents into ocular tissues. This review discusses the various types of nanoparticles, including liposomes, solid lipid nanoparticles, and polymeric nanoparticles, highlighting their unique properties that facilitate targeted delivery and controlled release of antibiotics. We explore recent advancements in nanoparticle formulation techniques, characterization methods, and in vitro and in vivo studies demonstrating their efficacy against common ocular pathogens. Additionally, the potential of nanocarriers to improve patient compliance and reduce side effects is examined. Challenges such as biocompatibility, regulatory hurdles, and scalability are also addressed. This review underscores the transformative potential of nanoparticle-based systems in the field of ocular medicine, paving the way for more effective and patient-friendly treatments for ocular infections.

Keywords;

Nanoparticles, ocular drug delivery, antibacteriotherapy, bioavailability, liposomes, solid lipid nanoparticles, controlled release, ocular infections.

INTRODUCTION ;Ophthalmic drug delivery presents major challenges for pharmaceutical and medicinal sciences.For several decades, progress has been achieved to im

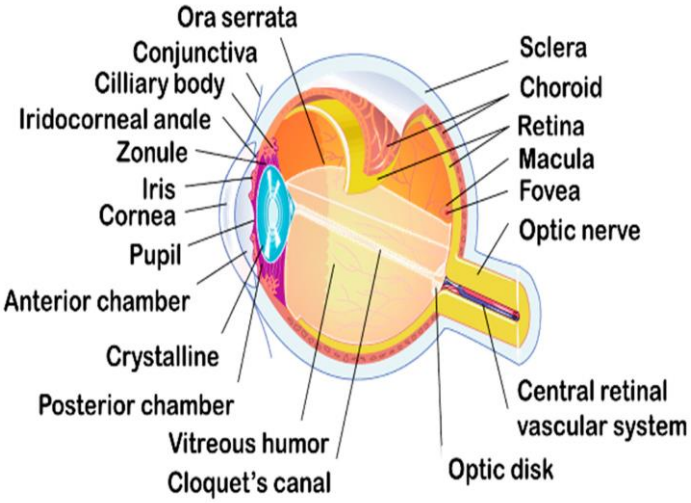
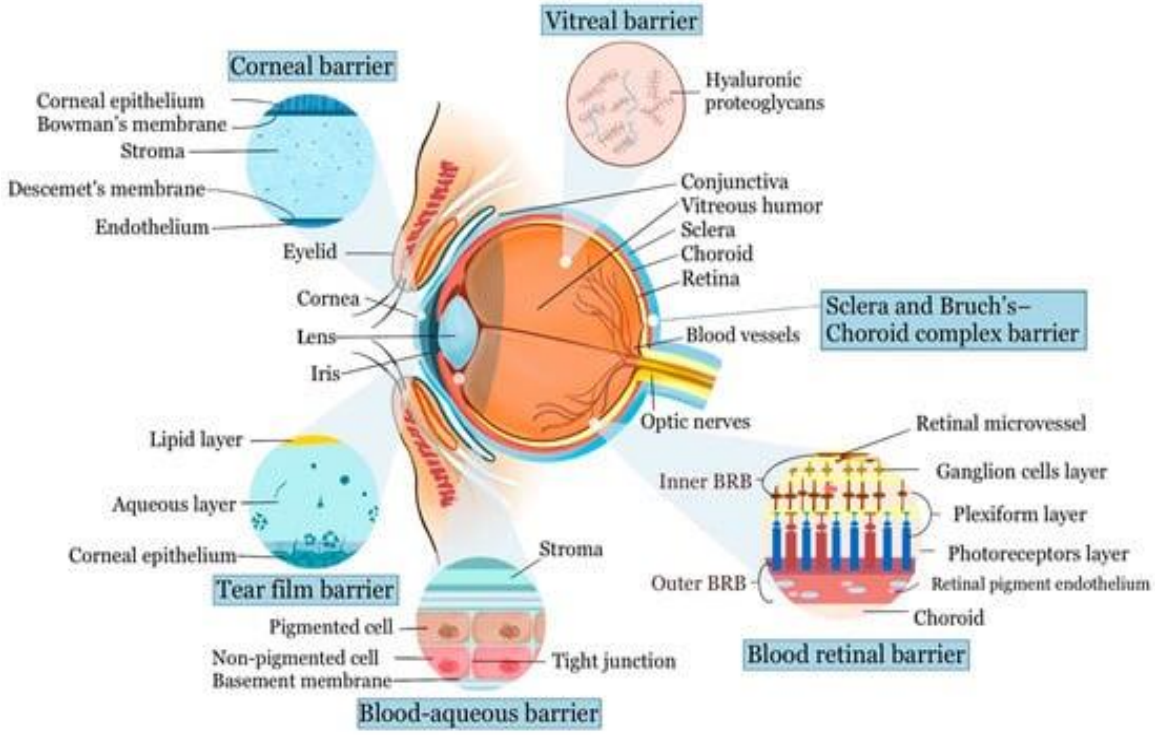


Fig. Interanal Anatomy Of The Eye

prove the currently dosage forms. Ocular diseases complicated to treat, and ocular forms need to be safe, non-allergic for the patient and sterile.Topical forms represent 90% of the marked formulation [1]. The tear fluid turnover, the nasolacrimaldrainage, the corneal

epithelium and the blood-ocular barriers are decreasing the local bioavailability of drugs and residence time on the ocular surface in topical application. Only 5%–10% of the drug crosses the corneal barriers. Anterior segment diseases as blepharitis, conjunctivitis, scleritis, keratitis and dry eye syndrome are resolved with topical or periocular administration. The delivery of drug to the posterior segment of the eye for glaucoma, endophthalmitis or uveitis and to the anterior segment has the same issue of poor bioavailability of the drug and barriers. However, intraocular administration might be preferred despite its risk of complication [2]. In addition, compared to the oral route,
ocular drug delivery provided equivalent or better bioavailability in the eye [3]. Approaches have been made for the improvement of the bioavailability of the drug, the controlled release and the
improvement of the therapeutic effect [4].

Anatomy and Barriers of Ocular Drug Delivery



Tear Film Barrier

The tear film on the ocular surface forms an initial barrier, impeding drug delivery, while drainage through the nasolacrimal system can dilute and remove drugs, affecting their efficacy. This tear film, around 3 μm thick and 3 μL in volume, comprises three layers: an outer lipid layer, a middle aqueous layer, and an inner mucous layer [12]. The outer lipid layer prevents water evaporation but also hinders drug absorption into the cornea and sclera [13]. Meanwhile, the mucous layer in the tear film acts protectively, forming a hydrophilic barrier that efficiently removes debris and pathogens

Cornea and Conjunctival Barrier

The cornea, the outermost transparent avascular layer of the eye, has essential refractive and barrier functions. It consists of three cell layers: the lipophilic epithelium, the hydrophilic stroma, and the lipophilic endothelium, along with two interfaces: The Bowman layer and Descemet's membrane. The corneal epithelium, comprising 5–7 lipid-rich cell layers with tight junctions and desmosomes, forms a robust barrier against drug penetration and microbial invasion [14,16].

Blood–Aqueous Barrier

The blood–aqueous barrier (BAB) is formed by tight junctions in the ciliary process's non-pigmented epithelium, endothelial cells in the iris vasculature, and the inner wall endothelium of Schlemm's canal. The tight junctions regulate paracellular transport, controlling the movement of ions and small substances between adjacent cells. The BAB is not completely impermeable; instead, it serves as a specialized gateway for controlled molecule movement [20].

Vitreal Barrier

The vitreous is a gel-like, transparent substance that fills the space between the lens and the retina. It mainly consists of water, collagen types II, IX, V/XI, hyaluronic acid, and other extracellular matrix components. Positively charged nanomaterials may interact with the negatively charged components of the vitreal network and thus block its diffusion ability, while negatively charged particles, based on the example of poly lactic-co-glycolic acid (PLGA) or human serum albumin, can distribute successfully across the vitreous humo

Blood–Retinal Barrier

The blood–ocular barrier (BOB) system includes two key barriers: the BAB and the blood–retinal barrier (BRB). The BRB is highly selective, controlling the passage of ions, proteins, and water to and from the retina. It comprises two parts: the outer BRB (oBRB), which includes the choroid, Bruch's membrane (BM), and the retinal pigment epithelium (RPE), and the inner BRB (iBRB), formed by tight junctions among retinal capillary endothelial cells [**23**

ADVANTAGE ;

Enhanced Bioavailability: Nanoparticles improve the solubility and stability of poorly water-soluble antibiotics, leading to higher concentrations at the target site.

Controlled Release: They allow for sustained and controlled release of the drug, reducing the frequency of administration and improving patient compliance.

Targeted Delivery: Nanoparticles can be engineered to target specific ocular tissues, minimizing systemic exposure and potential side effects.

Increased Penetration: The small size of nanoparticles enhances their ability to penetrate ocular barriers, such as the cornea, enabling better drug absorption.

Reduced Toxicity: By delivering drugs more precisely, nanoparticles can help minimize toxicity to surrounding tissues, leading to a better safety profile.

Ease of Administration: Advanced formulations can be designed for easy application (e.g., eye drops, gels), improving the overall patient experience.

DISADVANTAGE ;

Complex Manufacturing: The production of nanoparticles can be complicated and costly, requiring specialized equipment and processes that may limit scalability.

Regulatory Challenges: Nanoparticle formulations face stringent regulatory scrutiny, which can delay their approval and market availability.

Stability Issues: Some nanoparticle formulations may suffer from stability problems over time, leading to aggregation or degradation that affects drug efficacy.

Biocompatibility Concerns: While many nanoparticles are designed to be biocompatible, certain materials may still induce immune responses or toxicity in ocular tissues.

Limited Penetration of Certain Nanoparticles: Despite their small size, some nanoparticles may not effectively penetrate all ocular barriers, depending on their composition and surface properties.

Potential for Inflammation: The introduction of foreign nanoparticles can provoke inflammatory responses in the eye, potentially leading to complications.

Mechanism of action

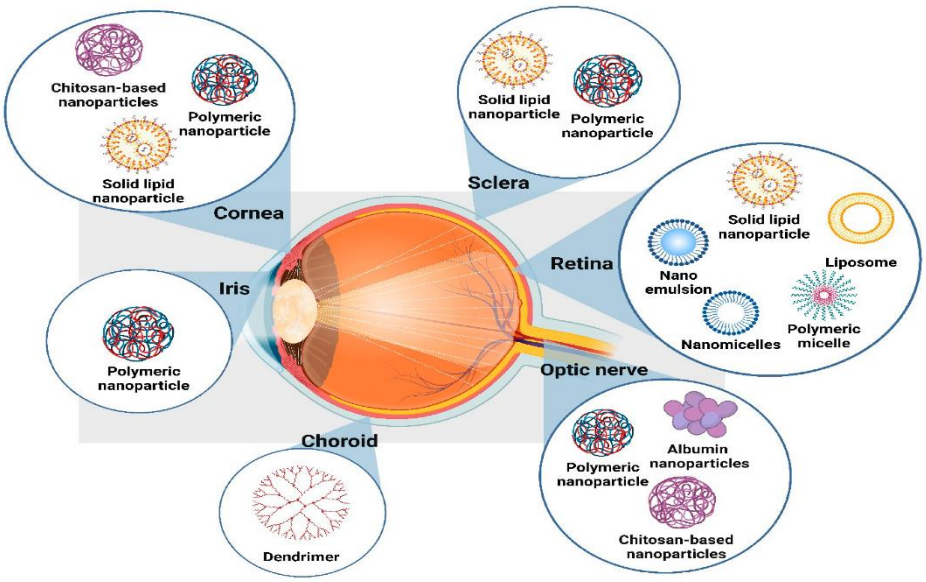


Fig. Targeted Ocular Drug

Nanoparticle-based drug delivery systems are increasingly being used for ocular drug delivery due to their ability to improve the bioavailability, and controlled release of drugs. In ocular antibiotics therapy, nanoparticles offer several advantages over traditional delivery methods such as eye drops, including better drug penetration, prolonged action, reduced systemic side effects, and targeted therapy.

Nanoparticle Types: Common nanoparticle types used for ocular delivery include liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions.

Surface Modification: Surface modification (e.g., with polyethylene glycol, surfactants, or targeting ligands) can enhance the stability, ocular retention, and cellular uptake of the nanoparticles.

Antibiotic Encapsulation: Antibiotic drugs (e.g., ciprofloxacin, gentamicin) are encapsulated in nanoparticles to protect them from degradation and control the release rate.

Controlled Release: Nanoparticles allow for the sustained release of the drug, which increases drug retention in ocular tissues and reduces the frequency of dosing.

Corneal Penetration: The small size of nanoparticles enables them to penetrate through the corneal epithelium, stroma, and endothelium, which are the main barriers for ocular drug delivery.

Passive diffusion: Nanoparticles can passively diffuse across these barriers due to their small size.

Endocytosis: Nanoparticles may also be internalized by corneal cells via endocytosis (e.g., clathrin-mediated, caveolae-mediated).

Uses

Nanoparticle Types: Common nanoparticle types used for ocular delivery include liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions.

Antibiotic Encapsulation: Antibiotic drugs (e.g., ciprofloxacin, gentamicin) are encapsulated in nanoparticles to protect them from degradation and control the release rate.

Corneal Penetration: The small size of nanoparticles enables them to penetrate through the corneal epithelium, stroma, and endothelium, which are the main barriers for ocular drug delivery.

Release Mechanism: Once the nanoparticles reach ocular tissues, they release the encapsulated antibiotic through various mechanisms:

Targeting the Infected Area: Nanoparticles can be functionalized with ligands (e.g., antibodies, peptides, or small molecules) that specifically target infection sites or overexpressed receptors on bacterial cells or inflamed tissues.

Active Targeting: The nanoparticles are directed to infection sites by binding to specific markers or receptors, such as those found on bacterial membranes or inflamed ocular tissues.

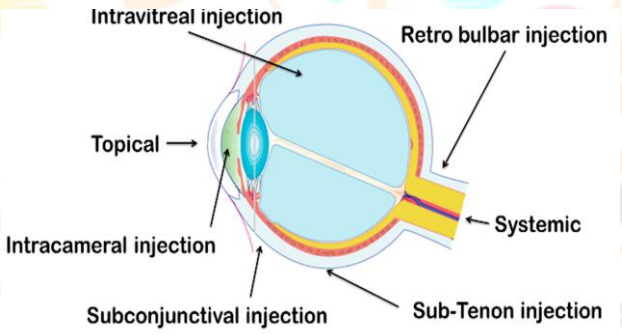
APLICATION

Chronic Ocular Diseases and Inflammation

Dry Eye Disease (DED):Nanoparticle-based drug delivery systems can be used to Ainfection often coexist. Nanoparticles can carry anti-inflammatory drugs (e.g., corticosteroids) alongside antibiotics to reduce inflammation and manage bacterial infections of the ocular surface.The sustained release of drugs can alleviate symptoms of dry eye by providing prolonged hydration and improving drug retention.

Blepharitis: Nanoparticles are used to treat blepharitis, a common condition involving inflammation of the eyelids, often caused by bacterial infections. Antibiotic nanoparticles can be applied to the eyelid area to combat the infection and inflammation while providing extended release, reducing the frequency of application.

Routes of ocular administration ;



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 allow the improvement of drug solubilization (hydrophilic and lipophilic) and dissolution efficiency of poorly water-soluble drugs. Its long shelf life, easy preparation (spontaneous formation) and improvement of bioavailability make it a potential ocular drug delivery system [8.9].

Anterior segment delivery challenges ;For ailments of the eye, topical administration is usually preferred over systemic administration, because before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route has to cross the precorneal barriers.
Posterior segment delivery challenges: Topical ocular medications do not reach the posterior segment drug targets because of the high efficiency of the blood-retinal barrier (BRB). The delivery of drugs to the posterior segment of ocular tissue is prevented by the same factors that are responsible for the poor ocular bioavailability. In addition, the BRB limits the effectiveness of the intravenous route in posterior drug delivery.[16]

Method of prepration

The topical use of the macerated fruit of *Atropa belladonna* L. by the Egyptians is the first known use of a nature-derived agent to treat an ophthalmic disease (Duncan and Collison, 2003 ▶).(24) The main chemical constituent of this plant is atropine, chemical structure is shown in . Chia et al. investigated in a randomized clinical trial that atropine at a low concentration (0.01% eyedrops) was more effective in slowing myopia progression with less visual side effects compared with higher doses (Chia et al., 2016 ▶). The exact mechanism of non-accommodative anti-myopic activity of atropine is still unknown but there are three possible echanisms of action

FORMULATION ;

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.

Gel ; Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers which leads to slight prolonged precorneal residence time. It has advantage like reduced systemic exposure. Despite the extremely high viscosity, gel achieves only a limited improvement in bioavailability, and the dosing frequency can be decreased to once a day at most

Future consideration ;

In future, much of the emphasis will be given to achieve noninvasive sustained drug release for eye disorders in both segments. A clear understanding of the complexities associated with tissues in normal and pathological conditions, physiological barriers, and multicompartmental pharmacokinetics would greatly hasten further development in the field. An ideal system should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure. In addition, the system should be both comfortable and easy to use. Patient acceptance will continue to be emphasized in the design of future ophthalmic drug delivery systems. A reasonable strategy to circumvent the drawbacks of individual technologies is to combine technologies. Most of the currently marketed ocular drugs were initially developed for nonocular applications, hence their low or nonspecificity. So, there is a need to develop new drug candidates primarily intended for ocular use.

Appropriate design and packaging of these delivery systems needs further research. There are several scientific and technological advances that are driving the progress in this field. Especially the advances in nanotechnology and biomaterials science may provide new smart technologies to augment ophthalmic drug delivery

CONCLUSION ;

In conclusion, nanoparticle-based drug delivery represents a significant advancement in ocular antibiotherapy, offering numerous benefits over traditional delivery methods. By enhancing drug solubility, enabling targeted delivery, and allowing for sustained release, nanoparticles can improve therapeutic outcomes while minimizing side effects. As research continues to evolve, the potential for these systems to revolutionize the treatment of ocular infections is considerable, promising improved patient compliance and effectiveness in combating resistant pathogens. Future studies should focus on optimizing formulations and evaluating long-term safety to fully realize the potential of nanoparticle technology in ocular medicine.

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