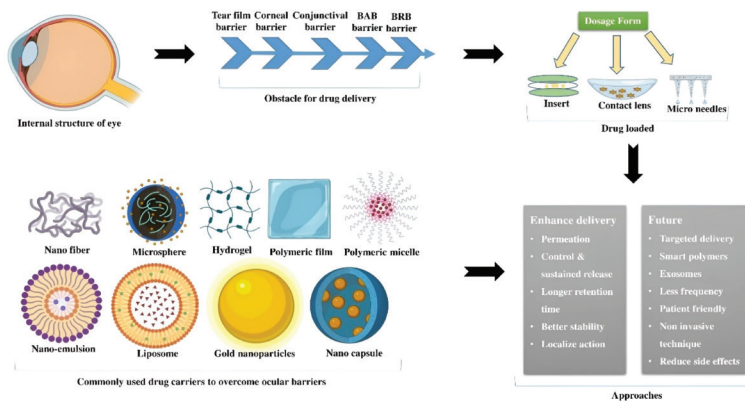


Ocular Delivery: Innovations in Ocular Inserts, Contact Lenses, and Microneedles

Graphical abstract



Highlights

- A brief discussion of the anatomy and physiology of the eye, including ocular barriers, is presented.
- Recent advances in ocular inserts for sustained and targeted drug delivery are reviewed. Innovative drug-eluting contact lenses for improving ocular bioavailability are discussed. Progress in microneedle-based systems for minimally invasive ocular delivery is highlighted.
- Challenges, clinical potential, and future perspectives of advanced ocular drug delivery systems are summarized.

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In brief

Recent advances in ocular drug delivery systems (ocular barriers, drug carriers and inserts, contact lenses, and microneedle advances for enhanced delivery).

Ocular Delivery: Innovations in Ocular Inserts, Contact Lenses, and Microneedles

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Abstract

Ocular drug delivery systems are essential for treating various eye conditions. Ocular conventional drug delivery techniques, such as eye drops (topical administration), often face challenges, like rapid drainage and low bioavailability. To overcome these challenges, scientists have developed ocular inserts with sustained delivery systems. Biocompatible materials, such as hydrogels, polymers, and biodegradable nanoparticles, have been investigated for insert manufacturing. These materials provide controlled release, improved retention time in the outer surface of the eye, and enhanced penetration of active pharmaceutical ingredients passing through the corneal barrier. Innovations in contact lens technology have made it possible to develop drug-loaded lenses that can deliver drugs in a sustained manner directly to the ocular surface by enhancing drug retention time and therapeutic efficacy. Microneedle-based ocular delivery, a relatively new methodology, has made progress by open-hollow and biodegradable microneedles that permit minimally invasive penetration to the sclera or cornea. Microneedle-based ocular delivery provides high bioavailability with prolonged release of drugs. The introduction of smart polymers, nanotechnology, and 3D printing with these systems has enhanced accuracy, patient comfort, and therapeutic efficacy. Together, these advances represent an evolution from current topical ocular treatment options to long-acting, patient-comfort ocular therapies with high efficacy and accuracy.

Keywords

Contact lenses; glaucoma; hydrogels; intravitreal injection; microneedles.

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Introduction

Ocular drug delivery systems deliver active pharmaceutical agents to the eye to treat various diseases or disorders. Ocular drug delivery represents one of the most challenging, yet indispensable interests in pharmaceutical research [1]. The main objective of ocular drug delivery systems is to treat diseases and disorders in a localized manner. Several drug delivery systems have a unique feature in which drugs are delivered in a site-specific manner, but due to the complex physiology and anatomy of the eye, ocular drug delivery is difficult [2–4].

The eye is a unique organ in the body with a complex anatomic structure and physiology. The eye contains various biological barriers that perform different independent functions and make it highly resistant to foreign objects [5]. The cornea and lens are two parts of the eye that do not have a blood supply. The strong connections between the corneal epithelium and the mucosal surface protect the interior components and tissues of the eye from

the outside world. The stroma contains hydrophilic cells which act as a barrier to hydrophobic drugs. The main challenge for ocular drug delivery is to pass through these protective barriers and ensure that the drug reaches the intraocular tissues to achieve a therapeutic effect. Most of the applied drugs are washed out by lacrimal fluid and tear secretions. Indeed, <5% of a drug enters the deeper layer of the eye. For this reason, researchers try to deliver ocular drugs to the specific target tissue at a specific therapeutic dose [6].

The bioavailability of drugs administered through the ocular route depends on physicochemical properties of the drug and physiologic factors. The physiologic factors are protein binding, drug metabolism, and lacrimal drainage [7]. Topical application of drugs is mainly used to treat various eye diseases, like eye flu, dryness, redness, and conjunctival infections. Greater than 70% of over-the-counter ophthalmic dosage forms are in the form of eye drops. Anti-inflammatory medications, antibacterial medications, and angiogenesis inhibitors are most likely utilized to treat different kinds of local infections in the eyes.

Recent advanced ocular drug delivery systems are improving drug bioavailability, residence time, and drug penetration. Advanced ocular drug delivery systems also minimize toxicity with some modifications, including novel formulations, like nanoparticles, liposomes, hydrogels, and *in situ* gels that release the active ingredients more accurately into the target ocular tissues. These dosage forms are commonly used for treatment of anterior and posterior segments of the eye. Moreover, ocular inserts, implants, and contact lenses with drug reservoirs are new strategies designed as alternatives to conventional methods. For example, diclofenac sodium is an anti-inflammatory drug that is used to prepare diclofenac sodium ocular inserts. Gene therapy, exosomes, and self-nano emulsifying drug delivery systems (SNEDDS) have been introduced in current treatments, which illustrates the technologic advances in ocular drug delivery.

Approximately 2.2 billion people are affected by visual impairment, according to the World Health Organization (WHO). Polymeric nanoparticles efficiently target conditions, such as age-related macular degeneration, cytomegalovirus (CMV) retinitis, diabetic retinopathy, posterior uveitis, and retinitis pigmentosa in the posterior portion of the eye. These nanoparticles can be used in the form of eye drops in place of semisolid ointments to reduce discomfort and blurred vision in the extra outer part of the eye [8]. Currently, the therapeutic potential of biodegradable polymers for ocular delivery are being investigated in *in vitro* and *in vivo* studies. Notably, these drug-loaded biodegradable formulations have various limitations, such as difficulty in drug loading, high cost, ocular irritation, and stability issues [9]. Stem cell therapy is one of the important treatments for ocular problems in which damaged ocular tissues are regenerated. Personalized ocular delivery systems, which treat ocular diseases in individual patients according to gene structure, gene types, lifestyle, and environment factors, are also being developed. The main aim of personalized medicine is to reduce the toxicity and side effects of pharmaceuticals [10].

In this review we focused on recent advances in ocular drug delivery system. First, the anatomy of the eye is reviewed and main challenges of ocular drug delivery systems are introduced. Then, the process to overcome the different barriers to ocular drug delivery systems are discussed. The present review provides a comprehensive overview of ocular inserts, ocular lenses, and ocular microneedles.

Merits of ocular drug delivery systems

- Drug delivery systems provide direct delivery of drugs to the eye which helps to achieve high drug concentration at the targeted site.
- Traditional routes of drug delivery face challenges due to the presence of various barriers but ocular delivery systems can bypass these barriers and enhance bioavailability.
- Drug delivery systems have local therapeutic actions, which does not allow any drug to reach the systemic circulation.

Drug delivery systems reduce side effects in other parts of the body.

- Drug delivery systems provide controlled and sustained release of drugs, which reduces dosing frequency.
- Ocular drug delivery methods, like encapsulation of nanoparticles and liposomes, protect medication from environmental factors [11].
- Some drug delivery systems are prepared to deliver genetic materials, like DNA and RNA, to treat genetic eye disorders.
- Drug delivery systems are easy to self-administer.
- Drug delivery systems increase the residence time of drug in the eye.
- Drug delivery systems provide better housing of delivery systems [12].

Limitations of conventional ocular drug delivery systems

Ocular delivery systems have been limited by the following limitations, which are:

- The eye has natural defence systems, such as tears, blinking, nasolacrimal drainage, and enzymatic degradation, which significantly limits the retention and absorption (approximately 5% drug can reach the target site only) of drugs on the ocular surface. [11].
- Frequent dosing results in patient non-compliance, especially in chronic conditions, like glaucoma [12]. To overcome these challenges, recent innovations, like nanotechnology and polymer-based systems, have been developed but these systems also face significant challenges. The actual use of nanotechnology-based delivery in the hospital setting is limited by concerns over safety, scalability, and regulatory aspects [5], while polymeric systems (hydrogels and microneedles) face challenges in manufacturing complexity and patient tolerability [13].
- Intravitreal injections provide direct delivery to the posterior segment but are invasive, painful, and carry risks of complications, like infections and retinal detachment [14].
- Emerging technologies, like smart contact lenses and biodegradable implants, promise controlled drug release. However, widespread adoption is constrained by high costs, regulatory requirements, and limited long-term safety data [15].

Anatomy of the eye

The eye is a complex organ made up of various sensitive tissues. The anatomy of the eye is an obstacle to drug delivery systems because some parts impede drug absorption and distribution [16]. The anatomic structure of the eyeball is divided into two parts:

- a. anterior segment (cornea, conjunctiva, iris, ciliary body, aqueous humor, and lens); and
- b. posterior segment (sclera, choroid, retina, and vitreous body).

Cornea

The cornea is a clear, transparent, outer layer of the eye that covers the iris (the colored part of the eye), pupil (the opening in the center of this layer), and anterior chamber (**Figure 1**) [17]. The cornea is avascular with the following five layers: epithelium; Bowman’s membrane; stroma; Descemet’s membrane; and endothelium. The corneal epithelium contains tight junctions in the surface layer [18]. CYP450 and a drug efflux pump is present in the epithelial cell layer, which reduces the bioavailability of drugs. Gap junctions are also present in the aqueous layer, which act as a leakage barrier. Gap junctions are lipophilic in nature and do not allow penetration of hydrophilic drugs. Gap junctions are the biggest obstacle of drug penetration [19].

Conjunctiva

The conjunctiva is a thin, vascularized membrane that covers the sclera and lines the inside of the eyelids (**Figure 1**). The conjunctiva is divided into three main parts (bulbar, forniceal, and palpebral). In addition, the fourth part is the marginal conjunctiva. The conjunctival cell layer consists of stratified, non-keratinized epithelial cells [20]. Conjunctival cells are connected by desmosomes at the epithelial surface and linked by intercellular junctions, which disrupts drug transport in the deeper layer. Goblet cells are also found as apocrine cells, which are larger than epithelial cells [21].

Aqueous humor

The aqueous humor is watery fluid in the anterior chamber of the eye and via the pupillary aperture to the posterior chambers. The aqueous humor lies between the cornea and lens (**Figure 1**). The aqueous humor functions in nutrient transportation and maintains the intra-ocular pressure (IOP) throughout the eye [22]. The aqueous humor is produced

by the ciliary body. The aqueous humor mainly consists of water and electrolytes, like sodium, potassium, various metabolites, glucose, and proteins [23, 24].

Lens

The lens is a vital component of the eye. The lens is a transparent and biconvex in structure posterior to the iris and pupil (**Figure 1**). The lens focuses light entering the eye, which is transmitted towards the retina. The lens is made up of tightly packed elongated cells containing crystalline protein. The primary function of the lens is to refract light rays. The lens acts as a filter protecting against translation of drugs from the aqueous humor into the vitreous humor [25–27].

Sclera

The sclera is a hydrated and white portion of the eye (**Figure 1**). The sclera consists of fibrous, thick connective tissue. The sclera also contains collagen fibers, which gives strength to the sclera. The sclera is divided into three parts (episcleral, stroma, and lamina fusca). The main function of the sclera is to provide a protective barrier to the inner parts of the eye and help maintain the proper shape of the eye [26].

Vitreous humor

There is a gel-like substance that fills the eyeball behind the lens. The vitreous humor is located posterior to the lens and anterior to the retina (**Figure 1**). It is mainly composed of water, collagen fibers, hyaluronic acid, and various proteins [27].

Retina

The retina is a multi-layered structure that includes the photoreceptors (rods and cones) and is necessary for vision. The retina converts the light into neural signals that the brain interprets as images. Cone and rod cells make up this structure. Cone cells are responsible for vision in bright light, while rod cells are used for vision in low light. The retina contains a photoreceptor layer, bipolar cells, ganglion cells, and pigment epithelium cells [28].

Choroid

The choroid is a vascular layer lying between the retina and sclera (**Figure 1**) that provides nutrients to the retina. The choroid is made up of blood vessels, connective tissues, and pigment cells (melanocytes). Melanin is present in high amounts, which helps absorb more light. The choroid contains three layers (outer, middle, and inner). The choroid supplies essential oxygen to the outer layer [29].

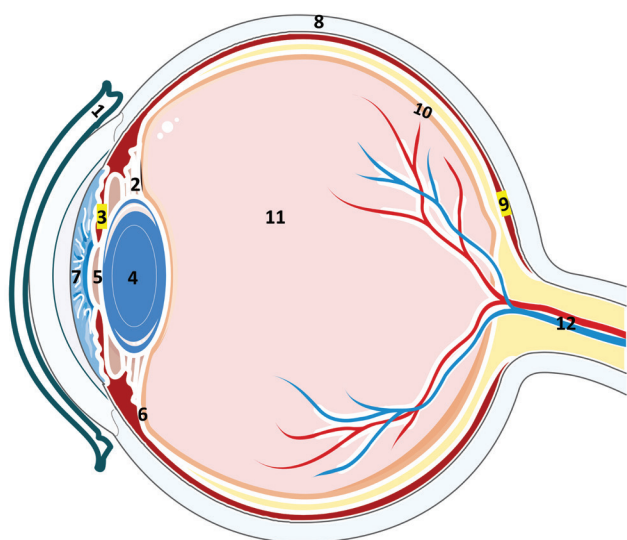


Figure 1 Schematic presentation of the eye (1. conjunctiva, 2. ciliary body, 3. iris, 4. lens, 5. pupil, 6. suspensory ligament, 7. aqueous humor, 8. sclera, 9. choroid, 10. retina, 11. vitreous humor, and 12. optic nerve).

Ocular barriers

There are various types of barriers (Figure 2) present in the eye which protect the internal structures of the eye and does not allow foreign particles into the deep layers of the eye. These barriers are discussed below.

Corneal epithelial barrier

The corneal epithelial barrier is the outermost layer of the cornea. The corneal epithelial barrier acts as a primary barrier that prevents the entry of foreign particles and maintains a sterile environment in the anterior segment of the eye. The corneal epithelial barrier prevents approximately 90% of drugs with a molecular weight >500 Da from penetrating deep layers of the cornea. This barrier is composed of tight junctions formed by occludin and claudin at the epithelial surface, which shows high resistance against permeation of drugs. This barrier has a sandwich construction with three layers (epithelium-lipid, stroma-aqueous, and endothelium-lipid) [30, 31]. This construction also serves as an obstacle of hydrophilic drugs that cannot cross through the epithelium layer. Lipophilic drugs cannot cross the stroma layer. For example, fluorescein remains on the surface of the epithelium but penetrates the stroma layer. The epithelium layer is negatively charged, so nucleic acid, which has a negative charge, cannot cross easily [32, 33].

Conjunctival-scleral barrier

The conjunctival-scleral barrier is a non-corneal pathway that includes the sclera and conjunctiva (Figure 3). The conjunctiva is a mucous layer located on the outer part

of the cornea in the posterior region. The conjunctiva is 17 times larger than the cornea and is therefore more suitable for drug absorption than the cornea. The conjunctival-scleral barrier consists of tight junctions (claudins, occludin, JAM-A, and tricellulin). This barrier admits compounds with molecular weights of 20–40 kDa. A drug can be eliminated by rapid vascular drainage after administration by this route [34, 35]. After clearance of the drug from the conjunctiva, A drug crossed the sclera to reach the anterior segment via the trans-scleral route after administration by this route [36]. The conjunctival-scleral barrier has a greater surface area and a comparatively high permeability compared to the cornea. The size of the drug molecule has a greater impact on the capacity to penetrate the sclera than lipophilicity [37].

Blood-aqueous barrier (BAB)

The BAB is a combination of a non-pigmented ciliary body and the iris endothelium (Figure 3). The BAB serves as a barrier that prevent solutes from entering the intraocular space [38]. The ciliary body, which is present from the iris root-to- the retina, forms a ring around the globe. The ciliary body has two major components (pars plicata and pars plana). The pars plicata is present in the anterior part and the pars plana is located between the retina and pars plicata. Due to the fenestrated and leaky nature of choroidal capillaries, the ciliary body is highly vascularized [39]. The physicochemical characteristics of the drug molecules influence osmotic pressure, which allows medications to pass through the BAB. Smaller, lipophilic medications can pass through the BAB faster than larger, hydrophilic medications. For example, pilocarpine is eliminated more rapidly than inulin [31]. Ocular drug delivery remains challenging due to the specialized tissue barriers that can provide an

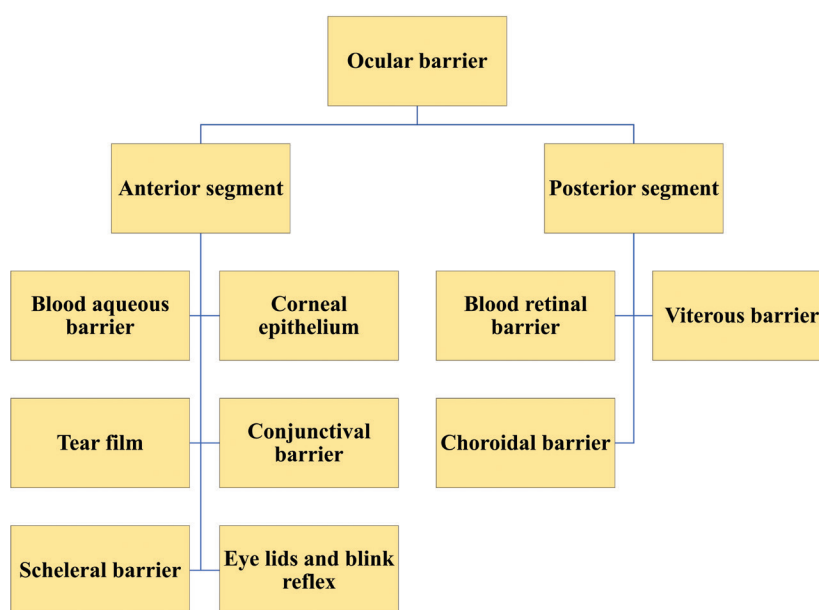


Figure 2 Classifications of barriers in ocular system (blood aqueous barrier, corneal epithelium barrier, tear film, conjunctival barrier, scleral barrier, blood retinal barrier, vitreous barrier, and choroidal barrier).

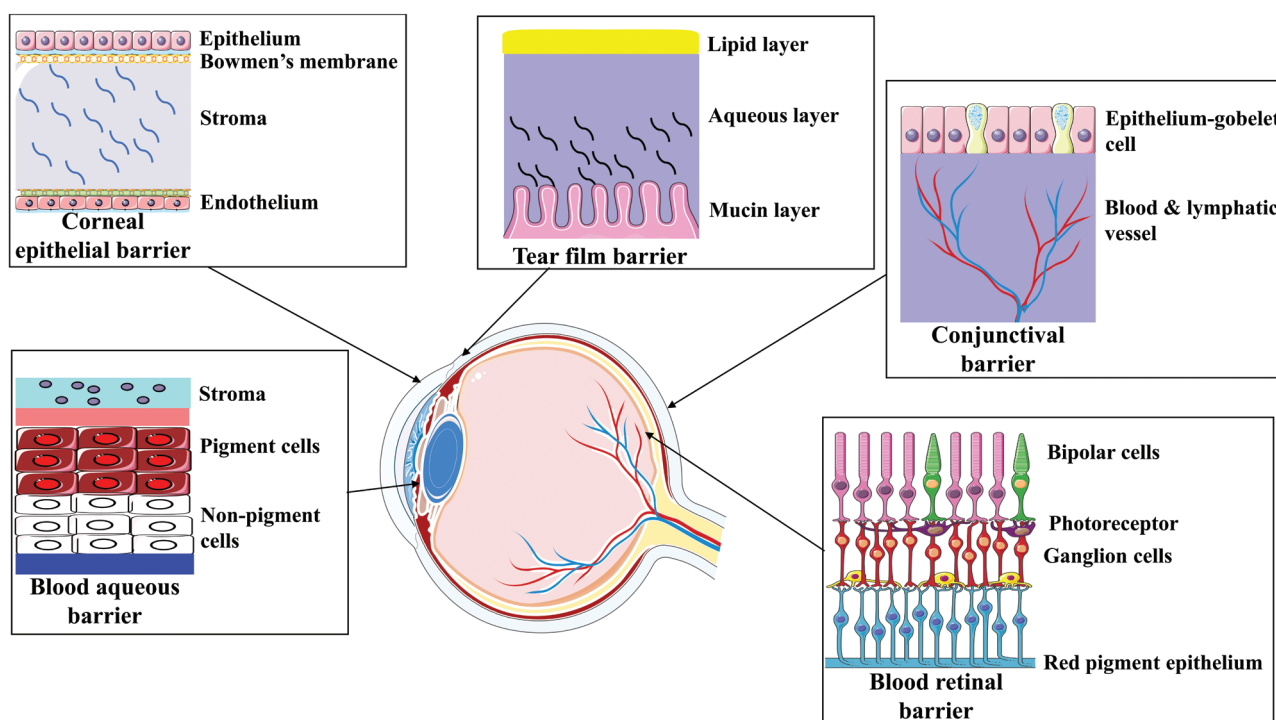


Figure 3 Schematic representation of ocular barriers; specifically, anatomic and physiologic structures in drug penetration in anterior and posterior segments of the eye (corneal barrier, tear epithelium barrier, blood aqueous barrier, blood retinal barrier, and conjunctival barrier).

impact of therapeutic effectiveness. The BAB mainly consists of non-pigmented epithelium, the ciliary body, and the capillary endothelium. The protein concentration is low in the aqueous humor (AH) with only a small portion of plasma protein [40]. Plasma proteins that pass through the capillaries of the ciliary body are unable to enter the posterior chamber because plasma proteins are blocked by the non-pigmented epithelium of the ciliary body. Similarly, these proteins cannot access the anterior chamber due to the tight junctions present in the iris capillary endothelium [32]. Non-pigmented epithelium cells act as physical barrier more than pigmented cells because tight junctions are present between the cells [39].

Blood-retina barrier (BRB)

Consequently, the BRB is the most important barrier in the back of the eye. The outer BRB is composed of tight junctions of retinal pigment epithelial cells, while the inner BRB is produced by tight junctions of endothelial cells and retinal capillaries (Figure 3) [36]. Muller cells, astrocytes, and pericytes cells, which are present in the retinal barrier, have a critical role in maintenance of the retinal barrier and regulation of nutrient uptake by cells in the BRB [41]. The BRB is formed when retinal glia and pericytes interact with the endothelium. The BRB regulates the flow of metabolites and waste products between the vascular lumen and the neural retina. Pericytes secrete angiopoietin 1 and induce tight junctions to support endothelial cells [42]. Water, plasma components, and other dangerous substances cannot get through this barrier and penetrate the retina. In contrast, the BRB can also stop medication molecules to enter the intraocular space. Thus, preservation of the eye as a favored location for typical visual function depends on the BRB. Adult human

retinal pigment epithelium (RPE) has tight connections (approximately $40 \Omega \cdot \text{cm}^2$), making the RPE a low-resistance epithelium [34].

Eyelids and tear film

The eyelids act as a physical barrier which prevent bacterial agents, foreign bodies, and other external particles from entering the eye (Figure 3). The reflex blink has a significant role in elimination of applied eye drops in the outermost layer of the eye epithelium [43]. The optimum pH for eye formulations should be 6.5–7.8. Another range of eye formulations may cause immediate discomfort. Because of the physicochemical characteristics of the outermost layer of the eye epithelium and the fact that the outermost layer of the eye epithelium contains proteins and enzymes that are antibacterial and anti-inflammatory, the tear film acts as a barrier [44]. The outermost layer of the eye epithelium has three separate layers (the inner mucin layer, which is released by the mucous glands and conjunctival glandular cells, the middle aqueous layer, which is secreted by the lacrimal glands, and the outer lipid layer, which is created by the meibomian glands). The lipid layer helps reduce tear evaporation, thereby maintaining the osmolarity [33, 34].

Challenges of ocular drug delivery systems

The major challenges in ocular delivery systems are delivery in the anterior part and another delivery in the posterior part of the ocular cavity [12]. After application of drug in the anterior segment of eye the drug must first pass through

the tear film and conjunctiva, which are the first barriers in the pathway and slow the rate of penetration of the active component in the eye. Poor drug bioavailability in most ocular formulations is caused by pre-corneal loss of factors (Figure 4). [45]. The BRB prevents ocular medications administered topically in the posterior segment of the eye. The BRB is permeable to more lipophilic molecules, so only these lipophilic drugs can enter the posterior portion of the eye. The repeated use of highly concentrated medication solutions may result in harmful side effects and ocular surface cellular damage [45].

Route of administration in the eye

There are different administration routes (Figure 5) available for ophthalmic drug delivery systems. Drugs can be administered by any of the below routes.

Topical administration

Topical drug administration is the most frequently used route of administration. Eye drops, ointments, and pastes are mainly used in this approach because the preparations can be easily administered to the patient [46].

Systemic administration

Systemic administration is one of the suitable administration routes that allows drug delivery to the posterior segment

of the eye but also faces significant challenges due to the presence of the BRB and BAB, which blocks the penetration of drug molecules. As a result, a high dose is required to achieve the target therapeutic effects [47, 48].

Intravitreal administration

Ocular drugs are directly injected into the vitreous humor using a 30 G needle in this approach, which enhances drug absorption compared to topical or systemic methods. While intravitreal administration achieves high drug levels in the retina, intravitreal administration also presents several technical challenges, such as intravitreal hemorrhage, endophthalmitis, and injury to the lens [48].

Periocular implants

Periocular implants are usually placed on the surface of the eye in areas, like the conjunctiva, retrobulba, and peribulba spaces. These implants deliver medications directly to the vitreous, retina, and choroid via the trans-scleral route [23]. These routes largely provide a good way to treat retinal disorders. The challenges associated with these routes are the barriers, such as the RPE, choroid, and sclera, and blood and lymph in the surrounding tissues [49].

Subconjunctival

The subconjunctival injection route is commonly used for delivering drugs to the anterior part of the eye to achieve higher drug concentrations compared to topical and other applications. The most frequent use of this method is to treat

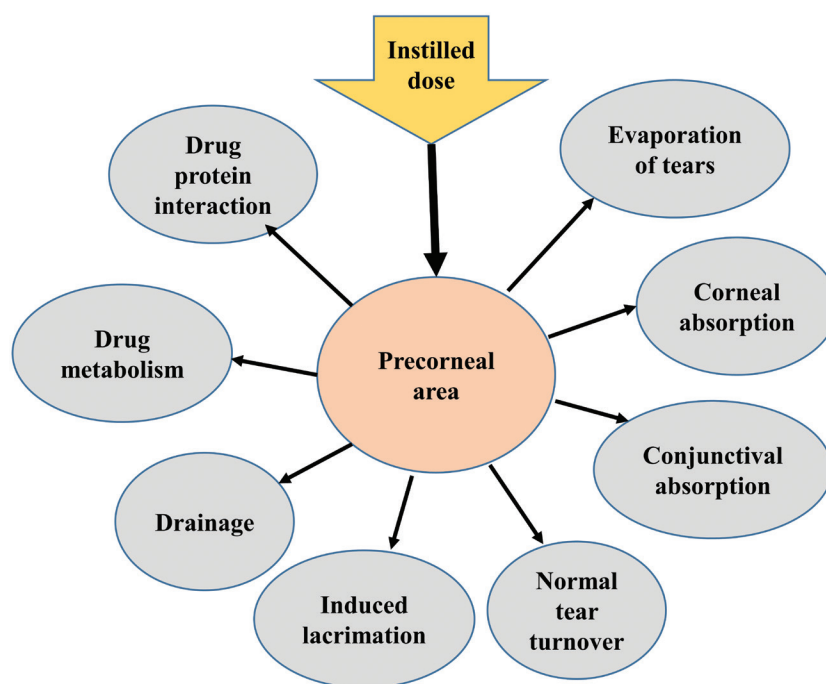


Figure 4 Precorneal factors influencing loss of optically applied dosage forms.

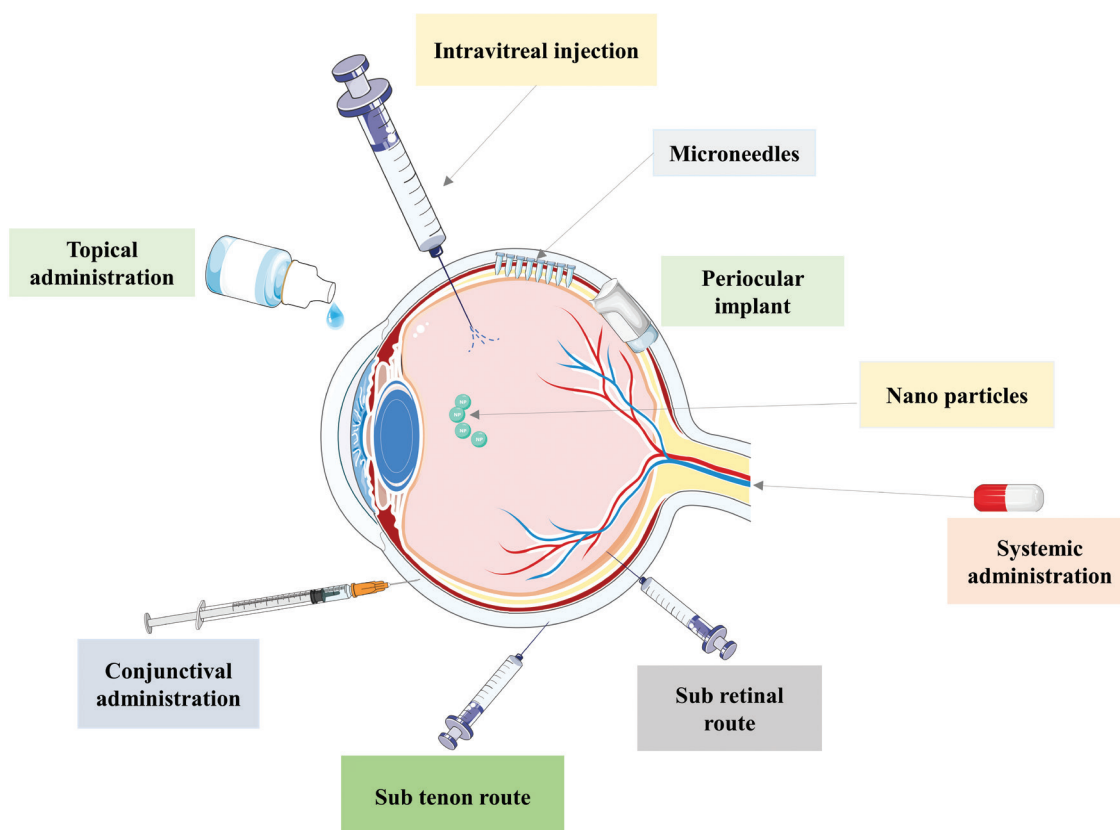


Figure 5 Schematic illustration of ocular administration routes in the anterior and posterior segments of the eye (topical administration, conjunctival administration, sub tenon, sub-retinal administration, systemic administration, periocular implant, nano particles, and microneedles).

retinal disorders. Blood flow and tear production can lead to decreased bioavailability, limiting the effectiveness of the treatment [50].

Suprachoroidal

This route involves drug delivery using microneedles into the supracervical space. The applied pressure helps spread the formulation throughout the suprachoroidal space during the injection. This approach has been studied to deliver drugs into the eye via surgical techniques using microneedles. The suprachoroidal approach provides long-term treatment by targeting the retina and choroid directly at the injection site. There are several challenges present in the suprachoroidal route, such as the risk of choroidal detachment and suprachoroidal haemorrhage. These challenges have made it difficult to implement the suprachoroidal approach in practice [50].

Sub-tenon

This route involves drug delivery using an injection technique that delivers medication into the space between the tenon capsule, a protective membrane, and the sclera (the white of the eye). This method is generally considered to be safer than intravitreal injections because microneedles are not used. The subtenon route remains an important

option for uveitis specialists, especially in cases in which intravitreal administration may not be feasible or requires special consideration. Like other intra- or peri-ocular steroid injections, subtenon or subconjunctival delivery can still lead to cataract progression and ocular hypertension [49, 50].

Strategies to overcome eye barriers

To overcome barriers in ocular drug delivery systems is difficult due to the unique challenges present in the eye, like various barriers. Below are some strategies to overcome eye barriers.

Enhancement formulations with carriers

- **Nano-carriers:** Nanoparticles are used in formulations to improve drug solubility, stability, and bioavailability due to the small size of the drug. Nano-carriers, like liposomes, niosomes, and phytosomes, provide protection to the drugs from environmental and biological factors [11, 51].
- **Polymeric micelles:** Polymeric micelles are tiny, specialized carriers that facilitate drug absorption and remain

active in the specific site for a longer time. This feature means patients can benefit from more effective treatments with several doses [4].

- **Hydrogels:** Hydrogels provide sustained release and improve contact time and prolong action at the ocular surface [52].

Improving bioavailability

- **Permeation enhancers:** Permeation enhancers are added to achieve easier penetration in the deeper layer of the eye so the drug can work better and faster [53].
- **Liposomes:** Liposomal medications are mainly used to enhance drug bioavailability. These liposomal medications are mainly tiny bubbles which keep the drug at a specific site to provide full therapeutic action of the active pharmaceutical ingredient (API) [54].

Targeted delivery systems

- **Prodrugs:** Prodrugs are inactive in nature but when administered, bind to the specific site and produce therapeutic actions. The proper design of a prodrug is necessary in targeted delivery.
- **Tissue-specific ligands:** Ligands that target specific receptors and bind to ocular tissues are used for more effective therapeutic action locally [55].

Innovative delivery methods

- **Intraocular implants:** Sustained-release implants release drug slowly that provide long-term drug delivery directly to the site of action.
- **Microneedle arrays:** Microneedle technology delivers medications that produce minimal discomfort. These tiny needles gently pierce the outer layer of the eye and inject the medicine [5].

Prolong retention time

- **Viscosity modifiers:** Viscosity-enhancing agents are added to increase the retention time of eye drops on the ocular surface [11].
- **Mucoadhesive agents:** Mucoadhesive polymers are used that prolong the contact time of the drug with the eye [53].

Controlled release mechanisms

- **Biodegradable polymers:** Biodegradable drug delivery systems have been developed using biodegradable polymers that release the drug at controlled rates over time.
- **Stimuli-responsive systems:** Stimuli-responsive systems are devices that can release medications in reaction to

stimuli, such as temperature or pH. These are intelligent drug delivery devices [56].

Patient compliance strategies

- **User-friendly formulations:** Formulations have been prepared that patients can use, such as gels or ointments, that require less frequent application.
- **Education and training:** Education and training are provided to patients regarding the importance of adherence and correct administration techniques of the ocular dosage form, such as pastes, ointments, and eye drops [53].

Regulatory and research support

- **Collaboration with regulatory bodies:** Patient treatment is developed and more safety is achieved by complying with the regulatory authorities.

Clinical trials and feedback

- **Clinical trials:** Clinical trials are conducted focusing on user experience to collect data on ease of use, effectiveness, and patient preferences.
- **Feedback mechanism:** Channels for patient feedback are established to recorrect and improve drug delivery systems after trials [57].

By using these strategies, researchers and developers can enhance the effectiveness of ocular drug delivery systems and improve patient outcomes.

Recent developments in ocular drug delivery systems

Recent developments in ocular drug delivery systems have focused on improved efficacy and patient compliance. Some notable advancements include ocular inserts, nanoparticle hydrogels, smart polymers, microneedle patches, contact lenses, implantable devices, and ocular injections. Below is a detailed overview of ocular inserts, contact lenses, and microneedles in this section of the review.

Ocular inserts

In the 19th century squares of dry filter paper impregnated with dry solutions, such as atropine sulphate or pilocarpine hydrochloride, were used as the first solid medication (the forerunners of today's insoluble inserts) [58].

Merits of ocular inserts

- Ocular inserts offer sustained and controlled release of medications to the site of action, e.g., ketorolac ocular inserts with a microsphere carrier platform (Table 1).

Table 1 Summary of Recent Experimental Studies on Ocular Inserts

Sl. No.	Model Drug	Dosage Form	Carrier Platform/Type Of Insert	Result	References
1.	Triamcinolone acetanide	Ocular insert	Nanofiber carrier	Decrease particle size, systemic absorption, and side effects.	[11]
2.	Ketorolac	Ocular insert	Microsphere	Prolonged drug release	[11]
3.	Tenoxicam	Ocular insert	Nanostructured formulation	Superior drug diffusion, <i>ex vivo</i> and <i>in vivo</i> permeation	[11]
4.	Pilocarpine	Ocular insert	Niosome, hydrogel	Enhanced bioavailability and extended release	[112, 113]
5.	Timolol maleate	Ocular insert	Ocular films	Improved ocular retention and reduced frequency of dosing	[114]
6.	Dexamethasone	Ocular insert	Intra-canalicular insert	Controlled release with reduced side effects	[115]
7.	Fluorescein acetanide	Ocular insert	Intravitreal insert	Enhanced visibility and extended diagnostic effectiveness	[116]
8.	Diclofenac sodium	Ocular insert	Nanoparticle system	Controlled anti-inflammatory effect and reduced systemic absorption	[117]
9.	Loteprednol etabonate	Ocular insert	Microsphere formulation	Prolonged therapeutic action with lower incidence of side effects	[118]
10.	Chloramphenicol	Ocular insert	Hydrogel	Broad-spectrum antibiotic used in eye infections	[119]
11.	Ciprofloxacin	Ocular insert	Polymeric film	Increased stability and prolonged antibacterial effect	[120]
12.	Brimonidine	Ocular insert	Polymeric film	Controlled release	[121]
13.	Valacyclovir	Ocular insert	Lipid-based system	Enhanced corneal penetration and prolonged antiviral activity	[122]
14.	Prednisolone	Ocular insert	Thermo-sensitive gel	Sustained release with reduced intraocular pressure	[123]
15.	Ketorolac tromethamine	Ocular insert	<i>In situ</i> gelling insert	Prolonged anti-inflammatory effects with minimized side effects	[124, 125]
16.	Moxifloxacin	Ocular insert	Liposome	Increased ocular bioavailability and reduced dosing frequency	[125, 126]
17.	Acyclovir	Ocular insert	Polymeric film	Controlled drug delivery	[127]
18.	Brinzolamide	Ocular insert	Hydrogel	Improved solubility and sustained carbonic anhydrase inhibition	[128]
19.	Bimatoprost	Ocular insert	Polymeric film	Enhanced bioavailability and prolonged intraocular pressure (IOP) lowering effects	[129]
20.	Timolol maleate	Ocular insert	Nano-emulsion	Improved penetration and sustained release	[130]
21.	Cyclosporine A	Ocular insert	Nano-micelle polymeric insert	Controlled release with reduced immune response	[131]
22.	Amino acid-based peptides	Ocular insert	Biodegradable film	Targeted delivery for retinal diseases	[132]
23.	Indomethacin	Ocular insert	PVA insert	Prolonged antibacterial effect with reduced toxicity	[133]
24.	Dorzolamide	Ocular insert	Chitosen hydroxyl ethyl cellulose insert	Sustained release of drugs for glaucoma treatment	[134]
25.	Pilocarpine nitrate	Ocular insert	Hydrating gel	Prolonged tear film stability and ocular comfort	[135]
26.	Azithromycin	Ocular insert	Nanoparticles	Enhanced penetration and sustained antibacterial activity	[136]
27.	Norfloxacin	Ocular insert	Polymeric film	Controlled release for bacterial infections with minimal side effects	[137]
28.	Betaxolol	Ocular insert	Microsphere formulation	Prolonged effect on corneal healing and repair	[138]
29.	Epinephrine	Ocular insert	Biodegradable polymer	Sustained effect for glaucoma management	[139]
30.	Gentamicin	Ocular insert	Nanoparticle delivery	Increased stability and prolonged antibacterial effect	[140]
31.	Levobunolol	Ocular insert	Thermo-sensitive gel	Reduced side effects with controlled release	[141]

- Drug bioavailability is increased by increasing the corneal residency period.
- The therapeutic performance of a drug can be improved to provide comfort and better patient compliance.
- Ocular inserts have a longer shelf life compared to aqueous solutions.
- Protective barriers, like drainage, lacrimation, and conjunctival absorption, are avoided [58, 59].

Limitations of ocular inserts

- Ocular inserts may undergo sporadic and unintentional loss during sleeping or while massaging the eyes. In addition, visual disturbances and difficulty with proper ocular implant placement further limit patient acceptability.
- One major drawback of ocular inserts is the solid structure, which causes the patient to sense the insert as a foreign object in the eye.
- Once inserted, the release rate is often fixed, which may not be ideal for all patients, especially if dose adjustment is needed [59].

Classification

It can be classified as: Ocular insert drug release mechanisms can be classified into diffusion, osmosis, and bioerosion (Figure 6).

Ocular insert drug release mechanism

A. **Diffusion:** The drug is released externally through the membrane at a controlled rate (Figure 7). It has been shown that when a drug is dispersed within a solid, non-erodible body consisting of pores, the drug is released through pores by diffusion. The solid dispersed medication is distributed to dissolve gradually into the

matrix; this slow immersion of the aqueous solution provides controlled drug release [58]. True dissolution in these soluble devices mostly occurs by the swelling of the polymer. The active substance in these swelling-controlled devices is evenly distributed throughout a glassy polymer. Because glassy polymer proteins are densely cross-linked, there is little or no diffusion in the dry matrix of the polymer. After the insert containing the drug is placed in the eye, water from tear fluid will be able to swell and ultimately relax the polymer chains, allowing for drug diffusion. The rates of matrix dissolution and matrix swelling are influenced by the chemical structure of the polymer. Linear amorphous polymers dissolve faster compared to cross-linked or partially crystalline polymers [59].

B. **Osmosis:** The ocular insert is comprised of an elastic membrane that is embedded into the structure and acts as a barrier between two compartments (Figure 7). The first compartment is a liquid containing a solute, which is unable to permeate through the semi-permeable membrane. The second compartment is a gel or liquid drug containing-compartment, where the elastic membrane only surrounds the second partition. An ethanol port exists within the impermeable structure of the insert. The insert structure is such that when it submerged in water, one side of fills with water, which causes pressure to build up. This pressure enables the drugs to come out from one port. The introduction of water into the first chamber allows the elastic foil to be stretched. With the introduction of pressure in the second chamber, some ethanol is forced into the polymer matrix, which enables the embedded drug to diffuse out [59, 60].

C. **Bioerosion:** The drug is contained within the polymer matrix that holds shape. When dried, the shape is fixed, which allows the drug to be dispersed throughout the surface of the structure. The drug-filled matrix containing insert enables drug polymers to slowly dissolve and release throughout the drug coated with polymer. When

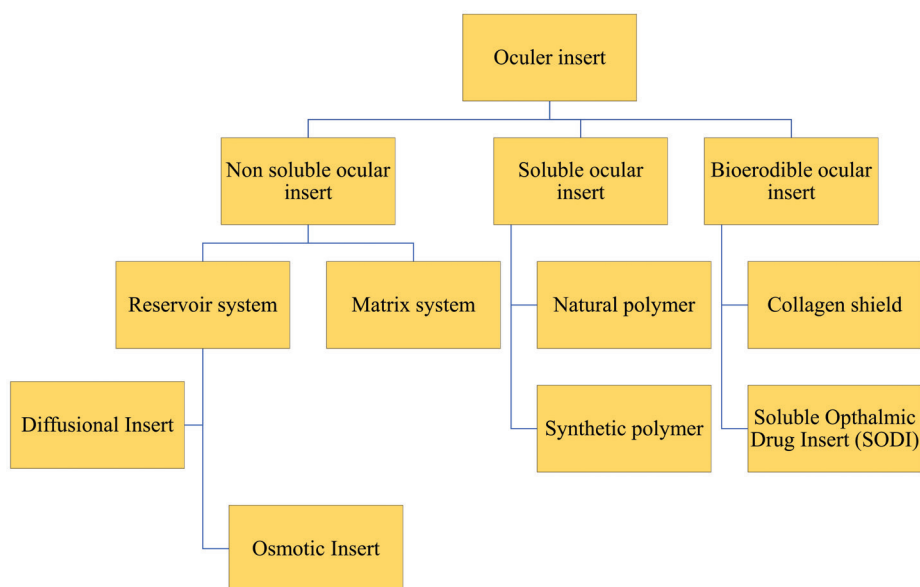


Figure 6 Types of ocular inserts (non-soluble inserts: diffusion system, osmotic system, and hydrophilic contact lens; soluble inserts: natural and synthetic polymers; bio-erodible inserts: non-erodible and erodible).

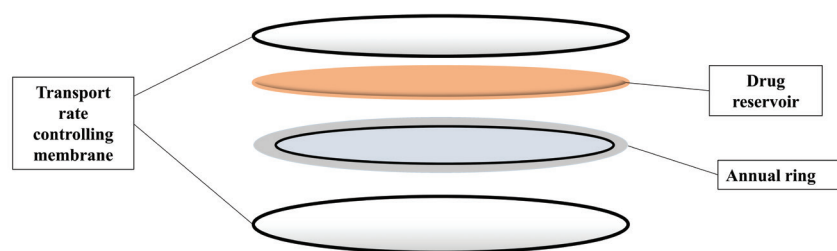


Figure 7 Structural representation of ocular inserts with drug reservoir, annual ring, and transparent rate controlling membrane.

tear fluid come in contact during drug release, the matrix begins to weaken at a slow rate, which prevents burst effects. The drug release mechanism of erodible (E-type) devices relies on chemical or enzymatic hydrolytic reactions that cause the polymer to dissolve or break down into smaller, water-soluble molecules. If the medication has low water solubility and the devices retain a constant surface geometry, these polymers increase hydrophilicity and the drug is released by zero-order release kinetics [61, 62].

Recent advances in ocular inserts

- A. **Hydrogel-based ocular insert systems for hydrophobic drugs:** Hydrophobic drug delivery to the eye has been improved by systems that are hydrogel-based, which increases the solubility of hydrophobic drugs. Hydrogels overcome several anatomic and physiologic barriers, which provide effective absorption of drugs and make the therapy long-lasting. For example, the pilocarpine hydrogel-based ocular insert increases bioavailability by enhancing residence time (Table 1) [4].
- B. **Nanofiber-based ocular insert:** A nanofiber-based ocular insert has been developed with electrospinning technology. A nanofiber-based ocular insert increases the drug contact time, control, and extended release of the drug. For example, triamcinolone acetonide-containing ocular insert reduces systemic absorption and side effects (Table 1) [63].
- C. **Ocular delivery of CRISPR/Cas genome editing components:** The genome editing method CRISPR/Cas components can be targeted directly to the eye to treat disease in short time. This new approach has the potential to treat not only inherited but also multifactorial eye disorders [64].
- D. **Biodegradable and non-biodegradable ocular inserts:** Researchers have developed contact lenses that are mucoadhesive, which can release the drug mixture (moxifloxacin and dexamethasone). These contact lenses improve the bioavailability and ensure sustained drug release for the cure of ocular infections [65, 66].
- E. **Development of magnetically actuated glaucoma drainage devices:** There is a novel glaucoma drainage implant that employs magnetic actuation in the postoperative regulation of intraocular pressure. This minimally invasive device leads to personalizing treatments and better postoperative results, such as the BIM ring® (Table 2) [67].

Patent information of the ocular insert

The development of ocular inserts has focused on numerous patents (Table 3). Patented technologies often address challenges, like controlled drug release, extended retention time in the eye, and compatibility with sensitive ocular tissues. Innovations include biodegradable polymers, osmotic systems, and sustained-release mechanisms.

Contact lens

Contact lenses are devices made up of hard or soft polymers that are designed to fit in cornea and correct refractive problems. Either hydrophilic or hydrophobic or both polymers are used to make contact lenses [68]. Hydrogel contact lenses are better at absorbing aqueous solutions, so contact lenses appear to be an effective way to deliver medications to the eye [69]. Contact lenses are present so close to the cornea that contact lenses have higher drug bioavailability than other non-invasive ophthalmic treatments, like eye drops or ointments. In addition, contact lenses offer a notable dose advantage over topical eye drops [62]. Drug-loaded contact lenses are recently a novel way to improve corneal permeability and ophthalmic drug bioavailability [70].

By using contact lenses as drug delivery platforms the efficacy of a drug has been improved when compared to boosting ocular bioavailability alone; patient adherence and prolonged drug release time is improved to conventional dosage forms. Conventional dosage forms deliver only 1%–5% of the drug to the targeted tissues where contact lens increases bioavailability up to 35%–50% with reduced systemic side effects [71]. For example, dexamethasone-containing contact lenses deliver 200 times more drug to the eye than conventional drops. Drug-loaded contact lenses provide high patient compliance compared to topical drops. Up to 29% of glaucoma patients struggle to self-administer drops properly in which drug-eluting contact lenses remove the dose instillation process and reduce dose frequency [72] eg., MediPrint™ contact lens is used to treat glaucoma (Table 4). Traditional soaking methods release most of the drugs within 1–3 h. To overcome this limitation, various advanced techniques, like molecular imprinting, drug-loaded nanocarriers, and vitamin E diffusion barriers have been developed that release drug over hours or even weeks in a controlled manner. We suggest

Table 2 Overview of Marketed Ocular Insert-Based Drug Delivery Products

Country	Ocular Insert	Manufacturing Company	Purpose	Approved Indications	Technology Platforms	Reference
USA	Ocusert®	Alza Corporation	Developed for delivering pilocarpine to treat glaucoma	Reduction of intraocular pressure in glaucoma patients	Diffusion-controlled membrane system	[142]
USA	Dextenza® OTX-CSI	Ocular Therapeutix, USA	Post-surgical ocular inflammation and pain	Pain and inflammation following ophthalmic surgery	Hydrogel-based intra-canalicular insert releasing dexamethasone	[58]
	Lacrisert®	Bausch and Lomb, USA	Treatment of dry eye syndrome	Moderate-to-severe dry eye, keratoconjunctivitis	Hydroxypropyl cellulose-based slow-dissolving insert	[11]
Russia	BIM ring®	LLC NCK-Progress, Russia	Glaucoma	Reduction of intraocular pressure	Drug-eluting ring insert	[106]
France	Mydriaserit®	Laboratoires Théa, France	Diagnosis (pupil dilator)	Mydriasis for diagnostic and pre-surgical use	Reservoir insert releasing tropicamide & phenylephrine	[106]
Spain	Mydriaserit®	Laboratoires Théa, France	Diagnosis (pupil dilator)	Mydriasis for diagnostic and pre-surgical use	Reservoir insert releasing tropicamide & phenylephrine	[106]
Sweden	Mydriaserit®	Laboratoires Théa, France	Diagnosis (pupil dilator)	Mydriasis for diagnostic and pre-surgical use	Reservoir insert releasing tropicamide & phenylephrine	[106]
Finland	Mydriaserit®	Laboratoires Théa, France	Diagnosis (pupil dilator)	Mydriasis for diagnostic and pre-surgical use	Reservoir insert releasing tropicamide & phenylephrine	[106]
Canada	Dextenza®	Ocular Therapeutix, USA	Post-surgical ocular inflammation and pain	Pain and inflammation following ophthalmic surgery	Hydrogel-based intra-canalicular insert releasing dexamethasone	[143]

that drug delivery using contact lenses enhances efficacy compared to the drug alone [73].

Merits of contact lenses

- Contact lenses provide a controlled and sustained release of drug to the site of action. Contact lenses enhance therapeutic efficacy compared to conventional eye drops, which have low bioavailability due to continuous tear drainage [73].
- Contact lenses ensure better drug absorption to the cornea and reduces drug wastage [74].
- Contact lenses provide better patient compliance.
- The main advantage of contact lenses include correcting vision and delivery of drug at the same time.
- Contact lenses provides protection to the ocular surface [75].
- Contact lenses minimize the systemic absorption and reduces the risk of side effects [76].

Limitations of contact lenses

- Contact lenses have limited drug loading capacity. The quantity of drug that may be delivered through a contact lens is often limited, which limits utility for more serious conditions [77].
- Extended wear or the elution of some drugs from contact lenses may induce irritation or adverse responses in sensitive patients [78].
- The drug-loaded contact lenses are more expensive and require sophisticated manufacturing techniques, making drug-loaded contact lenses less accessible [79].
- Some drugs may interact with the lens material, which may lead to suboptimal release or degradation [80].
- Storage and use of drug-loaded lenses can be complicated as sterility and stability have to be ensured [81].

Mechanism of drug release

Release of drug from contact lenses mostly involves physical and chemical phenomena, which is often associated with the characteristics of lens materials, drug characteristics, and the surrounding environment. The mechanisms involved are detailed below.

A. Diffusion

Drugs are incorporated into the contact lens matrix during manufacturing. When the contact lens comes into contact with tear fluid, the drug diffuses out of the lens material into the tear film and onto the eye (Figure 8). The diffusion rate depends on the porosity of the lens material, hydrophilicity, and the size of the drug molecule.

For example, hydrogels allow the drug to diffuse out as the hydrogels swell in the aqueous tear environment [82].

B. Swelling-controlled release

Contact lenses, especially hydrogels, absorb water from the tear film and swell. Swelling increases pore size that lets the drug out. This mechanism is especially relevant for hydrophilic drugs [83].

Table 3 Summary of Patents Related to Ocular Insert Technologies [144]

Sl. No.	Patent Number	Title	Patent Information
1.	Wo2024180472a1	Ocular insert	Dissolvable ocular insert that releases lubricants and drugs into the eye for extended time
2.	Wo2024180453a1	Dissolvable polymeric eye inserts with a non-ionic cellulose derivative	When inserted into eye may absorb tears and dissolve and slowly release lubricants into tear film
3.	Us20240207174a1	Dissolvable polymeric eye inserts	Eye insert release humectants and drugs into the eye
4.	Us 10,835,416 b2	Ocular insert apparatus and methods	Comprised of a retention structure sized for placement under the eyelids and along at least a portion of the conjunctival sac
5.	Us 10, 042, 183 b2	Ophthalmic device molds formed from water-soluble vinyl alcohol copolymer, ophthalmic devices molded therein, and related methods	Ophthalmic device molds made from at least one water-soluble vinyl alcohol copolymer; ophthalmic devices, such as ocular inserts
6.	Us 9, 849, 085 b2	Devices for sustained release medication delivery, applications, and production techniques	The technique involves carefully giving a mammalian creature in need of such therapy; a sustained release medication delivery device
7.	Wo2017137934a1	Non-invasive ocular drug delivery insert technology	This ocular insert allows releasing of at least one drug under suitable concentration levels during suitable periods of time

Table 4 Overview of Marketed Contact Lens based Drug Delivery Products

Sl. No.	Product Name	Company	Application	References
1.	Acuvue Theravision with Ketotifen	Johnson & Johnson Vision	Drug-eluting contact lens for delivering anti-histamines to treat allergic eye conditions	[145]
2.	MediPrint™	Leo lens pharma	Treatment of prostaglandin and glaucoma	[146]
3.	OcuMedic Therapeutic Lenses	OcuMedic, Inc.	Contact lenses designed for post-surgical recovery and drug delivery to the ocular surface	[147]
4.	Medidur™	pSivida Corp	Used to treat posterior uveitis	[148]

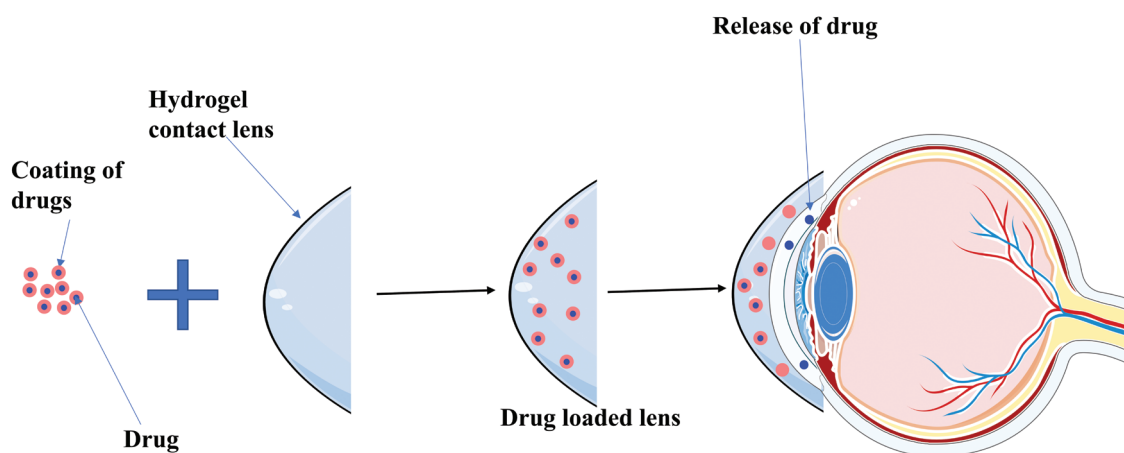


Figure 8 Structural representation of drug-loaded contact lenses and mechanism of action of drug release from the lens-to-the cornea.

C. Erosion-controlled release

Drugs are released as the polymer matrix progressively erodes in biodegradable lenses.

This process is less common for contact lenses but is being explored for advanced drug delivery systems [84].

D. Ion-exchange mechanism

Lenses are made of ionically charged polymers that attract oppositely charged drugs. The drug is released through ion exchange with the tear fluid.

For example, cationic drugs bound to negatively charged hydrogel lenses are displaced by positively charged ions in tears, thus releasing the cationic drugs.

Recent advances in contact lenses

Contact lenses have come a long way since being invented, starting from simple vision correction devices to sophisticated devices that could revolutionize eye care. Some of the recent advances in contact lenses are described below [85].

A. Silicone hydrogel lenses: Silicone hydrogel lenses are advanced compared to traditional hydrogels because silicone hydrogel lenses allow better oxygen permeability. Therefore, more oxygen will come to the cornea and decreased probability of hypoxia complications and

increased comfort of wearing [86]. Modern silicone hydrogel contact lenses have a surface treatment or contain hydrophilic materials that improve wettability to minimize dryness and discomfort. For example, resveratrol contact lens provide antioxidant and anti-inflammatory effects (Table 5) [87].

- B. **Multifocal and presbyopia-correcting lenses:** Multifocal and presbyopia-correcting lenses address the age-related decline in near vision. The wearer will be able to see clearly at both near and far distances with multifocal and presbyopia-correcting lenses. Recent developments in lens design involves materials that have been associated with better visual acuity and fewer visual disturbances compared to multifocal lenses [88].
- C. **Smart contact lenses:** Smart contact lenses are under development. Such lenses are equipped with in-built sensors and technologies to assist in monitoring health parameters and deliver medication [89]. One of the promising applications is smart contact lenses, which can be designed to monitor glucose levels continuously in tears, providing real-time data for diabetes management [90].
- D. **Toric lenses for astigmatism:** Toric lenses are designed to specifically correct astigmatism, a condition arising from an irregular shape in the cornea, among other causes. Modern toric lenses are designed using advanced stabilization technologies to enable proper lens orientation on the eye, thus optimizing visual correction [91].

E. **Nanotechnology:** Nanotechnology has been used to introduce nanomaterials into contact lenses, improving characteristics, such as wettability, oxygen permeability, and protection against UV. The traditional contact lenses will sometimes dry out, thereby causing discomfort and reduced vision. Incorporating nanomaterials in the lens surface can give a hydrophilic or water-loving coating, which enhances moisture retention property of the lens, hence making contact lenses comfortable and minimizing dryness. The cornea requires oxygen to remain healthy. Traditional contact lenses restrict oxygen flow, thus causing discomfort and complications. Nanomaterials can be embedded within the lens material to create microscopic channels that allow more oxygen to penetrate and ensure proper oxygenation of the cornea, such as brimonidine noisome-based contact lens (Table 5) [92].

These advances in contact lens technology have significantly improved the quality of vision correction and the overall experience for millions of wearers worldwide.

Microneedles

Dr. Ernst Kromayer provided the earliest known proof of microneedle use in 1905 when he proposed using motorized dental burs to cure hyperpigmentation and scarring. There was an increase in interest in the delivery of medications by microneedle platforms in the 1960s.

Table 5 Summary of Recent Experimental Studies on Ocular Contact Lens

Sl. No.	Model Drug	Dosage Form	Carrier Platform	Result	References
1.	Timolol	Contact lens	Gold nanoparticles	Encouraged outcomes in animal model to treat glaucoma	[149]
2.	Flurbiprofen	Contact lens	Nanoaggregates	Sustained release of the drug	[150]
3.	Phomopsidione	Contact lens	Nanoparticles	Sustained release of drug for 48 h	[151]
4.	Brimonidine	Soft contact lens	Niosome	Reduced intraocular pressure and treat glaucoma	[152]
5.	Latanoprost	Soft contact lens	Nano-emulsion	Sustained release for glaucoma	[153]
6.	Cyclosporine A	Soft contact lens	Nanoparticles	Treatment of dry eye	[154]
7.	Resveratrol	Contact lens	Hydrogel	Anti-inflammatory and antioxidant effects	[155]
8.	Diclofenac	Contact lens	Nanocapsules	Treatment of ocular inflammation	[156]
9.	Ketorolac	Soft contact lens	Drug –bandage lens	Pain relief	[157]
10.	Ciprofloxacin	Soft contact lens	Nanoparticles	Treatment of bacterial keratitis	[158]
11.	Gentamicin	Soft contact lens	Nanoparticles	Treatment of bacterial conjunctivitis	[159]
12.	Voriconazole	Soft contact lens	Nanoparticles	Treatment of fungal keratitis	[160]
13.	Erythromycin	Soft contact lens	Nanoparticles	Treatment of bacterial blepharitis	[161]
14.	Pilocarpine	Soft contact lens	Nanoparticles	Treatment of glaucoma	[162]
15.	Travoprost	Soft contact lens	Microemulsion	Reduced intraocular pressure	[163]
16.	Bimatoprost	Soft contact lens	Nanocapsules	Treatment of glaucoma	[164]
17.	Dorzolamide	Soft contact lens	Nanoparticles	Used in the eye to treat open-angle glaucoma and high pressure in the eye	[165]
18.	Brinzolamide	Soft contact lens	Nanoemulsion	Reduced intraocular pressure	[166]
19.	Timolol + Brimonidine	Soft contact lens	Nanoparticles	Treatment of glaucoma	[167]
20.	Bimatoprost + Timolol	Soft contact lens	Nanoparticles	Used to treat glaucoma and ocular hypertension	[168]
21.	Dorzolamide + Timolol	Soft contact lens	Nanoparticles	Pressure in the eye lowered by decreasing the production of natural fluids in the eye	[169]

Microneedles are increasingly showing promise as a delivery device to provide precise, less invasive, and localized pharmaceutical administration for ocular illnesses [93]. Administering microneedles to delicate organs, like the eye, can be difficult. To effectively deliver drugs to the eye using microneedles, a number of challenges must be addressed, including the restricted surface area for drug deposition, sensitivity to pressure changes, and variability in the biomechanical properties of ocular tissues. Using conventional hypodermic needles for drug delivery to the intraocular part of the eye is very difficult because of associated pain, irritation, and discomfort [94].

Merits of microneedles

- As possible drug delivery systems, microneedle arrays have many benefits, including minimum invasiveness, the capacity to bypass the human body’s external barriers that reduce the effectiveness of topical formulations, and ease of administration without expert assistance. Poor bioavailability is typically one of the most significant issues that arises when administering drugs to the eyes [94, 95].
- Some types of microneedles, including dissolving microneedles, can be engineered to have a sustained delivery of large molecules, including biologics in ocular tissues. This attribute may allow reduced frequency of administrations for chronic ocular conditions [96].
- Due to the small size, microneedles cause the least discomfort, which may lead to the improvement of needle phobia and patient compliance, especially when administered intravitreal injections. Use of microneedles reduce needle stick injuries and provide safety [96].
- A drug can also be delivered specifically to a chosen ocular site, such as the suprachoroidal space, therefore providing targeted therapy with possibly fewer systemic exposures and side effects [96].
- It provides localized action and reduces tissue trauma compared to conventional hypodermic needles [97].

Limitations of microneedles

- Dissolving microneedles have low mechanical strength, which complicates tissue penetration. Some of the polymers used in fabrication are hygroscopic, reducing the physical stability of the final product [96].
- Small size limits the capacity of microneedles for drug loading and hence might require multiple injections to reach therapeutic levels, especially in the case of chronic ocular diseases.
- Hollow microneedles are more brittle because of the material and small size. The risk of blockage and breakage is more likely to occur during insertion, which would compromise the safety and efficacy of the drug delivery system.
- Fixing microneedle patches onto the ocular surface is not easy. Microneedle patches intended for sustained drug delivery may lose efficacy if the microneedle patches fall off from the application site [97].

- The invasive nature of microneedles is likely to cause irritation and discomfort, which may impact patient compliance. For successful adherence to treatment regimens, ensuring patient comfort with microneedle-based ocular therapy is critical [97]

Types of microneedles in ocular delivery system

Different criteria can be used to classify microneedles, which come under vaccine delivery and diagnostics. Microneedle categorizations are mainly dependent on geometry, the base material used to fabricate the systems, fabrication technology, and drug-loading technique for targeted delivery of intended drugs [97]. The different types of microneedles are as follows: solid microneedles; solid-coated microneedles; dissolving microneedles; hollow microneedles; and hydrogel-forming microneedles.

Of these types of microneedles, solid-coated, dissolving, and hollow microneedles are frequently used for ocular therapy according to recent trends.

- Solid-coated microneedles:** Coated microneedles are designed on the “coat-and-poke” principle, where therapeutic agents are loaded onto the tips of solid microneedles, then inserted into the target ocular tissue (Table 6). Coated microneedles dissolve quickly after application to directly deliver the drug upon insertion. This method overcomes the structural barriers in the eye, enables efficient delivery, and significantly reduces the dose compared to traditional methods of drug administration. Solid-coated microneedles create micron-sized channels for easier and more effective drug delivery in a controlled manner in the sclera and cornea tissue. The needles are removed after dissolution of the coating and leave the pores for drug penetration. These coated microneedles frequently are made of non-biodegradable materials, such as stainless steel and silicon probes that provide excellent mechanical properties. Coated microneedles also have limitations. The needle imposes a limited drug-loading capacity and hence may require frequent administration with limited sustained-release ability (only limited by the surface area of the needle). Moreover, an uneven distribution of coatings or improper coating materials can also cause the release of drugs to be inconsistent and ineffective in targeting chronic ocular diseases. In addition, the process of coating can leave needle tips less sharp, which reduces the ability to penetrate and deliver [98].
- Dissolving microneedles:** Dissolving microneedles are fabricated by incorporating drug molecules into biodegradable and biocompatible polymers, such as polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), and hyaluronic acid (Table 6). These polymeric microneedles rapidly dissolve in the presence of tear fluid in a few minutes and release the therapeutic agents into the target site. While carrying the drug directly to the eye, administration of dissolving microneedles is quite simple (patient-friendly). Typically only gentle thumb pressure is required on top of eye surface to place contact

Table 6 Summary and Comparative Overview of Microneedle Types and Applications in Targeted Ocular Drug Delivery

Sl. No.	Microneedle Types	Characteristics	Specific Applications	Recent Approaches	References
1.	Solid (uncoated) microneedles	Sharp solid MNs fabricated from metals or silicon that create micro channels upon insertion; typically followed by topical drug application over pores.	Enhancing permeability of drug patches by forming micro pores in the cornea or sclera	Enhanced delivery of anti-glaucoma drugs (e.g., timolol) and imaging agents into sclera for diagnostics	[93]
2.	Coated microneedles	Solid needles coated with drug formulations that dissolve immediately upon insertion ("coat-and-poke"); limited by surface-area drug loading	Fast deposition of small molecules (pilocarpine and fluorescein) and macromolecules (proteins and DNA) into ocular tissues with high bioavailability	Delivery of anti-VEGF biologics and corticosteroids for macular degeneration and uveitis	[170]
3.	Dissolving microneedles	Made from biodegradable polymers (PVA, PVP, and hyaluronic acid); dissolve within minutes in aqueous environment; leave no sharp waste; limited drug load and patch curvature issues	Patient-friendly delivery—e.g., contact lens-based MNs—for small molecules (like pilocarpine); sustained release via formulation tuning	Nanoparticle-loaded dissolving MNs for sustained delivery of latanoprost in glaucoma models	[107]
4.	Hollow microneedles	Miniaturized hollow needles (150 µm+, 27–35 gauge) fabricated from glass, metals, or polymers; costly and brittle with risk of blockage or breakage	Direct injection of liquid formulations, including nanoparticles/microparticles into ocular tissues; also used in transdermal vaccines/insulin	Suprachoroidal delivery of gene therapy vectors and long-acting anti-inflammatory drugs	[97]
5.	Hydrogel-forming microneedles	Swellable, crosslinked hydrogel MNs (e.g., chitosan, hyaluronic acid, and PVA); absorb interstitial fluid, forming a drug-laden gel network for sustained release	Controlled and sustained ocular drug release; potential replacement for frequent intravitreal injections	Extended release of antibiotics for corneal infections using hydrogel MN patches	[171]

lens. Indeed, dissolving microneedles have been used in lens-based contact lenses to improve drug penetration as a familiar mode of treatment delivery for patients. This method has been shown to deliver small molecules, such as pilocarpine to the anterior segment of the eye. The major benefit of dissolving microneedles is biocompatibility and biodegradability. Because the microneedles degrade *in situ* there are no biohazardous sharps to dispose of, which can leave fragments of a solid microneedle behind in the eye in the case of breakage [99].

C. Hollow microneedles: Hollow microneedles are micro-scale needles that are used to inject liquid formulations into the skin, similar to conventional hypodermic needles. Normally hollow microneedles are made of stainless steel, silicon, glass, or biodegradable polymers (Table 6). Hollow microneedles are much smaller than traditional hypodermic needles, ranging from 27–35 gauge (outer diameter) and 150 µm in length compared to conventional needles size (usually 26–30 gauge and ≥ 2 mm in length). The smaller size also enables localized and minimally invasive ocular delivery, increasing patient comfort and possibly improving treatment compliance. For ocular applications, hollow microneedles are configured to contain and maintain the drug formulation inside the lumen of the needle, providing direct delivery into ocular tissues upon insertion. It is very useful to have these systems in place with nanoparticles and microparticulate formulations, which mediate target-infused release. Hollow microneedles have also been used in post-ocular therapy for transdermal delivery (e.g., insulin and vaccines) [96]. Hollow microneedles are fabricated using various methods, such as the micropipette puller technique, where a borosilicate glass micropipette tube is stretched and formed to develop the hollow wish. Although borosilicate tubes could be applied in experimental settings but the poor resistance would make hollow microneedles subject to easy breakage. Thus, hollow microneedles are inappropriate for regular clinical use. Materials, like stainless steel and some biodegradable polymers, are used for stronger material and safety [100].

Recent microneedle advances

Recent advances in microneedle technology have greatly improved ocular drug delivery, providing a precise, minimally invasive treatment for a range of eye diseases.

A. Minimally invasive for ocular delivery: Bypassing the barriers, like the tear film and conjunctiva, microneedles can transport medications straight into ocular tissues, such as the cornea, sclera, or retina. By directing the medication to the eye, all of the systemic adverse effects linked to traditional administration methods are reduced [97]. Recent advances in microneedle fabrication techniques, materials, dimensions, delivery routes, and therapeutic applications for ocular drug delivery are summarized in Table 7. Several microneedle-based products for ocular drug delivery have reached clinical development or commercialization, targeting both anterior and posterior

Table 7 Summary of Different Materials and Fabrication Techniques for Ocular Microneedles

Sl. No.	Materials	Fabrication Technique	Materials Properties	Dimension	Volume	Target Location	Applications	Clinical Implications	References
1.	Glass	Micro-pulling process	Biocompatible, smooth surface	700-800 μm , 25° bevel angle	10-35 μL	Sclera	Distribution of solution and nanoparticles in sclera	Enhanced drug distribution without tissue damage	[172]
2.	Glass	UV lithography	Transparent, mechanically robust	300 μm long array of MNs	10-35 μL	Sclera	Delivery of rose bengal dye in porcine sclera	Precise dosing for anterior segment therapies	[173]
3.	Glass	Thermal technique	High accuracy in nanoparticle delivery	750 μm	50 μL	Supra-choroidal spaces	Delivery of nano- (20 and 200 nm) and micro-particles (2 and 10 μm)	Improved posterior drug targeting	[174]
4.	Metal	Laser cutting	High tensile strength, corrosion-resistant	400, 500, and 600 μm , 27, 29, and 30 G	<10 μL	Sclera	Delivery of sunitinib-loaded Cs-g-PNIPAAm hydrogel	Sustained drug release with minimal tissue disruption	[94]
5.	Metal	CNC machining	Customizable bevel angles, strong materials	<1 mm, 30 and 33 G	200 μL	Scs	Gravity-mediated targeting of perfluorodecalin encapsulated with fluorescein-tagged polystyrene nanoparticles to SCS	Effective treatment for macular edema	[100]
6.	Metal	Precision casting	Robust and flexible for repetitive use	750 μm long, 33 G	50 μL	Scs	Distribution of nanoparticles (200 nm) in SCS	Reduced complications in posterior delivery	[175]
7.	Metal	Electrochemical etching	High biocompatibility, sharp edges	700 μm long, 30 G	50 μL	Scs	Trans scleral/sub retinal delivery of adeno-associated virus (AAV8) vectors	Gene therapy delivery with enhanced targeting	[176]
8.	Metal	Microfabrication	Adjustable flow rates, resilient	750 μm long, 33 G	50 μL	Scs	Distribution of viscous non-Newtonian solutions in SCS	Delivery of rheologically challenging solutions	[177]
9.	Metal	Laser ablation	Thermo-sensitive, adaptive designs	750 μm long, 27, 29, and 30 G	30, 50, and 100 μL	Sclera	Delivery of thermo-responsive depot-forming hydrogels	Long-term drug depot for chronic conditions	[20]
10.	Metal	CNC machining	Lightweight, biocompatible	750 μm , 30 G	10–20 μL	Supraciliary route	Distribution of brimonidine-loaded microspheres (20–45 μm) in various supranasal and temporal locations	Improved intraocular pressure reduction	[178]

Table 8 Overview of Marketed Microneedle Products for Ocular Drug Delivery Products

Sl. No.	Product Name	Company	Application	References
1.	SCS Microinjector™	Clearside Biomedical	Delivering drugs to the suprachoroidal space for retinal and choroidal diseases	[179]
2.	Microneedle array	Re-Vana Therapeutics	Sustained drug delivery for diseases, like glaucoma and macular degeneration	[98]
3.	Eyedropper microneedles	Georgia Tech	Delivering drugs directly into the cornea or conjunctiva	[180]
4.	NanoJect™	Microdermics	Minimally invasive delivery of ophthalmic drugs to anterior or posterior segments	[181]
5.	EyeMN™	Ophthalmic Innovations	Painless delivery of drugs for retinal diseases and uveitis	[182]

segment diseases. An overview of marketed and advanced microneedle products is provided in **Table 8**.

- B. Enhanced drug delivery systems:** Microneedles allow targeted delivery of drugs into ocular tissues, which enhances the therapeutic outcome. Microneedles can penetrate through barriers, such as the cornea and sclera, to ensure effective drug administration [101].
- C. Polysaccharide-containing microneedles:** Polysaccharides are vital structural components of the eye that have a crucial role in maintaining the normal physiologic state [102]. Polysaccharide-based microneedle systems are said to be studied for the development of ocular drug delivery because these biocompatible materials may improve the profile of drug release and reduce adverse effects. Polysaccharides, for example, hyaluronic acid, offer structural support and hydration to the cornea, and therefore maintain the cornea as a transparent, refracting tissue. Polysaccharides with collagen make a matrix that gives elasticity and toughness to the sclera and protects the eye against outer pressure and injury [103, 104].
- D. Autonomous insertion:** Innovations in autonomous microneedle insertion techniques have improved precision in delivering drugs to specific intraocular sites, enhancing treatment efficacy and safety. Access of the suprachoroidal space by microneedles to the back of the eye continues to allow targeted delivery. This method has proven efficacy in treating posterior segment diseases [105].

Clinical translation bottlenecks

The clinical translation of ocular drug delivery systems, such as ocular inserts, contact lenses, and microneedles, face several tailbacks. Sometimes it is difficult to recruit and maintain the active participation of patients because it may lead to increased risks of irritation, infections, or tissue damage or blurred vision. These effects may reduce patient compliance and adherence to the therapy. Regulatory aspects are another challenge that requires long-term safety and efficacy for drug device combination products. Technical challenges include large-scale production, which maintains the sterility and stability for the shelf life of the product. All these challenges slow the journey of these new delivery systems from research labs to real patient use [106, 107].

Regulatory perspectives

Ophthalmic formulations are considered a class of complex products challenging in chemistry, manufacturing, and control by the US Food and Drug Administration (FDA). The extended-release oral medicines for ocular disease were issued by the US FDA in 1997 [108]. The WHO, the FDA, and the European Medicines Agency (EMA) are prominent and highly respected regulatory bodies, but according to the Federal Food, Drug & Cosmetic Act (FD & C Act [1938]), the FDA only has legal authority to regulate medical devices in the US [109].

Regulatory strategies for ocular inserts ensures its safe, effective, and easy use for patients. The FDA requires ocular inserts to be sterile under 21 CFR 200.50 and to pass biocompatibility tests (ISO 10993-1) to ensure ocular inserts will not cause irritation or allergic reactions. Stability testing, as per ICH Q1A-Q1E, must confirm that the product maintains quality over time and a quality-by-design (QbD) approach under ICH Q8 (R2) helps fine-tune the formulation and manufacturing to consistently deliver safe, high-quality inserts [108]. Title 21 CFR, Parts 800-1299, contains information about medical devices as well as products that generate radiation. The Premarket Notification (510K) Guidance Document for Class II Daily Wear Contact Lenses was published by US regulatory authorities in 1994. In the US contact lenses have been regulated by the FDA since the 1960s with soft hydrogels. Following the 1976 Medical Device Amendment, extended-wear lenses became Class III devices, which require pre-market authorization. Daily-wear and RGP lenses were classified as Class II in 1994 with all contact lenses falling under Class II by 1997. Both are low-risk and need Institutional Review Board approval [110]. The first regulatory policy for microneedle-products was issued in 2017 to guide industries on such products under section 201(h) of the federal FD&C Act, 21 U.S.C. § 321(h). The guidance outlines the regulatory pathway for marketing these devices for aesthetic use [111].

Methodology of data collections

This comprehensive review search was conducted on recent advances in ocular delivery systems with a focus on ocular inserts, contact lenses, and microneedles. The databases and search engines used included Google Scholar, PubMed,

NCBI, NIH, Taylor & Francis, and the Wiley Online Library. The search covered publications from 2003–2025 by using combinations of keywords, such as “ocular delivery systems,” “ocular inserts,” “drug delivery contact lenses,” “ocular microneedles,” “sustained release,” and “recent advancements.” Reference lists of selected articles were also screened to identify additional relevant publications. Data from the included studies were synthesized to highlight current progress, key innovations, and gaps for future research and the images were drawn using Biorender.com.

Conclusion

The recent advances in ocular inserts, contact lenses, and microneedles have shown significance translational value and promise for sustained drug release, site-specific delivery, and enhanced patient compliance over conventional therapy. These innovations represent a potential kinetic middle ground from basic laboratory research to clinical outcome improvements by improving bioavailability, decreasing dosing frequency, and minimally invasive administrations. The major challenges with these systems are large-scale manufacturing, long-term biocompatibility, patient compliance, and adherence. Increase integration of diagnostic, monitoring, or adjunct therapeutic functions in these devices would likely require better effectiveness.

Future perspectives

The future trends would aim at combining current advances in ocular drug delivery systems with modern day smart drug delivery system. The delivery systems in our body should be able to discriminate and respond to real time physiologic signals, like intraocular pressure, composition of tears, or a state of disease progression for timely drug release. This will allow for an individualized therapeutic approach, enabling drug type, dose, and delivery route to be matched with genetic profiling as well as patient-specific disease biomarkers to achieve the best benefit-risk profile. In addition, next-generation delivery platforms, such as biotechnical ocular inserts, nanocarrier-based microneedles, and multi-functional

contact lenses are projected to bring together the benefits of sustained release, targeted delivery and diagnostics all in one system offering high efficacy patient-centric ocular disease management.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Consent for publication

Not applicable.

List of abbreviations

SNEDDS	self-nano emulsifying drug delivery systems
IOP	intraocular pressure
BAB	blood-aqueous barrier
BRB	blood-retinal barrier
RPE	retinal pigment epithelium
HA	hyaluronic acid
SCS	suprachoroidal space
WHO	World Health Organization
FDA	Food & Drug Administration
EMA	European Medicine Agency
IRB	Institutional Review Board

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