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Recent Advanced Technologies for Ocular Drug Delivery: The Transformative Impact of Nanotechnology on Treating Eye Disorders

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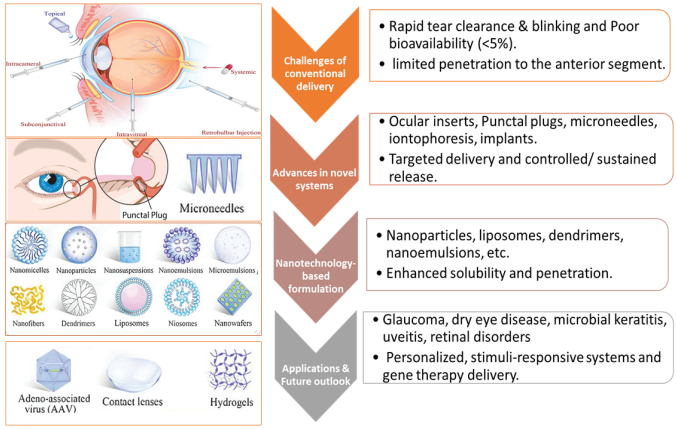
ABSTRACT:

Ocular drug delivery is profoundly challenging due to natural barriers like the corneal epithelium and blood-ocular barriers, which restrict drug penetration, resulting in low bioavailability (<5%) and frequent dosing required by conventional eye drops, thus hindering therapeutic efficacy. To overcome these limitations, innovative delivery platforms, most notably nanotechnology-based systems (including nanoparticles, liposomes, and cubosomes) and advancements like microneedles and sustained-release implants, are being developed to ensure longer residence duration, tailored drug release, and improved penetration for diseases spanning the anterior and posterior segments. While these nanocarriers have demonstrated clinical potential and are already licensed for use, significant obstacles related to long-term safety, cost-effectiveness, and large-scale manufacturing must be standardized. Ultimately, the future integration of smart stimuli-responsive systems, gene therapy, and personalized platforms promises to transform ophthalmic care by delivering safer, more effective, and sustained patient-specific treatments.

KEYWORDS:

Ocular, Nanotechnology, Nanoparticles, Glaucoma, Retinopathy.

Graphical Abstract:



1. Introduction:

The challenge of delivering drugs to the eye

1.1. The Eye's Fortifications

The eye is comprised of three layers: connective, vascular, and neural tissues. The connective tissue consists of the transparent cornea, which is connected to the white sclera through the limbus. The vascular tissue is composed of the choroid, as well as two ciliary bodies in the middle, connected at the front by the iris. The retina constitutes the neural tissue, which functions to transmit electrical impulses to the brain through the optic nerve (1).

The lens is another key transparent structure inside the eye. It is located beneath the iris and is suspended between the ciliary bodies by two ligaments known as the zonule of Zinn (2). The ocular globe is divided into two segments: an anterior segment (filled with aqueous humour)

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and a posterior segment (filled with vitreous humour). The anterior portion of the eye is composed of the cornea, conjunctiva, iris–ciliary body (ICB), lens, and aqueous humour. The posterior segment, on the other hand, is the primary ocular structure, consisting of the sclera, choroid, and retina, which surround the vitreous cavity filled with vitreous humour (3,4).

The eye has various distinct anatomical and physiological barriers that dramatically reduce the bioavailability of medicines, particularly those applied topically. The cornea is one of the principal barriers, as it is part of the static anatomical barriers and is made up of tightly packed epithelial cells and stromal tissue that prevent medicines from entering the anterior chamber of the eye. Furthermore, tear film dynamics, such as tear turnover, nasolacrimal drainage, and blinking, serve as crucial physiological barriers that rapidly wash away delivered medicines, minimizing their contact duration with ocular surfaces (5). Another key barrier is the blood-ocular barrier (BOB), which consists of both the blood-aqueous barrier (BAB) and the blood-retinal barrier (BRB). These barriers consist of tight junctions between retinal capillary endothelial cells and the retinal pigment epithelium (RPE), thereby preventing systemically or topically administered medications from entering the retina and vitreous compartments (6,7,8). The BRB, in particular, is essential for maintaining retinal homeostasis and preventing harmful substances from reaching sensitive neural tissues.

Furthermore, the mucin layer on the corneal and conjunctival surfaces functions as an additional permeability barrier, especially for large molecules, although the exact impact on topical medication bioavailability is unknown (9). Efflux transporters such as P-glycoprotein (P-gp), multidrug resistance protein (MRP), and breast cancer resistance protein (BCRP) actively expel medicines from intraocular tissues, creating another layer of defense that prevents efficient medication absorption (10). These complex and interrelated barriers underscore the inherent difficulties in attaining therapeutic medication concentrations in ocular tissues.

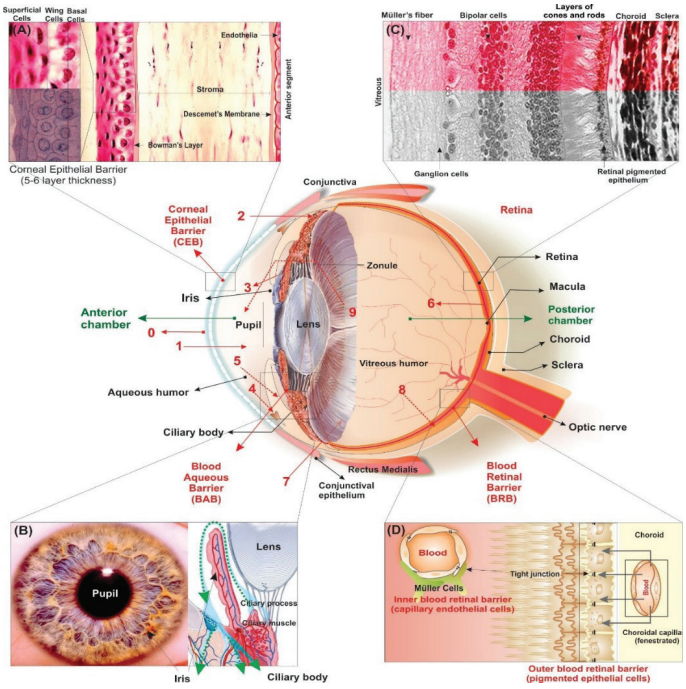

Figure 1: Overview of the anatomical structure of the eye, highlighting physiological barriers that hinder drug delivery (11).

1.2. *The downfall of Droplets*

Conventional methods of ocular drug delivery systems, such as eye drops and ointments, make up about 70% of the ophthalmic medications available in the pharmaceutical market. Among these, eye drops represent nearly 95% of marketed ocular products and remain the most commonly used method. However, despite their widespread use, eye drops are associated with various limitations (12, 13).

Eye drops are favored because they are noninvasive, practical, and safe. However, they suffer from a pulsatile release pattern, where the drug concentration spikes immediately after instillation and then rapidly declines due to physiological clearance, preventing sustained therapeutic levels (14, 15, 16).

Besides the liquid eye drops, there are other forms, such as suspension and emulsion. Ocular suspensions depend on the dispersion of the hydrophobic drug in aqueous solvent; therefore, particle size will be crucial for the physicochemical properties of the formulation. Generally, it's preferred to maintain a particle size <10 µm due to greater solubility, enhanced dissolution rates, but still exhibiting poor retention on the ocular surface. On the other hand, ocular emulsions are a solubilized biphasic system by the presence of surfactants; they provide delivery of hydrophobic drugs as oil-in-water emulsions (O/W), which

exhibit enhanced contact time, bioavailability, and less irritation if compared to water-in-oil emulsions (W/O). In ocular drug delivery, anionic surfactants are generally preferred. Cationic surfactants interact strongly with the negatively charged ocular tissues. This interaction can disrupt cell membranes and cause irritation and toxicity. In contrast, anionic surfactants are much safer and better tolerated.

Another form of eye medication is ointments, which are made with semisolid hydrocarbons that melt at body temperature, to make them more comfortable and less irritating for the patient. Once applied, the ointment melts into small droplets that collect in the cul-de-sac, creating a reservoir for the medication and allowing sustained release. While ointments offer some advantages, they also have some drawbacks. Common problems include blurred vision and discomfort. An alternative to ointments is eye gels, which are also a semisolid dosage form with added polymers to enhance the viscosity and increase bioavailability. They still cause mild and temporary blurred vision, but less prominently than ointments (13). A more comparative overview of conventional ocular drug delivery systems, highlighting their respective advantages, limitations, and future prospects, is illustrated in **Table 1.**

Table 1: Comparative overview of different conventional ocular drug delivery systems.

Types	Brief description	Bioavailability	Advantages	Limitations	Applications	Future Prospects
Eye Drops [17,18]	Clear, sterile aqueous solutions in which the drug is completely dissolved. The most widely used ocular dosage forms are due to simplicity and ease of use. Simplicity.	Very low, around 1–5%, due to rapid precorneal elimination by tear drainage and blinking.	Rapid onset, good tolerability, and excellent patient compliance; ideal for acute treatment of anterior eye conditions.	Necessitates frequent dosing, ineffective for poorly water-soluble drugs.	- Glaucoma - Ocular Infections such as bacterial and viral conjunctivitis or keratitis. - Ocular inflammation due to surgery, trauma, or uveitis. - DED (Dry Eye Disease) to improve lubrication.	- Personalized eye drops based on diagnostic AI tools. - Eye drop delivery of gene-editing technology, such as CRISPR (Clustered regularly interspaced short palindromic repeats), to treat genetic ocular disorders - The delivery of biologics such as Anti-VEGF (anti-vascular endothelial growth factor) is now being explored for delivery through eye drops.
Eye Suspension [19]	A dispersed system containing micronized solid particles intended for drugs with limited water solubility.	Slightly improved over solutions due to slower dissolution and longer retention, especially when particle size is optimized.	Formulations of lipophilic agents can remain longer on the ocular surface due to slower dissolution.	Coarser particles may trigger a foreign-body sensation or mild irritation.	Common in the treatment of ocular inflammation, such as *Pred Forte®* (Prednisolone Acetate Ophthalmic Suspension 1%).	The use of Nanosuspensions containing 100% pure drug in the nano range, by reducing the particle size, increases the surface area and concentration of the drug in the infected area.
Eye Emulsion [20, 21, 22]	Biphasic systems, typically (O/W), are used to solubilize lipophilic drugs for ocular delivery.	Enhanced bioavailability due to better corneal penetration, prolonged contact time, and interaction with the tear film lipid layer.	Ideal for hydrophobic drugs and chronic inflammatory conditions, with low irritation potential.	Require emulsifying agents for stability; may cause mild blurring post-application.	Treatment of dry eye syndrome with an anionic lipid emulsion containing cyclosporine A 0.05% *Restasis™* was approved for clinical use by the FDA (Food and Drug Administration) in December 2002. Also, a non-medicated anionic emulsion formulation, *Refresh Endura®*, for moderate to severe dry-eye syndrome.	- A new generation of artificial tears based on emulsions supplements the tears with lipids acting as a lubricant and, more importantly, as a barrier against evaporation and a tear film stabilizer. - Microemulsions and nanoemulsions, which enhance ocular penetration.

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Eye Gels [19,23,24]	Semisolid formulations with added polymers (e.g., polyacrylic acid, acrylic acids) to enhance the viscosity.	Gels offer higher bioavailability than drops or suspensions.	Gels reduce the frequency of administration, increase patient compliance, and can be tailored for controlled release.	May cause temporary blurring or irritation; formulation challenges include ensuring optimum gelling and clarity.	- Topical anesthesia for surgery or foreign body removal (e.g., *Akten®* FDA-approved ophthalmic gel). - Postoperative inflammation (e.g., *LOTEMAX®* loteprednol etabonate).	- The use of hydrogel-based drug carriers for the delivery of biologic agents in the eye. - The use of in situ-forming gel as a vehicle for loading nano and micro particles to treat ocular diseases.
Eye Ointments [25]	Semisolid formulations using petrolatum or lanolin as a base are ideal for lipophilic drugs and long-term ocular residence.	High bioavailability due to extended retention on the ocular surface and protective barrier effect.	Good choice for lipophilic and moisture-sensitive drugs. Provides prolonged release, enhances drug absorption, and protects the eye post-surgery or during sleep.	Their greasy nature causes vision blurring, limiting daytime use and reducing patient compliance.	- Herpetic keratitis treatment via Avaclyr®, an ocular ointment containing the antiviral acyclovir that was approved in 2019. - Prophylaxis of ophthalmia neonatorum in newborns via Erythromycin 0.5% ophthalmic ointment.	Ointments are currently said to follow a patient-centric approach, with the advancements in nanotechnology and bioengineering.

1.3. The Dawn of a New Era

These previously discussed challenges have created a demand for more advanced, targeted, and sustained release drug delivery technologies. Recent advancements, particularly in nanotechnology, have marked the dawn of a new era in ocular therapeutics. Nanotechnology-based systems, which use nanoscale carriers to increase drug solubility, stability, and targeted administration while minimizing systemic side effects, are among the most promising advances (19, 21, 26). These techniques have shown tremendous promise in both preclinical and clinical contexts, with certain nanocarriers currently approved for use in ophthalmology. The purpose of this review article is to investigate the most recent technological advances in ocular drug delivery, with a special emphasis on nanotechnology, and to assess their therapeutic influence on the treatment of various eye diseases, paving the way for more successful and patient-specific therapies.

2. Advances in Ocular Drug Delivery: Beyond the Nanoscale

For decades, the treatment of ocular disorders has heavily relied on conventional ocular drug delivery systems. As previously discussed, these systems present multiple limitations, including poor drug bioavailability, rapid tear clearance, and issues with patient compliance. Consequently, there has been a pressing need for more advanced ocular drug delivery platforms that offer prolonged residence time, targeted delivery, and enhanced patient adherence. This shift marks the beginning of a new era in ophthalmic care.

2.1. Ocular inserts

Ocular inserts are sterile, thin, multilayered devices with either solid or semisolid consistency. They are designed for placement in the conjunctival cul-de-sac, with careful consideration of Size and shape to ensure suitability for ophthalmic use. These inserts are generally composed of polymers, which may or may not be drug-loaded.

Ocular inserts aim to overcome several disadvantages associated with conventional delivery systems, most notably the “pulse entry” drug release profile. In contrast, they provide controlled, sustained, and continuous drug delivery. A significant advantage of ocular inserts is the reduction in dosing frequency, which contributes to improved patient compliance. However, one of the main limitations of ocular inserts is their solid nature. Patients may perceive them as a foreign body, which can be a barrier to both physical comfort and psychological acceptance. Ocular inserts can be broadly classified based on their solubility into three types: insoluble, soluble, and bioerodible, as shown in **Figure 2.**

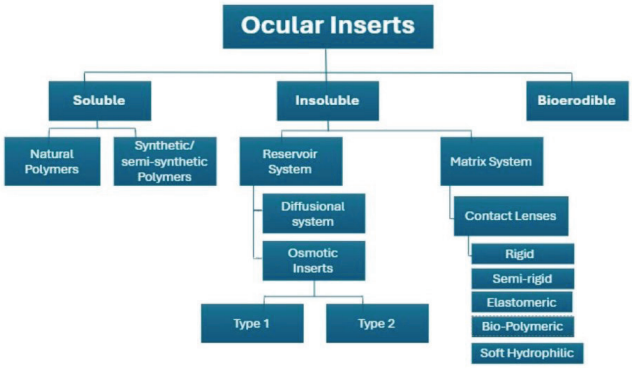

Figure 2: Classification of medicated ocular inserts.

Insoluble inserts are made up of insoluble polymers and may be classified as a reservoir or matrix system, where each system follows a different releasing pattern. Reservoir systems release drugs through either diffusion or osmosis. A prominent example is the *Ocusert®* system, which is a novel ocular delivery platform featuring a porous membrane that regulates the release of a drug reservoir through diffusion at a constant rate, as illustrated in **Figure 3.** The *Ocusert®* pilocarpine system is designed to deliver time-independent drug concentration to ocular tissues. This controlled delivery minimizes side effects such as miosis and myopia, while maintaining effective intraocular pressure (IOP) reduction in glaucoma patients (27).

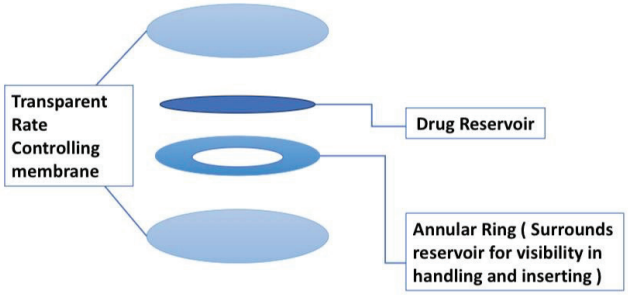

Figure 3: Structure of a reservoir-type ocular insert system, specifically the Ocusert® system.

On the other hand, the osmotic inserts include a central core surrounded by a peripheral layer and exist in two types, as shown **in Figure 4.**

Type 1: Contains a single compartment in which the drug is dispersed throughout a polymer matrix. As osmotic pressure builds, small ruptures form in the semipermeable membrane, allowing the drug to be released near the surface.

Type 2: Consists of two compartments, one for the drug and another for the osmotic solute. Tear fluid enters the solute chamber, generating pressure that stretches an elastic membrane and compresses the drug chamber, facilitating drug release (27).

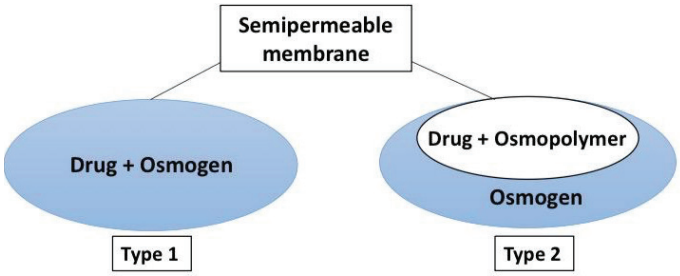

Figure 4: Comparative representation of the two fundamental osmotic insert designs.

Matrix systems are primarily represented by contact lenses. Although traditionally used for vision correction, contact lenses have been repurposed for drug delivery by presoaking them in medicated solutions. They are categorized into five types as mentioned in **Figure 2.**

Rigid lenses, typically made from polymers such as polymethyl methacrylate (PMMA), have poor moisture and oxygen permeability, often causing discomfort. Gas-permeable alternatives, such as cellulose acetate butyrate, offer improved breathability but remain unsuitable for sustained drug delivery. To address this, soft hydrophilic contact lenses have been developed. These offer greater comfort and prolonged drug release for agents including pilocarpine, chloramphenicol, tetracycline, and prednisolone sodium phosphate. Common materials include hydroxyethyl methacrylate, often copolymerized with polyvinylpyrrolidone to increase water content, or ethylene glycol dimethacrylate to reduce it. Drug loading depends on the lens's hydrophilicity, soaking time, drug concentration, and water content.

Now, for the soluble inserts, they dissolve completely in the ocular environment, eliminating the need for removal. These inserts are classified based on the type of polymer used. Type 1 is the Natural polymers (e.g., collagen), while type 2 uses Semi-synthetic polymers (e.g., cellulose derivatives) or Synthetic polymers (e.g., polyvinyl alcohol). Their complete solubility makes them convenient and well-tolerated by patients. However, they may offer lower drug loading capacity and mechanical strength compared to insoluble systems (28).

Bioerodible inserts are formed from polymers that undergo hydrolysis and dissolve over time. A major advantage of these systems is that their erosion rate can be modulated through structural modifications during synthesis and by the addition of anionic or cationic surfactants. However, erosion rates can vary significantly

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based on individual patient physiology. Several commercial and experimental systems include:

SODI (Soluble Ophthalmic Drug Insert): A small, oval, bioerodible insert made from a specially engineered ABE copolymer. This type of copolymer contains Acrylmide derivatives for hydrophilicity and softness, Butyl for controlled erosion, and Ethyl-based monomer for mechanical strength. It softens quickly upon insertion and dissolves within an hour, releasing the drug in a controlled manner.

Collagen Shields: Made from purified animal collagen, these inserts resemble contact lenses and slowly dissolve on the ocular surface. Providing high drug levels in ocular tissues comparable to subconjunctival injections. However, they can cause discomfort, affect vision, and are unsuitable for damaged corneas.

Ocufit: A rod-shaped, insoluble silicone-based insert designed to fit in the conjunctival fornix. It offers extended retention (up to two weeks) and sustained drug release. The cylindrical design improves comfort and reduces the risk of expulsion (28).

Table 2: Comparison between soluble inserts and bioerodible inserts.

Feature	Soluble Inserts	Bioerodible Inserts
Drug-Release Duration	Short-term (minutes to a few hours). For rapid, bulk drug release.	Long-term (hours to days). For sustained, controlled drug release.
Primary Use Case	Acute conditions: postoperative care, infections, immediate relief.	Chronic conditions: glaucoma, dry eye, long-term inflammation.
Patient Tolerance	Generally high. Due to rapid dissolution, minimizing foreign body sensation is important.	Variable; may cause initial discomfort.
Mechanical Strength	Lower. Softer, more fragile polymer structure.	Higher. More durable and robust.
Drug Loading Capacity	Lower. Limited by the small, fast-dissolving matrix.	Higher. Larger and durable matrix supports higher dose.
Example Systems	Basic polymer inserts (e.g., polyvinyl alcohol).	SODI, collagen shields.

2.2. Punctal plugs and Intraocular injections

Another contributor to the advancement in ocular drug delivery is Punctal Plugs, initially developed for the treatment of DED. Punctal plugs are miniature medical implants placed at the punctal opening with an umbrella-like design, with a head, narrow neck, and conical base, which facilitates retention and removal, as seen **in Figure 5.** They are manufactured from materials such as collagen, silicone, hydrogel, polydioxanone, and acrylic. Their primary function is to occlude the lacrimal drainage system, thereby enhancing tear retention and improving the efficacy of artificial lubricants and medications. Punctal plugs have recently gained attention as potential drug delivery systems, especially for conditions like glaucoma. By improving drug retention on the ocular surface, they offer a promising route for sustained therapy. However, they are relatively contraindicated in patients with ocular inflammation, as blocked tear drainage can lead to the accumulation of inflammatory cytokines, worsening symptoms.

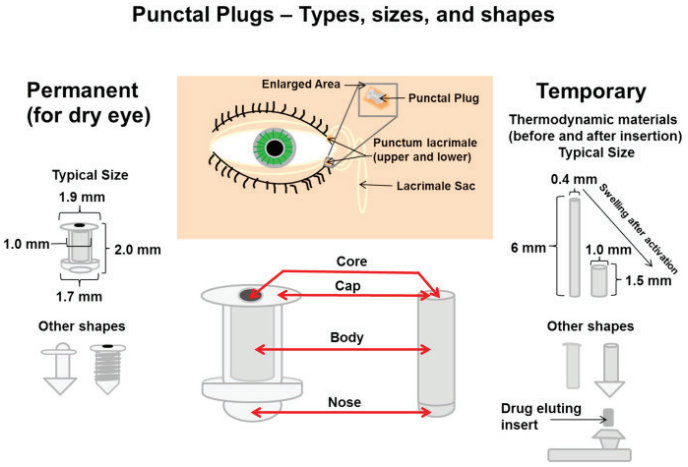

Figure 5: Types, sizes, and structural components of punctal plugs (30).

Among the various novel drug delivery systems, injectable formulations known as intraocular injections have the most impactful application as they can deliver the right amount of drug in the desired area of the eye. Considering this, some of the disadvantages associated with intraocular injections are their invasive nature, frequent application of injections leads to non-compliance, and also less bioavailability, which is where iontophoresis and micro needles came in display (31).

2.3. Iontophoresis and Microneedles

Iontophoresis is a noninvasive drug delivery technique that employs a low-intensity electric current to enhance the penetration of the drug through physiological barriers. By following the basic electrochemical principle that like charges repel and opposite charges attract, iontophoresis facilitates the targeted migration of charged

molecules through biological membranes, including skin, mucosa, joints, nails, and ocular tissues. Compared to conventional topical administration, this approach can achieve drug delivery rates 10–2000 times greater, with dosing directly proportional to the applied current, duration of application, and surface area in contact with the drug reservoir (32).

Two principal electrical modalities are utilized: direct current (DC), which remains the most widely applied in clinical and experimental contexts, and alternating current (AC). The drug transport process is governed by three complementary and synergistic mechanisms. The direct-field effect (Nernst–Planck effect) refers to the electrophoretic movement of charged molecules in response to the applied potential gradient, with ionized substances migrating toward the oppositely charged electrode. This mechanism is particularly significant for small ions. Electro-osmosis involves bulk solvent flow induced by a potential difference across a charged membrane, promoting the movement of both ionic and neutral drugs, and is especially relevant for the delivery of large monovalent ions. Electro-permeabilization describes the transient alteration of membrane porosity and transport pathway characteristics under an electric field, thereby increasing permeability to both charged and neutral molecules during and after current application.

In ophthalmology, iontophoresis has been extensively investigated as an alternative to invasive intravitreal injection for both anterior and posterior segment drug delivery. Transcorneal iontophoresis targets the anterior segment, enabling delivery of antibiotics such as gentamicin, tobramycin, ciprofloxacin, and vancomycin across the cornea despite the formidable barrier posed by its stratified squamous epithelium and tight junctions, as shown in **Figure 6**, but still due to the lens barrier, drugs administered transcorneally rarely achieve therapeutically relevant concentrations in the posterior segment.

To address this limitation, transscleral iontophoresis has been developed, capitalizing on the sclera's higher hydration, lower cellular density, and larger surface area (~17 cm^2 vs. ~1.3 cm^2 for the cornea) to facilitate diffusion of both small and high molecular weight compounds. This route enables drug passage to the posterior segment via the choroid, bypassing the lens and iris diaphragm, as shown in **Figure 6**. Low current transscleral iontophoresis using hydrogel probes has been shown to achieve high intravitreal and retinal drug concentrations in short treatment times, offering a promising therapeutic alternative for posterior uveitis, scleritis, and endophthalmitis conditions traditionally managed by invasive intravitreal injection with associated pain and risk of complications (33).

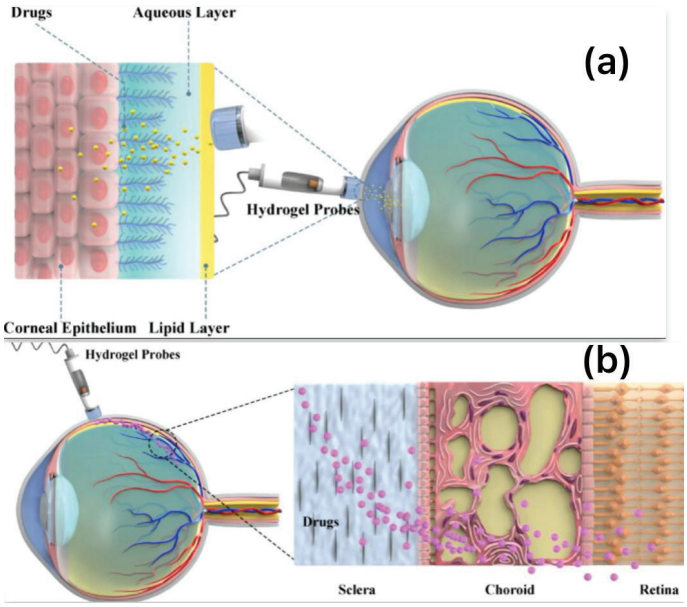

Figure 6: Drug release and penetration by: (a) Transcorneal Iontophoresis (b) Transscleral Iontophoresis (33).

Microneedles are devices made up of polymer or metal having dimensions in the range of a few micrometres to 200 μm, offering a minimally invasive strategy for enhancing ocular drug penetration by creating micro-scale channels in the cornea or sclera, thereby improving tissue permeability and targeted delivery. These microneedles are able not only to overcome the disadvantages associated with conventional delivery systems but also to cross the ocular barriers to specifically target the drugs at the needed site of action. There are three main microneedle types that play a substantial role in drug delivery to ocular tissues. These types include solid coated, hollow, and microneedles of dissolving polymers, as illustrated in **Figure 7**.

Solid coated microneedles are fabricated from non-biodegradable materials such as stainless steel or silicon, and function by piercing ocular tissue, after which the surface coating rapidly dissolves to release the drug. While manufacturing complexity limits their use, they have demonstrated efficacy in enhancing the absorption of agents such as pilocarpine for glaucoma and bevacizumab for corneal neovascularization.

Hollow microneedles, typically made from borosilicate or stainless steel, encapsulate the drug formulation within their lumen.

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Upon insertion, the drug is delivered directly into ocular tissues. These devices can be loaded with nanoparticles, liposomes, emulsions, or microparticles to enhance therapeutic activity. For example, hollow microneedle delivery of triamcinolone acetonide (TA) into the suprachoroidal space effectively managed posterior uveitis for up to three days without elevating intraocular pressure or damaging retinal structures.

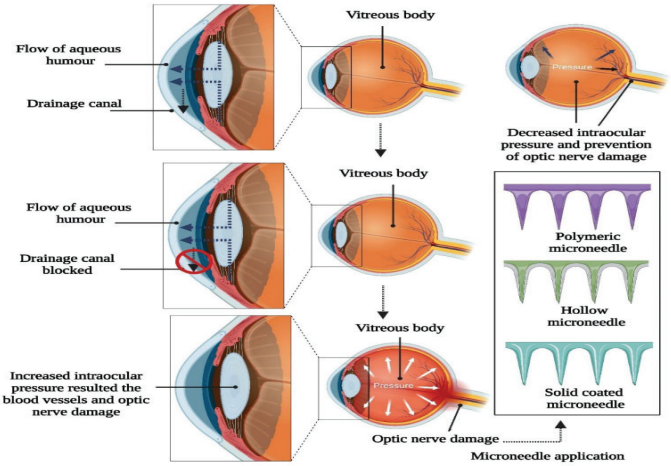

Figure 7: Main types of microneedles and their application in glaucoma treatment (34).

2.4. Ocular Implants

Ocular implants are solid drug delivery devices designed to provide controlled, sustained release of therapeutic agents from either biodegradable or non-biodegradable polymeric matrix over extended periods ranging from several months to years. Implants can be positioned at multiple ocular sites, and they possess the advantage of bypassing the BOB, delivering precise drug doses directly to the target tissue for prolonged durations. Intravitreally placed implants, in particular, can localize therapy to the vitreous with minimal systemic exposure, potentially reducing risks such as infection or retinal detachment.

Biodegradable implants, fabricated from polymers such as polycaprolactone, polyglycolic acid, polylactic acid, polylactic-co-glycolic acid (PLGA), and polyanhydrides, gradually degrade in situ, eliminating the need for surgical removal, a requirement for non-biodegradable counterparts. However, biodegradable systems may exhibit variable drug release kinetics.

By providing continuous medication delivery, ocular implants reduce the frequency of interventions and are therefore well-suited for managing chronic ophthalmic conditions. One notable platform, Durasert™, utilizes a solid polymer matrix capable of releasing small molecule drugs for up to three years. This technology underpins three FDA-approved products, Iluvien®, Retisert®, and Vitrasert®, which have demonstrated clinical utility in long-term treatment of ocular diseases (35).

3. Nanotechnology in Ocular Drug Delivery

In recent decades, the field of ophthalmology has witnessed a transformative shift towards nanotechnology-based formulations for drug delivery to both the anterior and posterior segments of the eye. This innovative approach leverages the unique properties of nanomaterials to overcome the inherent challenges associated with conventional ocular drug administration, offering enhanced therapeutic outcomes and improved patient compliance.

3.1. Why go Nano?

The small Size of nanoparticles, typically ranging from 10 nm to 1000 nm, allows for improved drug penetration into the deeper layers of the ocular structure, including the aqueous humor. This enhanced penetration is crucial for treating conditions affecting the posterior segment of the eye, which are often difficult to reach with conventional formulations (36, 37). Furthermore, nanoparticles can be designed to facilitate enhanced cellular uptake, allowing for more efficient delivery of therapeutic agents into target cells. This ability to overcome ocular barriers and increase drug penetration is a significant advantage over traditional eye drops, which often suffer from limited drug absorption.

(37). Also, one of the critical challenges in ocular drug delivery is the rapid clearance of formulations from the eye due to tear fluid turnover and blinking. Nanoparticles have various types, as seen in **Figure 8**, and some types showcase mucoadhesive properties.

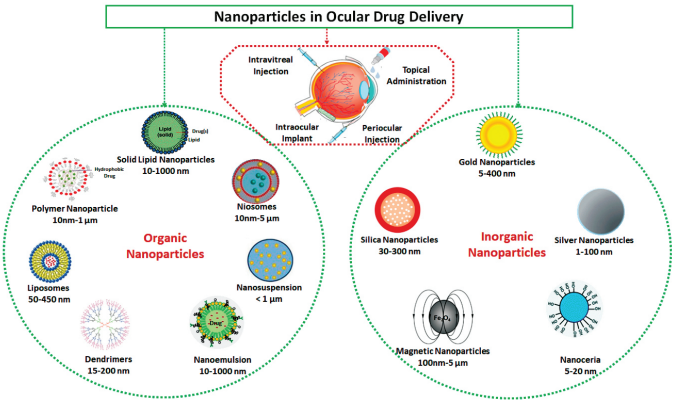

Figure 8: Overview and classification of nanoparticles in ocular drug delivery (38).

3.2. A Menagerie of Nanocarriers

3.2.1. Liposomes

Liposomes are spherical vesicles composed of one or more lipid bilayers, which encapsulate an aqueous core. They vary in Size, ranging from 10 nm to over 1 µm. This unique structure allows them to carry both hydrophilic drugs within their aqueous core and hydrophobic or amphiphilic drugs embedded within their lipid bilayers. They are highly versatile, biocompatible, biodegradable, and generally non-toxic, making them attractive candidates for drug delivery (39).

Structurally, they are classified as unilamellar vesicles (ULVs), possessing a single lipid bilayer, or multilamellar vesicles (MLVs), which consist of multiple concentric lipid bilayers separated by aqueous compartments. ULVs are further categorized by Size into small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), and giant unilamellar vesicles (GUVs). Liposomes with multiple compartments (MLVs) generally have a greater capacity for entrapping hydrophilic drugs due to their larger aqueous volume (39).

The primary building blocks of liposomes are phospholipids, which can be naturally occurring (e.g., egg phosphatidylcholine, brain and synthetic phosphatidylserine, sphingomyelin, ovolecithin) or synthetic (e.g., synthetic dipalmitoyl-dl-α-phosphatidylcholine). To introduce surface charge, other lipids are often incorporated: stearylamine for positive charge, and diacetylphosphate, phosphatidyl glycerol, or phosphatidylserine for negative charge. One of the major limitations is their stability. Liposomes may become chemically unstable due to hydrolysis or oxidation of their constituent unsaturated lipids. They may also become physically unstable due to the leakage of the entrapped drug. Therefore, Incorporation of Cholesterol is frequently added to enhance stability, improve fluidity, and reduce drug leakage (39).

Liposomes still may aggregate to form larger particles that interfere with ocular absorption and also make them susceptible to phagocytosis by phagocytic cells. In general, charged liposomes resist aggregation and fusion better compared to uncharged liposomes, and positively charged liposomes provide greater duration of action and higher drug delivery compared to negatively charged liposomes. This is because positively charged liposomes intimately interact with the negatively charged cornea, leading to prolonged residence time. It has also been suggested that a cationic vehicle slows down the drug drainage with lacrimal fluid by increasing the viscosity and interaction with negative charges of the mucus. The effect of the surface charge of liposomes on ocular irritation has also been evaluated. Positively charged liposomes significantly increase the rabbit eye blinking rate compared to neutral liposomes; however, the mean total score on the Draize test remains below "practically non-irritating level," and no corneal histological changes appeared. Cationic liposomes can also serve to deliver genetic material; they consist of positively charged lipids that interact with and neutralize the negatively charged deoxyribonucleic acid (DNA) and hence, condense the DNA into a more compact structure. Such lipid complexes provide protection to entrapped genetic material and enhance its intracellular delivery. They are of sufficient flexibility to allow synthesis in various sizes and can be formulated as eye drops, gels, and ointments for topical delivery.

3.2.2. Nanoparticles

Polymeric nanoparticles are solid colloidal particles ranging from 10 to 1000 nm, formed from natural or synthetic polymers. They are widely explored for drug delivery due to their versatility, stability, and ability to provide controlled release of encapsulated therapeutics. These nanoparticles are typically composed of biodegradable or non-biodegradable polymers. Common examples include poly (lactic-co-glycolic acid) (PLGA), a synthetic biodegradable polymer widely used due to its biocompatibility and tunable degradation rates, and chitosan, a natural biodegradable polymer derived from crustacean exoskeletons and fungal cell walls. Other polymers like polycaprolactone (PCL) are also utilized (40).

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Drugs can be loaded into polymeric nanoparticles either by encapsulation within the polymer matrix during their formation or by adsorption onto the nanoparticle surface. The method depends on the drug's properties and the desired release profile. For instance, hydrophobic drugs are often encapsulated within the polymer core, while hydrophilic drugs might be loaded onto the surface or within a hydrophilic matrix.

Surface functionalization is a key strategy to enhance the targeting, stability, and drug delivery efficiency of polymeric nanoparticles. This involves modifying the nanoparticle surface with specific ligands, polymers, or other molecules. For example, chitosan's positively charged nature allows for strong mucoadhesive interactions with the negatively charged ocular mucosa, enhancing drug retention and permeability by transiently relaxing tight junctions between cells. The molecular weight and deacetylation degree of chitosan can influence its mucoadhesion to ocular tissues (40). Surface functionalization can also help in evading the body's immune response, improving cellular uptake, or enabling specific targeting to diseased cells or tissues.

Polymeric nanoparticles offer a wide range of advantages, including biodegradability and biocompatibility, especially those made from PLGA and chitosan, leading to minimal toxicity, Controlled and Sustained Release. Therefore, these systems help reduce dosing frequency and improve patient compliance. Polymers like chitosan enhance drug permeability by modulating tight junctions, leading to improved penetration. Chitosan-based nanoparticles also exhibit strong mucoadhesive properties, which increase bioavailability. However, despite these advantages, several limitations exist. The synthesis and functionalization of polymeric nanoparticles can be complex, requiring precise control over formulation parameters. Ensuring consistent particle size, drug loading, and release profiles is often challenging, leading to batch-to-batch variability. Moreover, while generally biocompatible, some synthetic polymers or their degradation products might pose toxicity concerns at high concentrations or over long periods.

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) represent advanced lipid-based colloidal drug delivery systems. SLNs are typically spherical nanoparticles with a solid lipid core matrix at both body and room temperatures. This solid core can effectively solubilize lipophilic drug molecules. The lipid component can be a triglyceride, diglyceride, monoglyceride, fatty acid, steroid, or wax. The solid lipid core is stabilized by surfactants, which prevent aggregation and maintain particle size. SLNs are prepared from physiological lipids, contributing to their low bio-toxicity (41). NLCs are a second generation of lipid nanoparticles, designed to overcome some limitations of SLNs. Unlike SLNs, NLCs are composed of a mixture of solid and liquid lipids in their core. This blend creates an imperfect crystal structure within the lipid matrix, which provides more space for drug loading and reduces the risk of drug expulsion during storage. Similar to SLNs, NLCs are stabilized by surfactants and water (42).

As shown in **Table 2**, both SLNs and NLCs primarily load lipophilic drugs by dissolving them within their lipid core during the formulation process. For hydrophilic drugs, strategies like surface adsorption or creating a hydrophilic shell around the lipid core can be employed. The unique structure of NLCs, with their disordered lipid matrix, allows for higher drug loading capacity and prevents drug leakage more effectively than SLNs.

NLCs offer several advantages over SLNs, making them a preferred choice in many applications. The blend of solid and liquid lipids in NLCs creates an amorphous or imperfect crystal structure, leading to more void spaces within the lipid matrix. This allows for a higher incorporation of drug molecules compared to the highly ordered crystalline structure of SLNs. The disordered matrix of NLCs minimizes drug expulsion during storage, a common issue with SLNs, where drugs can crystallize out of the solid lipid matrix over time, and the disordered matrix can also lead to a more controlled and sustained release of the encapsulated drug, as the drug molecules have to diffuse through a more complex and less uniform matrix. This leads to better long-term stability of the encapsulated drug (42).

3.2.3. Nanoemulsions and Nanosuspensions

Nanoemulsions are submicron emulsions of oil and water stabilised using surfactants. They are especially useful in ocular drug administration because they increase the solubility of poorly water-soluble medicines, improve corneal penetration, and prolong precorneal residency (43, 44). Their small droplet size improves the bioavailability and stability of labile compounds. However, they require rather high concentrations of surfactants, which may cause irritation, and their long-term stability might be influenced by environmental conditions (45).

Nanosuspensions are dispersions of pure

medication nanoparticles stabilised with appropriate agents, making them suited for pharmaceuticals with low water solubility. Compared to conventional formulations, they allow for larger drug loading, faster dissolution, and better absorption (46, 47). Furthermore, they are rather simple to prepare. Nonetheless, the drawbacks of nanosuspensions include particle agglomeration, burst release, and inadequate control over sustained drug administration (48).

3.2.4. Dendrimers

Dendrimers are three-dimensional, highly branched macromolecules with a well-defined architecture and surface groups that can be modified. Their distinct structure allows for significant drug-loading capacity via both encapsulation and surface conjugation, making them appealing carriers for eye therapy (49, 50). They can stay on the ocular surface for longer periods of time, increase corneal permeability, and be functionalised with ligands to deliver drugs to specific tissues (51). Several studies have shown that dendrimers can help manage glaucoma, ocular inflammation, and retinal disorders by increasing therapeutic efficacy and decreasing dose frequency (52, 53). However, their manufacturing is complicated and expensive, and higher-generation dendrimers with positively charged surfaces may cause cytotoxicity or ocular discomfort. Surface changes like PEGylation or acetylation can mitigate these negative effects, increasing their clinical applicability (54).

3.2.5. Niosomes and Cubosomes

Niosomes are vesicular systems composed of non-ionic surfactants and cholesterol, similar in structure to liposomes but more stable and cost-effective. They can encapsulate both hydrophilic and lipophilic medicines, increasing bioavailability and providing prolonged release, thus lowering the need for frequent ocular dosage. Their advantages include high biocompatibility and biodegradability; nevertheless, they sometimes have poorer drug entrapment efficiency than liposomes and may aggregate during storage (52).

Cubosomes, on the other hand, are nanoparticles with a cubic liquid crystalline structure that provide a large surface area, strong bioadhesion, and diversity in drug encapsulation. They show considerable potential in ocular administration because of their capacity to sustain release and increase corneal penetration (53). Despite these advantages, difficult production procedures and stability issues limit cubosomes' clinical application (54, 55).

Table 3: Comparison of different nanoparticle-based drug delivery systems.

Types	Composition	Size and Surface Properties	Drug Loading and Release	Biocompatibility and toxicity	Targeting ability	Applications
Liposome nanoparticles [39]	Spherical vesicles composed of one or more lipid bilayers encapsulating an aqueous core. With other lipids like stearylamine (positive charge), phosphatidyl glycerol, or phosphatidyl serine (negative charge) for surface modification. Cholesterol is often added for stability.	- Size: from 10 nm to over 1 µm. - Surface Properties: Can be cationic or anionic depending on the incorporated lipids. Cationic liposomes show strong interaction with the negatively charged cornea.	It can encapsulate both hydrophilic drugs and hydrophobic/amphiphilic drugs. Stability issues due to hydrolysis/oxidation of unsaturated lipids and drug leakage can occur, but cholesterol addition improves stability and reduces leakage.	Generally biocompatible, biodegradable, and non-toxic. Positively charged liposomes can increase ocular irritation, but often remain below the 'practically non-irritating level'.	Cationic liposomes show enhanced interaction with the negatively charged cornea, leading to prolonged residence and potentially better targeting to the ocular surface.	- Investigated for cancer chemotherapy, it can be formulated as eye drops, gels, and ointments for topical delivery. - Cationic liposomes can deliver genetic material by condensing negatively charged DNA.
Polymeric nanoparticles [40]	Solid colloidal particles formed from natural or synthetic polymers. Common examples include PLGA and chitosan.	- Size: 10 to 1000 nm. - Surface Properties: Surface functionalization is key to enhancing targeting, stability, and drug delivery. Chitosan's positive charge allows for strong mucoadhesive interactions with the negatively charged ocular mucosa.	Drugs can be encapsulated within the polymer matrix or adsorbed onto the surface. They provide controlled and sustained release.	Many are biodegradable and biocompatible, leading to minimal toxicity. Some synthetic polymers or their degradation products might pose toxicity concerns.	Surface functionalization can enhance targeting. Chitosan can improve permeability by relaxing tight junctions.	Widely explored for drug delivery due to its versatility and stability. Chitosan-based nanomedicines are explored for ocular applications in glaucoma.

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SLNs & NLCs [41, 42]	- SLNs: Spherical nanoparticles with a solid lipid core matrix stabilized by surfactants. - NLCs: Composed of a mixture of solid and liquid lipids in their core, creating an imperfect crystal structure, also stabilized by surfactants and water.	- Size: both generally range in Size from 50 to 1000 nm. - Surface Properties: Both are stabilized by surfactants. NLCs show good interaction with corneal mucosa due to biocompatibility and mucoadhesive properties.	Both primarily load lipophilic drugs by dissolving them in the lipid core. Hydrophilic drugs can be loaded via surface adsorption or a hydrophilic shell. NLCs offer higher drug loading capacity and reduced drug expulsion compared to SLNs due to their disordered lipid matrix. Both provide prolonged drug release.	Both are prepared from physiological lipids, making them highly biocompatible and non-toxic.	Both achieve targeting through passive EPR-based accumulation, active ligand-mediated uptake, and stimulus-triggered release. NLCs generally have an edge in loading efficiency and flexibility for functionalization, enhancing their targeting abilities compared to SLNs.	- SLNs: anti-glaucoma drugs (e.g., Methazolamide) and anti-inflammatory drugs (e.g., Cyclosporine A). - NLCs: ocular delivery of poorly water-soluble drugs (e.g., hydrocortisone, estradiol, pilocarpine, propranolol hydrochloride).
Nanoemulsions & Nanosuspensions [43, 44, 46, 47]	- Nanoemulsions are composed of oil and water stabilized by surfactants. - Nanosuspensions are pure drug nanoparticles dispersed with stabilizers.	- Size: for nanoemulsions 20-200nm, nanosuspensions <1000 nm. - Surface Properties: both have High surface area; stability depends on surfactants.	Nanoemulsions and nanosuspensions are both suitable for lipophilic drug loading.	Both are generally biocompatible, but in nanoemulsions, surfactants may cause irritation, and in nanosuspensions, there's a risk of aggregation.	Nanosuspensions achieve targeting mainly through surface modification, charge control, and Size for passive or active delivery, whereas nanoemulsions rely on droplet composition, surface ligands, and Size to direct lipophilic drugs to specific tissues or enhance lymphatic transport.	- Nanoemulsions enhance solubility and corneal penetration, and sustained ocular delivery. - Nanosuspensions improve dissolution and absorption; simple prep for hydrophobic drugs.
Dendrimers [49, 50]	Highly branched synthetic macromolecules (e.g., Polyamidoamine (PAMAM)).	Size: 1-10 m (depends on generation) Surface Properties: Functional surface groups modifiable with ligands.	High encapsulation & conjugation.	Biocompatible if surface-modified; risk of cytotoxicity at higher generations.	High targeting abilities via surface ligand conjugation.	For treatment of glaucoma, uveitis, and retinal diseases, sustained release is required.
Niosomes & Cubosomes [51, 52, 57, 58]	Niosomes are made of non-ionic surfactants + cholesterol vesicles, while Cubosomes are Cubic liquid crystalline lipid nanoparticles.	- Size: Niosomes range from 100-1000 nm and Cubosomes from 100-300nm. - Surface Properties: Niosomes are Similar to liposomes, stable and flexible. Cubosomes have a high surface area and strong bioadhesion.	Niosomes' drug loading is moderate for hydrophilic and lipophilic drugs. On the other hand, Cubosomes' drug loading is high and diverse.	Both are Biocompatible, but niosomes suffer from lower entrapment efficiency than liposomes, and cubosomes may face some stability issues.	Generally limited for both unless modified.	- Niosomes can be used for Glaucoma management, sustained-release eye drops - Cubosomes offer sustained ocular delivery and improved corneal penetration.

4. Clinical Impact of Nanotechnology in Ocular Diseases

The unique properties of nanoparticles offer a promising solution by enhancing drug penetration into the anterior segment of the eye and enabling targeted delivery, thereby improving therapeutic outcomes for chronic eye conditions.

Glaucoma is a known cause of irreversible blindness; the main goal in managing glaucoma is to decrease IOP. However, the efficacy of standard treatments, which are mainly through topical hypotensive agents, is fundamentally limited by previously discussed barriers. Surgical interventions, on the other hand, are effective but compromised by the body's natural fibrotic response (56).

Current research leverages more advanced, biocompatible materials such as biodegradable polymers and specially functionalized nanoparticles. Among the most promising are polymer-based carriers and lipid nanoparticles (LNPs), which have demonstrated excellent biocompatibility for ocular use. Polymeric nanoparticles, especially those made from PLGA, have shown success in preclinical models for the sustained release of IOP-lowering agents like brimonidine.

LNPs are found to be beneficial for glaucoma treatment. Their lipid structure enhances penetration, shields drugs from degradation, and allows for controlled and sustained release. This reduces the need for frequent applications, a major benefit for patient adherence. Furthermore, LNPs can be modified with a polyethylene glycol (PEG) coating to improve their bioavailability and targeting ability. These carriers are now being used to deliver a wide range of small-molecule drugs like prostaglandin analogs to advanced nucleic acid-based therapies, including DNA, small-interfering RNA (siRNA), and messenger RNA (mRNA). For example, siRNA delivered via LNPs has been shown to silence genes responsible for fibrosis, a common complication of glaucoma surgery, leading to better surgical outcomes. Despite this progress, challenges remain in ensuring the long-term stability of lipid formulations, as degradation could compromise drug effectiveness. Additionally, formulations must be carefully designed to avoid triggering an immune response and to optimize drug release for sustained effect (57).

DED is a growing health issue characterized by a loss of homeostasis in the tear film, leading to discomfort and visual problems. Several topical treatments are commonly used to treat DED; however, poor bioavailability is achieved by the majority of eye drops in the market. In this context, there's an indication for enhancing the drug's ability to overcome ocular barriers. Several nanotechnology-based products for DED have already received FDA approval and are available to patients (60).

Restasis®, the first FDA-approved nanoemulsion for DED, delivers cyclosporine (CsA) in an (O/W) formula. Other products like Cationorm® and Ikervis® use the Novasorb technology, which employs electrostatic attraction to prolong the drug's residence time on the negatively charged ocular surface.

Cequa®, a nanomicellar formulation of CsA, was developed to improve drug solubility and bioavailability, demonstrating a higher concentration of CsA in ocular tissues compared to earlier nanoemulsions.

Liposomal sprays such as Tears Again® (marketed as Optrex ActiMist™ in the UK) are applied to the closed eyelids, allowing phospholipids to migrate to the tear film and enhance its stability. Other liposomal products deliver vitamins A, E, and B12 to address deficiencies associated with DED.

Hydrogel formulations like Vidisc® and GelTears® are commercially available and valued for their biocompatibility and ability to provide sustained drug release. Eysuvis®, another innovation, uses mucus-penetrating nanoparticles to deliver loteprednol etabonate for the short-term treatment of DED (58).

Researchers are also exploring novel nanocarriers like niosomes, which are cost-effective and can entrap both water-soluble and fat-soluble drugs, and cubosomes, which offer a large surface area for drug delivery (59).

Microbial keratitis (MK) is a severe infection of the cornea that is caused by a range of microorganisms, such as bacteria, viruses, fungi, and protozoa. It can lead to blindness if not treated promptly and effectively. The rise of antimicrobial resistance has made conventional treatments less reliable, creating an urgent need for new therapeutic strategies. Nanotechnology offers powerful tools to manage MK by improving drug delivery and introducing novel treatment modalities (60).

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Beyond simply acting as delivery vehicles, some nanoparticles have intrinsic therapeutic properties. Innovations in nanomedicine have led to the development of several advanced treatments, including Photothermal Therapy (PTT) and Photodynamic Therapy (PDT). These therapies use nanoparticles that, when activated by light, either generate heat in the case of PTT or produce reactive oxygen species (ROS) in the case of PDT to destroy pathogens. Gold nanoparticles, for example, can convert light energy into heat to kill bacteria and fungi. PDT, which uses a light-activatable dye, has shown promise as an alternative to traditional antibiotics.

Another promising therapy is the use of nanozymes, which are nanomaterials with enzyme-like properties that can combat infection by reducing oxidative stress and promoting tissue repair. Treatments based on multienzyme-like nanozymes are being explored to provide combined antibacterial and anti-inflammatory effects.

Moreover, there are other distinct treatments that differ based on the anatomical target. For instance, in treating anterior segment diseases like infectious keratitis, metal ion therapy has emerged as a powerful antimicrobial strategy. Nanoparticles composed of metals such as silver, copper, or zinc exhibit potent, broad-spectrum activity by generating reactive oxygen species (ROS) and disrupting microbial cell membranes, making them effective against a wide range of pathogens (61).

In contrast, for diseases affecting the posterior segment, nanotechnology focuses on overcoming drug delivery challenges. Anti-VEGF nanocarriers, for example, are designed to manage retinal conditions that currently require frequent intravitreal injections. By encapsulating anti-VEGF compounds in platforms like PLGA microspheres or liposomes, these nanocarriers provide sustained drug release over an extended period. This approach reduces the treatment burden associated with injections every 4–8 weeks, marking a significant improvement in patient care for chronic retinal diseases (62). However, they also share common hurdles, as critical challenges related to toxicity, biocompatibility, and regulatory approval must be addressed to ensure their safe and effective clinical translation. For example, PLGA nanospheres and microspheres can inhibit VEGF for a long time following intravitreal injection (63), whereas pegylated liposome–protamine–hyaluronic acid nanocarriers loaded with siRNA against VEGFR1 have considerably reduced choroidal neovascularisation in animal models (64). Dendrimer-based carriers also have shown long-term suppression of CNV after intravitreal administration (64). Such technologies have the potential to increase treatment intervals and improve patient adherence while remaining effective.

Sustained corticosteroid delivery is essential for treating posterior uveitis because it reduces inflammation while avoiding repeated injections and systemic complications. Nanoparticles and implanted devices have been studied to administer medications such as TA and dexamethasone directly to the vitreous. Ozurdex® (dexamethasone) and Retisert® (fluocinolone acetonide) are FDA-approved implants that offer long-term medication release (months to years) and have been used successfully to treat uveitis (64, 66).

Emerging nanocarrier technologies, such as thermo-responsive hydrogels loaded with PLGA microspheres, can encapsulate drugs like ranibizumab, aflibercept, or corticosteroids and release them for up to 200 days (65). Such platforms reduce the risk of ocular hypertension and cataract advancement caused by repeated corticosteroid bolus injections, providing a safer and more long-lasting treatment option.

5. From bench to bedside: challenges in clinical translation

5.1. The Regulatory Hurdle

The regulatory approval process for ocular nanomedicines is particularly complex, owing to the unique barriers of the eye, as well as the inherent novelty of nanoscale drug delivery systems. Nanomedicines have very different pharmacokinetics (PK) and pharmacodynamics (PD) than standard drug molecules. This is due to their complex nature, which varies significantly in structure, shape, Size, surface properties, and other physicochemical characteristics. This inherent complexity makes it difficult for regulatory agencies, such as the United States FDA and the European Medicines Agency (EMA), to define, classify, and establish standardized PK and PD profiles across the wide range of nanomedicine types.

A significant challenge is the lack of definitive and standardized protocols for assessing nanotoxicity across various ocular layers. Given the human eye's delicate and intricate structure, developing robust in vitro and in vivo protocols is critical for ensuring accurate

and comprehensive safety assessments of nanomedicines. The risk of retinal accumulation, which could cause toxicity in various retinal layers, as well as systemic accumulation that could impair normal ocular functions, highlights the importance of rigorous toxicity testing. Many nanomedicine formulations, particularly those that combine a drug and a delivery device (for example, a sustained-release eye implant), are classified as combination products. This classification introduces new regulatory criteria and frequently necessitates a collaborative review by multiple centers within regulatory bodies. For example, in the United States, the FDA's Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) work together to determine the primary mode of action and the appropriate regulatory pathway. Similarly, in Europe, the EMA's Committee for Medicinal Products for Human Use (CHMP) assesses the proportion of drug and device components in such combined products. Ensuring manufacturing consistency is especially important for nanomedicines (67).

The physicochemical characteristics of nanoparticles can be dramatically changed by slight changes in the production process. To ensure batch-to-batch consistency, regulatory bodies require that manufacturing processes be thoroughly designed and verified. This includes thorough stability testing, guaranteeing sterility for ocular formulations, and adhering to stringent Good Manufacturing Practice (GMP) guidelines for scaling up nanoparticle production. Verifying the final product's quality frequently calls for specialized analytical methods, which further complicates the manufacturing and quality control procedures. As of right now, there isn't a single, internationally consistent regulatory framework for the clinical use of nanomedicines.

This lack of consistency can present additional challenges for developers seeking global market access, as they must navigate varying requirements and guidelines across jurisdictions. Both the FDA and the EMA have strict requirements for demonstrating the safety, efficacy, and manufacturing consistency of ocular nanomedicines. Extensive preclinical studies on safety are expected, including acute and chronic toxicity assessments, detailed ocular histopathology, and PK data that show drug distribution and elimination profiles within the eye. Efficacy demonstration necessitates strong clinical data demonstrating therapeutic benefit, with clinical endpoints relevant to patients. Manufacturing consistency necessitates validated processes that ensure batch-to-batch reproducibility, adhere to GMP guidelines, and employ specialized analytical techniques.

Developers must address these challenges proactively by generating robust safety and efficacy data, ensuring reproducible manufacturing processes, and collaborating early with regulatory bodies to clarify requirements and streamline the approval pathway for advanced therapies (67).

5.2. Safety and Biocompatibility

Clinical trials of nanomedicine formulations for ocular diseases provide important information about their safety and biocompatibility. Phase I/II trials focus on safety and biocompatibility, measuring visual comfort, vital signs, visual acuity, intraocular pressure, and the frequency of adverse events. Safety data for intravitreal injections focuses on inflammation, increased intraocular pressure, and retinal detachment, as well as monitoring for systemic effects. While nanoparticle formulation can prolong drug release and reduce injection frequency, it is critical to monitor for inflammation and immune responses. Dexamethasone intravitreal implants, for example, show sustained release and a consistent safety profile, but common side effects include increased intraocular pressure and cataract formation. Patient feedback is critical for improving delivery methods and formulations, informing the regulatory approval process, and refining therapeutic strategies.

Due to the delicate tissues of the eye, biocompatibility is an important consideration for ocular nanomaterials. This includes assessing nanoparticles' interactions with ocular structures such as the cornea, conjunctiva, vitreous humor, and retina. In vitro and in vivo models are used to assess safety by measuring oxidative stress, cellular viability, tissue integrity, and the absence of inflammatory responses. Nanoparticle toxicity is linked to their biophysical characteristics. Size, for example, influences nanoparticles' entry, cellular uptake, and overall toxicity. Research indicates a direct relationship between nanoparticle size and distribution, as well as the generation of ROS in organs such as the kidneys. Smaller nanoparticles frequently exhibit greater tissue distribution and more severe toxic effects. Beyond Size, nanoparticle shape influences distribution, deposition, and clearance; long, fibrous particles, such as single-walled nanotubes, are particularly difficult for the body to clear, resulting in significant organ deposition. Surface chemistry has a significant impact on pharmacokinetics, as charged nanoparticles accumulate more in target organs than uncharged counterparts. The dissolution of

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nanoparticles, particularly inorganic ones, can also influence acute toxicity, with the release of free ions contributing to the toxic effects (68).

Biodegradable biocompatible polymers are frequently chosen for ocular applications due to their documented safety and non-toxic byproducts. Surface modification, such as PEGylation or anti-inflammatory coatings, is used to reduce toxicity and inflammation. Another strategy is to adjust the surface charge, as highly positively charged particles cause more irritation.

Different types of nanoparticles, such as liposomes, polymeric, and metallic, can elicit a variety of immune responses. Nanoparticles can disrupt the eye's immune privilege, resulting in conditions such as uveitis or increased intraocular pressure. Metallic nanoparticles may cause greater oxidative stress and inflammation than biodegradable polymeric carriers. Understanding these interactions is critical for developing nanoparticles with minimal immunogenicity while maintaining therapeutic efficacy (67).

5.3. Scalability and Cost

Significant scalability and cost issues further complicate the development and commercialization of nanomedicines. Because nanomedicine products are inherently complex, they require careful engineering and design, rigorous physicochemical property characterization, and the development of repeatable scale-up and manufacturing procedures. These steps are critical for achieving a consistent product with stable physicochemical properties, biological behaviors, and pharmacological profiles.

Scaling nanoparticle production from laboratory research to commercial manufacturing presents a number of challenges. Stability and reproducibility are critical, as maintaining consistent nanoparticle physicochemical properties and drug encapsulation efficiency can be difficult during large-scale production. Small variations in process parameters, such as temperature and mixing speed, can have a significant impact on nanoparticle properties, affecting their safety and efficacy. Quality control is also critical, necessitating powerful analytical methods to monitor key characteristics and ensure batch-to-batch consistency. Furthermore, high production costs due to specialized equipment, raw materials, and quality control processes create economic challenges. Addressing these issues through process optimization and advanced manufacturing techniques is critical to the clinical success of nanoparticle-based therapies (67).

6. Future Perspectives in Ocular Drug Delivery

As eye disorders become more common and complex, the future of ocular therapeutics lies in the integration of modern biomaterials, molecular methods, and patient-specific tactics to create safer, more effective, and more convenient treatments. This section emphasises three promising directions: smart response systems, gene therapy delivery platforms, and personalized ocular drug delivery.

6.1. smart systems

Smart ocular drug delivery systems are designed to respond to local physiological cues (pH, temperature, enzymes, and light) or external stimuli, allowing regulated, on-demand drug release. Stimuli-responsive hydrogels can undergo sol-gel transitions or changes in mesh size in response to pH or temperature changes, allowing for reduced dosing frequency and enhanced patient adherence (69, 70). Contact lenses with drug reservoirs or integrated biosensors are another transformative approach: they can continuously monitor tear biomarkers and release therapeutic agents in a feedback-controlled manner, enabling both prophylactic and reactive treatment strategies for chronic ocular conditions (71). These platforms aim to improve local bioavailability while reducing systemic exposure and adverse effects.

6.2. Gene therapy delivery

Gene therapy has previously demonstrated therapeutic promise for hereditary retinal diseases, and optimizing delivery vehicles remains critical to building on these results. Viral vectors, notably adeno-associated viruses (AAVs), have been shown to produce effective transduction and long-term expression in retinal cells in landmark clinical studies (72). However, viral delivery can be hampered by cargo size, immunogenicity, and manufacturing complexity, prompting the development of non-viral nanocarriers. Lipid nanoparticles, polymeric nanoparticles, and dendrimer-based systems provide scalable, customizable, and potentially safer methods of delivering DNA, mRNA, or gene-editing components to retinal tissues (73, 74) Advances in ligand targeting, surface modification, and particle design are enhancing penetration into retinal layers and improving

cellular selectivity, which will be crucial for treating a wider range of inherited and acquired retinal diseases.

6.3. Personalized medicine

In ocular treatments, personalized medicine entails adapting both the drug and the delivery system to each patient's genetics, disease subtype, ocular surface features, and lifestyle. Integration of pharmacogenomic data with tear/blood biomarkers can inform drug selection and dosing, while modular delivery technologies (e.g., adjustable sustained-release implants, sensor-guided contact lenses) allow for therapeutic modifications over time (75). Long-acting ocular implants, for example, may help patients with rapid drug clearance or poor adherence, whereas biosensor-responsive devices may be better suited to individuals with changing disease activity. Personalized approaches have the potential to increase efficacy, reduce adverse effects, and optimize resource utilization in clinical practice; however, widespread implementation will require comprehensive biomarker validation, cost-effectiveness studies, and regulatory frameworks (76).

7. Conclusion

This review highlights the substantial progress made in developing ocular medication delivery systems, particularly those based on nanotechnology, which have shown significant potential to overcome the limitations of conventional eye treatments by enhancing drug penetration, residence time, and targeted delivery. Despite these promising developments, several critical gaps are preventing their widespread clinical adoption.

A primary concern is the lack of long-term safety data, especially regarding the potential for nanoparticle accumulation and chronic inflammation in sensitive ocular tissues. The majority of research remains in the preclinical stage, highlighting a pressing need for well-designed, large-scale human trials to validate both efficacy and safety. Furthermore, significant manufacturing challenges, including high costs, difficulty in scaling up production, and batch-to-batch variability, persist. Delivering drugs to the posterior segment of the eye non-invasively also remains a major, unsolved obstacle.

To move forward, future research must prioritize comprehensive long-term toxicity studies and the development of standardized, GMP-compliant manufacturing processes. Expanding clinical trials is essential to confirm therapeutic outcomes in humans. Looking ahead, the development of "smart" stimuli-responsive systems and the integration of gene therapies could offer even greater precision.

In summary, while nanotechnology is set to transform ophthalmic therapy, its successful clinical translation hinges on overcoming these key scientific, manufacturing, and regulatory hurdles. Continued collaboration between researchers, clinicians, and regulatory bodies is crucial to ensure these advanced treatments become safe, effective, and accessible for patients.

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