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Nanotechnology Based On Management of Glaucoma: Review

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ABSTRACT

Nanotechnology has transformed medical disciplines, creating tools and materials for molecular control and repair of human biological systems. It can improve ocular bioavailability and drug residence in glaucoma treatment, increase surgical success, and minimize postoperative scarring. Further research is needed to fully understand nanotechnology's therapeutic effects. The purpose of this review is to compile the research on nanotechnology advancements, with a focus on ocular devices used to treat. Glaucoma is a leading cause of blindness, affecting the delicate human eye. Traditional eye therapies, such as implants, eye drops, and injections, face complications due to low bioavailability or adverse effects. Nanoscience technology offers a novel approach to ocular disease treatment, modifying active molecules to react with nanocarriers. This review explores nanotechnology's therapeutic and diagnostic prospects in ophthalmology, specifically glaucoma, focusing on efficiency, safety, and potential applications in glaucoma.

Introduction

Nanotechnology is a scientific field that manipulates matter on a nanoscale. It was first proposed by Richard Feynman in 1959 and gained momentum in 1981 with the invention of the scanning tunneling microscope. Since then, research and development in nanotechnology have accelerated, with global investments reaching $150.5 billion between 2000 and 2019[2-4]. Nanotechnology has various applications, particularly in medicine, where it enables targeted treatment and diagnostics at the molecular level[5].

Glaucoma is a chronic eye disease and the leading cause of irreversible blindness worldwide. By 2020, it's estimated to affect 80 million people, with 11 million bilaterally blind. Nanotechnology may offer a promising alternative to overcome these challenges[6-9]. Glaucoma is a group of eye conditions that cause irreversible vision loss due to damage to the optic nerve and retinal ganglion cells. The disease progresses slowly, often without symptoms, making it difficult for patients to detect until the late stages.

Glaucoma is a degenerative eye disease requiring lifelong treatment, presenting in acute or chronic forms. Acute glaucoma is a medical emergency, causing rapid vision loss due to blocked aqueous humor flow, leading to increased intraocular pressure, retinal degeneration, and optic neuropathy. If untreated, permanent vision loss can occur within hours or days. Although chronic glaucoma is more common, acute glaucoma causes severe visual impairment in a larger proportion of patients[10-12].

Despite its complex causes, most treatments focus on reducing intraocular pressure (IOP) to slow disease progression. Current treatments for reducing intraocular pressure (IOP) have limitations[13]. Topical therapies require strict patient

compliance, have low bioavailability, and may cause side effects. Surgical options, like trabeculectomy, can enhance aqueous humor drainage but may lead to complications like scarring[14].

According to the World Health Organization (WHO), approximately 76 million people worldwide suffered from glaucoma in 2020, with predictions suggesting this number will increase to 111 million by 2040. In China, the annual cost of treating glaucoma is substantial, ranging from $945 for early treatment to $12,520 for bilateral vision loss[15-16].

Glaucoma, the leading cause of irreversible blindness worldwide, affects approximately 95 million people globally, with 10 million experiencing blindness in at least one eye. Despite treatment, most patients retain functional vision throughout their lives, but with ongoing vision loss. The economic burden of glaucoma is substantial, with annual treatment costs in China ranging from $945 to $12,520[17]. Glaucoma can be categorized into primary and secondary types, with secondary glaucoma often resulting from medical interventions, medications, or underlying health conditions. Glaucoma has several forms, including primary open-angle glaucoma (POAG) and angle-closure glaucoma. POAG accounts for 75% of global glaucoma cases and is characterized by increased ocular pressure due to blocked aqueous humor outflow. Angle-closure glaucoma occurs rapidly when the lens presses against the iris, blocking drainage. A less common form, primary normotensive glaucoma, involves vision loss without increased intraocular pressure. Glaucoma is highly heritable, with first-degree relatives being eight times more likely to develop the disease. Glaucoma's increased intraocular pressure and oxidative stress damage retinal ganglion cells and optic nerves [18-19]. Neurovascular dysfunction and neuroinflammation also contribute to glaucoma's progression. Current treatments have poor bioavailability, requiring frequent dosing and compromising patient compliance. Novel drug delivery systems using nanotechnology aim to overcome ocular barriers, enhancing drug absorption and efficacy. Glaucoma is a chronic, progressive optic neuropathy that accounts for the main cause of irreversible blindness globally. By 2020, it is expected to impact about 80 million people, with 11 million bilaterally blind. Despite being a multifactorial disease in which a complex combination of risk factors, such as intraocular pressure (IOP), increasing age, genetic, ethnic, and structural ocular variations, lead to progressive retinal ganglion cell and axon loss, the majority of therapies used today are focused on lowering IOP, the only modifiable parameter in the previous equation, in order to slow the progression of the disease [20]. Topical IOP-lowering medications aim to lower 1OP by either boosting aqueous humor (AH) drainage or decreasing AH formation. However, the need for strict patient compliance, limited intraocular bioavailability, and the possibility of substantial topical and systemic adverse effects may make administration unappealing [21]. Outflow-increasing operations, such as trabeculectomy, glaucoma drainage devices (GDD) implantation, nonpenetrating surgeries, and other minimally invasive surgical surgeries, lower IOP by improving AH drainage [22-23].

Nanomaterials have several appealing properties, the most important of which may derive from their namesake: most particles are in the range of 1-100 nm, which allows them to penetrate smaller capillaries and be absorbed by surrounding cells, allowing for efficient drug accumulation at target sites. Furthermore, these particles can be influenced to show more sites for chemical reactions.

For these reasons, the interest in the investigation of nanotechnology applied to the treatment of diverse diseases, including glaucoma. There are currently no FDA-approved or clinically available sustained drug delivery systems (DDS) for glaucoma treatment, including those based on nanotechnology [24-26]. Furthermore, the bulk of nanotechnology-based ocular devices for glaucoma treatment are still in the preclinical stage of development. This study attempts to outline and emphasize the achievements and benefits of nanotechnology in ocular devices used to treat glaucoma, with the goal of stimulating and accelerating research activities in this field [27-28].

Anatomy and Barriers of eye

The human eye is a complex and highly specialized organ that facilitates vision. It detects pressure and light, creating a three-dimensional image typically perceived in color during daylight hours [29]. The retina contains cone cells and rod

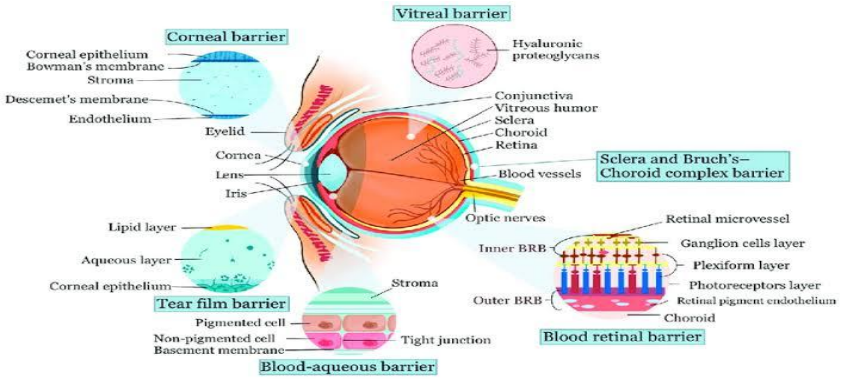
cells, which play a crucial role in light detection and vision perception. This enables the eye to distinguish approximately 10 million colors and potentially detect individual photons.

Similar to other mammalian eyes, human eyes possess non-image-forming photosensitive ganglion cells in the retina. These cells receive light signals, regulating pupil size and influencing the production of melatonin and the body's circadian rhythm [30-31].

The human eye's structure deviates from a perfect sphere, instead comprising two distinct segments: the anterior and posterior. The anterior segment includes the cornea, lens, and iris, while the posterior segment contains the retina and other vital structures [32].

The human eye, measuring 22-27 mm axially and 69-85 mm in circumference, is a complex organ divided into anterior and posterior segments [33]. The anterior segment includes the cornea, conjunctiva, iris, ciliary body, and lens, while the posterior segment comprises the vitreous humor, retina, choroid, sclera, and optic nerve. The eye's unique anatomy and protective mechanisms, such as the blood-retinal barrier, create challenges for drug delivery, especially for treating disorders affecting the posterior segment [in Fig.1]. This barrier, similar to those found in immune-privileged organs like the brain, isolates the eye from systemic circulation, making it difficult to administer drugs systemically.

Fig 1. Schematic diagram of ocular anatomy and physiological barrier to ocular drug delivery



Barriers of the Anterior Segment

Tear Film Barrier

The anterior segment of the eye features several barriers that hinder drug delivery. One of the primary obstacles is the tear film, a thin layer covering the ocular surface. This film, approximately 3 μm thick and 3 μL in volume, consists of three distinct layers: an outer lipid layer, a middle aqueous layer, and an inner mucous layer [34]. The outer lipid layer prevents water evaporation but also impedes drug absorption into the cornea [35]. Conversely, the mucous layer acts protectively, forming a hydrophilic barrier that efficiently removes debris and pathogens from the ocular surface [36].

Cornea and Conjunctival Barrier

The cornea, the eye's outermost transparent layer, serves as a barrier to drug penetration and microbial invasion. It comprises three cell layers: the lipophilic epithelium, hydrophilic stroma, and lipophilic endothelium, along with two interfaces: the Bowman layer and Descemet's membrane [36-37].

The corneal epithelium forms a robust barrier due to its tight junctions and desmosomes. The Bowman layer allows drug passage into the stroma, which facilitates permeation and diffusion of hydrophilic drugs. Descemet's membrane filters macromolecules and particles, protecting the endothelium [37-38].

The corneal endothelium maintains stromal dehydration and regulates water and solute transport through active and passive mechanisms.In contrast, conjunctival drug absorption is hindered by capillaries and the lymphatic system,

leading to reduced bioavailability. Tight junctions in the conjunctival epithelium impede hydrophilic molecule movement [38].

The sclera, composed of collagen fibers and proteoglycans, exhibits permeability similar to the corneal stroma. Drug permeation through the sclera is inversely correlated with molecular size, with linear dextrans showing lower permeability than globular proteins [39].

Blood-Aqueous Barrier (BAB)

The blood-aqueous barrier (BAB) is a selectively permeable structure formed by tight junctions in the non-pigmented epithelium of the ciliary process, endothelial cells in the iris vasculature, and the inner wall endothelium of Schlemm's canal. This barrier regulates the movement of ions and small molecules between adjacent cells, controlling paracellular transport. While not completely impermeable, the BAB functions as a specialized gateway, allowing controlled movement of molecules [40].

Barriers of the Posterior Segment

Vitreal Barrier

The vitreous is a transparent, gel-like substance filling the space between the lens and retina. Its composition includes water, collagen types II, IX, V/XI, hyaluronic acid, and other extracellular matrix components.

Positively charged nanomaterials may interact with the negatively charged vitreal network, hindering diffusion. In contrast, negatively charged particles, such as poly lactic-co-glycolic acid (PLGA) or human serum albumin, can successfully distribute across the vitreous humor [41]. The vitreous provides structural support, maintaining the eye's shape against intraocular pressure. The vitreoretinal interface acts as a barrier, restricting substance passage into retinal layers. This interface consists of three main components: the cortical vitreous, inner limiting membrane (ILM), and expanded Müller cell footplates [42].

Blood-Retinal Barrier (BRB)

The blood-retinal barrier (BRB) is a highly selective barrier controlling the passage of ions, proteins, and water to and from the retina. It consists of two parts: the outer BRB (OBRB) and the inner BRB (iBRB) [43].

The OBRB comprises the choroid, Bruch's membrane, and the retinal pigment epithelium. The choroid supplies nutrients and removes waste from the outer retinal layers. Bruch's membrane allows size-selective passive diffusion but blocks larger molecules.

The iBRB is formed by tight junctions among retinal capillary endothelial cells. It restricts molecule permeation based on size, charge, and lipophilicity. The iBRB and OBRB have specific systems for substance entry and exit, including influx transporters and efflux pumps. Designing drugs that mimic substances recognized by influx transporters or evade efflux pumps can improve drug delivery to the retina [42].

Sclera and Bruch's-Choroid Complex Barrier

The choroid, situated between the retinal pigment epithelium (RPE) and the sclera, acts as a densely vascularized barrier. Its five distinct layers include Bruch's membrane, the choriocapillaris layer, two vascular layers, and the suprachoroidal layer [39-45]. The choroid hinders hydrophilic compounds but allows positively charged lipophilic drugs to bind and create slow-release depots.

Bruch's membrane, approximately 2-4 μm thick, primarily consists of collagen and elastin fibers. The choriocapillaris layer features highly fenestrated capillaries, allowing larger molecules to pass through.The sclera, the eye's outer opaque

layer, comprises collagen fibers, proteoglycans, and glycoproteins. Its average thickness is 0.5-1 mm. Factors such as molecular weight, size, charge, and lipophilicity influence drug permeability through the sclera [46].

Pathogenesis of Glaucoma

Glaucoma's various clinical types share a common thread: optic nerve damage. This damage occurs through retinal ganglion cell (RGC) apoptosis, triggered by two main mechanisms:1. Mechanical injury from increased intraocular pressure (IOP), disrupting axonal flow and blocking neurotropic proteins. 2. Local vascular insufficiency at the optic nerve head, leading to ischemic damage and reduced neurotrophic factors [Fig A & B] [47-50]. Additional factors contributing to glaucomatous optic nerve damage include mitochondrial dysfunction, abnormal cerebrospinal fluid pressure, excitotoxicity, and oxidative stress [50-51].

Urgent glaucoma treatments primarily focus on reducing intraocular pressure (IOP), despite multiple contributing factors. Effective IOP reduction significantly slows glaucoma progression [52]. Methods for reducing IOP include:1. Medical therapy: Topical eye drops that lower IOP through two mechanisms - reducing aqueous humor production or enhancing outflow. 2. Surgical options: Trabeculectomy or drainage devices to drain excess aqueous humor when medication is insufficient [53-55].

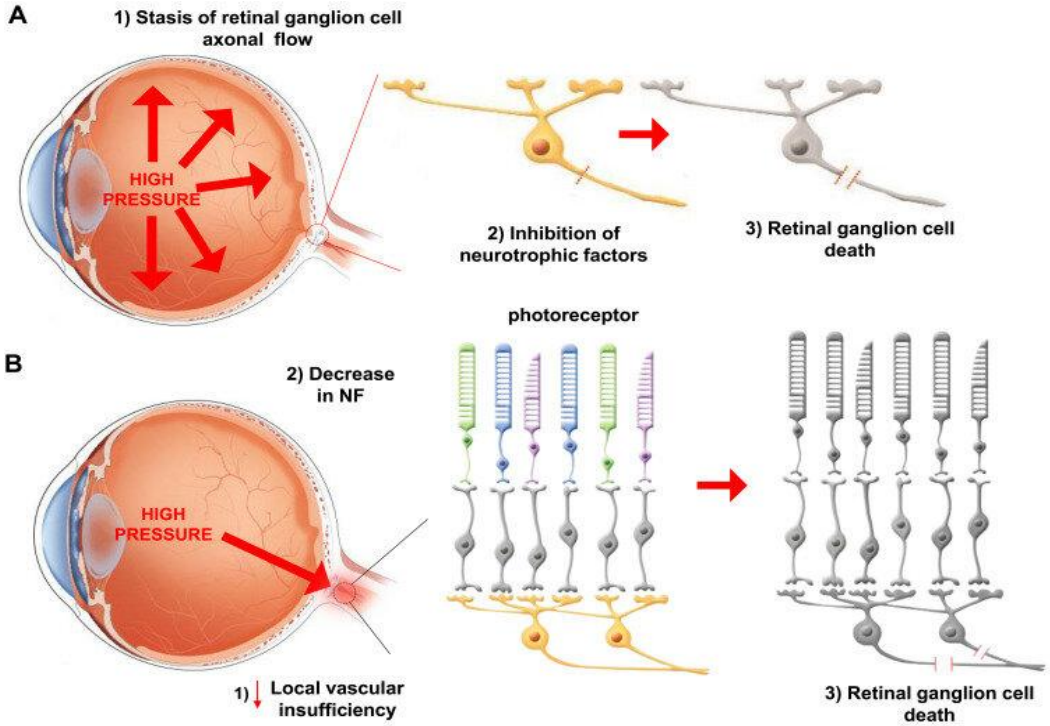


Fig A & B. Two main mechanism of glaucomatous optic nerve damage (A). The elevation of IOP and (B) deficiency of vascular result in the blockage of neurotrophy factors and proteins to induce the death of RGCs.

Limitations of Current Glaucoma Treatment

Topical eye drops, despite their effectiveness, have several drawbacks. These include poor patient compliance due to frequent administration cycles and ocular discomfort. Additionally, the bioavailability of these drops is extremely low, with only 5-10% of the drug being absorbed into the eye [Table 1] [56-57].

The ocular system's natural clearing mechanisms and the corneal epithelium's barrier function further limit drug absorption. As a result, most of the delivered drug is either absorbed into the bloodstream or eliminated through the lacrimal secretion [58].

Surgical treatments, such as drainage devices, also have limitations. Fibrosis around the devices can lead to surgical failure, and antifibrotic treatments can increase the risk of infection.

Furthermore, current treatments for glaucoma are unable to reverse visual loss, and retinal ganglion cell death can continue to progress despite intraocular pressure reduction. This highlights the need for novel strategies, such as nanotechnology-based approaches, to overcome these limitations and improve glaucoma treatment outcomes [59-64].

Mechanism of glaucomatous optic nerve damage	Increased IOP	Stasis of RGC axonal flow →Block NF →apoptotic RGC death
	Local vascular insufficiency	Ischemic damage →Decrease in NFs →RGC death

Table 1 Limitations of Current Glaucoma Medical Treatments

Nanotechnology-Based Ocular Drug Delivery Systems for the Management of Glaucoma

Nanotechnology has revolutionized ocular drug delivery by enabling precise and targeted administration of therapeutic agents. Nanoscale carriers, such as nanoparticles and nanocarriers, have been designed to transport drugs to specific sites within the eye, enhancing solubility, stability, and release while minimizing side effects [55-56].

Over the past two decades, ocular nanotechnology has gained significant attention for its potential to overcome ocular barriers and improve drug bioavailability. Several nanocarriers have received FDA approval and are commercially available for treating various ocular diseases.

This innovative approach has opened up new avenues for treating eye disorders, offering improved treatment outcomes and potential future developments. Recent exploratory studies have demonstrated the clinical applications of nanotechnology-based ocular delivery methods, providing valuable insights into the treatment of various eye diseases [67].

Nanomicelles

Nanomicelles are self-assembling nanoparticles with a hydrophobic core and hydrophilic shell, allowing them to load and deliver hydrophobic drugs. These nanoscale colloidal dispersions can be categorized into three types: polymer, surfactant, and multi-ion composite nanomicelles [68].

Nanomicelles exhibit stimuli-responsive behavior, releasing drugs in response to various triggers such as pH, temperature, or light. This property enhances their potential in pharmaceutical and biomedical research.

Polymer nanomicelle carrier materials can be natural or synthetic, with natural polymers like hyaluronic acid and chitosan offering biocompatibility and non-toxic breakdown products. Synthetic polymers like polyethylene glycol (PEG) and polyacrylamide (PAM) comprise the hydrophilic sections of polymer nanomicelles [68-70].

Recent advances in ocular drug delivery have led to the development of nanomicelle-based treatments, including approved therapies for immune rejection, fungal eye infections, and dry eye syndrome. However, comprehensive toxicology testing is essential to assess the potential cytotoxicity, genotoxicity, and immune response of these nanocarriers before clinical use [70-72].

Nanoparticle

Nanoparticles (NPs) are tiny particles, typically ranging from 1 to 1000 nanometers, composed of various materials such as metals, polymers, lipids, or ceramics. They come in diverse shapes and may have a core-shell structure. NPs can encapsulate both hydrophobic and hydrophilic drugs, protecting them from degradation and enhancing targeted delivery, absorption, and controlled release [73].

In ophthalmic drug delivery systems, NPs are often made from lipids or polymers, including natural and synthetic options. Natural polymers like chitosan and hyaluronic acid offer biocompatibility and minimal toxicity, while synthetic polymers can be engineered for specific properties but may raise clinical concerns [74].

Solid lipid nanoparticles and nanostructured lipid carriers are lipid-based NPs used in drug delivery. NP size significantly affects drug loading and delivery, with smaller NPs offering better stability and biodistribution. NPs between 50-400 nanometres are preferred for ocular drug delivery, with 200-nanometer particles easily absorbed by the cornea and conjunctiva. Surface charge is also crucial, as cationic NPs interact with negatively charged tissues, extending their ocular surface retention [75].

Nanosuspensions for Ocular Drug Delivery

Nanosuspensions (NSs) are a promising approach for delivering hydrophobic drugs to the eye. These formulations consist of pure drug nanoparticles stabilized in a liquid phase, enhancing solubility in both aqueous and organic environments [76-77].

Key Characteristics

- Average diameter below 1 μm (typically 200-500 nm)

- Can be formulated in aqueous or non-aqueous liquid phases

- Require stabilizing agents to maintain particle stability [78-79]

Fabrication Methods

- Top-down techniques: wet milling, dry milling, high-pressure homogenization, co-grinding

- Bottom-up methods: anti-solvent precipitation, liquid emulsion, sono precipitation

- Combination of approaches often employed

Clinical Applications

- Ocular drug delivery: treating conditions like glaucoma, macular degeneration, diabetic retinopathy, and uveitis
- Other routes: oral, brain-targeted, topical, buccal, nasal, transdermal [80-81]

Benefits and Challenges

- Benefits: enhanced drug delivery efficiency, bioavailability, patient comfort
- Challenges: stability, particle size distribution control, safety, toxicity concerns

By optimizing Nano suspension formulations and addressing these challenges, researchers aim to improve ocular disease treatment and expand the potential of NSs in various drug delivery applications [82].

Nanoemulsions and Microemulsions for Ocular Drug Delivery

Nanoemulsions (NEs) and microemulsions (MEs) are promising formulations for ocular drug delivery. NEs are emulsions with sizes ranging from 20-500 nm, composed of two immiscible liquids stabilized by an amphiphilic surfactant. MEs are isotropic and thermodynamically stable dispersions with small droplet sizes (5-200 nm) [84].

Key Characteristics of NEs

- Transparent or translucent

- Thermodynamically unstable but kinetically stable

- Categorized into oil-in-water (o/w), water-in-oil (w/o), and bi-continuous NEs [85].

Advantages of NEs in Ocular Drug Delivery

- Extended pre-corneal retention times

- Increased ability to penetrate ocular tissues

- Enhanced ocular drug bioavailability

- Consistent drug levels in the eye [86].

Clinical Applications of NEs

- Treating anterior segment disorders

- Topical, ocular, and intravenous delivery

- Templates for producing nanocrystals of hydrophobic pharmaceutical ingredients [87].

Challenges and Future Directions

- Need for significant amounts of surfactants

- Concerns about potential toxicity

- Limited capacity to solubilize high-melting-point substances

- Susceptibility to environmental factors affecting stability

- Careful component selection and safety evaluation are essential for pharmaceutical developments [88].

Nanofibers for Biomedical Applications

Nanofibers are one-dimensional nanostructures with unique properties, including high surface-to-volume ratio, porous structure, mechanical strength, flexibility, and resemblance to the extracellular matrix [89].

Key Characteristics

- Diameter: tens to hundreds of nanometers

- Composition: natural polymers (e.g., hyaluronic acid, chitosan), synthetic polymers (e.g., PLA, PLGA, PCL), carbon, or ceramics

- High aspect ratio

- Fabrication methods: electrospinning and non-electrospinning [90].

Clinical Applications

Nanofiber composites are used in various biomedical applications, including:

- Medical implants

- Wound dressing

- Tissue scaffolds

- Drug delivery systems [91].

Nanofibers in Ocular Drug Delivery

Nanofibers offer significant advantages in ocular drug delivery, including:

- High drug loading capacity

- Extended drug release profiles

- Reduced need for frequent dosing [92]

Recent Research

Recent studies have explored the use of nanofiber-based ocular drug delivery systems for both anterior and posterior segment disorders, demonstrating promising results [93].

Dendrimers for Ocular Drug Delivery

Dendrimers are highly branched, nanoscale polymer structures with a three-dimensional design, making them versatile and biocompatible for various applications [94].

Key Characteristics

- Highly branched structure

- Numerous functional groups on their surface

- Can be synthesized to control size, surface charge, and solubility

- Can carry various therapeutic drugs [95].

Clinical Applications

Dendrimers have shown promise in ocular drug delivery, including:

- Topical, intravitreal, and subconjunctival administration

- Treatment of ocular surface disorders, such as dry eye and corneal inflammation

- Posterior segment diseases, including age-related macular degeneration (AMD)

- Corneal tissue engineering

- Genome-editing technology for genetic disorders [96].

Benefits and Challenges

Dendrimers offer several benefits, including:

- Improved drug targeting and reduced systemic side effects

- Prolonged drug half-lives

- Potential for treating various ocular diseases

However, dendrimers also pose challenges, such as:

- Potential cytotoxicity, depending on generation, surface charge, and terminal moiety type

- Need for careful design and synthesis to minimize adverse effects [97]

Liposomes and Niosomes for Ocular Drug Delivery

Liposomes and niosomes are vesicular drug delivery systems designed to encapsulate and deliver drugs in a controlled manner. While they share similar structures, they differ in composition [98].

Key Characteristics of Liposomes

- Spherical vesicles made of phospholipid bilayers

- Can encapsulate hydrophilic and lipophilic drugs

- Biocompatible and biodegradable

- Can be modified for targeted delivery [99].

Key Characteristics of Niosomes

- Composed of non-ionic amphiphilic molecules

- More stable than liposomes due to absence of phospholipids

- Can co-deliver both hydrophilic and lipophilic drugs

- Easier formulation process and lower cost compared to liposomes [100].

Clinical Applications

Liposomes and niosomes are versatile and customizable for regulating drug release rates and targeting specific cells or tissues. Several FDA-approved liposomal products are available for clinical use, including:

- Visudyne® for photodynamic therapy in age-related macular degeneration (AMD)

- Lacrisek and Artelac Rebalance for dry eye disease treatment

Recent studies have explored the use of liposomes and niosomes in ocular drug delivery, highlighting their potential for improved therapeutic outcomes [101].

Nanowafers for Ocular Drug Delivery

Nanowafers are small, transparent disks containing nanoreservoirs filled with medication. These reservoirs release the drug gradually, improving absorption into nearby eye tissue [102].

Key Characteristics

- Contain nanoreservoirs filled with medication

- Release drug gradually, improving absorption

- Dissolve after desired drug release duration

- Made from biodegradable and non-immunostimulatory polymers [103].

Clinical Applications

Nanowafers have shown promise in treating various ocular conditions, including:

- Corneal neovascularization

- Corneal cystinosis

- Dry eye conditions

Studies have demonstrated the effectiveness of nanowafers in:

- Reducing frequency of dosing

- Minimizing systemic exposure and side effects

- Improving therapeutic efficacy

However, careful selection of materials is crucial to ensure biocompatibility and minimize toxicity [104].

Contact Lenses for Ocular Drug Delivery

Contact lenses with integrated nanoparticles or nanoscale materials offer a promising approach for controlled drug delivery directly to the ocular surface [105].

Key Characteristics

- Extend drug retention time and enhance ocular bioavailability

- Two main types: soft contact lenses (SCL) and rigid gas-permeable contact lenses (RGP)

- SCL parameters: transparency, oxygen permeability, and glass transition temperature

- Surface modifying methods: dip-coating, diffusion barrier insertion, molecular imprinting, and incorporation of nanoparticles [106].

Clinical Applications

Contact lenses as drug delivery systems offer numerous advantages, including:

- Sustained drug release

- Targeted delivery

- Improved patient compliance

- Reduced tear dilution

- Protection of sensitive drugs

- Potential for combination therapy

Recent applications include:

- Antibiotics

- Antihistamines

- Immunosuppressants

- Corticosteroids

- Glaucoma drugs

- Treatment of anterior segment ocular disorders

However, challenges remain, such as:

- Controlling drug release rates precisely

- Potential infection risk from improper handling [107]

Hydrogels for Ocular Drug Delivery

Hydrogels are three-dimensional networks of hydrophilic monomers and multifunctional linkers that form a flexible and water-laden structure. They can undergo swelling and shrinkage, facilitating controlled drug release [108].

Key Characteristics

- Composed of natural or synthetic monomers

- Natural hydrogels: biocompatible, biodegradable, but may exhibit weaker mechanical strength

- Synthetic hydrogels: customizable, good batch-to-batch reproducibility, but may face challenges related to clearance and toxicity

- Achieve cross-linking through physical or chemical mechanisms

- Can integrate functionalized components that respond to biological stimuli [109].

Clinical Applications

Hydrogels have been studied for drug delivery in various ocular conditions, including:

- Corneal injuries and fibrosis

- Ocular surface bandages

- Anti-VEGF therapy for retinal diseases

- Transscleral drug delivery for retinoblastoma [110]

Hydrogels can be used in combination with nano-based formulations to prolong drug retention and release. Researchers continue to explore and innovate in this field to improve the effectiveness and safety of ocular drug delivery systems using hydrogels material and design optimization [111].

Microneedles for Ocular Drug Delivery

Microneedles (MNs) are small patches with tiny needles that enable localized drug delivery, enhancing penetration through ocular barriers for improved therapy [112].

Key Characteristics

- Minimally invasive and relatively painless

- Various types: solid, hollow, coated, dissolving, and hydrogel-forming

- Enhance drug permeability and bioavailability [113].

Clinical Applications

MNs have been explored for various ocular conditions, including:

- Keratitis

- Glaucoma

- Age-related macular degeneration

- Uveitis

- Retinal vascular occlusion

- Retinitis pigmentosa

Recent studies have demonstrated the effectiveness of MNs in:

- Treating fungal keratitis with fluconazole-loaded dissolving MN patches

- Enhancing adhesion strength and penetration force with interlocking features

- Achieving controlled drug delivery with polymer-coated polymeric MNs

However, MNs for ocular drug delivery face challenges, including:

- Ensuring precise and consistent insertion and drug delivery

- Potential for eye damage

- Patient acceptance

- Regulatory approvals, standardization, and manufacturing costs [114].

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