

RECENT ADVANCES IN OCULAR DRUG DELIVERY SYSTEMS**Ankit Singh, Sunil Ahirwar*, Reena Shende, SatkarPrasad, Shailesh Kumar Ghatuuary****RKDF School of Pharmaceutical Sciences, BHABHA University, Madhya Pradesh, India***Corresponding Author's E mail: sunilahirwar687@gmail.com

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ABSTRACT

Ocular drug delivery remains challenging due to the eye's unique anatomy and protective barriers that limit drug bioavailability and target access. In recent years, advances in nanotechnology, long-acting biodegradable platforms, microneedles and suprachoroidal approaches, stimuli-responsive "smart" materials, and gene-/biologic-focused delivery strategies have substantially expanded therapeutic options for both anterior and posterior segment diseases. This review summarizes the latest developments (2022–2025) in formulation and device technologies, highlights translational milestones such as sustained-release intracanalicular inserts and emerging suprachoroidal/microneedle systems, and discusses remaining hurdles and future directions for achieving safe, effective, and patient-friendly ocular therapeutics.

Keywords: Ocular drug delivery, nanocarriers, sustained release, microneedles, suprachoroidal, intracanalicular insert, hydrogels, gene therapy.

INTRODUCTION

The human eye is a highly specialized sensory organ that enables vision, one of the most important senses for perceiving and interacting with the environment. Structurally, the eye is a nearly spherical organ measuring about 24 mm in diameter, housed within the protective orbit and supported by accessory structures such as the eyelids, eyelashes, conjunctiva, tear glands, and extraocular muscles. The wall of the eye consists of three principal layers: the outer fibrous coat (cornea and sclera), which provides shape and refractive power; the middle vascular coat or uvea (iris, ciliary body, choroid), which regulates light entry, accommodation, and blood supply; and the inner nervous coat (retina), which contains photoreceptor cells that convert light into electrical signals. Transparent ocular media including the cornea, aqueous humor, lens, and vitreous humor allow the transmission and focusing of light, while the optic nerve conveys the resulting neural impulses to the brain's visual cortex for image

formation (Figure 1). Because of its delicate structure and multiple protective barriers, the eye is prone to a variety of diseases such as glaucoma, age-related macular degeneration (AMD), diabetic retinopathy, dry eye disease, and infectious or inflammatory conditions^{1,2}.

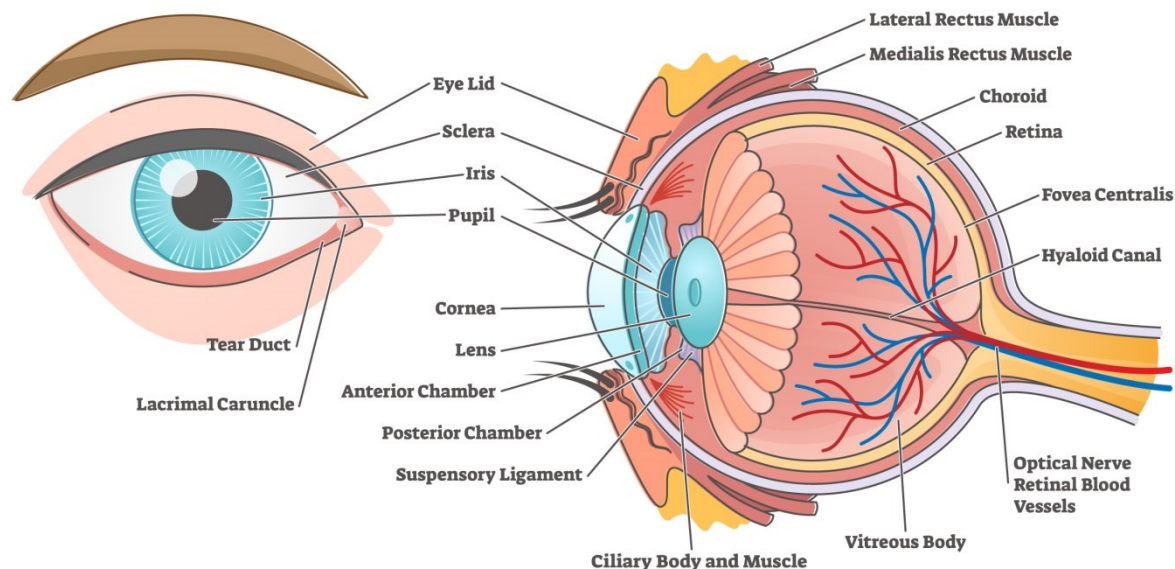


Figure 1: Structure of a human eye

Despite the clinical need, effective ocular drug delivery remains a major challenge. Conventional topical eye drops, which represent the majority of ocular therapies, typically deliver less than 5% of the administered dose to intraocular tissues due to tear turnover, blinking, nasolacrimal drainage, and the formidable corneal epithelium. Posterior segment diseases such as AMD and diabetic macular edema often require repeated intravitreal injections, which are associated with discomfort, risks of infection, retinal detachment, and poor patient compliance. These limitations have driven the search for novel and patient-friendly ocular drug delivery systems capable of enhancing bioavailability, improving targeting, reducing dosing frequency, and minimizing systemic exposure³.

In recent years, significant progress has been made in this field. Nanotechnology-based carriers (nanoparticles, nanoemulsions, micelles, and liposomes) have improved solubility, corneal penetration, and sustained release of drugs. Sustained-release devices such as intracanalicular inserts (e.g., DEXTENZA®) and biodegradable implants (e.g., Iluvien®) offer dropless therapy with better patient adherence. Drug-eluting contact lenses and in situ-forming hydrogels provide prolonged anterior segment delivery with improved comfort. Meanwhile, microneedle arrays and suprachoroidal injections

have emerged as minimally invasive approaches for targeted posterior drug delivery. In parallel, the advent of gene therapy and biologics has accelerated the development of advanced vectors and delivery routes for long-term treatment of inherited retinal diseases and neovascular disorders. Smart and stimuli-responsive platforms, as well as computational modeling tools, are also being investigated to refine release kinetics and predict ocular distribution⁴.

Effective ophthalmic therapy requires delivering therapeutic concentrations to target tissues (cornea, anterior chamber, vitreous, retina, choroid) while minimizing systemic exposure and dosing burden. Conventional topical drops suffer low bioavailability (often <5%) and frequent dosing, while intravitreal injections, though effective for posterior disease, are invasive and associated with complications and treatment burden. Recent innovations focus on raising ocular residence time, enabling targeted posterior delivery, and creating long-acting platforms to reduce dosing frequency. Several approaches spanning materials science, microscale device engineering, and biologic/gene-delivery technologies are now maturing toward clinical translation⁵.

Ocular barriers & design considerations

The eye presents multiple static and dynamic barriers (Table 1): tear turnover and nasolacrimal drainage (limiting topical retention), corneal epithelium (tight junctions restricting permeation), conjunctival/scleral clearance, blood–aqueous and blood–retinal barriers, and vitreous gel diffusion constraints for posterior tissues. Successful designs therefore aim to: (1) increase pre-corneal residence (mucoadhesives, viscosity modifiers); (2) enhance transcorneal/scleral penetration (nanocarriers, permeation enhancers); (3) target posterior tissues (intravitreal, suprachoroidal, or trans-scleral approaches); and (4) provide controlled, long-term release (biodegradable polymers, implants, inserts)^{7,8}.

Table 1: Ocular barriers to drug delivery

Barrier	Location / Structure	Role / Function	Impact on Drug Delivery
Tear Film & Tear Turnover	Precorneal surface; ~7–10 µm thick	Protects ocular surface, provides lubrication, removes debris	Rapid clearance of instilled drugs (half-life 2–5 min), very low drug residence
Conjunctival Epithelium	Covers sclera and inside eyelids	Permeable, rich vasculature	Significant drug loss into systemic circulation, reduced ocular bioavailability
Corneal Epithelium	Stratified squamous epithelium with tight junctions	Main rate-limiting barrier for hydrophilic drugs	Poor penetration of hydrophilic/macromolecules; favors lipophilic molecules
Corneal Stroma	Hydrophilic collagen matrix	Provides structural strength	Limits diffusion of lipophilic drugs
Corneal Endothelium	Single cell layer, leaky junctions	Maintains corneal hydration	Less restrictive, allows some drug passage
Sclera	Collagen-rich connective tissue	Provides structural integrity	Allows passage of hydrophilic drugs, but collagen density limits large molecules
Blood–Aqueous Barrier (BAB)	Tight junctions in ciliary body epithelium and iris vessels	Regulates exchange between blood and aqueous humor	Restricts entry of systemic and topical drugs into anterior chamber
Vitreous Humor	Gel-like matrix filling posterior segment	Maintains eye shape and supports retina	Hinders diffusion, especially of large/charged molecules
Blood–Retina Barrier (BRB)	Tight junctions in retinal pigment epithelium (RPE) & endothelium	Protects retina from blood-borne toxins	Strongly restricts systemic drug entry to posterior segment; major hurdle for retinal therapy
Lymphatic & Efflux Pumps	Widely distributed	Active transporters (P-gp, MRP) and lymphatic clearance	Actively efflux drugs, reducing intracellular drug accumulation

Nanocarriers: versatility for anterior & posterior delivery

Types & mechanisms

Nanoparticles (polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanocrystals, dendrimers) can encapsulate hydrophilic or hydrophobic drugs, protect labile molecules, and enable controlled release and enhanced tissue penetration. Surface modification (PEGylation, targeting ligands) and size/tortuosity tuning allow modulation of corneal uptake and scleral permeation. Several 2023–2024 comprehensive reviews summarize the progress and translational potential of these platforms⁹.

Clinical prospects & limitations

Nanocarriers have shown improved ocular bioavailability in preclinical models and early clinical settings for anti-inflammatory, anti-infective, and anti-VEGF payloads. Key limitations remain scale-up reproducibility, stability in ophthalmic formulations, ocular tolerability (irritation/immunogenicity), and regulatory pathways for complex nanomedicines¹⁰.

Long-acting biodegradable platforms, inserts and implants

Biodegradable implants and injectable depots (e.g., microspheres, in situ-forming gels) deliver drugs for months. These are useful for chronic posterior diseases; formulation work focuses on release kinetics, payload stability (small molecules and biologics), and minimizing inflammatory responses¹¹⁻¹³.

Table 2: Ocular drug delivery systems

System / Platform	Route / Placement	Examples	Mechanism	Advantages	Limitations
Conventional Eye Drops	Topical (corneal surface)	Antibiotics, antiglaucoma agents	Passive diffusion across cornea/conjunctiva	Simple, noninvasive, inexpensive	Low bioavailability (<5%), frequent dosing needed
Ointments / Gels	Topical	Artificial tear gels, steroid ointments	Increased viscosity prolongs residence	Longer contact time, useful for dry eye	Blurred vision, poor patient compliance
Nanoparticles / Nanomicelles	Topical, periocular, intravitreal	Polymeric nanoparticles, lipid nanoparticles, polymeric micelles	Enhance solubility, adhesion, sustained release	Better penetration, prolonged release, protection of labile drugs	Sterility, toxicity concerns, complex manufacturing
Liposomes /	Topical or	Liposomal	Encapsulation of	Biocompatible	Stability issues,

Nanoemulsions	intraocular	cyclosporine, lipid emulsions	hydrophobic drugs	, improve solubility, sustained release	cost
Microspheres / Implants	Intraocular / periocular	Retisert®, Iluvien® (fluocinolone acetonide implants)	Controlled/long-term release	Months–years of therapy, improved compliance	Invasive procedure, risk of complications (infection, detachment, migration)
Intracanalicular Inserts	Lacrimal canaliculus	DEXTENZA® (dexamethasone insert)	Biodegradable insert releasing drug over weeks	Droplless therapy, improved adherence	Device retention issues, cost
Drug-Eluting Contact Lenses	Corneal surface	Timolol-, bimatoprost-eluting hydrogel contact lenses	Drug reservoir releases drug during wear	Sustained anterior delivery, patient friendly	Manufacturing, sterilization, optical clarity concerns
Microneedles / Suprachoroidal	Minimally invasive periocular/posterior	Suprachoroidal triamcinolone delivery systems	Direct drug delivery to posterior segment	Targets retina/choroid, reduced systemic exposure	Requires precision devices, long-term safety still under study
In Situ Hydrogels	Topical / intraocular injection	Thermosensitive or pH-sensitive polymeric hydrogels	Sol–gel transition forms depot at site	Prolonged release, adaptable to many drugs	Biocompatibility, burst release risk
Gene & Biologic Delivery	Subretinal, intravitreal, suprachoroidal	Luxturna® (voretigenepa rvoec), anti-VEGF biologics with extended delivery	Viral/nonviral vectors, sustained biologic implants	Long-term correction of genetic defects, targeted biologic action	Expensive, immune response, complex regulatory pathways
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Intracanalicular inserts and contact-lens platforms

Biodegradable intracanalicular inserts (e.g., dexamethasone intracanalicular insert) and drug-eluting contact lenses provide sustained anterior segment delivery and remove the need for frequent topical

drops. DEXTENZA® (a PEG-based intracanalicular dexamethasone insert) is an example of a clinically approved sustained-release platform that supplies therapeutic levels for up to 30 days and has catalyzed interest in similar designs for anti-infectives, antiproliferatives, and antiglaucoma agents¹¹.

Intraocular implants for posterior disease

Biodegradable and non-biodegradable intravitreal implants deliver anti-VEGF agents, steroids, or gene therapies over months to years. Recent reviews highlight next-generation polymers (PLGA variants, hydrogels) and refillable or refill-port implants that seek to reduce injection frequency for AMD and diabetic macular edema. Extended-release platforms for the retina and choroid are actively being evaluated in preclinical and early clinical studies¹².

Microneedles & suprachoroidal delivery enabling targeted posterior access

Microneedles (solid, coated, hollow, dissolving) are emerging as minimally invasive tools for periocular and transscleral delivery. They can deposit drug or depot formulations into the sclera, suprachoroidal space, or subretinal vicinity with higher local bioavailability and lower systemic spread than topical routes. Suprachoroidal injections via microcannula or microneedles target the choroid and retina directly and are being developed for steroids, small molecules, and gene vectors. Recent high-impact studies (2024–2025) demonstrate improved posterior tissue concentrations and acceptable safety profiles in animal models; several device designs are progressing into early human testing¹³⁻¹⁵.

Smart & stimuli-responsive materials

Stimuli-responsive hydrogels, in-situ gelling systems, and light/temperature/pH-sensitive polymers enable on-demand or environment-triggered release. Smart contact lenses that respond to tear-film or ocular surface conditions and hydrogels that swell or degrade in response to enzymes or pH have been reported. These materials can improve residence time, provide pulsatile dosing, or release payloads in response to disease-specific signals (e.g., inflammation). Reviews in 2023–2024 highlight the potential of these materials but emphasize biocompatibility and reproducibility challenges before clinical translation¹⁶.

Gene therapy, biologics, and payload considerations

Gene therapies (AAV, lentiviral vectors) and biologics (monoclonal antibodies, peptides) demand delivery systems that preserve activity while minimizing immune responses. While intravitreal and subretinal injections remain primary routes for gene therapy, suprachoroidal and less invasive

platforms are being explored to reduce procedure complexity. Advances in vector engineering and targeted carriers have expanded therapeutic targets beyond rare inherited retinal dystrophies to common retinal vascular diseases. The delivery of large biomolecules accentuates the importance of release kinetics, sterility, and device compatibility¹⁷.

Modeling, imaging, and design optimization

Computational fluid dynamics (CFD), pharmacokinetic modeling, and high-resolution ocular imaging (OCT/OCTA, adaptive optics) are increasingly used to predict drug distribution, optimize implant geometry, and assess local tissue responses. These tools reduce reliance on lengthy empirical optimization and help match delivery kinetics to disease biology an approach reflected in several 2024–2025 engineering studies¹⁸.

Regulatory, safety, and translational challenges

Key barriers to translation include: (1) ensuring long-term ocular safety (chronic inflammation, glaucoma, cataract risks for steroid depots); (2) manufacturing and sterilization challenges for complex devices and biologic-loaded platforms; (3) demonstration of patient benefit versus standard-of-care in controlled trials; and (4) establishing scalable, cost-effective production particularly for nanocarriers and polymeric implants. Regulatory agencies have begun to issue guidances for combination products, but harmonized pathways for novel ocular devices and nanomedicines remain evolving¹⁹⁻²².

Future directions & perspectives

Combination platforms (e.g., nanocarrier-loaded implants, microneedle-assisted nanoparticles) that integrate targeting and sustained release are likely to accelerate clinical impact.

Minimally invasive posterior delivery (microneedles, suprachoroidal devices) could shift many intravitreal therapies toward office-based, lower-risk procedures.

Personalized dosing and smart release using stimuli-responsive materials and real-time ocular monitoring may reduce adverse events and optimize efficacy.

Focus on manufacturability, cost, and access, especially for long-acting therapies for chronic diseases (AMD, diabetic retinopathy, glaucoma), will determine global adoption.

CONCLUSION

Progress across materials science, micro-device engineering, and biologic delivery has delivered a pipeline of promising ocular drug delivery solutions aimed at improving efficacy, safety, and patient adherence. Approved sustained-release platforms (such as intracanalicular inserts) demonstrate the clinical feasibility of long-acting approaches, while cutting-edge microneedle/suprachoroidal systems and smart materials offer routes to safer, more targeted posterior therapy. Addressing translational challenges safety, manufacturability, and regulatory clarity will be essential for these innovations to reach patients at scale.

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