

Ocular Drug Delivery System A Review

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Abstract

The development of ocular drug delivery systems (ODDS) is a complex task because of the eye's anatomy and physiology that are barriers to drug penetration and retention. Current preclinical and clinical studies have shown that conventional eye drops, ointments, suspensions, and solutions have poor bioavailability due to precorneal drug loss, blinking, and nasolacrimal drainage with values less than 5%. Recently, new ocular drug delivery systems such as nanoparticles, in-situ gels, ocular inserts, and microneedles have been developed to increase the residence time of the drug in the eye, penetration, and patient compliance. This review aims to give an insight into ocular barriers, conventional and emerging ocular drug delivery systems, parameters of the preclinical and clinical evaluation, and future prospects to improve ocular therapy.

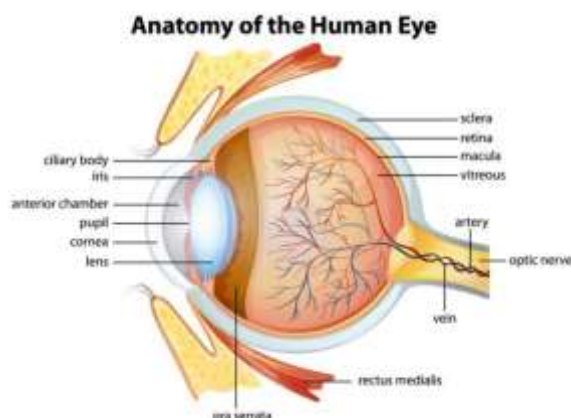
Keywords: Ocular drug delivery, bioavailability, nanoparticles, microneedles, sustained release, in-situ gel.

Introduction

The human eye is a highly specialized organ responsible for vision and protection from environmental factors. Its complex structure, while vital for function, presents considerable challenges for drug delivery. Most ocular diseases require localized and sustained therapeutic intervention, but conventional dosage forms such as solutions, suspensions, and ointments fail to maintain effective drug concentrations for prolonged periods. The bioavailability of topically applied drugs is extremely low because of protective mechanisms including blinking, tear dilution, and drainage into the nasolacrimal duct.

Ocular diseases, affecting either the anterior or posterior segments of the eye, require targeted drug delivery to achieve effective therapeutic concentrations while minimizing systemic exposure.¹

The global burden of ocular disorders is increasing, with millions affected by glaucoma, cataracts, AMD, diabetic retinopathy, and infectious diseases. Over the past decade, pharmaceutical scientists have turned to nanotechnology, biodegradable polymers, and minimally invasive devices to overcome these challenges. This article provides a comprehensive overview of ocular barriers, conventional delivery approaches, and recent innovations, while also highlighting clinical applications and future perspectives.²



[Fig. 1 Anatomy of the Human Eye]

Anatomy and Physiology of the Eye Relevant to Drug Delivery

The human eye is a highly specialized organ with distinct anatomical structures and physiological functions that significantly influence ocular drug delivery.

The outermost surface is covered by the tear film, a trilaminar structure consisting of lipid, aqueous, and mucin layers, which maintains ocular surface integrity, provides lubrication, and forms the first barrier to drug permeation due to its rapid turnover and dilution effects. Beneath the tear film lies the cornea, a transparent, avascular tissue composed of epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium, each exhibiting different permeability properties; the lipophilic epithelium restricts hydrophilic molecules, whereas the hydrophilic stroma limits lipophilic molecules, making corneal penetration highly selective. The sclera, composed mainly of collagen and water, allows diffusion of hydrophilic molecules but provides resistance to large macromolecules.³

The anterior chamber, filled with aqueous humor secreted by the ciliary body, acts as a reservoir for topically absorbed drugs, while the blood–aqueous barrier formed by tight junctions of ciliary epithelium and iris vasculature regulates drug entry from systemic circulation. Posteriorly, the vitreous humor, a gel-like matrix of collagen and hyaluronic acid, slows down the diffusion of large molecules and contributes to prolonged retention of intravitreally injected drugs.⁴

Barriers to Ocular Drug Delivery

The human eye has several protective mechanisms to prevent damage to its intricate system. While these barriers protect the eye from foreign toxins, they also impede the delivery of therapeutic agents.⁵

1. Precorneal Barriers

The precorneal space is comprised of the tear film, corneal surface, and conjunctival sac. This region is the first site of drug absorption.

Tear Film Dynamics: The tear film, which consists of lipid, aqueous, and mucin layers, is constantly renewed. Tear turnover ($\sim 1 \mu\text{L}/\text{min}$) and reflex tearing induced by drug instillation rapidly wash away instilled solutions, resulting in significant drug loss.

Blinking Reflex: Blinking distributes the tear film but simultaneously expels excess fluid, limiting the residence time of topically applied drugs.⁶

Limited Instilled Volume: The cul-de-sac of the conjunctiva can only accommodate 25–30 μL , while a standard eye dropper delivers about 30–50 μL , resulting in spillage and loss of drug.

2. Corneal Barrier

The cornea serves as the primary site for drug absorption into the anterior chamber, but its multi-layered structure presents a formidable obstacle.

Epithelium: The outermost lipophilic epithelial layer is composed of tightly packed cells connected by tight junctions, restricting the permeation of hydrophilic and large molecular weight drugs.

Stroma: The central hydrophilic stroma limits the transport of lipophilic drugs.

Endothelium: While more permeable than the epithelium, the endothelium still restricts the passage of macromolecules.

3. Conjunctival and Scleral Barriers

Conjunctiva: This highly vascularized tissue allows absorption, but extensive blood and lymphatic circulation result in significant drug clearance before reaching intraocular tissues.

Sclera: Although relatively permeable to hydrophilic drugs and macromolecules, the scleral barrier limits penetration due to its dense collagen fibril structure, particularly at the posterior segment. ⁴

4. Blood–Ocular Barriers

Two highly selective barriers regulate the exchange of substances between systemic circulation and ocular tissues:

Blood–Aqueous Barrier (BAB): Located at the ciliary body and iris vasculature, this barrier prevents the entry of many systemically administered drugs into the aqueous humor.

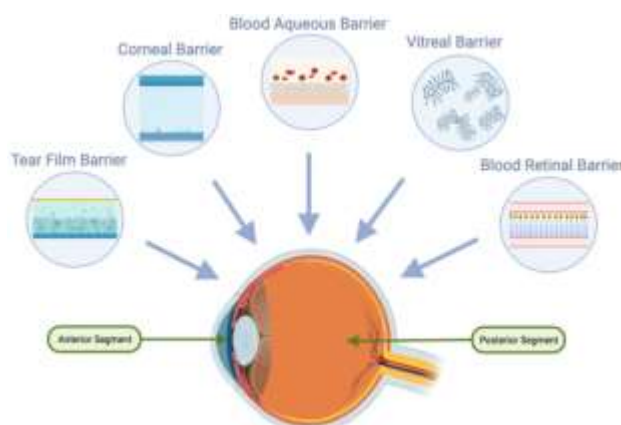
Blood–Retinal Barrier (BRB): Formed by retinal capillary endothelial cells and retinal pigment epithelium (RPE), this barrier protects the neural retina from harmful substances but severely restricts drug entry into the posterior segment. ⁷

5. Efflux Transporters

Active efflux pumps, such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRPs), are expressed in ocular tissues, including the corneal epithelium and retinal pigment epithelium.

6. Enzymatic Barriers

Ocular tissues contain various metabolizing enzymes such as esterases, peptidases, and oxidoreductases. These enzymes degrade drugs before they reach their site of action, leading to reduced bioavailability. For example, peptide-based drugs and prodrugs are highly susceptible to degradation in the tear film and corneal epithelium. ⁸



[Fig. 2: Diagram of Ocular Barriers]

Mechanism of Ocular Drug Absorption

The absorption of drugs into the eye is a multifactorial process determined by the interaction between drug physicochemical properties, ocular barriers, and physiological processes. Unlike systemic absorption, ocular absorption occurs in a highly compartmentalized environment, where precorneal and intraocular factors play dominant roles.

1. Precorneal Factors Governing Absorption

When a drug is instilled as an eye drop, it first encounters the precorneal environment (tear film, blinking, and nasolacrimal drainage). This stage significantly limits absorption.

Dilution in tear fluid: Tear film volume is about 7–10 μL , whereas commercial eye drops deliver ~30–50 μL , resulting in immediate spillage and dilution.

Tear turnover and drainage: Lacrimation and blinking rapidly remove the drug, reducing contact time.

Tear proteins and enzymes: Protein binding (e.g., Lysozyme, lactoferrin) and enzymatic degradation (esterases, peptidases) reduce active drug concentration.

Thus, only a small fraction of the instilled dose remains available for absorption.

2. Physicochemical Mechanism of Permeation

Drugs penetrate ocular tissues primarily via passive diffusion, but other mechanisms may also contribute depending on drug type.

Passive Transcellular Diffusion: Lipophilic drugs partition into the cell membrane lipids and diffuse across epithelial/endothelial cells down a concentration gradient.

Passive Paracellular Diffusion: Small hydrophilic molecules may pass through the tight junctions between epithelial cells, although this pathway is highly restricted in the cornea.⁹

Facilitated Diffusion: Some nutrients and drugs (e.g., glucose, amino acids) utilize carrier-mediated transporters expressed on corneal and conjunctival membranes.

Active Transport & Efflux Mechanisms: ATP-binding cassette (ABC) transporters such as P-glycoprotein and MRP actively efflux certain drugs, limiting absorption.

Endocytosis & Transcytosis: Macromolecules, peptides, proteins, and nanoparticles may enter cells via vesicular uptake mechanisms such as pinocytosis or receptor-mediated endocytosis.

3. Partitioning Across Ocular Layers

The corneal epithelium is lipophilic, the stroma is hydrophilic, and the endothelium is again lipophilic.¹⁰

4. Distribution within the Eye

Once absorbed, drug distribution depends on intraocular circulation:

Aqueous humor dynamics: Drugs enter the anterior chamber, circulate, and may be cleared through trabecular meshwork or uveoscleral outflow.

Binding to ocular pigments: Lipophilic and basic drugs may bind to melanin in the iris/ciliary body, influencing retention and prolonged release.

Posterior segment penetration: Conventional absorption mechanisms rarely allow significant drug levels in the retina or vitreous due to blood–aqueous and blood–retinal barriers.^{7, 11}

5. Rate-Limiting Steps in Absorption

Limited residence time on the ocular surface. Tight junctions in corneal epithelium restricting hydrophilic molecules. Efflux transporters pumping drugs back into the tear film. Enzymatic degradation in tears and corneal epithelium.^{8, 12, 13}

Conventional Ocular Drug Delivery Systems

Table 1. Conventional ocular dosage forms

Formulation Type	Advantages	Limitations
Eye drops	Easy to use, cost-effective	Rapid clearance, low bioavailability
Ointments	Prolonged contact time	Blurred vision, greasy feel
Solutions/Suspensions	Simple manufacturing	Irritation ,sedimentation
Eye washes	Large surface coverage	Short contact time

Novel Ocular Drug Delivery Systems

Eye drops, ointments, and suspended drug solutions are the most common types of formulations used today, but are often limited by rapid precorneal removal, poor corneal penetration, and low total bioavailability (<5% of instilled dose reach target intraocular tissues). Development of novel ocular drug delivery systems (NDDS) have been made to increase corneal/ conjunctival penetration, prolong residence time, achieve targeted posterior ocular segment delivery, and improve drug efficacy, with reduced dosing frequency to improve patient compliance.^{14, 15, 16}

1. Nanoparticles

Nanoparticles are submicron particles generally made of a biodegradable polymer such as poly (lactic-co-glycolic acid) (PLGA), chitosan or polycaprolactone. The small size allows intimate contact with the corneal epithelium and the addition of mucoadhesive polymers at the particle surface improves precorneal retention. Nanoparticles offer protection to the entrapped drug from enzymatic breakdown and provide controlled release by restricting drug diffusion or polymer erosion.^{17, 18}

2. Liposomes

Liposomes are spherical bilayer structures made of phospholipids which encapsulate hydrophilic and lipophilic drugs within the aqueous core and lipid bilayer respectively. Liposomes improve drug solubility and offer protection from degradation while facilitating penetration of the hydrophobic corneal epithelium. Studies have shown cationic liposomes to have electrostatic affinity to the negatively charged corneal surface leading to increased adhesion and sustained drug release from their surfaces.¹⁹

3. Niosomes

Niosomes are nonionic surfactant vesicles that mimic the properties of liposomes but have proven to offer better chemical stability, high entrapment efficiency and patient tolerance than liposomes. Niosomes improve ocular residence time and facilitate better penetration of various drugs.²⁰

4. Dendrimers

Dendrimers are monodisperse highly-branched macromolecules that have numerous functional groups on their surface, allowing for multiple drug attachment sites, encapsulation and targeted delivery. Polyamidoamine (PAMAM) dendrimers have been considered for ocular use due to enhanced solubility, controlled drug release and site specific targeting.²⁰

5. In-situ Gelling Systems

In-situ gelling systems are solutions that undergo sol to gel transition on exposure to physiological stimuli such as pH, temperature or ionic strength. Polymers such as gellan gum, carbopol and poloxamers have been used to develop such formulations.^{16, 21}

6. Microneedles

Microneedles are an interesting novel approach for posterior segment targeting. These fine needles can penetrate the tough sclera or corneal surface without causing damage to deliver the drug directly to intraocular tissues while avoiding systemic toxicity.¹⁶

7. Implants and Inserts

Ocular implants and inserts provide controlled prolonged release of drug and are beneficial in chronic diseases of the eye like glaucoma and macular degeneration.¹⁶

8. Contact Lens Based Delivery

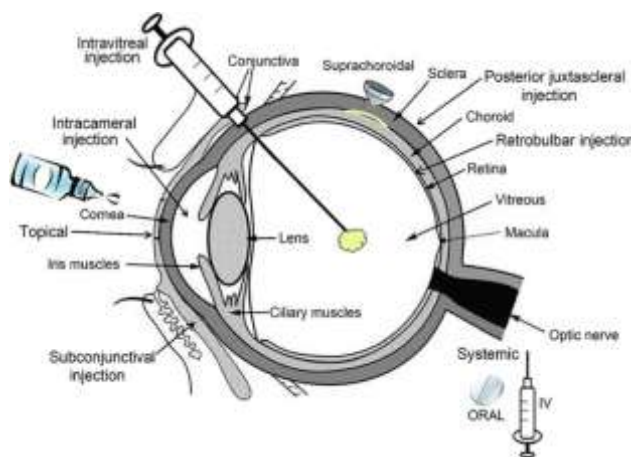
Drug loaded contact lenses are a patient friendly system that have been explored for sustained ocular drug delivery. Drugs can be incorporated into the contact lens material by soaking, molecular imprinting or through entrapment of nanoparticles within the material. Contact lenses have improved bioavailability and residence time of the drug in comparison to conventional eye drops, especially for antibiotics, anti-glaucoma and anti-inflammatory drugs.^{16, 22}

9. Nanomicelles

Nanomicelles are self assembled amphiphilic micelle structures with a hydrophobic core and hydrophilic surface. They improve solubility of hydrophobic drugs and facilitate their penetration into the cornea.¹⁶

10. Gene and Nucleic Acid based Delivery Systems

Molecular therapy has made it possible to target specific genes for ocular drug delivery. This can be achieved by using viral and non-viral vectors, lipid based delivery systems and dendrimers for targeted gene knock down or expression. Such systems can be used to treat genetic disorders and diseases that arise due to irregular expression of normal proteins like Retinitis pigmentosa and Leber's congenital amaurosis.^{15, 23}



[Fig. 3 : Novel Ocular Drug Delivery Systems Overview]

Marketed Products and Clinical Status

Several novel systems have already reached clinical use. Representative examples are summarised in Table 2.^{15, 16, 23}

Table 2. Representative marketed ocular products

Delivery system	Marketed example	Key feature
In-situ gel	Timoptic-XE (timolol maleate)	Gellan gum solution that gels in the eye; once-daily dosing

Ocular insert	Lacrisert (hydroxypropyl cellulose)	Rod-shaped insert placed in the lower fornix for dry eye
Implant	Ozurdex (dexamethasone)	Biodegradable intravitreal implant for macular oedema and uveitis
Liposome	Visudyne (verteporfin)	Liposomal photosensitizer for photodynamic therapy of AMD
Gene therapy	Luxturna (voretigene neparvovec)	AAV2 vector given subretinally for RPE65-mediated retinal dystrophy

Evaluation of Ocular Drug Delivery Systems

Evaluation of ocular drug delivery systems is important to ensure safety, efficacy, stability and patient acceptability prior to clinical trials. Since ocular formulations come into contact with delicate eye tissues, various in-vitro, ex-vivo and in-vivo tests are carried out to determine the physicochemical properties, drug release characteristics, permeability and irritation potential. Major evaluation parameters include:

1. Particle Size and Polydispersity Index (PDI)

Particle size and uniformity are crucial parameters for ocular formulations especially nanoemulsions and nanoparticles. Dynamic Light Scattering (DLS) is the most commonly used method for determining the average particle size and PDI of the formulation. A PDI of less than 0.3 is considered to indicate uniformity of size and improved corneal penetration and bioavailability. Particle sizes below 200 nm are preferred since they minimize foreign body sensation and prolong ocular residence time.

2. Viscosity: Viscosity of eye drop formulations plays an important role in their precorneal residence time. Formulations with higher viscosity prolong corneal contact leading to better absorption. Viscosity can be determined by measuring the flow rate with a Brookfield viscometer, which allows control over the shear rate, simulating eye blinking conditions.

3. In-vitro Drug Release Studies: Drug release studies are crucial to understand the drug release characteristics and predict in-vivo performance. Dialysis membrane diffusion method is a commonly employed method that provides useful information on release kinetics, drug diffusion mechanism and sustained release potential of novel ocular drug delivery systems.

4. Mucoadhesion: Mucoadhesive properties of formulations that are intended to adhere to the ocular mucosa are tested by tensile strength test to determine the adhesion forces. Better mucoadhesion translates to longer residence time and hence improved efficacy.¹⁷

5. Corneal Permeability: Corneal permeability studies are performed using Franz diffusion cells with excised animal or human corneal tissue to determine permeability and retention of various formulations in the corneal layers. Better permeability ensures higher chances of achieving therapeutic concentrations in the intraocular tissues.^{9, 10}

6. Ocular Irritation Studies: Various irritation tests such as Draize rabbit eye test are performed to determine the safety profile of new ocular formulations. However, ethical concerns have led to the use of alternative in-vitro methods like HET-CAM and cell culture based cytotoxicity assays.

7. Sterility and Stability Testing

Sterility is a critical parameter for any ophthalmic formulation. Microbiological tests such as membrane filtration and direct inoculation are performed to ensure that there are no microbial contaminants.²⁴

Future Perspectives

Future research is focusing on non-invasive and patient-friendly sustained release systems. Stimulus responsive in-situ gels and drug-eluting contact lenses are anticipated to reduce the need for frequent eye drops. Similarly, AAV based gene therapy offers a possible treatment option with a single dose for inherited retinal disease. Advanced manufacturing techniques such as 3D printing and hot-melt extrusion may help in producing personalized ophthalmic dosage forms. Some challenges still remain including long-term ocular safety profile of various nanocarriers, reproducibility in large scale production, maintaining sterility and regulatory approvals. Moreover, there is a need for better predictive in-vitro and ex-vivo models that can predict in-vivo performance. Addressing these issues will pave the way for future innovative ocular drug delivery systems that can transform the clinical management of various eye diseases.^{14, 15, 16}

Conclusion

Ocular drug delivery is hampered by several ocular barriers but is seeing an exponential growth due to development of novel formulation strategies. Sustained release systems, nanoparticles and microneedles offer much promise in achieving better therapeutic outcomes and patient compliance.

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